CLINICAL TRIAL EVALUATION

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Ticagrelor for the treatment of atherosclerotic disease: insights from the PARTHENON clinical development program

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Ticagrelor (P2Y₁₂ receptor antagonist) is presently indicated for preventing atherothrombotic events in patients with acute coronary syndrome and patients with a history of myocardial infarction. The PARTHENON clinical development program comprises five randomized, controlled, cardiovascular, indication-seeking outcome studies, aiming to evaluate ticagrelor across the spectrum of patients with atherothrombotic disease. Results of two large-scale trials support a benefit for ticagrelor in patients with acute coronary syndrome (PLATO; ClinicalTrials.gov: NCT00391872) and in patients with a history of myocardial infarction (PEGASUS-TIMI 54; ClinicalTrials.gov: NCT01225562). Ongoing trials will provide information on the efficacy and safety of ticagrelor in patients with acute ischemic stroke or transient ischemic attack (SOCRATES; ClinicalTrials.gov: NCT01994720), peripheral artery disease (EUCLID; ClinicalTrials.gov: NCT01732822) and coronary artery disease in patients with Type 2 diabetes mellitus (THEMIS; ClinicalTrials.gov: NCT01991795).

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Atherothrombotic disease

Cardiovascular disease (CVD) remains the leading global cause of death, claiming more lives than all cancer types combined. Consequently, the economic burden is significant, with direct and indirect costs of CVD and stroke totaling more than \$316 billion annually in the USA [1].

The most prevalent cause of CVD is atherosclerosis, defined as the process of plaque formation ultimately resulting in either stenosis and/or plaque rupture in the arterial vessel(s) affected. Atherosclerotic lesions typically occur in the large and medium-sized elastic and muscular arteries, and can remain silent, without clinical manifestation, for years. However, disruption of the plaque surface, as is observed in 60–80% of cases of acute coronary syndrome (ACS), can lead to thrombotic complications and a subsequent reduction or occlusion of blood supply resulting in downstream ischemia or permanent cell death [2].

The role of platelets in atherogenesis and in atherosclerosis progression remains unclear [3,4]. However, platelet activation and aggregation are ultimately responsible for manifesting atherothrombotic disease [5,6]. The outcome of an atherothrombotic event depends on the location of the affected vascular bed. For example, plaque rupture and subsequent thrombosis occurring in atherosclerotic coronary arteries can result in unstable angina or an ACS [7,8], whereas atherothrombosis in carotid or cerebral arteries can result in a transient ischemic attack (TIA) or ischemic stroke [9]. Atherosclerosis is a systemic disease and may also lead to peripheral artery disease (PAD). The most common symptom in patients with PAD is intermittent claudication, and 5–10% of these patients

KEYWORDS

- acute coronary syndrome
- atherosclerosis • coronary artery disease • diabetes mellitus • myocardial infarction • P2Y₁₂ receptor antagonist • ischemic stroke
- ticagrelor

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may develop critical limb ischemia [10]. Patients with PAD have an increased risk of myocardial infarction (MI), stroke and death [10]. Another group of patients who are also at an increased risk of CVD are those with diabetes. In these patients, atherosclerosis progresses rapidly, atherosclerotic complications are particularly common, and platelet function is abnormal [11].

Background to ticagrelor

Potent antiplatelet therapy has been proven in large clinical trials to reduce the risk of new infarctions following an MI, thereby saving patients' lives [12–15]. However, despite this success, the risks of a further MI and death are still high, and there remains a medical need for improved therapy. Following the results of the CURE study [16], clopidogrel with aspirin became the standard of care for ACS. However, certain properties of clopidogrel highlight the potential weaknesses of this antiplatelet agent. For the inhibition of platelet aggregation (IPA), clopidogrel has a slow onset of action, potentially

due to the need for metabolic activation as it is a prodrug [17]. Furthermore, variable and reduced antiplatelet effects are observed in patients with polymorphism in certain cytochrome P450 (CYP)2C19 alleles [18] and these patients may remain at risk of experiencing atherothrombotic events [19]. Additionally, the active metabolite of clopidogrel binds irreversibly to the platelet P2Y₁₂ receptor, resulting in prolonged recovery of platelet function as this is dependent on the formation of new platelets [20]. Prolonged loss of platelet function with clopidogrel, as well as its combined use with aspirin (which irreversibly inhibits its target COX1) and/or other antiplatelet/anticoagulant agents, is associated with increased bleeding [16,21].

Ticagrelor is the first in a new class of P2Y₁₂ receptor antagonists and has several characteristics that potentially address the shortcomings of the previous standard of care. The clinical development program is summarized in **Figure 1**. Overall, the development program up to the approval of ticagrelor included 41 clinical

Figure 1. Ticagrelor clinical development program. Studies: DISPERSE; DISPERSE-2; EUCLID (ClinicalTrials.gov: NCT01732822); ONSET/OFFSET (ClinicalTrials.gov: NCT00528411); PEGASUS-TIMI 54 (ClinicalTrials.gov: NCT01225562); PLATO (ClinicalTrials.gov: NCT00391872); RESPOND (ClinicalTrials.gov: NCT00642811); SOCRATES (ClinicalTrials.gov: NCT01994720); THEMIS (ClinicalTrials.gov: NCT01991795).

pharmacology (Phase I) studies, describing the pharmacologic characteristics of ticagrelor. After oral administration, ticagrelor is rapidly absorbed and demonstrates linear and predictable pharmacokinetics with minimal variability across a range of populations [22]. Ticagrelor is direct acting and does not require metabolic conversion for antiplatelet activity, although ticagrelor is extensively metabolized [22]. CYP3A is the major enzyme responsible for ticagrelor metabolism and the formation of the metabolite AR-C124910XX, which has a similar potency versus the P2Y₁₂ receptor as the parent ticagrelor [23]. Ticagrelor binds directly, selectively and reversibly to the P2Y₁₂ receptor (**Figure 2**) to mediate a rapid onset and offset of antiplatelet activity [24]. Furthermore, ticagrelor also inhibits adenosine uptake via selective inhibition of the ENT1, thereby increasing the local extracellular concentration of adenosine and its potential to activate adenosine receptors (**Figure 2**) [25,26]. Adenosine has several biological effects via its four receptors (A1, A2a, A2b and A3), including platelet inhibition, coronary vasodilation, modulation of inflammatory responses, cardioprotective effects and reduction of ischemia/reperfusion injury [25]. Thus, ticagrelor, via ENT1 inhibition and increasing extracellular adenosine concentrations, may have additional clinical benefits. Indeed, ticagrelor has been shown to limit infarct size in animal models [27,28], and to improve heart function postischemia reperfusion [29]. In addition, ticagrelor exhibits cell-specific effects on endothelial dysfunction independently of P2Y₁₂ or adenosine receptors, with additional implications for ticagrelor in CVD [30].

In the Phase II studies, ticagrelor's pharmacokinetic and pharmacodynamic profiles were further characterized, and the safety profile elucidated. In the dose confirmation study assessing antiplatelet effects of AZD6140 (prior drug identifier for ticagrelor) versus clopidogrel (DISPERSE) study, patients with atherosclerosis who received ticagrelor achieved a peak final-extent IPA (65–95%) within 2–4 h. However, clopidogrel had a slower onset of action and IPA was <20% 2–12 h postdosing. Bleeding events in the ticagrelor arms were dose related but, overall, were minor or mild-to-moderate in intensity [32]. In patients with non-ST-elevation ACS (NSTE-ACS, DISPERSE-2 study), ticagrelor exhibited higher levels of IPA than clopidogrel [33,34], as well as encouraging, initial findings on MI rates [33].

There was no significant difference in the rates of major bleeding, although an increase in minor bleeding was observed with ticagrelor. A higher frequency of mostly asymptomatic ventricular pauses (duration >2.5 s) was reported with ticagrelor versus clopidogrel [33,34]. Also, in both DISPERSE studies, a dose-dependent increase in dyspnea was observed with ticagrelor [32,33]. In patients with stable CAD, the assessment of the onset and offset of the antiplatelet effects of ticagrelor versus clopidogrel study (ONSET OFFSET; ClinicalTrials.gov: NCT00528411), ticagrelor exhibited a more rapid and consistent onset of action and a faster offset of action with a faster recovery of platelet function, compared with clopidogrel [35]. Furthermore, a study of the antiplatelet effects of ticagrelor in clopidogrel responders and nonresponders (RESPOND; ClinicalTrials.gov: NCT00642811) in patients with CAD showed that ticagrelor therapy overcame nonresponsiveness to clopidogrel [36].

Based on these encouraging Phase II results, AstraZeneca initiated PLATO, a confirmatory, Phase III trial in ACS patients at high risk of a recurrent atherothrombotic event [37,38]. Following positive results in PLATO, the PARTHENON program was expanded.

The PARTHENON program: Phase III clinical development of ticagrelor

The PARTHENON clinical development program comprises five indication-seeking, cardiovascular (CV) outcome studies (**Table 1**) evaluating ticagrelor across the spectrum of patients suffering from CVD (from high to very high risk of experiencing future CV events) in the various vascular beds affected (**Figure 3**). The program considers ticagrelor for the treatment of acute CVD, as well as for the primary and secondary prevention of CVD (**Figure 3**). In total, over 80,000 patients will be enrolled across the five randomized, controlled, double-blind studies. Key study characteristics and end points are summarized in **Table 1** [37–43]. Common exclusion criteria across the studies were an increased risk of bleeding, known bleeding diathesis or coagulation disorder, a history of intracranial bleeding, renal failure requiring dialysis and a requirement for concomitant therapy with other antithrombotic agents, strong CYP3A inhibitors or inducers, or oral anticoagulants. The primary efficacy end points are composites of MI, ischemic or all-cause stroke, and cardiovascular or all-cause

Figure 2. Dual mode of platelet aggregation inhibition by ticagrelor. Platelet aggregation is inhibited by antagonism of the P2Y₁₂ receptor by ticagrelor. This receptor (with the P2Y₁ receptor, not shown) mediates ADP-induced platelet activation/aggregation. In addition, ticagrelor inhibits ENT1, expressed on many cells including erythrocytes, thereby reducing cellular uptake of adenosine. Extracellular adenosine activates the platelet A_{2A} receptor, which stimulates cAMP by AC; cAMP inhibits platelet activation/aggregation. Ticagrelor via ENT1 inhibition has the potential to enhance all physiological responses to adenosine, which, besides platelet inhibition, includes: vasodilation, modulation of inflammation and cardioprotection [25].

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death. The primary safety end point across the studies is the rate of major bleeding.

• PLATO

ACS encompasses a spectrum of unstable CAD and is associated with significant morbidity and mortality [1]. Platelet activation, aggregation and thrombus formation are a hallmark of ACS, which typically involves the presence and/or rupture of an atherosclerotic plaque in the coronary arterial tree [8]. PLATO (ClinicalTrials.gov: NCT00391872; **Table 1**) evaluated ticagrelor in a broad population of ACS patients, who were randomized 1:1 to receive ticagrelor (180-mg loading dose, 90 mg twice daily [b.i.d.] thereafter) or clopidogrel (300–600-mg loading dose, 75 mg once daily [q.d.] thereafter). Key inclusion criteria were hospitalization for potential ST-segment elevation or non-ST-segment

elevation ACS, with onset during the previous 24 h documented by cardiac ischemia symptoms of ≥10 min duration at rest, and aged ≥18 years. Key exclusion criteria (further to those described above) were fibrinolytic therapy within 24 h, or a contraindication to clopidogrel therapy [37].

Principal results from PLATO are presented in **Table 2** & **Figure 4A**. The reduced rate of CV events with ticagrelor versus clopidogrel (hazard ratio: 0.84; 95% CI 0.77–0.92; $p < 0.001$) was achieved without an increase in the overall rate of major bleeding, although ticagrelor was associated with a higher rate of major bleeding not related to coronary artery bypass graft (CABG) surgery. Notably, ticagrelor was associated with a reduction in the rate of all-cause mortality at 1 year (hazard ratio: 0.78; 95% CI: 0.69–0.89; $p < 0.001$), which has not been reported for other oral antiplatelet agents [16,44].

The improved survival rate with ticagrelor is potentially explained by a combination of factors including the decreased risk of thrombotic events without an increase in the risk of major bleeding, and additional adenosine-related effects [38]. Consistent with Phase II study findings, dyspnea was reported more frequently in patients receiving ticagrelor versus clopidogrel. There was also a higher incidence of ventricular pauses during the first week in the ticagrelor group. Importantly, ventricular pauses in the ticagrelor group were not more common at day 30. Ventricular pauses were rarely associated with symptoms. The incidence of syncope and pacemaker implantation were similar between the ticagrelor and clopidogrel groups [38]. Not only increased survival but also dyspnea and ventricular pauses may be related to ticagrelor's effects on adenosine [25].

Based on the PLATO results, ticagrelor is licensed and recommended in guidelines for the prevention of atherothrombotic events in ACS patients [12–15]. To date, approximately 50 subanalyses of the PLATO data have been reported. Results comparing ticagrelor with clopidogrel are generally consistent with those in the overall cohort. Key subanalyses included patients: with a planned invasive strategy [45]; intended for noninvasive management [46]; with non-ST-segment elevation with or without revascularization [47]; with ST-elevation MI (STEMI) [48]; with a history of stroke or TIA [49]; with and without diabetes [50]; with chronic obstructive pulmonary disease [51]; undergoing CABG [52]; with PAD [53]; and an analysis of the effects on stent thrombosis [54]. Importantly, a landmark analysis demonstrated that the beneficial treatment effects with ticagrelor were consistent in the short- (days 1–30) and long-term (days 31–360) following an ACS (Table 2) [38], providing rationale for the PEGASUS-TIMI 54 study.

• PEGASUS-TIMI 54

Patients with atherothrombosis and a history of ischemic events (MI or stroke) have an elevated risk for subsequent ischemic events [55]. Two real-world, observational, retrospective, cohort studies in Sweden [56] and the USA [57] have recently shown that the risk of CV events was high beyond the first year post-MI, particularly in patients with additional risk factors.

The PEGASUS-TIMI 54 study (ClinicalTrials.gov: NCT01225562; Table 1)

Table 1. Summary of the cardiovascular outcome studies comprising the PARTHENON program.

Characteristics	PLATO (ClinicalTrials.gov: NCT00391872) [37,38]	PEGASUS-TIMI 54 (ClinicalTrials.gov: NCT01225562) [39,40]	SOCRATES (ClinicalTrials.gov: NCT01994720) [41]	EUCLID (ClinicalTrials.gov: NCT01732822) [42]	THEMIS (ClinicalTrials.gov: NCT01991795) [43]
Number of patients	18,624	21,162	~13,200	13,885	~19,000
Study duration	1 year [†]	3 years [†]	90 days	<40 months [‡]	<48 months [§]
Disease/population	ACS	Stable CAD, history of MI	Acute ischemic stroke or TIA	PAD	T2DM and CAD, no history of MI or stroke
Ticagrelor dose	90-mg bid (180-mg loading) [¶]	60 or 90 mg b.i.d. [#]	90 mg b.i.d. (180-mg loading)	90 mg b.i.d.	60 mg b.i.d. ^{††}
Comparator	Clopidogrel 75 mg q.d. (300–600-mg loading) [*]	Placebo [#]	Aspirin 100 mg q.d. (300-mg loading)	Clopidogrel 75 mg q.d.	Placebo ^{††}
End points					
Primary efficacy	MI, stroke or death from vascular causes ^{‡‡}	MI, stroke or death from vascular causes ^{‡‡}	MI, stroke or death from any cause ^{‡‡}	MI, ischemic stroke, death from vascular causes ^{‡‡}	MI, stroke or death from vascular causes ^{‡‡}
Primary safety	Major bleeding ^{§§}	Major bleeding ^{¶¶}	Major bleeding ^{##}	Major bleeding ^{†††}	Major bleeding

[†]Overall planned maximum duration (approximate).

[‡]The trial will continue until at least 1364 adjudicated primary end points occur.

[§]The trial will continue until at least 1034 adjudicated primary end points occur.

[¶]All patients received aspirin 75–100 mg/day (if tolerated).

^{*}All patients received aspirin 75–150 mg/day (if tolerated).

[†]With aspirin (if not contra indicated or not tolerated).

[‡]Composite end point.

[§]PLATO defined (adjudicated using TIMI definition).

[¶]TIMI defined.

^{##}PLATO defined.

^{†††}TIMI defined (and also adjudicated using PLATO, GUSTO and International Society on Thrombosis and Hemostasis definitions).

ACS: Acute coronary syndrome; b.i.d.: Twice daily; CAD: Coronary artery disease; PAD: Peripheral artery disease; MI: Myocardial infarction; q.d.: Once daily; TIA: Transient ischemic attack; T2DM: Type 2 diabetes mellitus.

Figure 3. The PARTHENON program: patient populations and cardiovascular risk. The active comparators are clopidogrel (75 mg once daily; for PLATO and EUCLID) and aspirin (100 mg once daily; for SOCRATES). Studies: EUCLID (ClinicalTrials.gov: NCT01732822); PEGASUS-TIMI 54 (ClinicalTrials.gov: NCT01225562); PLATO (ClinicalTrials.gov: NCT00391872); SOCRATES (ClinicalTrials.gov: NCT01994720); THEMIS (ClinicalTrials.gov: NCT01991795). ACS: Acute coronary syndrome; b.i.d.: Twice daily; CV: Cardiovascular; MI: Myocardial infarction; PAD: Peripheral artery disease; T2DM: Type 2 diabetes mellitus.

tested the hypothesis that long-term therapy with ticagrelor plus low-dose aspirin compared with aspirin alone reduces the risk of CV events in patients with stable CAD and a history of MI. Patients aged ≥ 50 years with a spontaneous MI 1–3 years before enrolment were randomized 1:1:1 to receive ticagrelor 90 mg b.i.d., ticagrelor 60 mg b.i.d. or placebo; all groups also had aspirin 75–150 mg daily. Patients were required to have at least one additional CV risk factor (aged ≥ 65 years; diabetes mellitus on medication; second prior MI; multivessel CAD; chronic renal dysfunction). Patients with planned revascularization were excluded (Table 1) [39].

The main results of the PEGASUS-TIMI 54 trial are summarized in Table 3 & Figure 4B [40]. Briefly, both doses of ticagrelor significantly reduced the risk of CV death, MI or stroke, to a similar extent, versus placebo. The benefit of ticagrelor with respect to the primary end point continued to accrue over time, with a median 33 months of follow-up (Figure 4B). Pharmacodynamic analysis confirmed similar high levels of IPA for both ticagrelor doses [58]. Both ticagrelor doses in PEGASUS-TIMI 54 increased the risk of major bleeding. The rate of dyspnea and the proportion of patients who discontinued due to dyspnea were greater in the

two ticagrelor arms versus placebo, however, the majority of dyspnea episodes with ticagrelor were mild or moderate in severity [40]. The rates of bleeding and dyspnea were numerically lower with ticagrelor at 60 mg b.i.d. versus the 90-mg b.i.d. dose. Given the observed similar benefit of both ticagrelor doses, but a more favorable tolerability profile of the 60-mg dose, the benefit–risk profile of the 60-mg dose of ticagrelor is considered to be better compared with the 90-mg dose. Additionally, a recent landmark analysis demonstrated that ticagrelor reduced the risk of MI, stroke or CV death during the first year, as well as in subsequent years [59].

The clinical profile of ticagrelor in the PEGASUS-TIMI 54 trial was consistent across subgroups including age, gender, race, history of percutaneous coronary intervention (PCI), presence or absence of diabetes, aspirin dose [40], stent history [60] and degree of renal dysfunction [61]. The significant reduction in MI with ticagrelor was also consistent across different MI subtypes and sizes [62]. Moreover, the efficacy of ticagrelor appeared to be greater in patients continuing on therapy with a P2Y₁₂ inhibitor (or restarting after only a brief interruption) compared with patients who were stable for more than 2 years post-MI and had not received

treatment with P2Y₁₂ inhibitors for more than a year [63].

Treatment guidelines have historically recommended treatment with a P2Y₁₂ receptor antagonist for up to 1 year post-MI [12,14–15]. However, the PEGASUS-TIMI 54 results provide evidence that long-term platelet inhibition with ticagrelor reduces CV events in patients with prior MI. Based on the findings of PEGASUS-TIMI 54 and the dual antiplatelet therapy trial [64], the European Society of Cardiology Guidelines for the management of NSTEMI-ACS were recently updated. The revised guidelines recommend that P2Y₁₂ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischemic and bleeding risks of the patient (class IIb, level A evidence) [13].

• SOCRATES

Thrombotic complications of atherosclerotic disease in the carotid or cerebral vasculature can manifest clinically as a TIA or ischemic stroke [9]. Patients who have experienced a

TIA or acute, minor ischemic stroke have an elevated stroke risk [65]. A meta-analysis of 40,000 patients from two large, randomized trials (the Chinese Acute Stroke Trial, and the International Stroke Trial) assessed aspirin monotherapy in patients with ischemic stroke [66]. In this analysis, aspirin significantly reduced the incidence of recurrent ischemic stroke, although hemorrhagic stroke was significantly increased [66]. Antiplatelet therapy is recommended in current guidelines, and aspirin is the current standard of care, for the prevention of recurrent ischemic events (including CV events) in patients with TIA or acute, ischemic stroke of noncardioembolic origin [67]. However, evidence on the use of more potent antiplatelet therapy to further reduce the risk of recurrent ischemia (including CV events) following acute stroke or TIA remains limited. Recently, in a Chinese only population, the CHANCE (ClinicalTrials.gov: NCT00979589) trial demonstrated a reduction in the relative risk of stroke (primary end point) at 90 days following treatment with clopidogrel

Table 2. Summary of PLATO study results.

End point n/total (%)	Ticagrelor 90 mg b.i.d.	Clopidogrel 75 mg q.d.	HR for ticagrelor group (95% CI)	p-value [†]
Primary efficacy[‡]				
MI, stroke, death from vascular causes	864/9333 (9.8)	1014/9291 (11.7)	0.84 (0.77–0.92)	<0.001 [§]
Secondary efficacy[‡]				
Death from any cause, MI, stroke	901/9333 (10.2)	1065/9291 (12.3)	0.84 (0.77–0.92)	<0.001 [§]
MI	504/9333 (5.8)	593/9291 (6.9)	0.84 (0.75–0.95)	0.005 [§]
Death from vascular causes	353/9333 (4.0)	442/9291 (5.1)	0.79 (0.69–0.91)	0.001 [§]
Stroke	125/9333 (1.5)	106/9291 (1.3)	1.17 (0.91–1.52)	0.22
Other efficacy analyses[‡]				
Primary end point, days 1–30	443/9333 (4.8)	502/9291 (5.4)	0.88 (0.77–1.00)	0.045
Primary end point, days 31–360	413/8763 (5.3)	510/8688 (6.6)	0.80 (0.70–0.91)	<0.001
Death from any cause	399/9333 (4.5)	506/9291 (5.9)	0.78 (0.69–0.89)	<0.001
Primary safety[‡]				
PLATO-defined major bleeding	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Life-threatening or fatal bleeding (PLATO defined)	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)	–	0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)	–	0.69
Secondary safety[‡]				
PLATO-defined non-CABG related major bleeding	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
PLATO-defined CABG-related major bleeding	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32

[†]p-values were calculated by means of Cox-regression analysis.

[‡]Percentages are Kaplan–Meier estimates of the rate of the end point at 12 months.

[§]Statistical significance was confirmed in a hierarchical testing sequence applied to the secondary composite efficacy end points.

b.i.d.: Twice daily; CABG: Coronary artery bypass graft; HR: Hazard ratio; MI: Myocardial infarction; q.d.: Once daily.

Data taken from [38].

plus aspirin for the first 21 days versus aspirin alone; this benefit persisted at 1 year [68].

The ongoing SOCRATES (ClinicalTrials.gov: NCT01994720; **Table 1**) trial aims to evaluate whether ticagrelor monotherapy is superior to aspirin monotherapy for the primary end point (composite of stroke [ischemic or hemorrhagic], MI and death) following an acute, ischemic stroke or TIA. Patients aged ≥ 40 years with a minor, ischemic stroke or high-risk TIA within the previous 24 h are being randomized 1:1 to receive ticagrelor (180-mg loading dose, 90 mg b.i.d. thereafter) versus aspirin (300-mg loading dose, 100 mg q.d. thereafter) for 90 days, with an

Figure 4. Cumulative Kaplan–Meier estimates of the composite of myocardial infarction, stroke or death from vascular causes (primary efficacy end point) in (A) PLATO and (B) PEGASUS-TIMI 54. HR: Hazard ratio.

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Table 3. Summary of PEGASUS-TIMI 54 study results.

End point n (%)	Ticagrelor 90 mg b.i.d.	Ticagrelor 60 mg b.i.d.	Placebo	Ticagrelor 90 mg b.i.d. versus placebo		Ticagrelor 60 mg b.i.d. versus placebo	
				HR (95% CI)	p-value	HR (95% CI)	p-value
Primary efficacy [†]	n = 7050	n = 7045	n = 7067				
MI, stroke, death from vascular causes	493 (7.85)	487 (7.77)	578 (9.04)	0.85 (0.75–0.96)	0.008	0.84 (0.74–0.95)	0.004
Secondary efficacy [†]	n = 7050	n = 7045	n = 7067				
Death from CHD, MI, stroke	438 (6.99)	445 (7.09)	535 (8.33)	0.82 (0.72–0.93)	0.002	0.83 (0.73–0.94)	0.003
MI	275 (4.40)	285 (4.53)	338 (5.25)	0.81 (0.69–0.95)	0.01	0.84 (0.72–0.98)	0.03
Death from vascular causes	182 (2.94)	174 (2.86)	210 (3.39)	0.87 (0.71–1.06)	0.15	0.83 (0.68–1.01)	0.07
Stroke (any)	100 (1.61)	91 (1.47)	122 (1.94)	0.82 (0.63–1.07)	0.14	0.75 (0.57–0.98)	0.03
Primary safety [†]	n = 6988	n = 6958	n = 6996				
TIMI-defined major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
Fatal bleeding or nonfatal ICH	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
ICH	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00

[†]Percentages are Kaplan–Meier estimates of the rate of the end point at 3 years.

b.i.d.: Twice daily; CHD: Coronary heart disease; HR: Hazard ratio; ICH: Intracranial hemorrhage; MI: Myocardial infarction.

Data taken from [40].

additional 30-day follow-up receiving standard of care. Patients with a severe, ischemic stroke, low-risk TIA or suspected cardioembolic pathology are excluded [41]. Recruitment has been completed and approximately 13,200 patients have been randomized in SOCRATES. Results from SOCRATES will be available in 2016.

• EUCLID

PAD is a risk factor for CV events and associated morbidity, and is specifically related to atherothrombotic complications occurring in the vasculature of the lower limbs [55,69]. Atherosclerosis often occurs in multiple vascular beds, and patients with PAD have a high risk of MI and CV death [55,70]. PAD is associated with high healthcare costs, these patients also tend to have other conditions, such as diabetes and hypertension [71]. Current guidelines recommend antiplatelet therapy (including aspirin or clopidogrel) to reduce the risk of CV events in patients with symptomatic lower-extremity PAD [72]. In the randomized study of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE), clopidogrel significantly reduced the annual risk of ischemic stroke, MI or CV death compared with aspirin [73].

EUCLID (ClinicalTrials.gov: NCT01732822; **Table 1**) aims to evaluate the use of ticagrelor versus clopidogrel monotherapy in patients aged >50 years with established PAD. Patients were randomized 1:1 to receive ticagrelor 90 mg b.i.d. or clopidogrel 75 mg q.d. Patients with planned revascularization or amputation, a requirement

for aspirin, a history of stroke within 3 months or poor metabolizer status for CYP2C19, were excluded. EUCLID is currently ongoing and will continue until at least 1364 adjudicated primary end points occur (**Table 1**) [42]. To date, EUCLID is the first large, prospective, CV outcome study to examine the use of potent antiplatelet therapy in PAD. The results of EUCLID, expected in 2016, will determine whether treatment with ticagrelor versus clopidogrel, both administered as monotherapy, can reduce the incidence of CV and limb-specific events in patients with symptomatic PAD.

• THEMIS

Atherosclerosis is a major cause of morbidity and mortality in patients with Type 2 diabetes mellitus (T2DM). However, there is conflicting evidence on whether antiplatelet therapy should be used in the primary prevention of CV events in patients with diabetes [74]. Current European guidelines do not recommend antiplatelet agents for the primary prevention of CV events in low-risk patients with diabetes, whereas there is a class IIb (level C) recommendation to consider antiplatelet therapy for primary prevention in high-risk patients [75]. Benefits of more potent antiplatelet agents have not been confirmed in high-risk patients with T2DM.

THEMIS (ClinicalTrials.gov: NCT01991795; **Table 1**) is evaluating ticagrelor for the prevention of CV death, MI or stroke in patients with CAD, but no prior MI or stroke at high risk of atherothrombotic events due to T2DM. Initially,

patients with CAD (aged ≥ 50 years) treated for T2DM with glucose lowering medication were randomized 1:1 to receive ticagrelor 90 mg b.i.d. or placebo. Based upon the successful treatment with ticagrelor 60 mg b.i.d. in PEGASUS TIMI 54, the ticagrelor dose in THEMIS was changed to 60 mg b.i.d. Study inclusion criteria include documented coronary artery occlusive disease or previous coronary revascularization. All patients should also take open-label aspirin (if not contraindicated or not tolerated). The study is exploring the effect of ticagrelor in the primary prevention of MI, stroke or death from vascular causes, as patients with a history of MI or any stroke will be excluded. The target sample size is approximately 19,000 patients (Table 1) [43]. Results are expected in 2018 and will provide direct evidence regarding the use of potent antiplatelet therapy for the prevention of CV death, MI or stroke in patients with CAD but no prior MI or stroke at high risk of atherothrombotic events due to T2DM.

Other randomized clinical studies

The clinical profile of ticagrelor has been studied extensively, with a large number of both AstraZeneca-sponsored studies, and external and investigator-initiated studies. ATLANTIC (ClinicalTrials.gov: NCT01347580) showed that prehospital administration of ticagrelor in patients with acute STEMI was safe but did not improve the coprimary study end points of pre-PCI coronary reperfusion and $\geq 70\%$ resolution of ST-segment elevation before PCI; however, this strategy may prevent postprocedural acute stent thrombosis [76]. TREAT (ClinicalTrials.gov: NCT02298088) is currently recruiting patients and will evaluate the use of ticagrelor versus clopidogrel following pharmacological thrombolysis in patients with STEMI. The ongoing TiCAB (ClinicalTrials.gov: NCT01755520) trial is a pivotal efficacy and safety study of ticagrelor monotherapy versus aspirin alone for the prevention of CV events in patients undergoing CABG (representing a current unmet need). The GLOBAL LEADERS (ClinicalTrials.gov: NCT01813435) and the TWILIGHT (ClinicalTrials.gov: NCT02270242) studies are evaluating ticagrelor monotherapy versus standard dual antiplatelet therapy following PCI. Additionally, patients with sickle cell disease are prone to CVDs. In this condition, hypercoagulability occurs and platelet activation is part of this

mechanism [77]. Thus, antiplatelet therapy may have a role in this condition. To this end, AstraZeneca has initiated a dedicated pediatric development program; HESTIA is a series of three studies in children (0–17 years) and a study in young adults (18–30 years) with sickle cell disease. HESTIA 1 (ClinicalTrials.gov: NCT02214121) is a ticagrelor, dose-ranging pharmacokinetic/pharmacodynamic study in children and adolescents (2–18 years old) with sickle cell disease. In summary, these randomized, controlled trials assessing the use of ticagrelor in a number of different CV settings aim to fill existing evidence gaps and further our understanding of the current treatment paradigm.

Switching antiplatelet therapies

In clinical practice, switching from one platelet inhibitor (e.g., clopidogrel) to another, such as ticagrelor, will often be indicated [78]. The RESPOND study in patients with stable CAD specifically addressed the effect of switching clopidogrel responders and nonresponders to ticagrelor. Platelet reactivity was assessed by light transmittance aggregometry, the VerifyNow® P2Y₁₂ assay and vasodilator-stimulated phosphoprotein phosphorylation [36]. Results of RESPOND showed that ticagrelor was not only able to overcome nonresponsiveness to clopidogrel, but that the antiplatelet effect of ticagrelor was the same in clopidogrel responders and nonresponders [36]. In addition a small, single-center study reported that switching from ticagrelor to clopidogrel did not result in an increase of adverse CV events [79]. The recent pharmacodynamic evaluation of switching from prasugrel to ticagrelor study (SWAP-3; ClinicalTrials.gov: NCT02016170) in patients undergoing PCI showed that this switch resulted in higher levels of platelet inhibition [80].

Conclusion & future perspective

Atherosclerosis is the key pathophysiology that underlies cardiovascular and cerebrovascular disease. Antiplatelet agents have been proven effective and, in many situations, represent the current standard of care for treating and preventing atherothrombotic disease in patients with different manifestations of this condition. Despite their effectiveness, a major unmet need for better therapy exists. This need for improvements in the prevention and treatment of CVD provided the rationale for the development of ticagrelor, a

potent antiplatelet agent with a dual mechanism of action. Ticagrelor has been studied extensively and the PARTHENON clinical development program will provide important information on whether ticagrelor can improve outcomes in patients across the spectrum of atherothrombotic CVD. To date, the results of two large-scale trials support a benefit for ticagrelor in patients with ACS (PLATO), and in patients with stable CAD who are receiving long-term treatment following MI (PEGASUS-TIMI 54). Ongoing trials in the program will provide data on the use of ticagrelor in patients with prior ischemic stroke or TIA, PAD and T2DM.

Financial & competing interests disclosure

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EXECUTIVE SUMMARY

Atherothrombotic disease

- The health and economic burden of cardiovascular disease remains substantial.
- Atherosclerosis underlies many cardiovascular diseases, which frequently manifest clinically following an atherothrombotic event.
- There is a large, unmet need for more effective treatments for atherothrombotic disease, providing the rationale for the development of new antiplatelet agents.

Background to ticagrelor

- Ticagrelor is a first-in-class, antiplatelet agent with a dual mechanism of action: inhibition of platelet aggregation via the P2Y₁₂ receptor and increase of extracellular adenosine concentrations via inhibition of ENT1.
- Based on the favorable pharmacokinetic, pharmacodynamic and safety profiles of ticagrelor in Phase II studies and PLATO, the PARTHENON clinical development program was expanded.

The PARTHENON program

- The PARTHENON program is aiming to evaluate ticagrelor across the breadth of patient populations suffering from cardiovascular disease.
- The program consists of five randomized, controlled, cardiovascular outcome studies, representing clinical manifestations arising from various vascular beds.

Other randomized clinical studies

- Ticagrelor has also been studied extensively outside of the PARTHENON program and several ongoing or recently completed, randomized trials aim to fill existing evidence gaps and further our understanding of the current treatment paradigm.

Conclusion & future perspective

- To date, the results of two large-scale trials support a benefit for ticagrelor in patients with acute coronary syndrome (PLATO), and in patients with stable coronary disease who are receiving long-term treatment following myocardial infarction (PEGASUS-TIMI 54).
- Ongoing trials in this program will provide data on the use of ticagrelor in patients with prior ischemic stroke or transient ischemic attack (SOCRATES), peripheral artery disease (EUCLID) and Type 2 diabetes (THEMIS).

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