Review

Ticagrelor: clinical development and future potential

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Platelets participate centrally in atherothrombosis, resulting in vessel occlusion and ischaemia. Consequently, optimisation of antiplatelet regimens has the potential to further reduce the residual burden of morbidity and mortality associated with atherosclerosis. Ticagrelor is a potent oral platelet $P2Y_{12}$ receptor antagonist that (1) inhibits a central amplification pathway of platelet activation directly as well as via an active metabolite, (2) has a rapid onset and offset of antiplatelet action that remains consistent in the circulation during twice-daily administration and is amenable to reversal, (3) has inverse agonist properties, and (4) demonstrates pleiotropic effects that contribute to anti-thrombotic, anti-inflammatory and vasodilatory properties. These advantageous characteristics of ticagrelor have translated to beneficial clinical outcomes in patients with acute coronary syndromes or ischaemic stroke, during prolonged maintenance therapy in specific high-risk populations, and following percutaneous coronary intervention but not definitively following coronary artery bypass graft surgery or in peripheral artery disease patients. Novel innovative strategies aim to reduce the risk of bleeding during dual antiplatelet therapy via shortening the duration of treatment and replacing the standard-of-care with ticagrelor monotherapy. In cases where aspirin is an essential component in secondary prevention, dose modification when combined with ticagrelor may hypothetically provide desirable clinical outcomes following appropriate clinical assessment as predicted by pharmacological studies. Overall, the future management of acute coronary syndromes could potentially involve the dichotomisation of antithrombotic therapies, whereby only those with high-risk of ischaemia, without a high-risk of bleeding, receive ticagrelor plus very-low-dose aspirin, while ticagrelor monotherapy is administered to the remaining majority.

Keywords

Ticagrelor; $P2Y_{12}$ receptor; Aspirin; Acute coronary syndrome; Dual antiplatelet therapy; Chronic coronary syndromes; Coronary artery disease; Percutaneous coronary intervention; Coronary artery bypass grafting

1. Introduction

The formation of atherosclerotic plaques increases the risk of arterial thrombosis that can result in vascular occlusion and subsequently ischaemia or infarction of the distal tissue. The most devastating conditions that manifest clinically as a result of this process include cardiovascular death, myocardial infarction (MI) and stroke, otherwise collectively known as major adverse cardiovascular events (MACE), markedly contributing to the global burden of premature morbidity and mortality [1]. In the coronary arteries, atherothrombosis may present rapidly as an acute coronary syndrome (ACS), which includes ST-elevation MI (STEMI) and non-ST-elevation ACS (NSTE-ACS). Subclinical atherothrombosis may also contribute to the progression of atherosclerotic disease in patients with chronic coronary syndromes (CCS), which includes so-called stable coronary artery disease (CAD) or an ACS event more than 1 year ago [2–6]. Platelets are central to this pathophysiological process and, therefore, the development of antiplatelets aims to reduce the risk of MACE by therapeutically antagonising various mechanisms involved in the activation and aggregation of platelets [7]. The combined inhibition of thromboxane A_2 (TXA_2) synthesis, a product of a chain of enzymes including platelet cyclo-oxygenase (COX)-1, and platelet activation by adenosine diphosphate (ADP) via the $P2Y_{12}$ receptor in dual antiplatelet therapy (DAPT) with aspirin and a platelet $P2Y_{12}$ receptor antagonist ('$P2Y_{12}$ inhibitor'), respectively, forms the cornerstone of management for ACS patients [2–6].

While contemporary advances have improved the control of modifiable risk factors, reduced complications associated with percutaneous coronary intervention (PCI) [8], and reduced the risk of recurrent ischaemia post-ACS, there remains a significant degree of residual risk in patients with CAD. Ticagrelor provides several hypothetical and pharmacological advantages over aspirin and other oral $P2Y_{12}$ inhibitors that have the potential to optimise patient outcomes in novel antiplatelet strategies by reducing the risk of ischaemia in DAPT or reducing the risk of bleeding as a monotherapy [9, 10]. In addition, these strategies may be extended to benefit patients with other atherosclerotic conditions, such as ischaemic stroke and peripheral artery disease (PAD). It has been almost a decade since our last review of the clinical uses of ticagrelor [11], since when numerous large-scale trials have been conducted (Table 1, Ref. [12–18], Table 2, Ref. [19–23] and Fig. 1). This review aims to summarise pharmacological and clinical characteristics of ticagrelor and highlight the latest guidelines, developments and future potential in clinical practice.

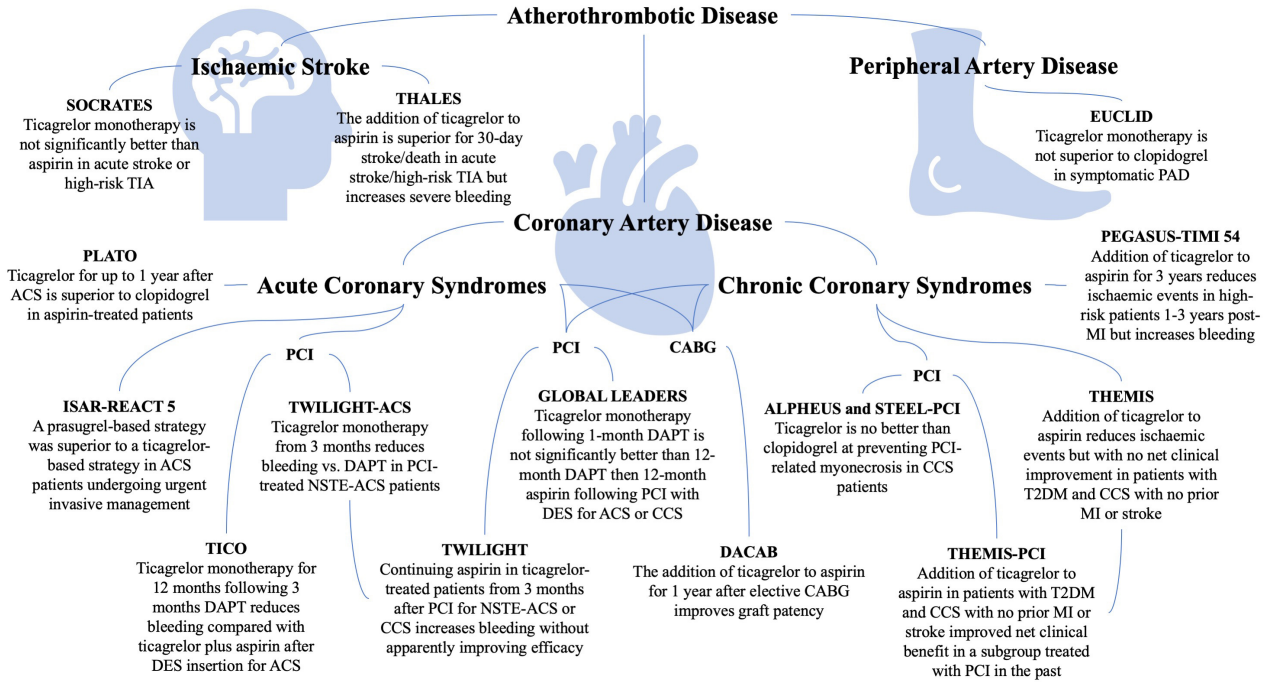

Fig. 1. Visual abstract of randomised clinical trials and pre-specified sub-studies relevant to the clinical development of ticagrelor in atherothrombotic disease, categorised by clinical disease and treatment strategy.

2. The role of the $P2Y_{12}$ receptor in platelet function

Platelets have a critical function within the vascular system to regulate haemostasis. Injury to the vascular endothelium exposes underlying extracellular matrix and prothrombotic factors, resulting in a cascade of events that stimulate platelet activation, a process involving structural shape change, degranulation, and platelet aggregation. Degranulation involves the release of pro-inflammatory and prothrombotic α-granules and dense granules, the latter containing a high concentration of ADP. Aggregation involves activation of the glycoprotein IIb/IIIa receptor, which allows adjacent platelets to bind to each other via fibrinogen. A number of agonists may initiate platelet activation including ADP, thrombin, TXA_2, von Willebrand factor and collagen [24, 25]. Subsequently, the release of ADP from dense granules amplifies the platelet response regardless of the initial stimulus and, therefore, ADP is considered a critical agonist involved in platelet activation.

The nomenclature assigned to G-protein-coupled receptors that are activated by nucleotides, such as ADP, is P2Y. To date, eight of these purinergic receptors have been identified [26], of which two are functionally present on the surface of platelets: G_q-coupled $P2Y_1$ and G_i-coupled $P2Y_{12}$. Both are required for ADP-induced platelet aggregation: $P2Y_1$ activation initiates platelet activation and shape change, including through mobilisation of intracellular calcium ions, whereas $P2Y_{12}$ activation amplifies this process [27, 28]. Inhibition of either receptor is sufficient to inhibit ADP-induced platelet aggregation [29].

The primary member of the G_i family that the $P2Y_{12}$ receptor couples with is $G\alpha_{i2}$ [25]. In response to ADP activation, the $G\alpha_i$ subunit inhibits adenylate cyclase which results in a reduction in cyclic adenosine monophosphate and consequently reduces the phosphorylation of vasodilator-stimulated phosphoprotein by protein kinase A. This subsequently leads to glycoprotein IIb/IIIa activation, the final mechanism involved in platelet aggregation [30–32]. Mediated via Gi $\beta\gamma$ subunits, $P2Y_{12}$ activation also leads to activation of phosphoinositide 3-kinase (PI3K), Akt, Rap1b and potassium channels, resulting in additional amplification of platelet activation [25]. The importance of the PI3K pathway in platelet activation and thrombosis has been emphasised in PI3Kγ deficient mice that were protected from lethal ADP-induced thromboembolism [33].

Antiplatelet drugs that targeted the $P2Y_{12}$ receptor were widely used before the receptor was cloned for the first time in 2001 [25, 34]. Several *ex-vivo* studies have established the $P2Y_{12}$ receptor as a key component involved in the process of haemostasis, particularly the potentiation of dense granule secretion [35], glycoprotein IIb/IIIa activation [36–38] and thrombosis [39, 40]. $P2Y_{12}$ receptors contribute to the generation of TXA_2 under certain experimental conditions [41] but this is of doubtful physiological relevance [42]. Importantly, $P2Y_{12}$ receptor activation also amplifies the secretion of α-granules, upregulating pro-inflammatory responses such as the expression of P-selectin on the platelet

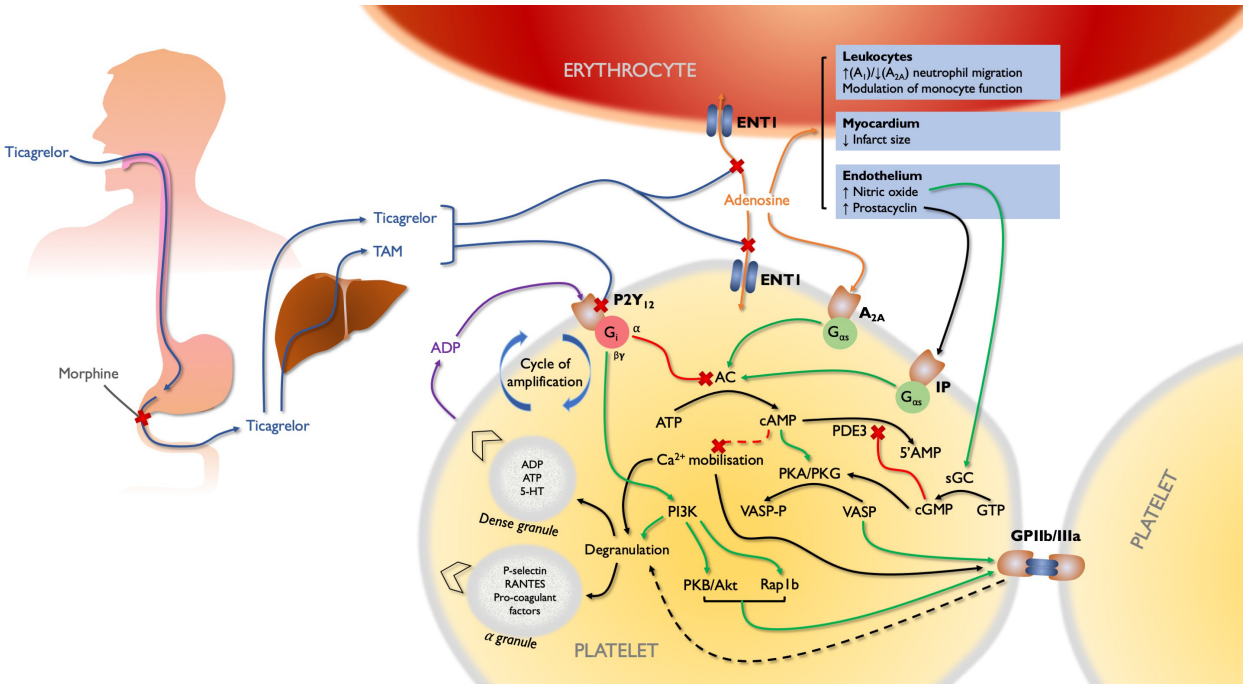

Fig. 2. Pharmacology of ticagrelor. Morphine slows gastric emptying and therefore may delay the onset of action of ticagrelor, which is absorbed in the small intestine. Once in the circulation, ticagrelor acts directly, as well as indirectly via ticagrelor active metabolite (TAM), as (1) a non-competitive antagonist and inverse agonist of the $P2Y_{12}$ platelet receptor; and (2) a weak antagonist of adenosine uptake via erythrocyte and platelet equilibrative nucleoside transporter-1 (ENT1). Platelet activation and subsequent degranulation leads to the release of ADP, which activates the $P2Y_{12}$ receptor and initiates intracellular G_i-coupled signalling pathways. Inhibition of adenylate cyclase (AC) reduces the cAMP/ PKA/PKG/ VASP-P pathway by $G_{i\alpha}$, or activation of the PI3K/PKB/Akt/Rap1b pathway by $G_i\beta\gamma$, results in the activation of the glycoprotein (GP) IIb/IIIa integrin, leading to platelet aggregation and amplification of degranulation via an 'outside-in' signalling pathway. Alternatively, ENT1 antagonism has the potential to elevate extracellular adenosine that acts via at least three distinct pathways that suppress the levels of VASP (A2A, IP and sGC activation) and therefore complement the effects of $P2Y_{12}$ inhibition by ticagrelor.

surface and consequent platelet-leukocyte interactions [43, 44]. Therefore, it is evident that activation of the platelet $P2Y_{12}$ receptor plays a central role in the initiation and amplification of platelet activation and all the prothrombotic and pro-inflammatory responses that accompany this (Fig. 2).

Considering that the $P2Y_{12}$ receptor is constitutively expressed on platelets and a limited number of other cell types, present in the central nervous system and on vascular smooth muscle cells, this receptor represents a desirable target for antiplatelet therapy [11].

3. Mechanism of action of ticagrelor

Ticagrelor, previously identified as AZD6140, belongs to the cyclopentyl-triazolopyrimidine class of $P2Y_{12}$ inhibitors that possess structural similarities to the natural $P2Y_{12}$ receptor antagonist adenosine triphosphate (Fig. 3). In contrast to other widely used oral $P2Y_{12}$ inhibitors in the thienopyridine subclass (clopidogrel and prasugrel), ticagrelor exerts its antiplatelet activity by reversibly binding to the $P2Y_{12}$ receptor at a site that is distinct from the ADP binding site, resulting in a non-competitive inhibition of the ADP-induced signalling pathway [45]. This effect is also achieved by ticagrelor active metabolite (TAM), which has similar potency [46]. Furthermore, ticagrelor demonstrates features of an inverse agonist, whereby maintained treatment reduces the basal G_i-coupled signalling in the absence of ADP stimulation [31, 47].

Interestingly, ticagrelor exerts a well-documented antagonistic effect on platelet and erythrocyte equilibrative nucleoside transporter (ENT)1 (Fig. 2), potentially resulting in an increase in extracellular adenosine by inhibiting cellular adenosine uptake [10, 47–49]. Due to its low potency as an ENT1 antagonist relative to its high potency as a $P2Y_{12}$ inhibitor, the extent of this effect is marginal at therapeutic concentrations of ticagrelor, as demonstrated by conflicting results from different studies, with some studies [49–53] but not others showing elevated plasma adenosine levels in ticagrelor-treated patients [54]. Enhanced levels of extracellular adenosine have the potential to contribute to the antiplatelet response via the activation of G_s-coupled A_{2A} receptors and resultant activation of adenylate cyclase [55]. Effects on adenosine metabolism have been purported to explain several advantageous pharmacological characteristics of ticagrelor that are considered pleiotropic when compared to thienopyridines, including: coronary vasodilation [56]; reduced myocardial infarct size secondary to the upregulation and activation of cardio-protective COX-2 and endothelial nitric oxide synthase [57]; and regulation of the innate immune system [48].

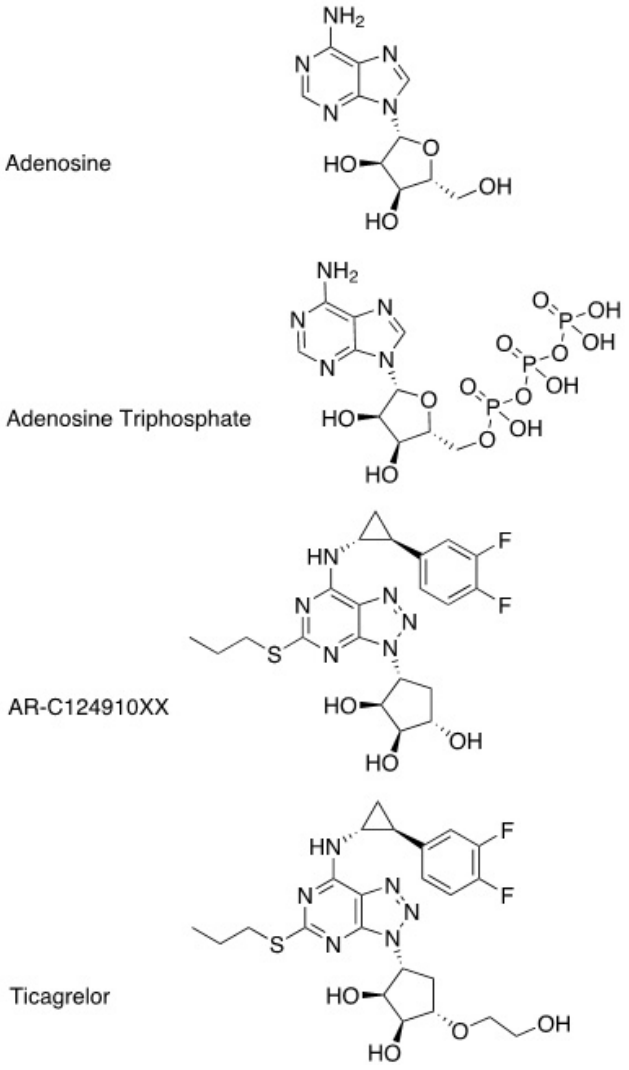

Fig. 3. Chemical structures of adenosine, adenosine triphosphate, AR-C124910XX (ticagrelor active metabolite) and ticagrelor.

Considering that studies have shown ticagrelor to impact coronary blood flow responses and severity of adenosine-mediated side effects during adenosine infusions [56, 58], it remains possible that ticagrelor affects adenosine concentrations in localised tissues. Hypothetically there may be local enhancement of adenosine concentration at the platelet cell membrane, which may produce therapeutic effects that are not reflected by measurements of systemic plasma adenosine level [31]; however, this mechanism remains to be proven and some preclinical studies have not confirmed a beneficial adenosine-mediated effect of ticagrelor on infarct size [59].

The anti-inflammatory effects of ticagrelor may be an important contributor to clinical outcomes. In an endotoxaemia model, there was evidence that ticagrelor exhibited greater anti-inflammatory properties when compared to clopidogrel. Both suppressed the release of tumour necrosis factor-α and interleukin (IL)-6, with greater effect of ticagrelor treatment reflecting the higher associated level of platelet $P2Y_{12}$ inhibition [60]. Other studies have also identified anti-inflammatory effects of ticagrelor in mouse [61] and human models [62]. The potential implications of this is highlighted in studies that have, firstly, suggested that ticagrelor inhibits thromboinflammatory processes and may improve lung function in patients with pneumonia [63] and, secondly, shown lower mortality as a result of pulmonary adverse events and sepsis associated with ticagrelor compared with clopidogrel treatment [64].

An *in vitro* study identified that ticagrelor, but not the clopidogrel active metabolite, activates endothelial nitric oxide synthase [65]. These effects were independent of $P2Y_{12}$ or adenosine receptor mediation and therefore suggests that alternative mechanisms are yet to be identified.

4. Pharmacokinetics of ticagrelor

Ticagrelor has a mean absolute oral bioavailability of 36% [66]. The absorption of ticagrelor is rapid and reaches a maximum plasma concentration (t_{max}) within 1.3–2 hours of ingestion [67, 68]. Once in the bloodstream, ticagrelor does not require hepatic transformation as it already exists as a pharmacologically active compound. There are ten metabolites of ticagrelor [46]. The predominant active metabolite is AR-C124910XX (ticagrelor active metabolite, TAM; Fig. 2), a product of the cytochrome P450 (CYP)3A4/5 enzymes [69], which reaches peak plasma concentration (C_{max}) in 1.5–3 hours (t_{max}). The peak plasma concentrations of TAM are approximately 30% of the parent compound. Ticagrelor exhibits linear and predictable pharmacokinetics with single oral doses up to 400 mg and multiple doses up to 300 mg twice daily (BD): the C_{max} and area under the curve (AUC) of ticagrelor and its active metabolite increase in a dose-dependent manner, while the t_{max}, terminal phase half-life ($t_{1/2}$)and plasma oral clearance are independent of the dose. These findings are broadly consistent in healthy participants [67, 68] and patients with stable CAD [70] or ACS [71]. The majority of ticagrelor and its metabolites are excreted via the biliary and intestinal system, while there is minor renal involvement [46]. The mean $t_{1/2}$ of ticagrelor and its active metabolite in healthy subjects are 7.1–8.5 hours and 8.5–10.1 hours, respectively [68].

There are several clinically significant pharmacological interactions between ticagrelor and other medications. While ticagrelor is primarily a substrate of CYP3A4, it also mildly inhibits the same isozyme [72], and therefore co-administration with CYP3A4 substrates with a narrow therapeutic index (e.g., ergot alkaloids) is discouraged due to an increased risk of elevated exposure [73]. In addition, strong CYP3A4 inhibitors (e.g., ketoconazole and clarithromycin) are contraindicated since they potentially lead to excessive ticagrelor levels and strong CYP3A inducers (e.g., phenytoin and carbamazepine) are discouraged since they may risk sub-therapeutic ticagrelor levels [50, 73]. With greater relevance to cardiovascular disease, the C_{max} and AUC of simvastatin 80 mg (also a CYP3A substrate) is increased by 81% and 56% respectively when co-administered with ticagrelor [74]. Sim-

vastatin doses greater than 40 mg therefore should not be co-prescribed with ticagrelor [73]. Encouragingly, there was no increase in statin-related adverse reactions reported in the 90% of patients in the PLATO study who received both a statin and ticagrelor [12].

Ticagrelor is also a substrate and inhibitor of the intestinal P-glycoprotein transporter and administration of ticagrelor during treatment with digoxin (a P-glycoprotein substrate) led to 75% and 28% increases in the C_{max} and AUC of digoxin, respectively [75]. Therefore, the combination requires appropriate monitoring to avoid digoxin toxicity [73].

Various studies have identified that the administration of morphine delays the absorption and onset of action of oral $P2Y_{12}$ inhibitors [76–79]. Opioid receptor agonists are associated with a marked delay in gastric emptying and intestinal absorption [80]; since oral $P2Y_{12}$ inhibitors are almost exclusively absorbed in the intestine [46], their absorption can be delayed for hours by opiates. This effect is particularly important to consider when aspirin and an oral $P2Y_{12}$ inhibitor such as ticagrelor are required to prevent acute stent thrombosis, with potentially catastrophic consequences [81–83]. In these patients, administration of a parenteral antithrombotic drug to cover the delayed absorption may reduce the risk of acute stent thrombosis, such as a 6-hour infusion of the glycoprotein IIb/IIIa antagonist tirofiban [84], the low-molecular-weight heparin enoxaparin [85, 86] or the intravenous $P2Y_{12}$ inhibitor cangrelor [87].

There is currently no evidence that the pharmacogenetic profile of ticagrelor impacts the clinical outcome in patients with ACS. In a genome-wide association study, three single-nucleotide polymorphisms were identified (SLCO1B1, UGT2B7, CYP3A4) that influenced the pharmacokinetics of ticagrelor and its active metabolite, but not to an extent that interfered with the safety or efficacy of the regimen [88]. In addition, common variations in the ENT1 genotype are not associated with altered clinical outcomes following the administration of ticagrelor or clopidogrel [89].

5. Pharmacodynamics of ticagrelor

Both ticagrelor and clopidogrel are widely used oral $P2Y_{12}$ inhibitors; however, there are a few important differences that highlight favourable characteristics of ticagrelor in the context of clinical practice.

As a feature of thienopyridines, clopidogrel irreversibly antagonises $P2Y_{12}$ receptors for the duration of the platelet's lifespan, which is approximately seven-to-ten days [90]. The implication of this is that, if urgent surgery is required in a patient taking clopidogrel, there is an increased risk of life-threatening bleeding if insufficient time elapses between drug cessation and surgery [91], particularly in those who are high responders to clopidogrel [92]. Thienopyridines are prodrugs that require hepatic transformation into pharmacologically active compounds by CYP isozymes. The formation of the active metabolite of clopidogrel is a two-step CYP-mediated process and, therefore, is susceptible to inter-individual variation in CYP activity, in particular that of CYP2C19, as well as various other factors [93–96]. This may be an important contributing factor to clopidogrel resistance, which leaves approximately 30% of patients susceptible to adverse cardiovascular events [97–101].

Unlike thienopyridines, ticagrelor binds reversibly to $P2Y_{12}$, resulting in declining levels of platelet inhibition from 24 hours after cessation, but also provides adequate platelet inhibition if a single dose is missed since the subsequent maintenance dose is sufficient to restore a high level of platelet inhibition [71, 102]. Because ticagrelor's chemical structure enables it to directly interact with the $P2Y_{12}$ receptor without requiring metabolism, the peak inhibition of platelet aggregation is achieved rapidly, with high levels of inhibition achieved within 30 minutes and reaching peak within 2 hours of a single dose in stable patients [102], in comparison to clopidogrel, which can take 4–8 days using a conventional maintenance dose or 4–6 hours after a high loading dose (600 mg) [103, 104]. The rapid onset and offset of ticagrelor are desirable qualities of an antiplatelet agent that provide greater flexibility in clinical practice. Furthermore, ticagrelor and its active metabolite, with equivalent potency [46], appear to provide consistent platelet inhibition at mean levels that are greater than with either clopidogrel, even in those who are most responsive to it [50, 102, 105, 106], or prasugrel during maintenance therapy [107]. Further work is required to determine if this is a result of pure potency or whether other mechanisms, including inverse agonism, are responsible. At steady state, ticagrelor is constantly present in the blood, resulting in inhibition of newly-produced platelets [71]. The concentration of ticagrelor in the plasma during long-term maintenance treatment with 60 mg or 90 mg BD is sufficient to achieve high levels of inhibition of platelet aggregation in patients with a previous MI [108], stable CAD undergoing PCI [50] or diabetes mellitus [109]. The sustained levels of platelet inhibition are greater when ticagrelor is administered BD rather than once daily (OD) [67].

To achieve acceptable outcomes, the antithrombotic efficacy must be balanced against the risk of bleeding and therefore a pharmacological agent that is capable of reversing the haemostatic effects of ticagrelor is highly desirable for use in emergency procedures where the risk of bleeding is increased. Bentracimab (PB2452) is an antigen-binding fragment antidote to ticagrelor that has demonstrated effective neutralisation properties both *in vitro* and in mice [110] and healthy volunteers [111]. A numerical improvement in ADP-induced platelet aggregation, blood loss and survival in response to PB2452 in pigs provides further encouragement [112], and pharmacological characterisation [113] and phase IIB and phase III studies are underway (ClinicalTrials.gov Identifier: NCT04122170 and NCT04286438 respectively). An alternative approach in patients undergoing urgent or emergency cardiopulmonary bypass surgery or ex-

tracorporeal membrane oxygenation is reducing ticagrelor plasma levels using haemadsorption with the CytoSorb cartridge system that can be linked with the bypass circuit and is CE-marked for this purpose [114] (ClinicalTrials.gov Identifier: NCT04131959).

6. Clinical outcomes in phase II studies

The Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction (DISPERSE)-2 study investigated the safety, tolerability and initial efficacy of two doses of ticagrelor (90 mg or 180 mg BD) plus aspirin, compared with standard clopidogrel (300 mg loading dose, 75 mg OD) DAPT in 984 patients with NSTE-ACS [115]. There was no difference in the incidence of overall bleeding at 4 weeks (ticagrelor 90 mg, 180 mg and clopidogrel; 9.8%, 8.0% and 8.1% respectively; $P = 0.43$ and $P = 0.96$, respectively, vs. clopidogrel) between the groups. The results also suggested good tolerability of ticagrelor, but showed a higher incidence of dyspnoea (10.5%, 15.8% and 6.4%; $P = 0.07$ and $P < 0.001$) and asymptomatic ventricular pauses >2.5 seconds (5.5%, 9.9% and 4.3%; $P = 0.58$ and $P = 0.014$), in a dose-dependent pattern, compared with clopidogrel. Encouragingly, there were numerically lower rates of MACE and bleeding after cessation for patients who required a coronary artery bypass graft (CABG). These findings paved the way for large-scale trials to further characterise the efficacy and safety of ticagrelor in the management of MI.

7. Phase III studies of ticagrelor in coronary artery disease

As a result of a worldwide collaborative effort, studies have highlighted the benefits of using ticagrelor-based DAPT for the secondary prevention of MACE in ACS patients, up to one year and beyond, in post-ACS patients at high risk of ischaemic events.

18,624 patients with ACS were recruited to the double-blind randomised Platelet Inhibition and Patient Outcomes (PLATO) study to compare the efficacy of ticagrelor and clopidogrel, administered with aspirin [12]. Ticagrelor not only proved superior at reducing the primary composite endpoint of vascular death, MI and stroke at 12 months (9.8% [ticagrelor] vs. 11.7% [clopidogrel]; HR, 0.84; 95% CI 0.77–0.92; $P < 0.001$; Table 1), but also cardiovascular mortality (4.0% vs. 5.1%; $P = 0.001$) and all-cause mortality (4.5% vs. 5.9%; $P < 0.001$). The study identified no statistically-significant difference in the rates of major bleeding (11.6% vs. 11.2%; HR, 1.04; 95% CI 0.95–1.13; $P = 0.43$) or CABG-related bleeding (7.4% vs. 7.9%; HR, 0.95; 95% CI 0.85–1.06; $P = 0.32$). This may be explained by the shorter biological $t_{1/2}$ of ticagrelor, despite having greater potency, whereby cessation prior to a procedure results in a quicker recovery to normal platelet function than clopidogrel. There was an elevated risk of spontaneous bleeding (4.5% vs. 3.8%; HR, 1.19; 95% CI 1.02–1.38; $P = 0.03$), including an increase in fatal intracranial bleeding (0.12% vs. 0.01%; $P = 0.02$) in the ticagrelor group. However, overall rates of fatal bleeding were not significantly different due to more non-intracranial fatal bleeds when receiving clopidogrel. The PLATO study was the first to show that more potent platelet inhibition with ticagrelor versus clopidogrel translated to improved overall clinical outcomes.

Before the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-) Thrombolysis in Myocardial Infarction (TIMI) 54 study, it was unclear if DAPT should be carried on beyond 12 months post-MI for patients at high risk of developing further ischaemic events [13, 116]. This prospective study investigated the efficacy of two doses of ticagrelor versus placebo, combined with low-dose aspirin, over a 3-year period in 21,126 stable patients with a history of MI (median 1.7 years prior), who were at least 50 years old and had an additional atherothrombotic risk factor (Table 1). Ticagrelor was studied for the first time at a dose of 60 mg BD in addition to further study of the 90 mg BD dose. Both ticagrelor doses significantly reduced the incidence of MACE (7.9% [ticagrelor 90 mg], 7.8% [ticagrelor 60 mg] and 9.0% [placebo]; $P = 0.008$ and $P = 0.004$ vs. placebo, respectively). Cardiovascular deaths alone were not significantly reduced versus placebo in the overall trial population although there was evidence of a reduced risk of CAD-related deaths (90 mg: HR, 0.73 [95% CI 0.56–0.95]; 60 mg: HR, 0.80 [95% CI 0.62–1.04]). Ticagrelor increased the incidence of major (2.6%, 2.3% and 1.1%; $P < 0.001$ for both) and minor bleeding, but there was no significant difference in fatal bleeding versus placebo. A subgroup analysis of the PEGASUS-TIMI 54 study identified a greater absolute risk reduction of MACE in patients with type 2 diabetes mellitus (T2DM) who received ticagrelor-based DAPT (1.5% vs. 1.1%) than those without [117]. The novel 60 mg dose of ticagrelor was chosen for this study to provide an intermediate level of antithrombotic protection, that would provide greater antithrombotic efficacy than clopidogrel 75 mg, but less of a bleeding risk than ticagrelor 90 mg [118]. Surprisingly, both doses of ticagrelor demonstrated similar overall efficacy at preventing ischaemic events, which was explored in a pharmacodynamic study that demonstrated similar magnitude of platelet inhibition at both doses [108]. The rates of bleeding, dyspnoea and discontinuation as a result of dyspnoea were numerically lower in the ticagrelor 60 mg group versus 90 mg. Therefore, in view of a similar efficacy and safety profile with better tolerability, this evidence suggests that ticagrelor 60 mg BD may be a more favourable option to 90 mg BD when combined with aspirin during long-term DAPT. Overall, the PEGASUS-TIMI 54 trial demonstrated that, for patients at high risk of recurrent ischaemic events, a longer duration of DAPT may derive benefit, but this needs to be weighed against the higher risk of non-fatal bleeding. In selecting those most likely to benefit from long-term DAPT, further subgroup analysis of PEGASUS-TIMI 54 supported

Table 1. Randomised clinical trials of ticagrelor-based dual antiplatelet therapy for secondary prevention in patients with atherosclerotic disease.

Short name (year published)	Study population	Intervention	Comparator	Primary endpoint(s)	Key safety endpoint(s)
PLATO (2009) [12]	18,624 patients hospitalised with ACS	Ticagrelor (180 mg LD, 90 mg BD MD) plus aspirin 75–325 mg OD for 12 months	Clopidogrel (300–600 mg LD, 75 mg MD) plus aspirin 75–325 mg OD for 12 months	Death from vascular cause, MI or stroke at 12 months: 9.8% vs. 11.7%; Hazard ratio (HR), 0.84; 95% confidence interval (CI) 0.77–0.92; $P < 0.001$	Major bleeding at 12 months: 11.6% vs. 11.2%; HR, 1.04; 95% CI 0.95–1.13; $P = 0.43$
PEGASUS-TIMI 54 (2015) [13]	21,162 patients with prior spontaneous MI in the last 1–3 years and an additional atherothrombotic risk factor*	Ticagrelor 90 mg (T90) or 60 mg (T60) BD plus aspirin 75–150 mg OD for 36 months	Placebo plus aspirin 75–150 mg OD for 36 months	CV death, MI, or stroke at 3 years: T90: 7.9% vs. 9.0%; HR, 0.85; 95% CI 0.75–0.96; $P = 0.008$ T60: 7.8% vs. 9.0%; HR, 0.84; 95% CI 0.74–0.95; $P = 0.004$	TIMI major bleeding at 3 years: T90: 2.6% vs. 1.1%; HR, 2.69; 95% CI 1.96–3.70; $P < 0.001$ T60: 2.3% vs. 1.1%; HR, 2.32; 95% CI 1.68–3.21; $P < 0.001$
DACAB (2018) [14]	500 patients with an indication for elective coronary artery bypass graft surgery. 1460 saphenous vein grafts were inserted	Ticagrelor 90 mg BD plus aspirin (100 mg OD) or alone for 1 year	Aspirin 100 mg OD for 1 year	Graft patency at 1 year: DAPT: 88.7% vs. 76.5%; RR, 0.48; 95% CI 0.31–0.74; $P < 0.001$ Ticagrelor alone: 82.8% vs. 76.5%; RR, 0.73, 95% CI 0.51–1.06; $P = 0.10$	Graft patency at 7 days: DAPT: 94.9% vs. 91.1%; RR, 0.58; 95% CI 0.30–1.14; $P = 0.11$ Ticagrelor alone: 94.3% vs. 91.1%; RR, 0.65, 95% CI 0.36–1.18; $P = 0.17$
ISAR-REACT 5 (2019) [15]	4018 patients hospitalised with ACS for whom an invasive evaluation was scheduled. Treatment: 84% PCI and 2.1% CABG	Ticagrelor (180 mg LD, 90 mg BD MD) based strategy for 12 months	Prasugrel (60 mg LD, 10 mg or 5 mg (if $\geq$75 years or $<$60 kg) OD MD) based strategy for 12 months	Death, MI or stroke at 1 year: 9.3% vs. 6.9%; HR, 1.36; 95% CI 1.09–1.70; $P = 0.006$	Bleeding Academic Research Consortium (BARC) type 3, 4, or 5 bleeding at 1 year: 5.4% vs. 4.8%; HR, 1.12; 95% CI 0.83–1.51; $P = 0.46$
THEMIS (2019) [16]	19,220 patients with stable CAD, type 2 diabetes and no prior MI or stroke	Ticagrelor (90 mg initially, then reduced to 60 mg) BD plus aspirin 75–150 mg OD for 54 months	Placebo plus aspirin 75–150 mg OD for 54 months	CV death, MI, or stroke: 7.7% vs. 8.5%; HR, 0.90; 95% CI 0.81–0.99; $P = 0.04$	TIMI major bleeding: 2.2% vs. 1.0%; HR, 2.32; 95% CI 1.82–2.94; $P < 0.001$
THALES (2020) [17]	11,016 patients with acute non-cardioembolic, non-severe ischaemic stroke (National Institutes of Health Stroke Score (NIHSS) $\leq$5) or high-risk transient ischemic attack (ABCD2 $\geq$6) or symptomatic arterial stenosis	Ticagrelor (180 mg LD, 90 mg BD MD) plus aspirin (300–325 mg LD, 75–100 mg OD MD) for 34 days	Placebo plus aspirin (300–325 mg LD, 75–100 mg OD MD) for 34 days	Stroke or death at 30 days: 5.5% vs. 6.6%; HR, 0.83; 95% CI 0.71–0.96; $P = 0.02$	GUSTO severe bleeding at 30 days: 0.5% vs. 0.1%; HR, 3.99; 95% CI 1.74–9.14; $P = 0.001$
ALPHEUS (2020) [18]	1910 patients with stable CAD with an indication for PCI and at least 1 high-risk feature†	Ticagrelor (180 mg LD, 90 mg BD MD) (87% on aspirin at admission) for 30 days	Clopidogrel (300–600 mg LD, 75 mg OD MD) (85% on aspirin at admission) for 30 days	PCI-related type 4 (a or b) MI or major myocardial injury at 48 h: 35% vs. 36%; OR, 0.97; 95% CI 0.80–1.17; $P = 0.75$	Major bleeding (BARC 3 or 5) at 48 h: $<$1% vs. 0%; $P = 0.50$ Minor bleeding (BARC 1 or 2) at 30 days: 11% vs. 8%; OR, 1.54; 95% CI 1.12–2.11; $P = 0.007$

* One of the following: $\geq$65 years old, diabetes treated with medication, a second prior spontaneous MI, multivessel CAD, chronic renal dysfunction (estimated creatinine clearance $<$60 mL per minute).

† $\geq$75 years old, renal insufficiency (clearance $<$60 mL per minute), diabetes mellitus, overweight (BMI $>$30 kg/m^2), history of ACS in last year, left ventricular ejection fraction $<$40% and/or prior episode of heart failure, multivessel (2–3) disease, multiple stents or total stent length $>$30 mm, left main stenting, ACC/AHA type B2 or C lesion, stenting of venous or arterial coronary graft.

the approach of excluding patients with anaemia or a history of prior hospitalisation in addition to the exclusion criteria for the trial related to bleeding, such as prior ischaemic or haemorrhagic stroke [119]. This analysis suggested significant cardiovascular mortality reduction from long-term DAPT in the patients with higher ischaemic risk and without high-bleeding-risk characteristics whereas those with anaemia or prior hospitalisation for bleeding did not appear to benefit.

In response to the publication of the PEGASUS-TIMI 54 study, all active or newly-enrolled participants in The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) [16] were switched to or started on, respectively, the lower dose of ticagrelor (60 mg BD). Primary and supplementary analysis showed consistent results independent of the dose. THEMIS was a randomised double-blind trial that sought to determine if adding ticagrelor to aspirin improves outcomes in patients with stable CAD and T2DM with no history of MI or stroke. The results showed that addition of ticagrelor to aspirin reduced the incidence of MACE (7.7% [ticagrelor] vs. 8.5% [placebo]; HR, 0.90; 95% CI 0.81–0.99; P = 0.04) but conversely increased major bleeding (2.2% vs. 1.0%; HR, 2.32; 95% CI 1.82–2.94; $P < 0.001$), after a median follow-up of 40 months. In an exploratory analysis featuring a composite of irreversible and harmful outcomes (all-cause mortality, MI, stroke, fatal bleeding or intracranial haemorrhage), there was no significant difference between the ticagrelor and placebo treatment groups (10.1% vs. 10.8%; HR, 0.93; 95% CI 0.86–1.02), leading the authors to conclude that ticagrelor plus aspirin may not be an acceptable form of secondary prevention of ischaemic events in this population, due to the poor benefit-to-risk ratio. However, the evidence supported the extension of the US label for ticagrelor to include stable patients at high risk of ischaemic events, including those without diabetes.

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial was a recent open-label randomised controlled trial (RCT) that compared two different treatment strategies in 4018 patients with ACS who were scheduled for invasive evaluation (i.e., coronary angiography) [15]. Following randomisation, a loading dose of ticagrelor was immediately administered to all patients randomised to ticagrelor whereas only STEMI patients randomised to prasugrel were intended to receive the loading dose of prasugrel before coronary angiography and those with NSTE-ACS underwent coronary angiography first, following which they received a loading dose of prasugrel only if proceeding to PCI, reflecting the evidence that prasugrel increases the risk of major bleeding if administered pre-PCI in this population [120]. ISAR-REACT 5 found that the ticagrelor-based strategy was less effective at preventing MACE (9.3% [ticagrelor] vs. 6.9% [prasugrel]; HR, 1.36; 95% CI 1.09–1.70; P = 0.006) compared to the prasugrel-based strategy and that there was no difference in major bleeding (5.4% vs. 4.8%; HR, 1.12; 95% CI 0.83–1.51; P = 0.46) after one year. This finding was unexpected as the trial was testing the hypothesis that ticagrelor would be superior to prasugrel. In addition to the open-label design of the study, there were a number of considerations that indicate the need for caution in translating the findings to clinical practice: (1) patients were randomised within 1–2 hours of coronary angiography and so any benefit of ticagrelor pre-treatment in patients waiting longer for coronary angiography was not assessed; (2) the majority of patients had femoral artery access for their procedure, which does not reflect contemporary optimal practice and would have disadvantaged the pre-treatment approach with ticagrelor; (3) approximately one-third of the benefit of prasugrel was through reduction in stent thrombosis, which is not consistent with the platelet inhibition profiles of the two drugs and therefore likely indicates poor adherence in the ticagrelor group, raising questions about the counselling and management of the study patients since better outcomes have been achieved in experienced centres; and (4) the better outcomes with prasugrel also partly reflected lower non-cardiovascular mortality, which is inconsistent with the results of the much larger phase-III studies and therefore suggests the play of chance. Poor adherence may have been a particular issue in the patients without diabetes since patients with diabetes did equally well with the ticagrelor-based and prasugrel-based strategies in the trial [121]. Large-scale observational data indicate similar outcomes with ticagrelor and prasugrel in PCI-treated MI patients [122, 123]. Reports of greater platelet inhibition with prasugrel compared with ticagrelor maintenance therapy are likely based on artefact related to the use of multiple electrode plate aggregometry since studies with other platelet function tests have demonstrated greater platelet inhibition during maintenance therapy with ticagrelor [107, 124] and this is consistent with the different development strategies for the two drugs [123].

8. Studies of ticagrelor in percutaneous coronary intervention

PCI is a procedure frequently performed in patients with CAD, usually involving the insertion of at least one drug-eluting stent (DES) to treat and prevent the progression of focal coronary artery stenosis. Approximately 60% of ACS patients undergo PCI when hospitalised [12]. A range of innovative studies involving ticagrelor have recently been conducted with the aim to optimise patient outcomes by reducing the burden of ischaemia and/or bleeding for those who have received PCI by tailoring the duration and combination of antiplatelet drugs.

Two meta-analyses [125, 126] collated ten RCTs to determine the length of time that DAPT should be administered following DES insertion during PCI. They both favoured a shorter duration of DAPT (<12 months) over long term (>12 months) therapy, based on the finding that a longer duration of DAPT was associated with higher rates of bleeding

complications and all-cause mortality, despite a reduction in MI and stent thrombosis. As these studies mainly involved thienopyridine-based DAPT, these data cannot be extrapolated to how ticagrelor may perform. Moreover, there is evidence to suggest that prolonged ticagrelor-based DAPT may benefit a specific high-risk subset of patients.

A prespecified subgroup analysis of the THEMIS study (median follow-up of 3.3 years) demonstrated an improved benefit-to-risk ratio for ticagrelor in patients with a PCI procedure in the past [127]. In this subgroup, there was a lower rate of both MACE (7.3% [ticagrelor] vs. 8.6% [placebo]; HR, 0.85; 95% CI 0.74–0.97; P = 0.013) and the exploratory net clinical benefit endpoint of irreversible harms (9.3% vs. 11.0%; HR, 0.85; 95% CI 0.75–0.95; P = 0.005), involving a composite of all-cause mortality, MI, stroke, fatal bleeding or intracranial haemorrhage. In contrast, patients with no history of PCI appeared to obtain no net clinical benefit from ticagrelor based-DAPT according to the latter composite endpoint (11.1% vs. 10.5%; HR, 1.06; 95% CI 0.93–1.21; P = 0.39). TIMI-defined major bleeding was significantly more frequent when receiving ticagrelor regardless of whether or not the patient had a history of PCI (2.0% vs. 1.1%; HR, 2.03; 95% CI 1.48–2.76; $P < 0.001$). Those specifically with a history of PCI, including implantation of a DES, appeared to derive an even greater reduction in MACE (6.9% vs. 8.6%; HR, 0.79; 95% CI 0.67–0.94; P = 0.008). This evidence raised the hypothesis that the addition of ticagrelor to aspirin reduces the risk of MACE in patients with stable CAD, T2DM and a history of PCI, especially with a DES, but not in those who do not have a history of PCI. However, the reasons for a selective effect in the PCI subgroup are unclear although prior tolerance of DAPT following PCI might explain the preferential efficacy.

Considering that increasing the efficacy of antiplatelet regimens is accompanied by a penalty in bleeding risk, another novel strategy that has gained attention is the discontinuation of aspirin, after a short period of DAPT, at an early stage after PCI (Table 2). While de-escalating antiplatelet therapy is unlikely to reduce ischaemic risk, it may improve safety yet maintain efficacy. This may be particularly important in the context of severe post-PCI bleeding, which poses a similar mortality risk compared with MI [128, 129].

The Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation (GLOBAL LEADERS) study sought to determine if ticagrelor-based DAPT for one month followed by ticagrelor monotherapy was superior to standard DAPT therapy (aspirin plus either ticagrelor for ACS or clopidogrel for CCS) for 12 months followed by aspirin monotherapy, over a two-year period following DES implantation in 15,968 patients [21]. The findings demonstrated no difference in the ambitious primary composite endpoint of all-cause mortality or new Q-wave MI (3.81% [1-month DAPT] vs. 4.37% [12-month DAPT]; risk ratio [RR], 0.87; 95% CI 0.75–1.01; P = 0.073) or the key safety endpoint of major bleeding (2.04% vs. 2.12%; RR, 0.97; 95% CI 0.78–1.20; P = 0.77). In a recent *post-hoc* subgroup analysis of the ACS cohort that evaluated clinical outcomes between 31 and 365 days post-randomisation, thereby exclusively comparing ticagrelor monotherapy with ticagrelor-based DAPT, there remained no significant difference in the primary endpoint (1.5% [monotherapy] vs. 2.0% [DAPT]; HR, 0.73; 95% CI 0.51–1.03; P = 0.073) but a significant reduction in major bleeding was observed (0.8% vs. 1.5%; HR, 0.52; 95% CI 0.33–0.81; P = 0.004) [130]. While the results of this analysis are encouraging, they must be considered as hypothesis-generating in light of their *post-hoc* nature, although the reduction in bleeding with aspirin cessation is predictable due to the subsequent increase in platelet reactivity and avoidance of aspirin-related gastrotoxicity [131].

Furthermore, in the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) study, 9006 patients who were determined to be at high risk of bleeding or ischaemia received DAPT with ticagrelor and aspirin for three months following PCI with DES for NSTE-ACS (65%) or CCS (35%) [22]. Of those who did not suffer from a disqualifying event, 7119 continued to take ticagrelor and were randomised to either receive placebo or continue with aspirin for a duration of 12 months. Reflecting the priority of the experimental regimen to provide a better safety profile than the standard-treatment comparator while maintaining safe antithrombotic protection, the primary endpoint was a composite of BARC (Bleeding Academic Research Consortium)-defined grade 2, 3 or 5 bleeding and the key secondary endpoint was a composite of all-cause mortality, non-fatal MI or non-fatal stroke. The results showed that the primary endpoint occurred significantly less frequently during ticagrelor monotherapy than DAPT (4.0% [monotherapy] vs. 7.1% [DAPT]; HR, 0.56; 95% CI 0.45–0.68; $P < 0.001$) without evidence for a difference in the key secondary endpoint (3.9% vs. 3.9%; HR, 0.99; 95% CI 0.78–1.25; P (noninferiority) < 0.001). The results suggest that DAPT for three months may be sufficient to cover the period of stent endothelialisation and stent thrombosis risk but there remains uncertainty in view of limited power of this study to assess the efficacy of the regimens in individuals at high long-term risk of ischaemic events.

In a pre-specified subgroup analysis, TWILIGHT-ACS highlighted that ticagrelor monotherapy provided greater magnitude of reduced bleeding in 4614 patients with NSTE-ACS (3.6% [monotherapy] vs. 7.6% [DAPT]; HR, 0.47; 95% CI 0.36–0.61; $P < 0.001$) than those with CCS (4.8% vs. 6.2%; HR, 0.76; 95% CI 0.54–1.06; P = 0.11; nominal $P_{interaction}$ = 0.03), while the risk of MACE was similar for both treatment groups and independent of the clinical presentation [132]. In support of these findings, but in a low-risk population, the Ticagrelor Monotherapy After three Months in the Patients Treated With New Generation Sirolimus-eluting Stent for ACS (TICO) study demonstrated that switching to ticagrelor monotherapy after three months of DAPT significantly reduced the frequency of the composite primary endpoint

Table 2. Randomised clinical trials of ticagrelor monotherapy for secondary prevention in patients with atherosclerotic disease.

Short name (year published)	Study population	Intervention	Comparator	Primary endpoint(s)	Key safety endpoint(s)
SOCRATES (2016) [19]	13,199 patients with acute, non-cardioembolic, non-severe ischaemic stroke (NIHSS $\leq$5) or high-risk TIA ($ABCD^2 \geq 4$)	Ticagrelor (180 mg LD, 90 mg BD MD) plus placebo for 90 days	Aspirin (300 mg LD, 100 mg OD MD) plus placebo for 90 days	Ischaemic or haemorrhagic stroke, MI or death at 90 days: 6.7% vs. 7.5%; HR, 0.89; 95% CI 0.78–1.01; $P = 0.07$	PLATO major bleeding at 90 days: 0.5% vs. 0.6%; HR, 0.83; 95% CI 0.52–1.34; $P = 0.45$
EUCLID (2017) [20]	13,885 patients with either previous revascularisation of lower limbs or haemodynamic evidence due to symptomatic PAD	Ticagrelor 90 mg BD for 36 months	Clopidogrel 75 mg OD for 36 months	CV death, MI or ischaemic stroke: 10.8% vs. 10.6%; HR, 1.02; 95% CI 0.92–1.13; $P = 0.65$	TIMI major bleeding: 1.6% vs. 1.6%; HR, 1.10; 95% CI 0.84–1.43; $P = 0.49$ TIMI minor bleeding: 1.2% vs. 1.0%; HR, 1.32; 95% CI 0.96–1.83; $P = 0.09$
GLOBAL LEADERS (2018) [21]	15,968 patients receiving a DES for stable CAD (53.1%) or ACS (46.9%), between angiography and PCI	Aspirin 75–100 mg OD plus ticagrelor 90 mg BD for 1 month, followed by ticagrelor 90mg BD for 23 months	Aspirin 75–100 mg plus either clopidogrel 75mg OD (stable CAD) or ticagrelor 90mg BD (ACS) for 12 months, then aspirin for 12 months	All-cause mortality or new Q-wave MI at 730 days: 3.81% vs. 4.37%; RR, 0.87; 95% CI 0.75–1.01; $P = 0.073$	BARC grade 3 or 5 bleeding: 2.04% vs. 2.12%; RR, 0.97; 95% CI 0.78–1.20; $P = 0.77$
TWILIGHT (2019) [22]	7119 high-risk patients* who underwent PCI for either stable CAD or NSTE-ACS, and 3 event-free months of ticagrelor 90 mg BD plus aspirin 81–100 mg OD	Ticagrelor 90 mg BD plus placebo for 12 months	Aspirin 81–100 mg OD plus ticagrelor 90 mg BD for 12 months	BARC grade 2, 3 or 5 bleeding at 1 year: 4.0% vs. 7.1%; HR, 0.56; 95% CI 0.45–0.68; $P < 0.001$	All-cause mortality, non-fatal MI or non-fatal stroke at 1 year: 3.9% vs. 3.9%; HR, 0.99; 95% CI 0.78–1.25; P (noninferiority) < 0.001
TICO (2020) [23]	3065 patients treated with DES for ACS	Aspirin 100 mg OD plus ticagrelor 90 mg BD for 3 months, then ticagrelor 90 mg BD for 9 months	Aspirin 100 mg OD plus ticagrelor 90 mg BD for 12 months	Net adverse clinical events† at 12 months: 3.9% vs. 5.9%; HR, 0.66; 95% CI 0.48–0.92; $P = 0.01$	TIMI major bleeding at 12 months: 1.7% vs. 3.0%; HR, 0.56; 95% CI 0.34–0.91; $P = 0.02$ MACE at 12 months: 2.3% vs. 3.4%; HR, 0.69; 95% CI 0.45–1.06; $P = 0.09$

* At least one additional clinical (at least 65 years old, female gender, troponin positive ACS, established vascular disease, diabetes treated with medication, CKD) and one angiographic (multivessel CAD, total stent length >30 mm, a thrombotic target lesion, bifurcation lesion treated with two stents, obstructive left main or proximal left anterior descending lesion, a calcified target lesion treated with atherectomy) feature.

† Composite TIMI major bleeding and adverse cardiac and cerebrovascular events (death, MI, stent thrombosis, stroke or target vessel revascularisation).

(TIMI major bleeding and major cardiac and cerebrovascular events [death, MI, stent thrombosis, stroke or target vessel revascularisation]; 3.9% [3-month DAPT] vs. 5.9% [12-month DAPT]; HR, 0.66; 95% CI 0.48–0.92; P = 0.01) compared with continuing DAPT for 12 months (n = 3065) [23]. The key secondary endpoints indicated a reduced risk of TIMI-major bleeding (1.7% vs. 3.0%; HR, 0.56; 95% CI 0.34–0.91; P = 0.02) and no significant difference in MACE (2.3% vs. 3.4%; HR, 0.69; 95% CI 0.45–1.06; P = 0.09). Notably, however, there are several important limitations of this recent study, which was open-label, did not monitor drug adherence, involved study sites that were exclusively based in South Korea and excluded any participants who were determined to be at high risk of bleeding. The collective evidence suggests that ticagrelor monotherapy has potential advantages over standard treatments following PCI and will be discussed in a subsequent section of this review.

Considering the evidence, it is becoming increasingly apparent that a tailored approach is required for ticagrelor-treated patients, particularly those with ACS. While the management of modifiable risk factors and development of thin-strut, biocompatible DES is improving clinical outcomes [8, 133], current evidence suggests the need for a dichotomization of treatment whereby those with unmodifiable risk factors for atherothrombotic events, but with a low risk of bleeding, receive long-term DAPT and those with controllable risk factors or a high risk of bleeding receive ticagrelor monotherapy following short-term DAPT [134].

Ticagrelor may not provide benefit in low-risk individuals undergoing elective PCI. With the aim to reduce prognostically-important periprocedural myonecrosis [135], the recently-published Assessment of Loading with the $P2Y_{12}$ inhibitor ticagrelor or clopidogrel to Halt ischaemic Events in patients Undergoing elective coronary Stenting (ALPHEUS) open-label study reported that ticagrelor showed no superiority over clopidogrel at preventing periprocedural MI or myocardial injury (35% [ticagrelor] vs. 36% [clopidogrel]; odds ratio [OR], 0.97; 95% CI 0.80–1.17; P = 0.75) within 48 hours of elective PCI in 1910 high-risk patients [18]. A similar lack of effect on periprocedural myonecrosis was also observed in a small study of elective PCI patients comparing ticagrelor 90 mg or 60 mg BD with clopidogrel [50]. Considering that ticagrelor showed no superiority over clopidogrel, despite greater potency of platelet inhibition, these studies suggest that much of the periprocedural myonecrosis in low-risk PCI patients occurs independently of platelet activation, such as due to embolisation of plaque contents into the coronary microcirculation.

9. Ticagrelor in ST-elevation myocardial infarction

The severity of ischaemia during STEMI and the susceptibility to further infarction of adjacent myocardial tissues makes it a particularly time-sensitive event, whereby the optimal choice of agent and timing requires careful consideration and elaboration. In a PLATO subgroup of patients with STEMI or left bundle branch block planned for primary PCI, ticagrelor remained superior to clopidogrel at preventing MACE at 12 months [136]. This benefit was independent of the extent of ST elevation at presentation and ticagrelor was not associated with any improvement in resolution of ST elevation, implying that its observed benefit was dependent on prevention of recurrent vascular events rather than superior effects on early perfusion or protection from reperfusion injury [137]. These observations were contrary to the findings from pre-clinical animal experiments demonstrating that early exposure of ticagrelor has pleiotropic cardioprotective effects that attenuate myocardial infarct size following coronary occlusion and reperfusion [138], to a greater degree than clopidogrel [139, 140]. This has implications for the choice of initial antiplatelet agent in the management of STEMI patients [141]. It has been observed that the enteric absorption of ticagrelor is often delayed in STEMI patients, especially when opiates such as morphine are co-administered for pain relief [76–79]. This phenomenon may explain the limited early benefit of ticagrelor and lack of difference in angiographic outcomes seen in the PLATO angiographic substudy, since rapid performance of PCI likely provided insufficient time to allow ticagrelor's effects to become apparent in opiate-treated patients [142]. Administration of a parenteral $P2Y_{12}$ inhibitor that reaches the circulation within minutes and prior to emergency PCI could potentially optimise the salvage of ischaemic myocardium and minimise reperfusion injury, in addition to providing early platelet inhibition to prevent stent thrombosis. Further work is therefore required to assess the benefit of intravenous cangrelor or subcutaneous selatogrel prior to stenting, followed by subsequent transition to oral ticagrelor [87, 141, 143, 144].

10. Ticagrelor in coronary-artery bypass graft surgery

Around 10% of patients diagnosed with an ACS event are treated by CABG [12], which is also an option for revascularisation in selected patients with CCS [2]. Factors that might favour CABG over PCI as a revascularisation strategy include triple-vessel or left main coronary artery disease, particularly in patients with diabetes mellitus and those with chronic total occlusions of major coronary vessels [145]. A common complication occurring after CABG is graft occlusion, which can lead to recurrent ACS (including manifestation as sudden death), angina, or heart failure [146]. As a major surgical procedure, CABG carries a significant risk of perioperative bleeding that must be balanced against any benefits of improved graft patency and broader protection from MACE that antiplatelet therapy may offer [147].

An analysis of ticagrelor vs. the then standard-of-care clopidogrel in aspirin-treated ACS patients undergoing CABG was included in the PLATO study [148]. Out of the trial population of 18,624, 1261 underwent CABG within seven days of receiving study medication. Though under-

powered to test robustly, there was evidence that the primary endpoint of MACE at 12 months occurred less frequently when receiving ticagrelor versus clopidogrel (10.6% vs. 13.1%, respectively; HR, 0.84; 95% CI 0.60–1.16; $P = 0.29$). Moreover, there was a strong signal of lower all-cause mortality (4.7% vs. 9.7%; HR, 0.49; 95% CI 0.32–0.77; $P < 0.01$), contributed to by both cardiovascular (4.1% vs. 7.9%; HR, 0.52; 95% CI 0.32–0.85; $P < 0.01$) and non-cardiovascular death (0.7% vs. 2.0%; HR, 0.35; 95% CI 0.11–1.11; $P = 0.07$). Importantly, there were no significant differences in CABG-related bleeding outcomes between the groups (e.g., major CABG-related bleeding 81.2% vs. 80.1%; HR, 1.07; 95% CI 0.80–1.43; $P = 0.67$).

Ticagrelor-based DAPT has also been compared with aspirin alone in patients undergoing CABG. In the Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB) trial, adding ticagrelor to aspirin led to better saphenous vein graft patency compared to aspirin alone (RR, 0.48; 95% CI 0.31–0.74; $P < 0.001$) [14]. DACAB also included an analysis of ticagrelor monotherapy vs. aspirin alone, finding no significant differences in outcomes. This comparison was further explored in the Ticagrelor in CABG (TiCAB) trial, which randomised 1893 patients undergoing CABG (around one-third for ACS) to receive single antiplatelet therapy with either ticagrelor 90 mg BD or aspirin 100 mg OD for 12 months after operation [149]. The study was prematurely terminated on futility grounds, there being no evidence of a benefit of ticagrelor over aspirin with regards to the primary composite endpoint of cardiovascular death, MI, repeat revascularization, and stroke (9.7% [ticagrelor] vs. 8.2% [aspirin]; HR, 1.19; 95% CI 0.87–1.62; $P = 0.28$). There were also no observed differences in bleeding outcomes.

Ticagrelor may offer advantages over thienopyridines to ACS patients awaiting CABG as, due to its reversible binding, it has a more rapid offset [104]. Furthermore, there are emerging strategies for more prompt reversal of ticagrelor's effects prior to CABG such as an haemadsorbent filter or infusion of a monoclonal antibody against the drug, neither of which are feasible for thienopyridines due to their irreversible action [111, 114]. Several observational studies have examined how long before CABG ticagrelor should be withheld in order to avoid excess bleeding risk. Data from a Swedish registry suggested that discontinuation <72 hours before surgery led to an increase in bleeding compared to >72 hours [150]. Furthermore, a single-centre study suggested discontinuation >72 hours before CABG led to no excess bleeding risk compared to patients who had received aspirin alone [151]. A further analysis from the European Multicentre Study on Coronary Artery Bypass Grafting (E-CABG) suggested that even discontinuing two days prior to surgery was not associated with an increased risk of severe bleeding, though there was a trend towards a greater need for platelet transfusion than when receiving aspirin alone [152]. Pharmacodynamic data suggest some recovery of ADP-induced platelet aggregation responses from 24 hours after discontinuation, but taking around four days for most patients to reach a level above that required to avoid excess bleeding risk [51]. Withholding ticagrelor for 3–5 days before CABG is currently recommended, compared to 5 or 7 days for clopidogrel and prasugrel, respectively [153, 154].

11. Studies of ticagrelor in ischaemic stroke

Ischaemic stroke is a common and often catastrophic condition. The thrombotic subtype shares a common pathophysiological mechanism and risk-factor profile with CAD [155]. Therefore, antiplatelet drugs may reduce the risk of thrombotic stroke, but conversely increase the risk of bleeding, including intracranial bleeding events. The mainstay of pharmacological management of those at high risk of stroke has been single antiplatelet therapy, which has demonstrated a clear benefit at reducing the risk of large-artery atherothrombotic stroke but not small vessel occlusion or cardiac thromboembolism [156], with either aspirin or clopidogrel. There is some evidence that clopidogrel may be modestly superior to aspirin, particularly in patients with a history of stroke or PAD [157]. Given ticagrelor may offer pharmacodynamic advantages over aspirin or clopidogrel, it has therefore been hypothesised that ticagrelor may offer superior clinical efficacy after ischaemic stroke.

The Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial was a multi-centre double-blind RCT involving 13,199 patients with acute (<24 hours onset) non-severe ischaemic stroke or high-risk transient ischaemic attack (TIA) [19]. Patients such as those treated with thrombolysis or thrombectomy, or with an indication for therapeutic anticoagulation, were not eligible. Though there was a trend towards lower MACE at 90 days when receiving ticagrelor monotherapy compared to standard aspirin monotherapy in this population, this did not reach significance (6.7% [ticagrelor] vs. 7.5% [aspirin]; HR, 0.89; 95% CI 0.78–1.01; $P = 0.07$), though nominal secondary analyses favoured ticagrelor with a lower incidence of recurrent ischaemic stroke (5.8% vs. 6.7%; HR, 0.87; 95% CI 0.76–1.00; $P = 0.046$), all stroke (5.9% vs. 6.8%; HR, 0.86; 95% CI 0.75–0.99; $P = 0.03$) and major bleeding (0.5% vs 0.6%; HR, 0.83; 95% CI 0.52–1.34; $P = 0.45$), but with higher incidences of minor bleeding and dyspnoea versus aspirin. Some of the possible benefit of ticagrelor was seen in patients treated with aspirin prior to randomisation, implying an overlap of effects in the first few days after randomisation to ticagrelor, and this raised the question of whether a DAPT approach may be more effective.

The Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death (THALES) study was a double-blind, placebo-controlled RCT [17] in a similar population to SOCRATES that also included patients with symptomatic arterial stenosis. This study showed that ticagrelor combined

with aspirin reduced the incidence of the composite endpoint of stroke or death compared with aspirin monotherapy at 30 days (5.5% [DAPT] vs. 6.6% [aspirin]; HR, 0.83; 95% CI 0.71–0.96; $P = 0.02$). DAPT also reduced the incidence of ischaemic stroke (5.0% vs. 6.3%; HR, 0.79; 95% CI 0.68–0.93; $P = 0.004$) versus aspirin alone; however, there was no difference in overall disability (23.8% vs. 24.1%; HR, 0.98; 95% CI 0.89–1.07; $P = 0.61$) between the two groups, and the rate of severe bleeding was significantly higher in the ticagrelor group at 30-days follow-up (0.5% vs. 0.1%; HR, 3.99; 95% CI 1.74–9.14; $P = 0.001$).

12. Studies of ticagrelor in peripheral artery disease

Atherosclerosis can also lead to PAD, for example manifesting as lower extremity artery disease or carotid artery stenosis. Patients with PAD are also at an increased risk of developing cerebral or myocardial ischaemia as a result of widespread atherosclerotic disease. Clopidogrel has previously demonstrated superiority over aspirin in reducing the risk of MACE (relative risk reduction, 23.8%; 95% CI 8.9–36.2; $P = 0.003$) in a subgroup of patients with PAD [157], and a post-hoc analysis of the PLATO study suggested similar beneficial trends during ticagrelor-based DAPT over clopidogrel-based DAPT in patients with ACS and PAD [158].

The Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease (EUCLID) double-blind, event-driven trial investigated the use of ticagrelor versus clopidogrel monotherapy on the composite risk of MACE in 13,885 patients with symptomatic PAD over a median period of 36 months [20]. The study showed that ticagrelor was not superior to clopidogrel in preventing MACE (10.8% [ticagrelor] vs. 10.6% [clopidogrel]; HR, 1.02; 95% CI 0.92–1.13; $P = 0.65$), acute limb ischaemia (1.7% vs. 1.7%; HR, 1.03; 95% CI 0.79–1.33; $P = 0.85$) or major bleeding (1.6% vs. 1.6%; HR, 1.10; 95% CI 0.84–1.43; $P = 0.49$). Ticagrelor did result in greater rates of discontinuation than clopidogrel (15.4% vs. 11.1%, respectively), mainly as a result of dyspnoea and bleeding. Based on this evidence, use of ticagrelor monotherapy cannot currently be recommended for event prevention in those with PAD, unless they have another indication. This is reflected in the European Society of Cardiology (ESC) PAD 2017 guidelines [159]. The lack of benefit of ticagrelor, which offers greater potency and consistency of platelet inhibition than clopidogrel, was surprising and further work is required to determine whether pleiotropic effects of clopidogrel may be relevant during long-term treatment in this population with extensive atherosclerotic disease, such as related to off-target anti-inflammatory effects [64].

13. Adverse effect profile

Throughout clinical trials, ticagrelor-associated dyspnoea has been consistently observed [16, 104, 115, 160]. In an analysis of the PLATO study, dyspnoea was reported in 14.5% of those receiving ticagrelor vs. 8.7% receiving clopidogrel, the excess being attributable to an effect of ticagrelor. Very few events were of severe intensity (0.4% vs. 0.3%, respectively). 27.3% vs. 20.1% of dyspnoeic events had no identifiable aetiology. Characteristics such as increased age and waist circumference as well as medical conditions including diabetes and chronic kidney disease (CKD) were associated with an increased risk of developing dyspnoea when treated with ticagrelor [160].

Dyspnoea during ticagrelor therapy does not appear to be associated with any changes in cardiac, pulmonary or metabolic function, whether in patients with CCS [161] or ACS [162]. Ticagrelor-related dyspnoea is typically of mild or moderate intensity, most often develops within one week of the initiation of treatment (median 23 days), and contributes to a low number of patients (approximately 1%) discontinuing the regimen and switching to a thienopyridine [160]. There appears to be a modest association between ticagrelor plasma levels and dyspnoea.

In patients who reported dyspnoea in the PLATO study, excluding those in whom it was MI-related, the effect of ticagrelor, compared with clopidogrel, on MACE appeared consistent with the main PLATO study results (8.8% vs. 10.4%; adjusted HR, 0.91; 95% CI 0.67–1.23; adjusted $P = 0.542$) [12]. There was also no impact on bleeding risk [160]. It therefore appears that ticagrelor-related dyspnoea is independent of any physical manifestations of disease and does not affect the efficacy or safety profile of ticagrelor therapy.

A perturbation in the afferent reflex carried by sensory chemoreceptor, mechanoreceptor or vagal C-fibres from the lungs and respiratory muscles may all contribute to an inappropriate perception of dyspnoea in the sensorimotor cortex of the brain [163]. Two main mechanisms have been proposed to explain how ticagrelor treatment can induce dyspnoea [164]. The first relates to ENT1 antagonism resulting in an elevated concentration of extracellular adenosine, a compound that has been associated with dyspnogenic effects in humans [165]. This is supported by the fact that theophylline, an adenosine receptor antagonist, blocks the potentiation of adenosine-induced dyspnoea by ticagrelor [56]. Against this theory is that dipyridamole, which has greater potency than ticagrelor at preventing adenosine reuptake, has not been associated with dyspnoea [166]. The second relates to the inhibition of putative $P2Y_{12}$ receptors on pulmonary C-fibres [167]. This is perhaps best supported by the observation that other reversible $P2Y_{12}$ inhibitors, belonging to different chemical classes (e.g., cangrelor, elinogrel and selatogrel), also induce dyspnoea. Though cangrelor main metabolite very weakly inhibits adenosine reuptake, there is no evidence that the other drugs or metabolites do [143, 144, 168]. The lack of effect of thienopyridine $P2Y_{12}$ inhibitors may be explained by the difference in pharmacological properties, relating to the ability of reversible $P2Y_{12}$ inhibitors to constantly antagonise newly synthesised receptors on nucleated C-fibres whereas therapeutic thienopyridine active metabolite levels are short-lived [167].

In terms of management, one of the major challenges facing clinicians is to determine whether dyspnoea in a patient is related to a serious pathology or a side-effect of the medication. Ticagrelor-induced dyspnoea is generally a diagnosis of exclusion, following a thorough history and examination, but some mild cases that are not associated with limitation of exercise capacity, orthopnoea or nocturnal dyspnoea can be readily attributed to ticagrelor and reassurance provided, particularly in patients who have been successfully revascularised. While persistent and intolerable ticagrelor-induced dyspnoea is uncommon, currently the only proven management strategy is discontinuation [166] although dose reduction from 90 mg BD to 60 mg BD may be an alternative option to try if dyspnoea is not severe.

In the PLATO study, ticagrelor was associated with a greater incidence of asymptomatic ventricular pauses of 3 seconds or more in the first week (5.8% [ticagrelor] vs. 3.6% [clopidogrel]; $P = 0.01$), and a greater increase in baseline levels of serum uric acid (mean $\pm$ standard deviation: 15 $\pm$ 52% vs. 7 $\pm$ 31%; $P < 0.001$) and creatinine (11 $\pm$ 22% vs. 9 $\pm$ 22%; $P < 0.001$) at 12 months compared with clopidogrel [12]. Of note, there was no significant difference between the treatment groups in the incidence of adverse events related to bradyarrhythmia, and the raised frequency of ventricular pauses subsided by one month. It is uncertain whether this effect of ticagrelor is associated with ENT1 blockade and increased extracellular adenosine levels. Uric acid is a product of purine (adenosine) metabolism [169], and can manifest clinically as a slightly increased risk of gout during long-term ticagrelor treatment, as demonstrated in the PEGASUS-TIMI 54 study [13]. Finally, adenosine can alter renal haemodynamics [170], resulting in a lower glomerular filtration pressure and a subsequent increase in serum creatinine.

14. Ticagrelor in conjunction with oral anticoagulant drugs

A major challenge facing clinicians is patients who have indications for both dual antiplatelet therapy and oral anticoagulant therapy, most commonly as a result of patients with atrial fibrillation being treated with PCI. Recent trials have indicated that vitamin K antagonists (VKA), such as warfarin, carry substantially higher risk of life-threatening bleeding, most notably intracranial haemorrhage, compared with non-VKA oral anticoagulants (NOAC), including when used in conjunction with antiplatelet drug regimens [171–174]. The 2 $\times$ 2 factorial design of the AUGUSTUS study permitted delineation of how much safety is improved by, firstly, using the factor Xa inhibitor apixaban (at its licensed dose for prophylaxis in atrial fibrillation) instead of a VKA and, secondly, dropping aspirin from combination with anticoagulant and a $P2Y_{12}$ inhibitor [173]. Both of these led to reductions in clinically-relevant bleeding, including in those with renal impairment [175], without significant impact on the combined endpoint of death and ischaemic events. However, there were numerical trends towards more stent thrombosis when aspirin was dropped from the antithrombotic regimen [176]. In AUGUSTUS and RE-DUAL, the majority of patients received clopidogrel as the $P2Y_{12}$ inhibitor [173] but a minority received ticagrelor, allowing some non-randomised comparisons of efficacy and safety outcomes [177, 178]. These analyses left some doubts about whether ticagrelor may safely and effectively substitute for DAPT with aspirin and clopidogrel in combination with a NOAC. The AUGUSTUS study suggested that a triple regimen with ticagrelor, aspirin and oral anticoagulant carries an unacceptable bleeding risk for routine use [178]. Whilst a dual regimen of ticagrelor and apixaban without aspirin makes pharmacological sense for optimising prevention of stent thrombosis whilst avoiding excessive bleeding, further work is required to assess this and compare with other options.

15. Ticagrelor monotherapy studies and studies of lower dose aspirin

This review has presented novel developments in antiplatelet therapy and has emphasised the role of ticagrelor. It is evident that the choice of pharmacological agents and the duration of treatment is dependent on the risk factors and clinical features of the individual patient. The clinical development of ticagrelor for use in CAD initially placed it as a substitute to clopidogrel in the context of DAPT i.e., in combination with baseline aspirin therapy. However, a *post-hoc* analysis of the PLATO trial found a significant interaction between high ($\geq$300 mg OD) aspirin dose and reduced benefit of ticagrelor over clopidogrel in preventing MACE [179], which led to questioning the benefits of aspirin alongside ticagrelor. The GLOBAL LEADERS *post-hoc* analysis, TWILIGHT and TICO studies indicate that the addition of low-dose aspirin to ticagrelor increases the risk of bleeding without an obvious benefit of anti-ischaemic protection after PCI, particularly in ACS patients. Bleeding is not only associated with an increased risk of mortality [128, 129], but mild cases can impact on quality of life and lead to premature discontinuation of treatment [20, 180].

Based on a variety of studies, it is clear that combining aspirin and ticagrelor has additive effects [42, 181] and may be required long term in certain patient populations that are at high risk of arterial thrombotic events. For example, PEGASUS-TIMI 54 and THEMIS-PCI consisted of high-risk individuals who derived greater antithrombotic benefit from DAPT than aspirin alone. In addition, the SOCRATES and THALES trials showed that patients with ischaemic stroke derived no benefit in ischaemic risk from ticagrelor alone vs. aspirin, but did benefit from DAPT. For three of these studies, the superior efficacy of DAPT also came at a cost of substantially increased risk of bleeding. Therefore, it appears that combining $P2Y_{12}$ inhibition by ticagrelor with COX-1 inhibition by low-dose aspirin is important in certain high-risk patients. A novel strategy aims to optimise aspirin dose in these patients to reduce the risk of bleeding [9]. Currently, the lowest standard dose of aspirin is 75–100

mg, but very-low doses (40 mg) have also demonstrated sufficient cumulative inhibition of platelet activation via the irreversible impairment of COX-1 derived TXA_2 [182, 183]. Aspirin dose-dependently inhibits COX-2 [184, 185], an enzyme that is associated with a cardioprotective function, whereby long-term inhibition may lead to adverse cardiovascular events [186, 187]. Therefore, lower-than-standard dose aspirin could hypothetically reduce the risk of bleeding and associated complications of COX-2 inhibition while maintaining anti-thrombotic efficacy. A recent study (WILLOW ACS) characterised a novel regimen of very-low-dose aspirin (20 mg BD) plus ticagrelor over two weeks in 20 patients with recent ACS [188]. Compared with standard-dose aspirin (75 mg OD) plus ticagrelor, the novel regimen reduced peak COX-1 inhibition, which was associated with a significant reduction in bleeding time and without a significant difference in arachidonic acid-induced platelet aggregation. In combination with ticagrelor, very-low-dose aspirin is likely to provide adequate antithrombotic coverage particularly when administered twice-daily. A recent single-centre, observational, non-randomised trial provides optimism for this potential strategy as the results indicated that aspirin 50 mg OD reduced the frequency of bleeding events compared with standard dose aspirin, without affecting the frequency of MACE, in 1066 patients with CAD on ticagrelor therapy [189]. Aspirin dose modification requires evaluation in large-scale RCTs, with sufficient power to determine any improvement in net outcomes before implementation into clinical practice.

16. ESC and AHA/ACC guideline recommendations

The European Society of Cardiology (ESC) and American College of Cardiology (ACC)/American Heart Association (AHA) publish regular guidelines that represent the views of experts in cardiology, based on the current knowledge and understanding of cardiac conditions and management at the time of publication. The following highlight the latest guidelines and represents the class of recommendation (I–III) and the level of evidence (A–C) that are relevant to the use of ticagrelor in CAD.

The ESC 2017 [5] and ACC Foundation/AHA 2013 [6] STEMI guidelines both recommend the use of ticagrelor (180 mg loading dose, then 90 mg BD maintenance dose) as a first-line $P2Y_{12}$ inhibitor to be combined with aspirin in the acute-phase management of patients undergoing primary PCI (ESC I, A; ACC/AHA I, B). For patients receiving fibrinolytic therapy and subsequent PCI, clopidogrel and aspirin are recommended initially (both I, A), but ESC states that if the index PCI is performed 48 hours after fibrinolysis, ticagrelor or prasugrel may be considered instead of clopidogrel (I, C). Maintenance antithrombotic therapy after PCI involving ticagrelor-based DAPT is recommended for at least one year after STEMI unless there is an excessive risk of bleeding (I, A; I, B), and ticagrelor plus aspirin may be considered for longer than a year (ESC state ticagrelor 60 mg beyond one year and up to three years; IIb, B; ACC/AHA state specifically following DES placement; IIb, C) in patients who tolerate DAPT and are at high risk of ischaemia.

The ESC 2020 [3] and AHA/ACC 2014 [4] NSTE-ACS guidelines state that aspirin plus a $P2Y_{12}$ inhibitor are recommended for one year after PCI (I, A; I, B). Ticagrelor is recommended for both invasive and conservative strategies and is preferred over clopidogrel; whereas prasugrel is only recommended for patients who are intended for PCI and are $P2Y_{12}$ inhibitor-naïve (I, B) although the ESC NSTE-ACS guidelines state that prasugrel should be considered in preference to ticagrelor in PCI-treated patients (IIa, B). The ESC 2020 guidelines do not recommend the routine use of $P2Y_{12}$ inhibitors prior to invasive management when the coronary anatomy is not known (III, A) but pre-treatment may be considered if patients are not planned for early invasive management (IIb, C). Following intervention for NSTE-ACS, ESC recommend a majority of patients receive DAPT for one year (I, A), although there is a degree of freedom for the prescribing clinician to select from various strategies that include prolonged duration, discontinuation or de-escalation of the maintenance regimen: $P2Y_{12}$ inhibitors are options long-term with aspirin for secondary prevention for those at high (IIa, A) or moderate (IIb, A) risk of ischaemia, without an excessive risk of bleeding; $P2Y_{12}$ inhibitors may be stopped after three months if there is a high risk of bleeding (IIa, B); aspirin may be stopped after three-to-six months depending on the balance between the risks of ischaemia and bleeding (IIa, A); prasugrel or ticagrelor may be switched to clopidogrel for patients who are not considered at high risk of ischaemia (IIb, A).

The ESC 2019 [2] CCS guidelines recommend that an oral $P2Y_{12}$ inhibitor or oral anticoagulant, in addition to aspirin, should or may be considered for long-term secondary prevention in CCS patients with sinus rhythm, who have a high (IIa, A) or moderately increased (IIb, A) risk of ischaemia, respectively, and are not at high risk of bleeding. Clopidogrel 75 mg OD and ticagrelor 60 mg BD are each indicated post-MI in patients who have tolerated DAPT for one year, while prasugrel requires an additional indication for the patient to have received PCI and its use is cautioned in patients over the age of 75 years. For post-PCI patients who are unable to tolerate DAPT due to aspirin intolerance, or with high-risk procedural features (e.g., suboptimal stent deployment, complex left main stem, multivessel stenting, or characteristics associated with a high risk of stent thrombosis), prasugrel or ticagrelor may be considered instead of clopidogrel (IIb, C).

According to ESC guidelines, for NSTE-ACS and CCS patients with an indication for long-term anticoagulation and a moderate or high risk of stent thrombosis, ticagrelor or prasugrel plus an oral anticoagulant in dual antithrombotic therapy may be considered as an alternative to triple antithrombotic therapy (IIb, C), and are not recommended for use in triple therapy (III, C) [2, 3].

Current ESC recommendations advise 12 months of DAPT with aspirin and a $P2Y_{12}$ inhibitor, preferably ticagrelor or prasugrel, after CABG for ACS (I, C) [153]. Prolonged DAPT beyond one year can be considered in those with a history of MI (IIb, C). However, if bleeding risk is high, only 6 months of DAPT after CABG is recommended and prasugrel should be avoided (IIa, C). In those undergoing CABG for CCS, there is no current recommendation for the routine use of DAPT or ticagrelor monotherapy and these patients should remain on aspirin alone unless there is another indication for an alternative regimen. ACC/AHA guidelines also recommend 12 months of DAPT (including the option of ticagrelor) after CABG for ACS (I, C) [190]. In contrast to the ESC guidelines, 12 months of DAPT after CABG for CCS is deemed reasonable (IIb, B) but clopidogrel is the only $P2Y_{12}$ inhibitor recommended in this scenario.

17. Future directions

Future work will exploit the reversibility of ticagrelor with the further characterisation and development of methods for reversing ticagrelor's effects in the event of patients needing urgent surgery or developing major bleeding complications. More work is required to identify which patients are best suited to ticagrelor monotherapy following PCI in order to tailor efficacy and safety according to individual characteristics. When dual antiplatelet therapy is required, further work will assess potential benefits of twice-daily very-low-dose aspirin regimens combined with ticagrelor. Tailoring of the ticagrelor dose according to body weight may also help refine short-term and long-term tolerability of ticagrelor in the future. Learning how ticagrelor can work alongside novel secondary prevention medications will provide opportunities for refinement of secondary prevention of cardiovascular disease.

18. Conclusions

Ticagrelor is an oral $P2Y_{12}$ receptor antagonist that demonstrates some desirable pharmacological advantages over thienopyridines, including reversibility of action. Its greater potency of platelet inhibition compared with clopidogrel translates to a reduction in MACE following ACS at the cost of increased spontaneous bleeding events. In this review, we have focussed on large randomised clinical trials and substudies that underpin the use of ticagrelor in clinical practice today, and highlight innovative antithrombotic strategies involving ticagrelor that aim to optimise clinical outcomes in specific patient populations by de-escalating the antiplatelet coverage that subsequently reduces bleeding and may maintain efficacy. Ticagrelor remains a key drug in the management of patients with CAD, and in particular ACS, that may be extended to other atherosclerotic conditions. As research continues in this field, pioneering clinical trials will establish further uses and constraints of ticagrelor within specific patient populations and management strategies, and will determine whether the aforementioned novel regimens are incorporated into standard clinical practice.

Abbreviations

AC, Adenylate Cyclase; ACC, American College of Cardiology; ACS, Acute Coronary Syndrome; ADP, Adenosine Diphosphate; AHA, American Heart Association; ALPHEUS, Assessment of Loading with the $P2Y_{12}$ inhibitor ticagrelor or clopidogrel to Halt ischaemic Events in patients Undergoing elective coronary Stenting; AUC, Area Under the Curve; BARC, Bleeding Academic Research Consortium; BD, Twice Daily; CABG, Coronary Artery Bypass Graft; CAD, Coronary Artery Disease; CCS, Chronic Coronary Syndrome; CI, Confidence Interval; CKD, Chronic Kidney Disease; C_{max}, peak plasma concentration; COX, Cyclooxygenase; CYP, Cytochrome P-450; DACAB, Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft; DAPT, Dual Antiplatelet Therapy; DES, Drug-Eluting Stent; DISPERSE, Dose ConfIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction; E-CABG, European Multicentre Study on CABG; ESC, European Society of Cardiology; ENT, Equilibrative Nucleoside Transporter; EUCLID, Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease; GUSTO, Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HR, Hazard Ratio; IL, Interleukin; ISAR REACT, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; LD, Loading Dose; MACE, Major Adverse Cardiovascular Event; MD, Maintenance Dose; MI, Myocardial Infarction; NIHSS, National Institutes of Health Stroke Scale; NOAC, Non-VKA Oral Anticoagulant; NSTE-ACS, Non-ST-Elevation Myocardial Infarction; OD, Once Daily; OR, Odds Ratio; PAD, Peripheral Artery Disease; PCI, Percutaneous Coronary Intervention; PEGASUS, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; PI3K, phosphoinositide 3-kinase; PLATO, Platelet Inhibition and Patient Outcomes; RCT, Randomised Controlled Trial; RR, Risk Ratio; SOCRATES, Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes; STEMI, ST-Elevation Myocardial Infarction; TAM, Ticagrelor Active Metabolite; THALES, Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and Acetylsalicylic Acid for Prevention of Stroke and Death; THEMIS, The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study; TIA, Transient Ischaemic Attack; TiCAB, Ticagrelor in CABG; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for ACS; TIMI, Thrombolysis in Myocardial Infarction; t_{max}, time to maximum plasma concentration; TWILIGHT, Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention; TXA_2, Thromboxane A_2; $t_{1/2}$, terminal phase half-life; T2DM, Type 2 Diabetes Mellitus; VKA, Vitamin K Antagonist.

Author contributions

NCS and WAEP drafted the manuscript under the supervision of RFS, who edited and approved the final version. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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