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REVIEW ARTICLE

A Comprehensive Review of the Pleiotropic Effects of Ticagrelor

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Abstract

Aims This review summarizes the findings of preclinical studies evaluating the pleiotropic effects of ticagrelor. These include attenuation of ischemia–reperfusion injury (IRI), inflammation, adverse cardiac remodeling, and atherosclerosis. In doing so, it aims to provide novel insights into ticagrelor's mechanisms and benefits over other $P2Y_{12}$ inhibitors. It also generates viable hypotheses for the results of seminal clinical trials assessing ticagrelor use in acute and chronic coronary syndromes.

Methods and Results A comprehensive review of the preclinical literature demonstrates that ticagrelor protects against IRI in the setting of both an acute myocardial infarction (MI), and when MI occurs while on chronic treatment. Maintenance therapy with ticagrelor also likely mitigates adverse inflammation, cardiac remodeling, and atherosclerosis, while improving stem cell recruitment. These effects are probably mediated by ticagrelor's ability to increase local interstitial adenosine levels which activate downstream cardio-protective molecules. Attenuation and augmentation of these pleiotropic effects by high-dose aspirin and caffeine, and statins respectively may help explain variable outcomes in PLATO and subsequent randomized controlled trials (RCTs).

Conclusion Most RCTs and meta-analyses have not evaluated the pleiotropic effects of ticagrelor. We need further studies comparing cardiovascular outcomes in patients treated with ticagrelor versus other $P2Y_{12}$ inhibitors that are mindful of the unique pleiotropic advantages afforded by ticagrelor, as well as possible interactions with other therapies (e.g., aspirin, statins, caffeine).

Keywords $P2Y_{12}$ inhibitor · Ticagrelor · Pleiotropic effects · Aspirin · Ischemia–reperfusion injury, Myocardial infarction · Coronary artery disease · Systematic review

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor, i.e., prasugrel, ticagrelor, or clopidogrel, is the cornerstone of treatment for patients who present with acute coronary syndrome (ACS) or undergo percutaneous coronary intervention (PCI) [1]. The latest European Society of Cardiology and American College of Cardiology/American Heart Association guidelines recommend a higher potency $P2Y_{12}$ receptor inhibitor (ticagrelor or prasugrel) over clopidogrel in patients with an ST-elevation myocardial infarction (STEMI) treated with primary PCI or non-ST-elevation myocardial infarction (NSTEMI) managed with either invasive or conservative measures [2–5]. The preference for ticagrelor over clopidogrel is informed by the landmark *Platelet Inhibition and Patient Outcomes* (PLATO) randomized controlled trial (RCT), which demonstrated superiority of ticagrelor to reduce a composite outcome of death from vascular causes, myocardial infarction (MI), or

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stroke, consistent in STEMI patients treated with primary PCI, and in NSTEMI managed with or without revascularization [6–9]. While ticagrelor did not increase the risk of major bleeding according to the primary endpoint definition, there was a higher rate of major bleeding not related to coronary-artery bypass grafting, including more instances of fatal intracranial bleeding [6].

However, most subsequent RCTs and meta-analyses comparing ticagrelor and clopidogrel failed to replicate the positive results seen in PLATO [10–18]. Notably, these studies did not account for two crucial observations from the PLATO trial. First, the positive effects of ticagrelor were absent in those who received maintenance therapy with high-dose (HD) compared to low-dose (LD) aspirin, a finding that was mostly confined to patients enrolled in North America [19]. Second, these effects were also attenuated in those off lipid-lowering drugs [6]. Understanding these interactions may provide the key to uncovering why subsequent trials and meta-analyses comparing ticagrelor to clopidogrel have yielded mostly neutral results.

Patients in RCTs assessing $P2Y_{12}$ inhibitors receive a loading dose followed by maintenance treatment and evaluated for major adverse cardiovascular events (MACE) months to years after initiation of therapy. Save for some landmark analyses, this study design is not conducive to distinguishing between acute versus chronic effects of ticagrelor, nor temporal interactions with other therapies [20]. Preclinical studies can better establish a temporal relationship between treatment and effects, as well as provide evidence of the possible mechanisms that mediate the observed outcomes [21]. This review aims to synthesize preclinical findings on the benefits of ticagrelor with those from the seminal RCTs and meta-analyses. In doing so, we provide insights into the mechanisms of action of ticagrelor, its benefits over other $P2Y_{12}$ inhibitors, and the failure of RCTs to reproduce the original results of PLATO.

The mechanisms that may underlie the advantages of ticagrelor over clopidogrel include faster and more complete platelet inhibition shortly after the first dose, and more efficient and sustained platelet inhibition during chronic treatment. Additionally, ticagrelor possesses unique adenosine-mediated pleiotropic effects that may also explain its greater efficacy, i.e., greater vasodilation of infarcted vessels, protection against ischemia–reperfusion injury (IRI), and reduced inflammation when ticagrelor is initiated after an acute MI or if an MI occurs on chronic treatment; and attenuation of recurrent cardiovascular events with maintenance ticagrelor therapy due to mitigation of inflammation, atherosclerosis, and adverse cardiac remodeling (Fig. 1). Furthermore, interactions with commonly used background therapy may attenuate or augment these non-platelet-mediated effects of ticagrelor.

Does Greater Platelet Inhibition from Acute Loading with Ticagrelor Explain Its Benefits?

Adenosine diphosphate (ADP) triggers platelet degranulation, thromboxane production, and eventual activation of the glycoprotein IIb/IIIa receptor leading to platelet aggregation. Clopidogrel is a prodrug that requires two-step activation by the liver to its active metabolite before irreversibly antagonizing the ADP-binding site on the $P2Y_{12}$ receptor. In contrast,

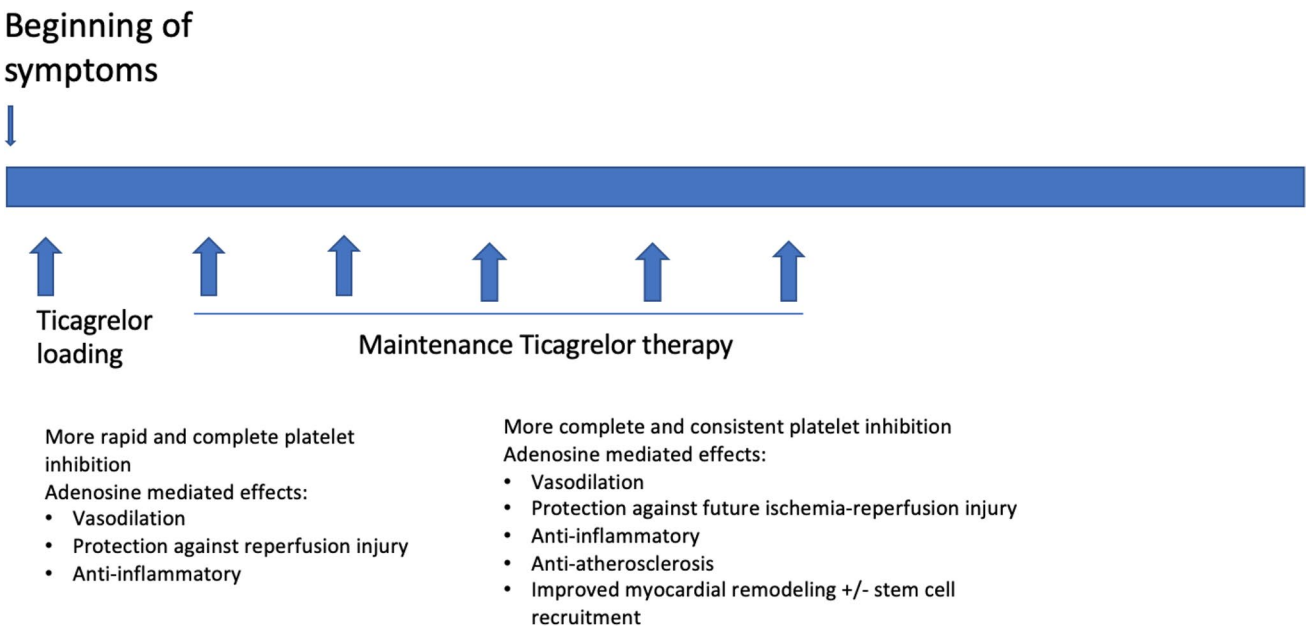

Fig. 1 Platelet- and non-platelet-mediated effects of ticagrelor with acute and chronic treatment

ticagrelor directly and reversibly binds to a site on the $P2Y_{12}$ receptor separate from the ADP-binding site which inhibits the ADP-induced receptor conformational change and G-protein activation preventing ADP downstream signaling. Consequently, ticagrelor inhibits platelet aggregation 0.5–2 h after ingestion compared to clopidogrel which takes 2–6 h before onset of action. Furthermore, ticagrelor leaves the receptor intact upon dissociation [22]. Theoretically, more potency and efficacy of platelet inhibition with ticagrelor loading can lead to faster and greater attenuation of atherothrombosis which improves coronary artery perfusion and may lead to acute benefits in the setting of a STEMI.

However, findings from preclinical trials do not support this hypothesis. A single dose of intraperitoneal ticagrelor 5 min prior to reperfusion reduced infarct size (IS) measured 24 h after reperfusion in rats more than clopidogrel. Ticagrelor and clopidogrel had *similar levels of platelet inhibition and comparable bleeding times* measured 2 h after reperfusion. This acute benefit translated to improved myocardial function with ticagrelor over clopidogrel 4 weeks post-MI [23]. Regardless of a similar platelet inhibitory effect, ticagrelor added to thrombolytic therapy significantly reduced the rate of coronary re-occlusion and limited IS minutes to hours after MI induction in dogs as compared to clopidogrel [24].

A single dose of ticagrelor 10 min before reperfusion or cangrelor 10 min before reperfusion followed by a continuous infusion equally limited IS at 2 h and 3 days postreperfusion [25]. A recent RCT that compared the effects on IS of a loading dose of ticagrelor to cangrelor followed by maintenance therapy with ticagrelor in patients presenting with a STEMI, corroborated these findings; despite cangrelor producing more potent platelet inhibition compared to ticagrelor at time of PCI, there was no improvement in coronary reperfusion or IS 12 weeks later [26]. Cangrelor is an intravenous (IV) $P2Y_{12}$ inhibitor that achieves maximal platelet inhibition within 15 min of administration [22]. If greater speed, potency, and efficacy of platelet inhibition were responsible for attenuation of IS, one would expect cangrelor to reduce IS more than ticagrelor. This was not observed, suggesting that greater platelet inhibition does not likely account for reduced IS with ticagrelor in comparison to clopidogrel therapy demonstrated by Ye and Wang [23, 24]. Indeed, minimizing delayed microvascular damage, which evolves over several hours after coronary reperfusion may be more important than platelet inhibition at time of PCI [27].

Ticagrelor, Adenosine, and Ischemia–Reperfusion Injury

IRI is myocardial damage that occurs after reperfusion due to oxidative stress, excess intracellular calcium, and inflammation [28]. Animal studies have shown that IRI may account for up to 50% of final IS [29]. Thus, attenuating IRI may be as consequential as shortening ischemic time.

Adenosine mitigates IRI and apoptosis, in addition to improving myocyte regeneration, contractility, and electrical stability [22]. Adenosine activates various receptors on endothelial cells and cardiomyocytes which lead to increases in cyclic adenosine monophosphate (cAMP) and nitric oxide production. These molecules induce vasodilation during ischemia which leads to improved metabolic function in both endothelium and coronary smooth muscle. Ischemic preconditioning, the phenomenon of repeated brief episodes of ischemia and reperfusion preceding sustained ischemia, also protects against IRI via adenosine-mediated activation of adenosine triphosphate (ATP)-sensitive potassium channels [30]. Adenosine attenuates production of free radicals and pro-inflammatory mediators during ischemia and reperfusion. In animal models, these effects of adenosine reduce myocardial stunning and improve long-term cardiac function [31].

Unique among the $P2Y_{12}$ inhibitors, ticagrelor has direct effects on adenosine metabolism (Fig. 2). Ticagrelor binds to equilibrate nucleoside transporter-1 (ENT-1) which blocks reuptake of adenosine into the cells and facilitates subsequent degradation to inosine [32]. In turn, higher levels of adenosine in the interstitial space at the site of ischemia mediates local vasodilation and reduction of free radicals and pro-inflammatory molecules that facilitate IRI [31]. Downstream, adenosine receptor activation leads to cyclooxygenase-2 (COX-2) activation, in addition to pro-survival kinases, e.g., Akt, extracellular signal-regular kinase (ERK) 1/2, and endothelial nitric oxide synthase (eNOS), which mediate cardioprotective effects [33, 34]. Adenosine receptor activation is the proposed mechanism for the sensation of dyspnea, a well-described side effect of ticagrelor, which in some cases leads to discontinuation of the medication [32, 35].

Statins upregulate 5′-nucleotidase, which leads to more adenosine export into the interstitial space [36, 37]. HD-aspirin administered prior to reperfusion—at doses comparable to those used in the clinical setting—dose-dependently inhibits COX-2 and production of cardioprotective eicosanoids and prostaglandins. This correlates with dose-dependent attenuation of the IS-limiting effects of atorvastatin in rats [38].

Ticagrelor Exhibits Adenosine-Mediated Protection Against Ischemia–Reperfusion Injury When Administered Prior to Reperfusion

As previously discussed, ticagrelor administered to rats 5 min prior to reperfusion reduced IS 24 h after reperfusion and preserved left ventricular (LV) function at 4 weeks

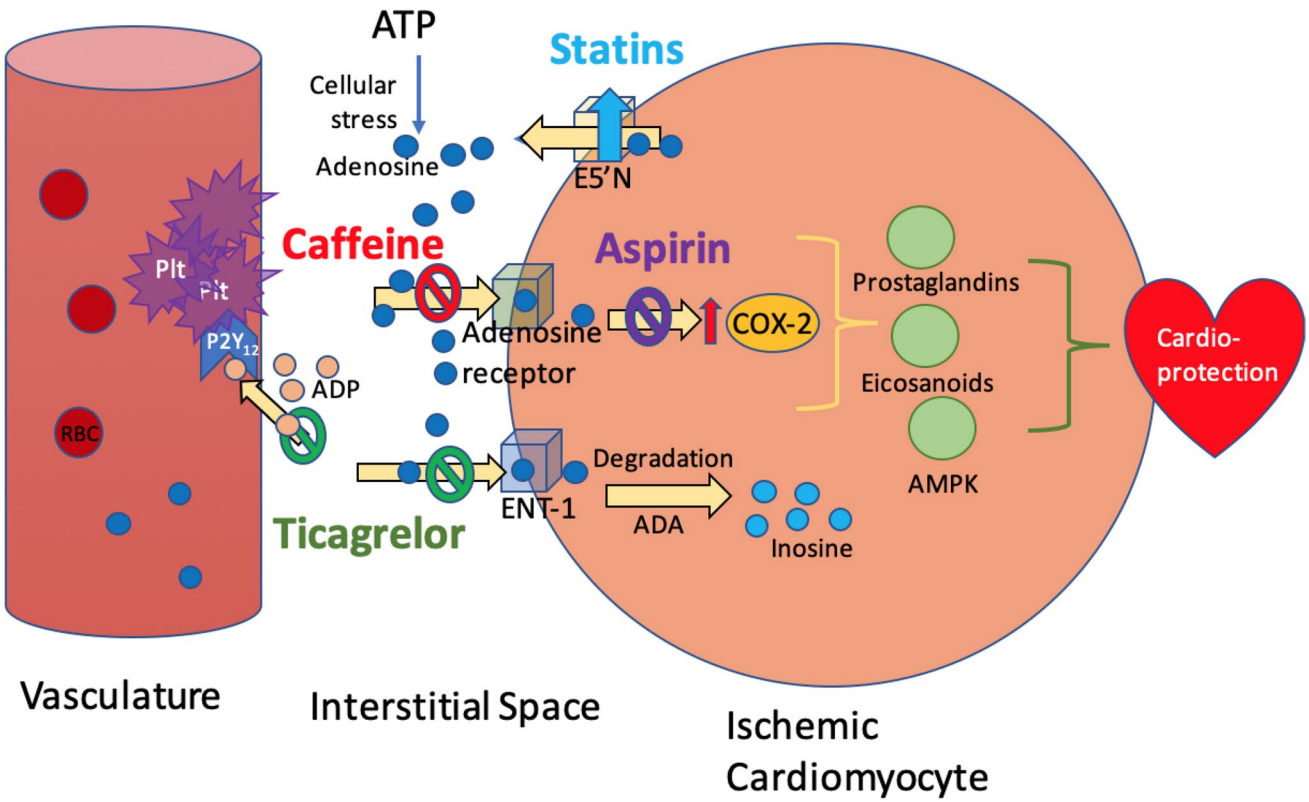

Fig. 2 The adenosine-mediated pleiotropic effects of ticagrelor and its interactions with statins, aspirin, and caffeine. ATP adenosine triphosphate, Plt platelet, RBC red blood cell, $P2Y_{12}$ $P2Y_{12}$, ADP adenosine diphosphate, ENT-1 equilibrate nucleoside transporter-1, E5'N ecto-5'-nucleotidase, ADA adenosine deaminase, COX-2 cyclooxygenase 2, AMPK adenosine monophosphate-activated protein kinase

compared to clopidogrel. This correlated with higher levels of adenosine and pro-survival kinases in ticagrelor-treated rats [23]. Adenosine levels have been shown to be higher in patients with ACS treated with ticagrelor as compared to clopidogrel due to inhibition of adenosine uptake by red blood cells [39]. It is possible that higher levels of adenosine in STEMI patients may protect against IRI acutely.

In a rat model, co-administration of ticagrelor and a caspase-1 inhibitor with a potent anti-inflammatory effect (VX-765) had significant additive effects of reducing IS at both 120 min and 3 days after reperfusion when given 5–10 min prior to reperfusion. Conversely, ischemic postconditioning in conjunction with ticagrelor administration had no additive effect, suggesting that $P2Y_{12}$ inhibitors already condition the heart in a similar manner rendering further postconditioning redundant [25].

In a dog study, IV ticagrelor exhibited a significant reduction in rates of coronary re-occlusion, quicker return to baseline coronary blood flow with reduced cyclic flow variation and reduced IS after 120 min of reperfusion compared to clopidogrel. All dogs received loading with 325 mg aspirin orally and tissue plasminogen activator (tPA) with reperfusion [24]. Another study demonstrated that ticagrelor dose-dependently inhibited adenosine uptake by erythrocytes and augmented the hyperemic response to temporary occlusion or direct intracoronary adenosine infusion [40]. Thus, the authors concluded that the improvement in coronary blood flow was possibly due to adenosine-mediated vasodilation induced by ticagrelor [24]. A summary of animal trials evaluating the effects of ticagrelor on IRI is available in Table 1.

Maintenance Ticagrelor Treatment Prevents Future Cardiovascular Events

The benefits of chronic ticagrelor therapy over clopidogrel may be attributed to its ability to prevent future cardiac events after an MI. The mechanisms by which this may occur include greater platelet inhibition in the long term leading to less recurrent ischemia, attenuation of inflammation thereby mitigating both adverse cardiac remodeling, and atherosclerosis progression [41].

Platelet Inhibition

In the chronic setting, it is also possible that greater long-term platelet inhibition can prevent atherothrombosis and subsequent coronary ischemia. Nanhwan demonstrated

Table 1 Interaction of ticagrelor, statins, caffeine, and aspirin in animal models of ischemia–reperfusion injury

Study	Animal model	Study drugs	Protocol	Ischemia/reperfusion method and timing	Infarct size (% of AR or LV) in treatment group	Infarct size (% of AR or LV) in control group	Effects on adenosine	Effect of ASA	Other pleiotropic effects
Administration of ticagrelor prior to reperfusion									
Ye [23]	Rat ($n=32$)	Ticagrelor, clopidogrel	Ticagrelor 10 or 30 mg/kg, clopidogrel 12.5 mg/kg IP–5 min before reperfusion	30 min/24 h	Ticagrelor 10 mg/kg: 31.5 ± 1.8% Ticagrelor 30 mg/kg: 21.4 ± 2.6% Clopidogrel: 42.4 ± 2.6%	45.3 ± 1.7%	Ticagrelor increased myocardial adenosine. Clopidogrel no effect	N/A	Ticagrelor increased phosphorylation of Akt, eNOS, ERK 1/2, reduced apoptosis
Wang [24]	Dog ($n=30$)	Ticagrelor, clopidogrel	Ticagrelor 1-min bolus (75 µg/kg) then 10 µg/kg/min for 2 h, clopidogrel 10 mg/kg IV bolus over 5 min; given 5 min before tPA	30 min electrolytic thrombus induction/120 min tPA and heparin	Ticagrelor: 11.7 ± 5.6% Clopidogrel: 32.7 ± 10.1%	28.0 ± 9.2%	N/A	N/A—all animals received ASA 325 mg orally	Ticagrelor reduced re-occlusion rate and cyclic flow variation, and improved blood flow compared to clopidogrel and control
Audia [25]	Rat ($n=40$)	Ticagrelor, cangrelor, VX-765	Ticagrelor 30 mg/kg IP once, cangrelor 60 µg/kg and continued at 6 µg/kg. Bolus given 10 min before reperfusion, VX-765, ticagrelor + VX-765, cangrelor + VX-765, ischemic postconditioning	60 min/120 min	Ticagrelor: 42.8 ± 3.3%, cangrelor: 43.8 ± 2.4%, VX-765: 29.2 ± 4.9%, ticagrelor + VX-765: 17.5 ± 2.3%, cangrelor + VX-765: 11.9 ± 1.9%	60.3 ± 3.8%	N/A	N/A	Addition of caspase 1 inhibitor, VX-765, further reduced IS with additive effect; ischemic postconditioning in conjunction had no additive effect; similar effect of IS at 3d
Chronic use of ticagrelor, statins, caffeine, and their effects on ischemia–reperfusion injury									
Nanhwan [34]	Rat ($n=47$)	Ticagrelor, clopidogrel	Ticagrelor 75, 150, or 300 mg/kg/day, clopidogrel 30 or 90 mg/kg/day for 7 days + either adenosine-receptor antagonist, ASA, or COX-2 inhibitor prior to reperfusion	30 min coronary ligation/24 h	Ticagrelor 75 mg/kg/day: 12.6 ± 0.3% Ticagrelor 300 mg/kg/day: 6.8 ± 0.5% Clopidogrel 30 mg/kg/day: 14.6 ± 0.4%, Clopidogrel 90 mg/kg/day: 15.0 ± 0.7% (IS as % of LV)	16.1 ± 0.9%	Ticagrelor increased myocardial adenosine levels. Adenosine receptor antagonist completely abrogated IS-limiting effect of ticagrelor (8.0 ± 1.6% vs. 13.4 ± 1.0%)	ASA dose-dependently attenuated IS reduction of ticagrelor (4.7 ± 0.4%, 6.5 ± 0.6%, 10.1 ± 0.8% for 5, and 25 mg/kg respectively as compared to 5.1 ± 0.5% with ticagrelor alone), Selective COX-1 inhibition had no effect	Ticagrelor increased COX-2 activity, ticagrelor increased levels of cNOS, cPLA2, and phosphorylation of Akt and eNOS
Birnbaum [38]	Rat ($n=49$)	ATV	3-day pretreatment with ATV (10 mg/kg/d) followed by either 1. ASA 5, 10, or 20 mg/kg after 27 min of coronary artery occlusion, or 2. ASA 20 mg/kg immediately after coronary artery occlusion or 15 min or reperfusion	30 min coronary artery occlusion/4 h reperfusion	ASA 20 mg/kg: 15.8 ± 1.8%, ATV: 4.9 ± 0.6%, ATV + ASA 5 mg/kg: 8.9 ± 0.5%, ATV + ASA 10 mg/kg: 12.6 ± 1.1%, ATV + ASA 20 mg/kg: 13.1 ± 2.0%; (IS as % of LV)	16.1 ± 1.1%	N/A	ASA dose-dependently attenuated IS of ATV with greater effects at occlusion (10.1 ± 0.3%) than reperfusion (6.8 ± 1.0%) as compared to 4.0 ± 0.7% with ATV and 12.4–13.2 ± 0.9% with ASA alone	ATV increased total COX activity, whereas ASA inhibited it, ASA attenuated the induction of COX-2 activity by ATV

Table 1 (continued)

Administration of ticagrelor prior to reperfusion									
Study	Animal model	Study drugs	Protocol	Ischemia/reperfusion method and timing	Infarct size (% of AR or LV) in treatment group	Infarct size (% of AR or LV) in control group	Effects on adenosine	Effect of ASA	Other pleiotropic effects
Birnbaum [42]	Diabetic Rat (ZDF) ($n=68$)	Ticagrelor, prasugrel, ROS	Ticagrelor (150 mg/kg/day), prasugrel (7.5 mg/kg/day), ROS (5 mg/kg/day), ticagrelor + ROS, or prasugrel + rosuvastatin for 3 days	30 min coronary occlusion/24 h reperfusion on day 4	Ticagrelor: 8.9 ± 0.9%, prasugrel: 17.3 ± 0.8%, ROS: 10.2 ± 0.6%, ticagrelor + ROS: 7.0 ± 0.6%, prasugrel + ROS: 12.3 ± 0.5% (IS as % of LV)	16.2 ± 0.9%	Ticagrelor increased myocardial adenosine in ischemic and nonischemic zone, additive when ROS was co-administered; blocked by adenosine receptor antagonist	N/A	Ticagrelor and ROS had additive effect in reducing IS, no effect on IS with prasugrel; Ticagrelor decreased pro-inflammatory mediators including IL-1β, IL-6, and increased anti-inflammatory eicosanoid: 15-epilipoxin A4
Ye [53]	Rat ($n=51$)	ATV	3-day ATV (10 mg/kg/d) with either water + sugar (7.5 g/100 ml), caffeinated coffee with sugar, or decaffeinated coffee with sugar	30 min of coronary artery occlusion/4 h reperfusion	ATV with water: 3.7 ± 0.3%, ATV with caffeinated coffee: 10.5 ± 1.2%, ATV with decaffeinated coffee: 3.6 ± 0.9% (IS as % of LV)	Water and sugar: 7.7 ± 1.4%, caffeinated coffee: 7.7 ± 0.9%, decaf coffee: 10.7 ± 0.9%	N/A	N/A	Increased myocardial levels of Akt phosphorylation in ATV and water + sugar treated rats was blocked by caffeinated but not decaffeinated coffee
Liu [54]	Rat ($n=75$)	Ticagrelor	Ticagrelor 150 mg/kg gavage immediately after LAD ligation, pretreatment with DDS (20 g/L) for 7 days, or ticagrelor + DDS	45 min LAD ligation followed by 24 h reperfusion, then, re-ligated at either 24 h, 3 days, or 7 days	Ticagrelor at 24 h: 34.5 ± 12.2%, 3 days: 17.4 ± 9.9%, 7 days: 14.0 ± 5.1%, DDS + ticagrelor at 24 h: 53.25 ± 10.0%, 3 days: 49.3 ± 8.7%, 7d: 50.7 ± 11.2%	24 h: 47.1 ± 12.4%, 3 days: 56.2 ± 9.4%, 7 days: 48.3 ± 19.0%	N/A	N/A	Ticagrelor reduced plasma cTnI, hs-CRP, NT-proBNP, downregulated NF-κB, galectin-3, IL-6, TNF-α; Pretreatment with DDS (an agonist of NF-κB) blocked these effects of ticagrelor
Hjortbak [61]	Rat ($n=48$)	Ticagrelor, prasugrel, clopidogrel	Clopidogrel 15 mg/kg given 4 h prior to injury, ticagrelor 20 mg/kg, or prasugrel 10 mg/kg 2 h prior to injury by oral gavage	30 min occlusion/2 h reperfusion	Ticagrelor: 37 ± 11% Clopidogrel: No effect (50 ± 11%) Prasugrel: No effect (49 ± 9%)	52 ± 8%	N/A	N/A	No additive effect of ticagrelor with ischemic preconditioning or remote ischemic conditioning
Vilahur [56]	Pig ($n=30$)	Ticagrelor, clopidogrel	Loading with Ticagrelor 180 mg 2 h, or clopidogrel 600 mg 4 h before MI induction; followed by ticagrelor 90 mg BID or clopidogrel 75 mg daily during reperfusion	60 min occlusion/24 h reperfusion	Ticagrelor: 16.4% (15.5–17.9) Clopidogrel: 20.9% (9.3–22.8) (IS as % of LV)	31.1% (25.9–39.1)	Co-administration of adenosine receptor antagonist reduced the effect of ticagrelor on IS (22.4% [21.8–23.9]	N/A	Ticagrelor significantly diminished myocardial edema, reduced aquaporin-4, and increased AMPK and COX-2 activity as compared to clopidogrel; these effects were blocked by adenosine receptor antagonist

Table 1 (continued)

Administration of ticagrelor prior to reperfusion									
Study	Animal model	Study drugs	Protocol	Ischemia/reperfusion method and timing	Infarct size (% of AR or LV) in treatment group	Infarct size (% of AR or LV) in control group	Effects on adenosine	Effect of ASA	Other pleiotropic effects
Vilahur [57]	Pig ($n = 24$) Ticagrelor, clopidogrel	Loading with Ticagrelor 180 mg 2 h, or clopidogrel 600 mg 4 h before MI induction; followed by ticagrelor 90 mg BID or clopidogrel 75 mg daily for 42 days	60 min balloon occlusion/deflation and recovery	Ticagrelor post-MI at 3 days: 16.3% (10.1–18.5), 42 days: 9.1% (8.3–10.3) Clopidogrel post-MI at 3 days: 20.7% (18.2–24.1), 42 days: 11.6% (10.2–15.1) (IS as % of LV)	Control post-MI at 3 days: 25.2% (22.2–27.3), 42 days: 13.0% (11.2–15.7)	Blood adenosine levels increased with ticagrelor but not with clopidogrel	N/A	See Table 2

AR area at risk, *ASA* aspirin, *ATV* atorvastatin, *BID* twice daily, *CI* 95% confidence interval, *cNOS* cytosolic nitric oxide synthase, *COX* cyclooxygenase, *cPLA2* cytosolic phospholipase A2, *cTnI* cardiac troponin I, *DDS* dextran sodium sulfate, *eNOS* endothelial nitric oxide synthase, *ERK* extracellular signal-regular kinase, *HD* high dose, hs-*CRP* high sensitivity C-reactive protein, *IL* interleukin, *IP* intraperitoneal, *IS* infarct size, *IV* intravenous, *LAD* left anterior descending, *LD* low dose, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *NF-κB* nuclear-factor kappa beta, *NT-proBNP* N-terminal pro hormone brain natriuretic peptide, *PKB* protein-kinase B, *ROS* rosuvastatin, *TNF-α* tumor necrosis factor-alpha, *tPA* tissue plasminogen activator, *ZDF* Zucker diabetic fatty

reduced IS after 24 h of reperfusion in rats pretreated with ticagrelor compared to clopidogrel 7 days prior to MI [34]. Birnbaum yielded similar results comparing ticagrelor to prasugrel after 3 days of dosing [42]. Superiority of ticagrelor over prasugrel to improve LV function measured by echocardiography at days 14 and 28 started 7 days after ischemia and reperfusion was further demonstrated [43]. Another animal model found attenuation of atherosclerosis progression in rats treated with ticagrelor or rosuvastatin compared to clopidogrel after 14 weeks of treatment [44]. All these results were seen in the setting of similar levels of platelet inhibition with ticagrelor compared to other $P2Y_{12}$ inhibitors. Thus, just as with acute ticagrelor loading, greater potency and efficacy with regards to platelet inhibition in the chronic setting does not appear to explain the benefits of reduced IS, attenuation of adverse remodeling, mitigation of atherosclerotic progression, or protection from IRI when reinfarction occurs on chronic ticagrelor treatment. However, in the clinical setting, better anti-platelet effects might contribute to improved clinical outcomes.

Attenuation of Inflammation and Adverse Cardiac Remodeling

Adenosine also protects against adverse cardiac remodeling. An increased neurohormonal response after infarction induces a release of catecholamines and growth factors which lead to fibrosis, beta-adrenoceptor-mediated myocardial hypercontractility, and myocyte hypertrophy [45]. Adenosine reduces the release of catecholamines and calcium overload, augments coronary blood flow, and prevents platelet and leukocyte activation. Adenosine also inhibits renin release and tumor necrosis factor (TNF)-α production in experimental models, processes that contribute to adverse cardiac remodeling [46, 47].

Ye assessed the effects of chronic ticagrelor treatment on myocardial function in rats when initiated after completion of IRI. They demonstrated that 4w of dosing started 24 h after reperfusion normalized LV internal diameter in diastole and systole, and preserved LV ejection fraction similar to a loading dose of ticagrelor before reperfusion. In the group of rats treated with both a loading dose and chronic treatment after reperfusion, there was an additive effect of improving these echocardiographic parameters. Increased levels of adenosine and pro-survival kinases, a reduction in fibrosis and lower levels of inflammatory cytokines (TNF-α, interleukin (IL)-1β, and IL-18) were also observed in ticagrelor-treated rats. None of these positive effects were seen with clopidogrel [23]. This study suggests that regardless of protection from IRI, chronic ticagrelor therapy attenuates inflammation, prevents adverse cardiac remodeling, and preserves myocardial function via an adenosine-mediated pathway.

In another study, rats were administered daily oral doses of ticagrelor, HD-aspirin, ticagrelor and HD-aspirin, or prasugrel 7 days after infarction and reperfusion. Ticagrelor and HD-aspirin independently attenuated the decrease in systolic function and remodeling measured on days 14 and 28, decreased levels of markers of fibrosis, and increased levels of the eicosanoid, 15-epi-lipoxin-A_4. These effects were not seen with prasugrel. Furthermore, only ticagrelor-treated rats had higher levels of progenitor stem cell markers and showed cardiac regeneration in the infarcted tissue. These benefits were found to be attenuated when HD-aspirin and ticagrelor were administered together [43]. The results suggest that HD-aspirin may block the effects of maintenance ticagrelor therapy to limit adverse cardiac remodeling and induce cardiomyocyte regeneration by inhibiting the production of cardioprotective eicosanoids.

Atherosclerosis

Atherogenesis involves complex interactions between lipids, endothelial cells, and the immune system [48, 49]. The following studies have shown that ticagrelor mitigates the progression of atherosclerosis through adenosine-mediated attenuation of pro-inflammatory cytokines.

Preusch demonstrated a significant reduction in the relative area of the necrotic core and increase in fibrous cap thickness in mice with advanced atherosclerotic lesions in the aortic sinus treated with ticagrelor for 25 weeks. An in vitro analysis revealed significant reduction in the prevalence of apoptotic macrophages and their uptake of oxidized low-density lipoprotein (LDL) [50]. Another study showed this reduction of oxidized LDL was dose-dependent, and that ticagrelor also decreased expression of proprotein convertase subtilisin/kexin type (PCSK9), a powerful regulator of LDL receptor degradation [51]. Less macrophage infiltration into the atherosclerotic intima and lower serum levels of pro-atherosclerotic markers were also observed in mice fed a high-fat diet treated with ticagrelor compared to clopidogrel for 16w [52]. These studies highlight not only ticagrelor's ability to mitigate atherogenesis, but also its increased efficacy over clopidogrel via non-platelet-mediated lowering of pro-inflammatory cytokines.

Ye assessed whether daily HD-aspirin can also block the anti-atherogenic effects of ticagrelor. After 14 weeks of treatment, aspirin, ticagrelor, and rosuvastatin each independently increased 15-epi-lipoxin-A_4 and decreased IL-1β, IL-6, TNF-α, as well as atherosclerotic plaque area in diabetic mice. The combination of rosuvastatin and ticagrelor augmented these effects, while aspirin interfered with the attenuation of inflammatory cytokine levels by both ticagrelor and rosuvastatin. Clopidogrel did not exhibit any of these beneficial effects [44]. Table 2 provides a summary of animal trials that evaluated the effects of ticagrelor and statins to reduce cardiovascular events.

Ticagrelor and Atorvastatin Pretreatment Protect Against Ischemia–Reperfusion Injury

As previously discussed, 7-day pretreatment with ticagrelor reduced myocardial IS in rats as compared to clopidogrel despite similar levels of platelet inhibition. This was associated with higher levels of adenosine, cytosolic phospholipase (cPLA2), an enzyme necessary to liberate AA, COX-2, 15-epi-lipoxin-A_4, and eNOS in myocardium. Co-administration of an adenosine receptor antagonist, COX-2 inhibitor, or HD-aspirin with ticagrelor 1 h before ischemia–reperfusion mitigated the reduction in IS and production of these molecules in a dose-dependent manner. However, no attenuation was seen when a COX-1 inhibitor or LD-aspirin were given [34]. This study indicates that HD-aspirin loading given as standard of care in the setting of ACS likely blocks the ability of maintenance ticagrelor therapy to protect from IRI.

The combination of rosuvastatin and ticagrelor, but not prasugrel, had an additive effect of increasing adenosine levels and reducing IS more than either rosuvastatin or ticagrelor alone. Ticagrelor and rosuvastatin also increased expression of COX-2, 15-epi-lipoxin-A_4, Akt, ERK 1/2, and eNOS. These outcomes were not observed in the group given ticagrelor and rosuvastatin in addition to an adenosine receptor antagonist 1 h prior to infarction [42]. Both ticagrelor and rosuvastatin (not prasugrel) also significantly attenuated the increase of caspase-1 following ischemia–reperfusion. Taken together with the results of the previous study that showed HD-aspirin administered to rats pretreated with atorvastatin 15 min prior to reperfusion blunted its reduction of IS [38], this suggests that aspirin loading prior to PCI could block the IS-limiting effects of both chronic ticagrelor and statins.

Another murine study evaluated whether caffeine blocks the pleiotropic effects of statins. IS was significantly reduced in rats pretreated for 3 days with atorvastatin and sugar water or decaffeinated coffee, but not caffeinated coffee when measured after coronary artery occlusion and 4 h of reperfusion on day 4 [53]. This was associated with inhibition of atorvastatin-mediated phosphorylation of Akt and subsequently less eNOS activation. The results of this study are evidence that the effects of statins to defend against IRI may be attenuated by adenosine receptor antagonism by caffeine via interference of the production of cardioprotective pro-survival kinases. Like statins, protection against IRI by ticagrelor has been shown to be adenosine mediated. It

is conceivable that caffeine may also attenuate the pleiotropic effects of ticagrelor, but this remains to be sufficiently addressed.

Rats treated with ticagrelor initiated after induction of initial infarction had significantly reduced IS and lower levels of nuclear factor-kappa B (NF-kB), galectin-3, IL-6, and TNF-α when reinfarction occurred at 24 h, 3 days, and 7 days later. Pretreatment with a known NF-kB agonist, dextran sodium sulfate, for 7 days prior to initial MI attenuated these protective effects. Thus, chronic ticagrelor therapy was demonstrated to reduce IRI from recurrent infarction by causing less activation of NF-kB in the ischemic myocardium [54]. Adenosine can inhibit NF-kB [55]. Thus, whether reduction of NF-kB represents a separate mechanism by which ticagrelor improves myocardial function in the setting of IRI, or it is further evidence of its adenosine-mediated effects has yet to be determined.

Studies of IRI utilizing large-animal models—with a higher translatability potential—yielded similar results to those seen in murine models. Cardiac MRI (CMR) evidenced that administration of a single dose of 180 mg ticagrelor prior to infarction in pigs reduced IS, edema formation and necrosis at 24 h post-MI to a larger extent than loading with clopidogrel. Concomitant administration of an adenosine receptor antagonist abolished these protective effects. Both drugs were given at doses that displayed comparable platelet inhibition, excluding any platelet-related effects [56]. In a second porcine study, a 180 mg loading dose of ticagrelor prior to MI induction followed by 90 mg twice daily reduced IS, scar formation, edema, and attenuated impairment in LV ejection faction 3 days after reperfusion—effects that persisted at 42 days. These benefits were not detected in pig hearts treated with clopidogrel. As in prior rat models, ticagrelor led to increased adenosine levels, and greater activation of COX-2 and adenosine monophosphate activated protein kinase (AMPK) in the ischemic myocardium [57]. AMPK is an energy sensor that exerts cardio-protection primarily via upstream activation of adenosine. Thus, acute and chronic ticagrelor treatment attenuates IRI and adverse cardiac remodeling via adenosine-mediated mechanisms in large animals, strengthening the case for ticagrelor's pleiotropic benefits and potential interactions that may affect these in the clinical setting.

Other Pleiotropic Effects

In an in vitro study, ticagrelor demonstrated bactericidal activity against gram-positive organisms, including drug resistant strains, i.e., glycopeptide intermediate-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus*. Although bactericidal concentrations were not reached systemically in patients receiving typical dosages for treating cardiovascular disease, the authors concluded that antibacterial activity at infection sites may still be achieved through local, possibly platelet-driven, drug accumulation [58]. In another study, extracellular vesicles derived from ticagrelor-pretreated rat cardiomyocyte precursor cells in vitro significantly decreased hyperglycemia-induced oxidative stress and prevented the development of apoptosis and endoplasmic reticulum stress in these cells. This suggests another non-platelet-mediated effect of ticagrelor to protect against diabetic cardiomyopathy through extracellular vesicular modulation [59]. Furthermore, a novel drug-target interaction between ticagrelor, and vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) receptors which may serve as potential targets for the development of new diagnostic and therapeutic tools for neuronal, metabolic, inflammatory, and malignant diseases was described. Cangrelor did not show a similar effect on VIP and PACAP receptors likely due to its slightly different molecular structure [60].

Analyzing Clinical Trial Outcomes in the Context of Preclinical Study Results

In a retrospective review of 1754 patients who presented with STEMI, troponin release was reduced in those treated with ticagrelor as compared to clopidogrel (adjusted 48 h area under the curve ratio: 0.67, 95% confidence interval (CI): 0.47–0.94). This correlated with lower rates of a composite endpoint of cardiac death or hospitalization for heart failure within 12 months in STEMI patients loaded with ticagrelor (hazard ratio (HR): 0.63, CI: 0.42–0.94) but not prasugrel (HR: 0.84, CI: 0.43–1.63), prior to primary PCI. Given the results of a concomitant rat study demonstrating reduced IS with ticagrelor but not prasugrel or clopidogrel administration after induction of acute MI, the authors concluded that the cardioprotective effects of ticagrelor in reducing IS may contribute to the clinical benefit observed in STEMI patients undergoing primary PCI [61].

Atlantic

In the 2014 multicenter double-blind RCT, *Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery*

Table 2 Effects of ticagrelor on adverse cardiac remodeling and atherosclerosis

Study	Animal model	Study drugs	Protocol	Results	Effects of ASA
Ye [23]	Rat ($n=32$)	Ticagrelor, clopidogrel	Acute dosing of ticagrelor (10 or 30 mg/kg IP 5 min before reperfusion), chronic dosing of ticagrelor (300 mg/kg per day for 4 weeks starting 1 day after reperfusion), acute + chronic, clopidogrel 12.5 mg/kg IP + 62.5 mg/kg per day oral for 4 weeks	After 4 weeks, ticagrelor improved LVEF: acute (69.5% ± 1.6%), chronic (69.2% ± 1.0%), acute + chronic (76.3% ± 1.2%), clopidogrel was similar to sham group (37.4% ± 3.7%). Ticagrelor attenuated fibrosis and decreased collagen-III mRNA levels 4 weeks after ischemia/reperfusion, attenuated the increase in proinflammatory TNF-α, iL-1β, and IL-18, and increased anti-inflammatory 15-epi-lipoxin-A4 levels. Clopidogrel had no effect on these markers	N/A
Husted [40]	Dog ($n=12$)	Ticagrelor	Ticagrelor 30 and 100 µg/kg/min IV	Ticagrelor dose-dependently inhibited adenosine uptake by erythrocytes and augmented the hyperemic response to temporary occlusion or direct intracoronary adenosine infusion	N/A
Birnbaum [43]	Rat ($n=44$)	Ticagrelor, prasugrel	Ticagrelor (300 mg/kg/day), ASA (20 mg/kg/day), Ticagrelor + ASA, or prasugrel (15 mg/kg/day) started 7 days after infarction	Both ticagrelor and ASA attenuated the decrease in systolic function and remodeling and increase in ANP, BNP, collagen-I and collagen-III, only ticagrelor increased markers of stem cells and regeneration, prasugrel had no effects	The combination of ticagrelor and ASA attenuated the improvement of systolic function and remodeling as well as the decrease in ANP, BNP, collagen-I and collagen-III, and increase in markers of stem cells and regeneration
Ye [44]	Mouse (ApoE double-knockout) ($n=77$)	Ticagrelor, clopidogrel, ROS	ROS (5 mg/kg/day), ASA (25 mg/kg/day), ticagrelor (300 mg/kg/day), or clopidogrel (75 mg/kg/day), or their combination for 14 weeks	ASA, ticagrelor, and ROS increased 15-epi-lipoxin A4 and decreased IL-1β, IL-6, and TNF-α levels, and reduced the area of atherosclerotic plaque. Ticagrelor + ROS provided additive effects	ASA attenuated the effects of ticagrelor and ROS including: increased 15-epi-lipoxin A4 levels, decreased TNF-α and reduced the area of atherosclerotic plaque; ASA had no effect on IL-1β or IL-6 levels

Table 2 (continued)

Study	Animal model	Study drugs	Protocol	Results	Effects of ASA
Preusch [50]	Mouse (ApoE/P2Y$_{12}$ double knock-out) ($n=25$)	Ticagrelor	Ticagrelor 270 mg/kg/day, or control for 25 weeks	Significant reduction in relative area of necrotic core and increase in fibrous cap thickness in ticagrelor-treated mice, trend toward reduction in total lesion size with ticagrelor, in vitro reduction of apoptotic macrophages and oxLDL uptake with ticagrelor	N/A
Xia [51]	Mouse (ApoE −/−) ($n=20$)	Ticagrelor	Ticagrelor 100 mg/kg/day intragastric for 10 days	Ticagrelor reduced ox-LDL-induced apoptosis, decreased atherosclerotic plaque area, inhibited the expression of PCSK9	N/A
Halim [52]	Mouse (LDL receptor −/− Apobec1 −/−) ($n=18$)	Ticagrelor, clopidogrel	Ticagrelor 180 mg/kg/day or clopidogrel 25 mg/kg/day for 16 weeks	Ticagrelor reduced macrophage infiltration to atherosclerotic intima, and apoptotic cytokines CCL4 and CXCL10, TNF-α as compared to clopidogrel, ticagrelor increased anti-atherosclerotic paraoxanase-1 as compared to clopidogrel	N/A
Vilahur [57]	Pig ($n=24$)	Ticagrelor, clopidogrel	Loading with ticagrelor 180 mg 2 h, or clopidogrel 600 mg 4 h before MI induction; followed by ticagrelor 90 mg BID or clopidogrel 75 mg daily for 42 days	Ticagrelor reduced edema, scar size, aquaporin-4 levels and increased AMPK, Akt/PKB activation as compared to clopidogrel. Ticagrelor also showed an improved regional wall motion of the infarcted segments and LVEF	N/A

ANP atrial natriuretic peptide, *ASA* aspirin, *BNP* B-type natriuretic peptide, *IL* interleukin, *IP* intraperitoneal, *LVEF* left ventricular ejection fraction, *oxLDL* oxidized low-density lipoprotein, *PCSK9* proprotein convertase subtilisin/kexin type 9, *ROS* rosuvastatin, *TNF-α* tumor necrosis factor-alpha

(ATLANTIC), of 1862 patients with ongoing STEMI of less than 6-h duration, administration of a 180 mg loading dose of ticagrelor en route to the hospital did not improve the coprimary endpoints of pre-PCI coronary reperfusion of the culprit artery nor ST-segment elevation resolution on electrocardiogram (ECG) 1 h post-PCI in patients as compared to ticagrelor administration in the catheterization laboratory. The original hypothesis of the study was that earlier ticagrelor administration would cause faster and stronger platelet inhibition, and lead to quicker resolution of acute coronary occlusion. The authors explained the lack of efficacy in the primary outcomes by pointing to a clinically non-significant time-to-PCI difference in both groups; the median time from randomization to angiography was 48 min, and the median time difference between the prehospital and in hospital group was only 31 min [62].

As has been demonstrated by preclinical trials, ticagrelor's acute cardioprotective effects are mostly attributed to protection from IRI rather than more potent and efficacious platelet inhibition. Given the effects of increased coronary blood flow and reduced IS demonstrated with ticagrelor loading in several animal studies, it would be expected that these findings would correlate with quicker resolution of ST-segment elevation or improved reperfusion. However, it is possible that 31 min was not enough time to make a clinical difference in protection from IRI. Another plausible yet unexplored explanation inferred from the preclinical trial findings is that HD chewable aspirin that was administered to all patients as standard of care blocked the ability of ticagrelor to attenuate IRI through the COX-2 pathway.

There were significantly more occurrences of the co-primary endpoints in patients treated with morphine [62]. One explanation is that delayed gastric absorption due to opioid-induced decreased gastric motility. This was corroborated by a sub-study of the ATLANTIC trial which demonstrated that platelet inhibition was unaffected by prehospital ticagrelor administration at the time of initial angiogram due to the short transfer delay, but that morphine administration was associated with delayed onset of platelet inhibition at 1 and 6 h post-PCI [63]. Another RCT of 195 patients who presented with STEMI and received crushed aspirin and ticagrelor prior to PCI found that IV acetaminophen in comparison to IV fentanyl was associated with significantly higher ticagrelor plasma levels, but no difference in platelet reactivity [64]. These trials raise the possibility that lower rates of ST resolution seen in the ATALNTIC trial in patients who received morphine may be due to other non-platelet-mediated interactions between morphine and ticagrelor.

Clinical Trials Evaluating Infarct Size and Adverse Cardiac Remodeling

Ubaid found that despite greater platelet inhibition by cangrelor compared to ticagrelor at time of balloon inflation during primary PCI, there was no improvement in coronary reperfusion or IS 13 weeks later in 100 STEMI patients [26]. Theoretically, more potent and efficacious platelet inhibition by cangrelor as compared to ticagrelor could result in improved reperfusion of infarcted tissue at the time of PCI which would manifest in reduced IS weeks to months later. As this was not seen, it is possible that other non-platelet-mediated mechanisms of ticagrelor may have compensated for its relatively weaker potency and efficacy of platelet inhibition resulting in no perceived difference in IS. Given the results of the preclinical trials showing that ticagrelor protects against IRI when initiated shortly after an acute MI [23–25], it may be expected that patients in the ticagrelor group, who received the drug several hours prior to those in the cangrelor group, would have had reduced IS. However, all patients who received cangrelor prior to primary PCI were also loaded with ticagrelor after intervention. Furthermore, all patients received HD-aspirin prior to randomization, which could have inhibited ticagrelor's ability to protect against IRI as suggested by the findings of Nanhawan et al. [34].

In another RCT of 203 patients presenting with STEMI, IS was smaller and myocardial salvage greater at 3 days when ticagrelor or prasugrel were administered prior to primary PCI as compared to clopidogrel [65]. A retrospective analysis of a RCT found similar results at 3-month follow-up [66] However, these trials did not separately analyze patients given prasugrel and ticagrelor, and so conclusions about the effects of the individual therapies cannot be discerned. Furthermore, Ubaid and Sabbah evaluated IS at 3 months in patients who received both acute and chronic ticagrelor therapy [26, 66]. Therefore, individual effects of acute protection from IRI and chronic effects of ticagrelor to prevent cardiac remodeling as demonstrated in the animal studies cannot be determined.

Resembling the findings of Ye [23], ticagrelor in comparison to clopidogrel was also associated with significant reductions in N-terminal pro-hormone B-type natriuretic peptide levels and a numerical index of LV remodeling at 6 months in 110 patients presenting with first-time STEMI treated with primary PCI [67]. This was despite similar levels of platelet inhibition with ticagrelor and clopidogrel therapy, and use of both HD-aspirin prior to and LD-aspirin after PCI [67]. It is notable that ticagrelor still attenuated adverse cardiac remodeling in the setting of concomitant LD-aspirin. This is like the findings of Nanhwan. that LD-aspirin given prior to reperfusion had no effect on IS attenuation by maintenance ticagrelor [34]. No significant difference was observed in pathological LV remodeling (defined as LV remolding index > 20%), but sample size was low, as was incidence of heart failure with reduced ejection fraction [68].

Insights from the PLATO Trial

The benefits of ticagrelor demonstrated in the PLATO trial were not homogenously distributed. Subgroup analysis revealed that ticagrelor was associated with greater MACE in the North American (HR: 1.25) and US populations (HR: 1.27) compared to the rest of the world (HR: 0.84). While the possibility of chance occurrence could not be definitively ruled out via statistical analysis, HD-aspirin (≥ 300 mg daily) was associated with more MACE than LD (≤ 100 mg daily) in patients who received ticagrelor. These patterns were absent in those who received clopidogrel [19].

As a result of this observation, the US Food and Drug Administration warn that "maintenance doses of aspirin > 100 mg reduce the effectiveness of [ticagrelor] and should be avoided" [69]. Mahaffey proposed that aspirin at daily doses of > 80 mg may have attenuated ticagrelor's antiplatelet effects via inhibition of endothelial release of prostaglandins, in a dose-dependent fashion [19, 33]. However, there are no specific recommendations regarding the loading dose of aspirin. Findings from the preclinical trials indicate that aspirin loading likely blocks the acute effects of ticagrelor to protect against IRI, while chronic HD-aspirin may mitigate protection against adverse cardiac remodeling, atherosclerosis, and IRI from reinfarction. Indeed, "the potential adverse effect of aspirin in attenuating protection has not yet been considered seriously in this regard" [70].

The PLATO investigators also observed that patients who were administered ticagrelor exhibited a significant reduction in the primary endpoint while on concomitant therapy with lipid-lowering drugs versus those who were not as compared to clopidogrel [6]. The study did not specify which lipid-lowering agents were used, though presumably these were statins [71]. Via increasing extracellular adenosine levels, statin medications augment ticagrelor's ability to protect against atherosclerosis and IRI. Thus, patients on both ticagrelor and statins likely had the added benefit of protection from complications of IRI and future cardiovascular events, including reduced atherosclerotic burden, reflected by a lower event rate compared to patients not taking statins.

The Effects of Caffeine on Ticagrelor

Caffeine is a widely used non-specific adenosine receptor antagonist [72]. In a prespecified analysis of 21,162 patients in the *Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction* (PEGASUS-TIMI 54) trial, caffeine was not associated with an excess risk for MACE, sudden cardiac death, or atrial fibrillation [73]. However, all patients received daily LD-aspirin which—albeit less compared to HD—still exhibits COX-2 inhibition [74]. A small prospective study of 23 patients treated with ticagrelor for ACS found that caffeine did not alleviate dyspnea. However, the investigators concluded that the adenosine hypothesis could not be refuted by these results, since the randomized assessment of adenosine antagonism in this setting could not be accomplished [75]. Adenosine antagonism, HD-aspirin, and caffeine have all been demonstrated in animal models to attenuate ticagrelor's protection against IRI and progression of atherosclerosis [23, 34, 38, 43, 56]. Theoretically, concomitant use of multiple agents that interfere with ticagrelor-mediated production of cardioprotective molecules, i.e., aspirin and caffeine, may have sufficiently inhibited these pleiotropic effects.

Ticagrelor in Acute and Chronic Coronary Syndrome

The PEGASUS-TIMI 54 trial demonstrated that in addition to LD-aspirin, ticagrelor started a median 1.7 years after an MI is associated with reduced cardiovascular death, recurrent MI, and stroke, but increased risk of major bleeding as compared to placebo. Patients who received ticagrelor 90 mg or 60 mg twice daily had significantly lower rates of recurrent MI (275, 4.40% and 285, 4.53%, respectively), as compared to LD-aspirin plus placebo (338, 5.25%) with a HR = 0.84, 95% CI = 0.72–0.98; $p = 0.03$ [76]. Another RCT found similar results in patients with type 2 diabetes and chronic coronary syndrome without a previous history of MI or stroke [77]. As suggested by the findings of the preclinical trials, these results may have been due to added attenuation of atherosclerosis and adverse cardiac remodeling by ticagrelor. If so, these cardio-protective benefits correlated with less recurrent MI and cardiovascular death in the clinical setting. Table 3 presents the findings of RCTs of ticagrelor.

In a post hoc analysis of the *Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome* (TICO) trial, which included 3056 participants, reduction of the primary end point (a composite of major bleeding, death, MI, stent thrombosis, stroke, or target-vessel revascularization) seen with ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT increased with age with a change point of 64 years of age. Significant decreases in rates of both major bleeding and major adverse cardiovascular and cerebrovascular events were observed in patients ≥ 64, but not < 64 years old [78]. A meta-analysis of 3 RCTs including 4175 participants undergoing complex PCI also demonstrated a significant reduction in the risk of cardiovascular death (incidence rate ratio (IRR): 0.52, 95% CI: 0.28–0.96; $p = 0.04$) likely driven by a numerical trend toward lower rates of MI (IRR: 0.79; CI: 0.61–1.01;

Table 3 Clinical trials of ticagrelor (in order of year published)

Clinical trial	Investigation	Design	No. of patients	Primary outcome	Primary outcome results	Safety (bleeding) outcome results
PLATO (2009) [6]	Ticagrelor vs. clopidogrel in patients w/ ACS (+/−STEMI) treated w/ or w/o PCI/CABG	Multicenter, randomized, double-blind, double-dummy	18,624	CV death, MI, stroke at 1 year	Ticagrelor 9.8%, clopidogrel 11.7% (HR 0.84, CI 0.77–0.92; $p<0.001$)	Ticagrelor: 11.6%, clopidogrel: 11.2%, $p=0.46$
ATLANTIC (2014) [62]	Pre-hospital vs in-hospital ticagrelor loading in patients w/ STEMI < 6 h	International multicenter, randomized, double-blind	1862	Proportion of pts w/o 70% or greater resolution of STE before PCI and proportion w/o TIMI grade 3 in infarct-related artery Secondary: MACE and definite stent thrombosis at 30 days	Absence of STE resolution ≥ 70% before PCI: prehospital 86.8% vs in-hospital 87.6% (HR 0.83, CI 0.69–1.25; $p=0.63$), absence of TIMI flow grade 3 in infarct-related artery: prehospital 82.6% vs in-hospital 83.1% (HR 0.97, CI 0.75–1.25; p = 0.82), definite stent thrombosis at ≤ 24 h after PCI: prehospital 0% vs in-hospital 0.8%, (p = 0.008) and at 30 days: prehospital 0.2% vs in-hospital 1.2% ($p=0.02$)	No difference in major or minor bleeding at ≤ 48 h or at 30 days
PEGASUS-TIMI 54 (2015) [76]	DAPT with ticagrelor 90 mg or 60 mg twice daily vs. placebo (1:1:1) in patients with MI within 1–3 years (median 1.7 years)	Randomized, double-blinded, placebo controlled	21,162	Composite of CV death, MI, or stroke after 3 years	Ticagrelor 90 mg: 7.85% (HR 0.85, CI 0.75–0.96), ticagrelor 60 mg: 7.77% (HR 0.84, CI 0.74–0.95, $p<0.01$) as compared to placebo, placebo: 9.04% There was no excess risk with caffeine for MACE (adjusted HR 0.78, CI 0.63–0.98; $p=0.031$), sudden cardiac death (adjusted HR 0.98, CI, 0.57–1.70; $p=0.95$), or atrial fibrillation (adjusted odds ratio 1.07, CI, 0.56–2.04; $p=0.84$)	TIMI major bleeding in ticagrelor 90 mg vs. ticagrelor 60 mg vs. placebo: 2.60% vs 2.30% vs. 1.06% ($p<0.01$ for each dose vs. placebo)
Khan et al. (2016) [65]	Sub-study of CvLPRIT (2015) assessing infarct size of prasugrel and ticagrelor compared to clopidogrel in STEMI patients treated with primary PCI	Multicenter, prospective, open-label, randomized, blinded end-point	203	Infarct size as percentage of left ventricular mass on CMR	Ticagrelor or prasugrel as compared to clopidogrel: 12.1% (4.8–20.7) vs. 16.1 (10.5–27.7), $p<0.01$	No statistical difference in bleeding endpoints

Table 3 (continued)

Clinical trial	Investigation	Design	No. of patients	Primary outcome	Primary outcome results	Safety (bleeding) outcome results
THEMIS (2019) [77]	Ticagrelor + ASA vs. Placebo + ASA in patients with stable CAD and diabetes w/o prior MI or stroke	Randomized, double-blinded, placebo-controlled	19,220	Composite of CV death, MI, or stroke after 40 months	Ticagrelor + ASA: vs placebo + ASA: 7.7% vs 8.5% (HR 0.90, CI 0.81–0.99; $p = 0.04$)	TIMI major bleeding in ticagrelor + ASA vs. placebo + ASA: 2.2 vs 1.0% (HR 2.32, CI 1.82–2.94; $p < 0.01$)
Ubaid et al. (2019) [26]	IV cangrelor vs ticagrelor in STEMI patients treated with primary PCI	Open-label, prospective randomized	100	Primary: platelet $P2Y_{12}$ inhibition at infarct vessel balloon inflation time at 4 and 24 h, secondary: index of microvascular resistance, infarct size	PRU for cangrelor: 145.2 ± 50.6, Ticagrelor 248.3 ± 55.1, no difference in mean PRU at 4 and 24 to 36 h post-dosing. IMR, index of microvascular resistance, angiographic and electrocardiographic measures of reperfusion were similar	No statistical difference in bleeding endpoints
HEALING-AMI (2020) [67]	Ticagrelor vs. clopidogrel on LV remodeling after reperfusion of STEMI	Randomized, open-label, assessor-blinded trial at 10 centers in Korea	278	LVRI and NT-proBNP level at 6 months	LVRI in ticagrelor vs clopidogrel: 0.6 ± 18.6% vs 4.5 ± 16.5%, $p = 0.09$. NT-pro BNP in ticagrelor vs clopidogrel: 173 ± 141 vs 289 ± 585 pg/ml, $p = 0.03$	BARC type 1 bleeding in ticagrelor vs clopidogrel: 54% vs 29.5% (HR 2.80, CI 1.71–4.59; $p < 0.01$)
Sabbah et al. (2020) [66]	Loading with ticagrelor or prasugrel vs. clopidogrel in STEMI patients treated with primary PCI	Multicenter, prospective, randomized, open blinded trial in Denmark	693	Infarct size calculated by CMR at 3-month follow-up	Median infarct size in ticagrelor or prasugrel vs clopidogrel: 10.0% vs 12.9% ($p < 0.001$)	N/A

ACS acute coronary syndrome, *ASA* aspirin, *BARC* Bleeding Academic Research Consortium, *CABG* coronary artery bypass grafting, *CAD* coronary artery disease, *CI* 95% confidence interval, *CMR* cardiovascular magnetic resonance, *CV* cardiovascular, *CvLPRIT* Complete versus Lesion-only PRimary PCI Trial, *DAPT* dual antiplatelet therapy, *HR* hazard ratio, *IV* intravenous, *LVRI* left ventricle remodeling index, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *NT-proBNP* N-terminal pro hormone brain natriuretic peptide, *PRU* $P2Y_{12}$ reaction unit, *PCI* percutaneous coronary intervention, *STE* ST elevation, *TIMI* thrombolysis in myocardial infarction

$p = 0.06$) and definite or probable stent thrombosis (IRR: 0.77, CI: 0.34–1.75; $p = 0.53$; $I^2 = 0\%$) with short-course (1–3 months) ticagrelor-based DAPT followed by ticagrelor monotherapy as compared to standard DAPT [79]. Thus, ticagrelor monotherapy after a short course of ticagrelor-based DAPT appears to be safer and more efficacious than 12 months of standard DAPT with either clopidogrel or ticagrelor in preventing recurrent MI and stent thrombosis, especially in patients with advanced age and high atherosclerotic burden.

Ischemic Stroke and Peripheral Artery Disease

In the *Examining Use of tiCagreLor In paD* (EUCLID) trial of 13,885 patients with symptomatic peripheral artery disease, ticagrelor was not shown to be superior to clopidogrel for the reduction of the primary endpoint of adjudicated cardiovascular death, MI, or ischemic stroke or major bleeding events as compared to clopidogrel after a mean follow-up of 30 months [80]. However, ticagrelor was associated with a significant reduction of ischemic stroke (OR: 0.78, 95% CI: 0.62–0.98; $p = 0.03$) which may be evidence of its ability to mitigated vascular inflammation and attenuate atherosclerotic progression. In a subgroup analysis of a RCT that compared 30-day use of aspirin plus either ticagrelor or placebo in patients with mild-to-moderate acute non-cardioembolic ischemic stroke or transient ischemic attack (TIA) and who were not undergoing thrombolysis or thrombectomy, net clinical impact factor favored the combination of aspirin and ticagrelor in the first week (absolute risk reduction: 0.97%, 95% CI: 0.17–1.77%) and remained constant throughout the 30 days [81].

On the other hand, another RCT of 13,199 patients with either a non-severe ischemic stroke or high-risk TIA presumed to not be due to a cardioembolic source and who did not receive IV or intraarterial thrombolysis did not find a significant difference between ticagrelor and aspirin administered 24 h after symptom onset with regard to the primary endpoint of stroke, MI, or death (HR: 0.89, 95% CI: 0.78–1.01; $p = 0.07$), or secondary endpoints of ischemic stroke (HR: 0.87, 0.76–1.01; $p = 0.046$) and ischemic stroke, MI, or cardiovascular death (HR: 0.89, 0.78–1.01; $p = 0.07$) [82]. However, patients were only followed for 90 days. Given the borderline CIs, it is possible a longer follow-up time as demonstrated in the EUCLID trial may have may have resulted in a statistically significant reduction of ischemic stroke, MI, and/or cardiovascular death. A future network meta-analysis will examine the efficacy of DAPT with ticagrelor versus clopidogrel in preventing recurrent stroke and mortality up to 30 days after an initial cerebrovascular ischemic event [83].

Antimicrobial Effects of Ticagrelor

Several studies have attempted to assess whether the observation that ticagrelor exhibits antimicrobial effects in vitro has real-world consequences. In an RCT, ticagrelor as compared with clopidogrel treatment did not significantly alter the risk of infections during hospitalization among 2116 STEMI patients undergoing PCI but was associated with a slightly lower risk of in-hospital all-cause death and major adverse cardiovascular and cerebrovascular events [84]. However, an observational cohort study of 26,606 Dutch patients who underwent urgent or emergent PCI found a reduced absolute 1-year risk difference of *S. aureus* bacteremia (−0.19%, 95% CI: −0.32 to −0.05%; $p = 0.006$), sepsis (0.50%, −0.86 to −0.14%; $p < 0.007$) and pneumonia (−1.43%, −2.03 to −0.82%; $p < 0.001$) when they received ticagrelor versus clopidogrel [85]. This may explain the lower mortality risk following pulmonary adverse events and sepsis in ACS patients treated with ticagrelor as compared to clopidogrel in a subgroup analysis of the PLATO trial [86].

A subgroup analysis of *A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation* (GLOBAL LEADERS) found that 1 month of DAPT followed by 23 months of ticagrelor monotherapy was associated with a significant lower incidence of the primary endpoint of all-cause mortality or new Q-wave MI at 2 years as compared with 24 months of DAPT in the cohort of patients with white blood cell (WBC) counts lower than the median of 7.8×10^9 cells/L (2.8% vs. 4.2%; HR: 0.67, 95% CI: 0.52–0.86) but not that with WBC counts greater than the median (4.8% vs. 4.7%; HR: 1.01, 0.82–1.25; P interaction = 0.013). The authors concluded that a higher inflammatory state at the time of index procedure likely reflected by increased WBC counts, may attenuate the anti-ischemic benefits of ticagrelor monotherapy observed in patients with lower WBC counts [87]. Adenosine also plays a role in modulating inflammatory cytokines and leukocyte chemotaxis [88]. Perhaps adenosine diverted toward these tasks depleted adenosine levels needed to facilitate the pleiotropic effects of ticagrelor at time of injury and reperfusion such as local vasoconstriction and protection against IRI.

Ticagrelor as Compared to Prasugrel

In the landmark *Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment* (ISAR-REACT 5) trial, the primary endpoint, a composite of death, MI, or stroke at 1 year, occurred in 184 of 2012 patients (9.3%) in the ticagrelor group and in 137 of 2006 patients (6.9%) in the prasugrel group (HR: 1.36, 95% CI: 1.09–1.70; $p = 0.006$). There was no significant difference in major bleeding events [89]. A study of platelet reactivity variability throughout the day in patients 4 days after an

acute MI demonstrated that ticagrelor has greater diurnal variability in platelet aggregation than prasugrel, likely due to the continuous increase of platelet inhibition after the morning maintenance dose. Despite this difference, both drugs provided adequate platelet aggregation inhibition throughout the day, including prior to the morning dose. The results challenge the hypothesis that less platelet inhibition by prasugrel at the time of the morning dose may be responsible for higher rates of stent thrombosis in the early morning hours, again suggesting that ticagrelor may possess further non-platelet-mediated anti-ischemic benefits beyond those of prasugrel [90]. In fact, in patients with an NSTEMI undergoing PCI administered incremental doses of adenosine, coronary blood flow velocity is augmented in those who receive ticagrelor as compared to prasugrel suggesting that ticagrelor's effects to increase adenosine levels may lead to greater perfusion in the setting of ischemia [91].

Meta-analyses

Most subsequent RCTs and meta-analyses comparing ticagrelor and clopidogrel (in addition to aspirin) found no significant difference in all-cause mortality, CV death, or MACE, but a slightly higher risk of major bleeding, especially in older patients [10–18]. Hong demonstrated that while all-cause mortality (driven primarily by lower rates of major bleeding) appears to be lower with ticagrelor monotherapy started after initial treatment with DAPT for 1–3 months as compared to continuation of DAPT, rates of MACE at 1–2-years were not significantly different [15]. However, a recent meta-analysis showed that both ticagrelor and clopidogrel monotherapy was associated with greater secondary prevention of recurrent MACE as compared to aspirin monotherapy in patients months-to-years post-PCI, coronary bypass, or stroke without an increased risk of major bleeding events [92]. Though there was no significant difference between ticagrelor and clopidogrel, no RCT analyzed directly compared the two agents. Concomitant use of statins and caffeine which may augment and attenuate the pleiotropic effects of ticagrelor, were also not evaluated. This may be one possible explanation for the lack of superiority of ticagrelor as compared to clopidogrel demonstrated.

In a network meta-analysis of 7 RCTs that reported separately the results of adults older > 70 years for at least the primary endpoint, i.e., a composite of death, MI, and stroke, comprising 14,485 patients, prasugrel was associated with a similar occurrence of the primary endpoint based on a Surface Under the Cumulative Ranking curve Analysis (SUCRA) of 54.5 as compared to ticagrelor (32.9) and clopidogrel (12.6). Ticagrelor was associated with the lowest risk of stent thrombosis (SUCRA: 55.6) as compared to prasugrel (42.4) or clopidogrel (27.8) [93]. If more efficacious platelet inhibition were responsible, one would suspect for prasugrel to also result in less chance of stent thrombosis than ticagrelor. This was not seen, suggesting an alternative explanation, e.g., an enhanced anti-inflammatory atherosclerotic environment.

Implications of the Findings Presented in This Review on Future Studies

Most RCTs and meta-analyses comparing ticagrelor and clopidogrel did not evaluate concomitant use of aspirin, statins, or caffeine (Table 4). Thus, the conclusion of these RCTs and meta-analyses should not be considered definitive. The findings presented in this review can be used to direct the design of future studies aimed at assessing the effects of ticagrelor as compared to other $P2Y_{12}$ inhibitors used to treat cardiovascular diseases. To begin, large animal models are needed to corroborate the findings of rodent studies that HD aspirin may attenuate the effects of ticagrelor to protect against IRI, adverse cardiac remodeling, and atherosclerosis. They should also assess the interaction between ticagrelor and statins, caffeine, opiates, and ischemic postconditioning (of which aspirin has also been shown to limit the IS-reducing effects) on these mechanisms [70]. If large animal models confirm the findings of the preclinical trials discussed in this review, it may be time for RCTs to compare patients who present with ACS receiving ticagrelor versus other $P2Y_{12}$ inhibitors with and without loading or maintenance dose aspirin. Guided selection of $P2Y_{12}$ inhibitor therapy and attention to genotypic variations in metabolism may further optimize ischemic benefits and limit bleeding with $P2Y_{12}$ inhibitor monotherapy peri-PCI [94, 95].

Limitations

The doses of ticagrelor in the animal studies were often several times higher than those used in the clinical trials discussed. As pharmacotherapies tend to exhibit greater pleiotropic effects at greater concentrations, it is unknown whether the effects of attenuation of infarct size, atherosclerosis, inflammation, and adverse cardiac remolding are exhibited in patients with clinically indicated doses. Differences in physiology and metabolism of the animals studied and humans further compound this issue. Furthermore, many of the studies discussed are post hoc and subgroup analyses of RCTs and thus meant to generate hypothesis rather than answer specific clinical questions. Regardless, the work within this manuscript provides a comprehensive review of the pleiotropic effects identified in preclinical studies, which can guide further discussion and design of future clinical trials aimed at assessing the efficacy of ticagrelor as compared to other $P2Y_{12}$ inhibitors.

Table 4 Meta-analyses evaluating $P2Y_{12}$ inhibitors

Study	Design/investigation	No. of patients (no. of trials included)	Efficacy outcome and results	Bleeding outcome and results
Gupta [10]	Retrospective cohort study of patients with ACS who underwent PCI and received ticagrelor or clopidogrel	5194 (5)	No significant difference compared to placebo, but trend toward lower overall mortality with clopidogrel (OR 0.75, CI 0.41–1.40; $p=0.75$) and prasugrel 30 mg (OR 0.77, CI 0.01–41.07; $p=0.61$) as compared to ticagrelor (OR 1.77, CI 0.35–8.92; $p=0.32$) and prasugrel 60 mg (OR 2.32, CI 0.22–24.38; $p=0.27$); For MI: prasugrel 60 mg (OR 0.69, CI 0.42–1.12; $p=0.75$), clopidogrel (OR 0.77, CI 0.56–1.07; $p=0.58$), ticagrelor (OR 0.79, CI 0.50–1.24, $p=0.53$)	Lower bleeding outcomes with clopidogrel (OR 1.34, CI 0.87–2.07; $p=0.63$ when compared to prasugrel (OR 1.92, CI 0.65–5.71; $p=0.45$) or ticagrelor (OR 2.65, CI 0.59–12.03; $p=0.32$)—not statistically significant
Zhao [11]	Ticagrelor vs. clopidogrel in elderly patients with ACS	4,429 (4)	Ticagrelor showed a significant advantage over clopidogrel with respect to all-cause mortality (HR 0.78, CI 0.63–0.96, $I^2=0\%$) and CV death (HR 0.71, 95% CI 0.56–0.91, I2 = 0%), no significant difference in MACE (HR 1.06, CI 0.68–1.65, $I^2=77\%$)	Ticagrelor associated with a higher risk of PLATO major and minor bleeding as compared to clopidogrel (HR 1.46, CI 1.13–1.89, $I^2=0\%$)
Abusnina [12]	Ticagrelor or prasugrel (potent $P2Y_{12}$ inhibitor) vs. clopidogrel in elderly patients with ACS	10,081 (8)	Ticagrelor or prasugrel demonstrated no significant differences between clopidogrel in MACE (HR 0.97, CI 0.82–1.15; $p=0.73$), all-cause mortality (HR 0.91, CI 0.75–1.10; $p=1.00$), MI (HR 0.95, CI 0.78–1.17; $p=0.64$), and stroke (HR 1.24, CI 0.82–1.86; $p=0.31$), but did show reduction in CV mortality (HR 0.82, CI 0.68–0.98; $p=0.03$)	Ticagrelor associated with increase in major bleeding events (HR 1.32, CI 1.09–1.59; $p<0.01$)
Tarantini [13]	Ticagrelor or prasugrel (potent $P2Y_{12}$ inhibitor) vs. clopidogrel in elderly and nonelderly patients with ACS	7860 elderly, 37,857 nonelderly (7)	Ticagrelor or prasugrel significantly reduced efficacy endpoint of a composite of CV death, nonfatal-MI, and nonfatal ischemic stroke in nonelderly patients (RR 0.85, CI 0.79–0.93) but no significant difference in elderly patients (RR 0.95, CI 0.86–1.05)	No significant differences were found between potent $P2Y_{12}$ inhibitors and clopidogrel in terms of safety endpoint (major bleeding using the prespecified definition of each trial) in nonelderly (RR 1.16, CI 0.95–1.41) or elderly patients (RR 1.19, CI 0.95–1.49)
Baldetti [14]	Clopidogrel, prasugrel, or ticagrelor in ACS	145,019 (14)	Prasugrel (OR 0.62; 0.50–0.78), ticagrelor (OR 0.77; 0.62–0.95) reduced all-cause mortality compared to clopidogrel, with trend toward prasugrel over ticagrelor (0.81; 0.65–1.01). No significant difference was found among clopidogrel, prasugrel, and ticagrelor with respect to 1-year MACE outcome	No significant difference in 30-day or 1-year major bleeding outcomes when comparing any of the $P2Y_{12}$ inhibitors to the others; ticagrelor compared to clopidogrel at 30 days: OR 1.03, CI 0.71–1.49; at 1-year: OR 1.08, CI 0.76–1.54
Hong [15]	Ticagrelor monotherapy after short-term DAPT after PCI vs conventional therapy	26,143 (3)	All-cause mortality was significantly lower with ticagrelor monotherapy (RR = 0.80, CI 0.65–0.98; $p=0.03$; NNTB = 320). No significant differences in stroke, acute MI, or ST	BARC type 3 or 5 bleeding was significantly lower with ticagrelor monotherapy (RR = 0.67, CI 0.49–0.92; $p=0.01$; NNTB = 156)

Table 4 (continued)

Study	Design/investigation	No. of patients (no. of trials included)	Efficacy outcome and results	Bleeding outcome and results
Ma [16]	Ticagrelor as compared to clopidogrel in East Asian patients with ACS	3597 (8)	Ticagrelor was associated with a significant reduced risk of stent thrombosis (RR 0.42, CI 0.19–0.92, $p=0.03$) compared to clopidogrel; no significant difference in all-cause death (RR 0.87, CI 0.64–1.24; $p=0.44$), CV death (RR 0.88, CI 1.60–0.30; $p=0.52$), MI (RR 0.89, CI 0.65–1.23; $p=0.49$), or stroke (RR 0.84, CI 0.47–1.50; $p=0.56$)	Compared with clopidogrel, ticagrelor had significantly higher incidence of any bleeding (RR 1.63, CI 1.33–1.99; $p<0.00001$], and PLATO major bleeding (RR 1.56, CI 1.15–2.12; $p=0.004$)
Sun [17]	Ticagrelor and clopidogrel in patients with ACS	270,937 (10 clinical, 18 observational trials)	No significant difference in MACE (OR 0.81, CI 0.60–1.08, $p=0.15$, $I^2=64.83\%$), ticagrelor showed better therapeutic effects in patients who underwent PCI (OR 0.38, CI 0.23–0.63; $p=0.00$, $I^2=0$) than those intended for PCI (OR 1.03, CI 0.76–1.38; $p=0.87$, $I^2=64.26\%$)	Ticagrelor as compared to clopidogrel associated with higher risk of bleeding (OR 1.46, CI 1.17–1.83; $p=0.00$, $I^2=61.66\%$) and minor bleeding (OR 1.71, CI 1.33–2.21; $p=0.00$, $I^2=4.65\%$) in clinical trials
Bergh [18]	Clopidogrel as compared to ticagrelor in patients with ACS	30,739 (29 RCTs)	In RCTs with zero-event arms, without major risk of bias, recruiting patients after PLATO, with 6–12-month follow-up, and not representing outlier populations, there was no difference between clopidogrel and ticagrelor in all-cause mortality (PRD 0.6%, − 0.03–1.30%), CV death (PRD 0.6%, 0.01–1.10%), MI (PRD 0.9%, 0.4–1.3%), and stent thrombosis (PRD 0.7, 0.4–1.1%). In the subgroup of older patients, there were also no differences regarding all-cause mortality, CV death, and MI	No significant difference between clopidogrel and ticagrelor in regards to clinically significant bleeding (PRD − 1.9%, − 3.7–0.2%) or major bleeding (PRD − 0.9%, − 1.6 to − 0.1%) in all subjects. In elderly patients, clopidogrel as compared to ticagrelor had lower risk of clinically significant bleeding (PRD − 5.9%, − 11 to − 0.9%) and major bleeding (PRD − 2.4%, − 4.4 to − 0.3%)
Aggarwal [92]	P2Y12 inhibitor as compared to aspirin monotherapy for the efficacy and safety of secondary prevention in patients with atherosclerotic CV disease	61,623 (9 RCTs: 5 clopidogrel, 4 ticagrelor)	Monotherapy with $P2Y_{12}$ inhibitors significantly reduced MACE (HR 0.89, CI 0.84–0.95; $I^2=0\%$), and MI (HR 0.81, 0.71–0.92; $I^2=0\%$) as compared with aspirin monotherapy, no significant difference in stroke (HR 0.85, CI 0.73–1.01) or all-cause mortality (HR 1.01, 0.92–1.11) *Results were consistent irrespective of the P2Y12 inhibitor used*	No significant difference in the risk of major bleeding with $P2Y_{12}$ inhibitor monotherapy compared with aspirin (HR 0.94, CI 0.72–1.22; $I^2=42.6\%$)
Galli [94]	Guided antiplatelet therapy, by means of platelet function testing or genetic testing, versus standard antiplatelet therapy in patients undergoing PCI	20,743 (11 RCTs)	Guided selection of antiplatelet therapy was associated with a reduction in MACE (RR 0.78, CI 0.63–0.95; $p=0.015$), CV death (RR 0.77, 0.59–1.00; $p=0.049$), MI (RR 0.76, 0.60–0·96; $p=0.021$), stent thrombosis (RR 0.64, 0.46–0.89; $p=0.011$), stroke (RR 0.66, 0.48–0.91; $p=0.010$)	Guided selection of antiplatelet therapy was associated with reduced bleeding, although not statistically significant (RR 0.88, 0.77–1.01; $p=0.069$), association with reduced minor bleeding was significant (RR 0.78, 0.67–0.92; $p=0.0030$)

ACS acute coronary syndrome, *BARC* bleeding academic research consortium, *CI* 95% confidence interval, *CV* cardiovascular, *DAPT* dual antiplatelet therapy, *HR* hazard ratio, *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *NACE* net adverse clinical events, *NNTB* number needed to treat for benefit, *OR* odds ratio, *PCI* percutaneous coronary intervention, *PRD* pooled risk difference, *RCT* randomized controlled trial, *RR* relative risk, *ST* stent thrombosis

Conclusion

When administered prior to reperfusion, small and large animal studies demonstrate that ticagrelor likely protects against IRI. Preclinical trials also show that chronic treatment with ticagrelor mitigates adverse cardiac remodeling and the development of atherosclerosis, while also protects against IRI from recurrent ischemia. These effects are likely mediated by ticagrelor's ability to increase local interstitial adenosine levels which activate downstream anti-inflammatory prostaglandins, eicosanoids and AMPK. RCTs suggest that these benefits may confer reduced rates of recurrent infarction and cardiovascular death.

HD-aspirin and adenosine-antagonism have been demonstrated to block these benefits of ticagrelor, as well as statin's ability to enhance them. Attenuation of ticagrelor's adenosine-mediated pleiotropic effects by aspirin likely explains the differential of outcomes among PLATO participants who received HD- versus LD-aspirin, and statin versus no statin therapy. Most RCTs and meta-analyses have not accounted for these interactions. We need more preclinical and RCTs comparing cardiovascular outcomes in patients who present with ACS treated with ticagrelor versus other $P2Y_{12}$ inhibitors that are mindful of the unique pleiotropic advantages afforded by ticagrelor, and possible interactions with other therapies (e.g., aspirin, statins, and caffeine).

Author Contribution Professor Birnbaum provided the concept for and guidance of the project. The bulk of the manuscript and analysis was written by Drs. Jeffrey Triska, Neil Maitra, and Faris Haddadin. Dr. Matthew Deshotels also helped write the manuscript and configuration of the tables. Drs. Dominick Angiolillo, Gemma Vilahur, Hani Jneid, Dan Atar, and Birnbaum provided expert commentary and significant edits to the manuscript. All authors read and agreed with the final version of the manuscript prior to submission.

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Declarations

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