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Ticagrelor in the prevention of coronary and non-coronary atherothrombotic events: A comprehensive meta-analysis of 10 randomized trials

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HIGHLIGHTS

- Ticagrelor has reduced acute and long-term mortality in patients with coronary artery disease.
- Recent data have suggested that the advantages of ticagrelor could be extended to non-coronary atherothrombotic disease.
- We provide the most comprehensive meta-analysis on the impact of ticagrelor *vs*. traditional antiplatelet regimens in atherothrombotic disease.
- Among 10 randomized clinical trials, ticagrelor is associated with a significant reduction in mortality and recurrent cardiovascular events.
- Ticagrelor therapy was associated with a significant increase in major bleeding complications.

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ABSTRACT

Background and aims: More potent antithrombotic strategies have significantly reduced the rate of recurrent ischemic events in cardiovascular disease. Ticagrelor, in particular, has significantly improved the outcome in patients with acute coronary syndromes, offering potential benefits also in terms of survival. In addition, more recent data have suggested that the advantages of ticagrelor could be extended also to non-coronary atherothrombotic disease, although with contrasting results, especially for mortality reduction. The aim of the present meta-analysis was to investigate the safety and effectiveness of a newer antiplatelet strategy with ticagrelor as compared to traditional antiplatelet regimens in patients with coronary or non-coronary atherothrombotic disease.

Methods: Literature and main scientific session abstracts were searched for studies comparing a ticagrelor-based antiplatelet regimen *vs*. different antiplatelet agents in the secondary prevention of cardiac, cerebral or vascular atherothrombotic events. The primary efficacy endpoint was mortality, primary safety endpoint was the occurrence of major bleedings. Secondary endpoints were myocardial infarction and stroke.

Results: We included 10 randomized clinical trials, for a total population of 73,121 patients, 54.9% randomized to ticagrelor. At a mean follow-up of 13.4 ± 12.6 months, a newer antiplatelet strategy based on ticagrelor was associated with a significant reduction in mortality as compared to a traditional therapy (OR [95%CI] = 0.92[0.86,0.99], $p = 0.02$; $p$het = 0.14), however, such benefits were more evident in patients with coronary artery disease, while not in non-coronary trials, with a significant interaction between patients' setting and the prognostic impact of ticagrelor (p int = 0.03). A similar result was achieved for cardiovascular mortality, recurrent myocardial infarction, while for the risk of stroke, the largest advantages were observed in patients with a previous cerebrovascular accident. Major bleeding events were increased in ticagrelor treated patients (OR [95%CI] = 1.11 [1.02, 1.20], $p = 0.01$; $p$het = 0.0003), although not affecting overall mortality, as confirmed by meta-regression analysis.

Conclusions: Based on the current meta-analysis, a newer antiplatelet strategy based on ticagrelor is associated with a significant reduction in mortality and recurrent cardiovascular events, as compared to a traditional treatment, among patients treated for coronary disease but not among those with non-coronary atherothrombotic disease. However, ticagrelor therapy was associated with a significant increase in major bleeding complications.

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1. Introduction

Atherosclerotic disease is still the leading cause of mortality worldwide. Despite the great improvement in percutaneous revascularization, the outcome is still unsatisfactory in high-risk subgroups of patients [1–3]. Antiplatelet drugs represent the key point in the secondary prevention of recurrent cardiac, cerebral or peripheral vascular ischemic events among patients with ascertained atherosclerotic disease [4,5]. Despite the largest data in the field are derived from trials on coronary artery disease (CAD), and mainly from the settings of acute coronary syndromes or percutaneous coronary intervention (PCI) [6,7], where dual antiplatelet therapy (DAPT) pharmacological platelet blockade is generally required, recent evidence has emerged of a potential benefit from a more aggressive antiplatelet therapy even among patients with non-coronary atherosclerotic disease [8]. Moreover, whereas acetylsalicylic acid and clopidogrel have represented for several decades the most preferred combination for dual antiplatelet therapy, the recent introduction of more potent antithrombotic drugs, allowing the achievement of a deeper, more prompt and predictable platelet inhibition, have provided significant anti-ischemic and outcome benefits [9–11], thus paving the way to different antiplatelet strategies, including various pharmacological combinations, dosing and duration [9], whose clinical implications are still largely unexplored.

Among new antiplatelet agents, the most widely addressed, so far, is ticagrelor, a directly active reversible antagonist of the P2Y12 receptor, not requiring metabolic activation and therefore providing a fast-onset and potent blockade of the adenosine-diphosphate mediated platelet aggregation. Several trials have documented the prognostic benefits of ticagrelor in CAD, both as acute or long-term therapy [12,13], therefore representing the only antiplatelet agent to have offered a reduction in mortality in these patients. However, such findings were not consistent in different trials, and especially in patients with non-coronary vascular disease [14,15]. Moreover, a potential raise in major bleeding complications has emerged in certain trials with ticagrelor [7,14].

Therefore, the aim of the present meta-analysis was to comprehensively evaluate the safety and efficacy of a newer antiplatelet therapy with ticagrelor as compared to a traditional antiplatelet regimen in patients with coronary or non-coronary atherothrombotic disease.

2. Materials and methods

2.1. Eligibility and search strategy

The literature was scanned by formal searches of electronic databases (MEDLINE, Cochrane and EMBASE) for clinical studies and the scientific session abstracts, searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org), and ESC (www.escardio.org) websites, for oral presentations and/or expert slide presentations from January 2007 to September 2018. The following key words were used: “ticagrelor”, “randomized trial”, “mortality”; “outcome”.

No language restrictions were enforced. Inclusion criteria were: 1) studies with randomized allocation to different antiplatelet regimens, comprising the allocation to ticagrelor (as single or dual therapy) as experimental strategy; 2) availability of complete clinical and outcome data after discharge. Exclusion criteria were: 1) follow-up data in less than 90% of patients, 2) ongoing studies or irretrievable data; 3) use of a new antiplatelet agent (ticagrelor or prasugrel) in the control arm.

2.2. Data extraction and validity assessment

Data were independently abstracted by two investigators (MV, GDL). In case of incomplete or unclear data, the authors were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle. Data on cardiovascular mortality were collected if data on overall mortality were not available.

2.3. Outcome measures

Primary efficacy endpoint was overall mortality. Primary safety endpoint was the rate of major bleeding complications (according to protocol definition).

Secondary endpoints were: 1) cardiovascular mortality, 2) recurrent myocardial infarction, and, 3) stroke.

2.4. Data analysis

Statistical analysis was performed using the Review Manager 5.3 freeware package, SPSS 23.0 statistical package. Odds ratio (OR) and

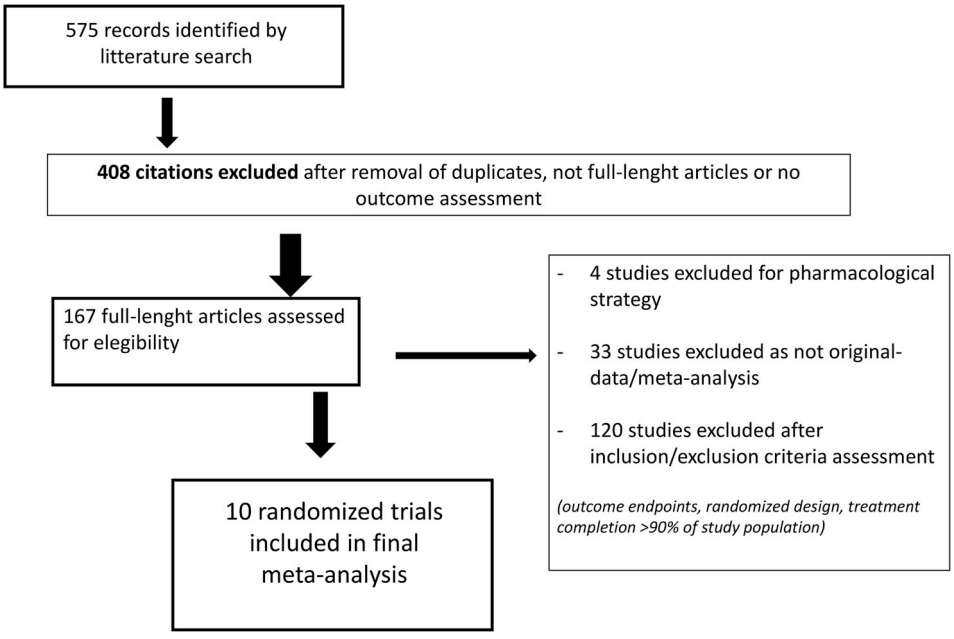

Fig. 1. Flow diagram of the systematic overview process.

Table 1
Characteristics of included randomized studies.

Study	Publication	Type	Antiplatelet treatment				Inclusion	Exclusion	Quality score
			New antiplatelet strategy	Dose	Standard antiplatelet strategy	Dose			
Coronary artery disease									
DISPERSE-2	2007	RCT-multicentric	Ticagrelor + ASA	T: 90 mgx2 (± 270 mg load-randomized); A: 75–100 mg	Clopidogrel + ASA	C: 75 mg (300 mg load); A: 75–100 mg	1. age ≥18 years; 2. hospitalized for NSTE-ACS within the preceding 48 h (defined as a) ischemic symptoms of ≥10 min duration at rest, b) troponin T or I, creatine kinase [CK]-MB elevation greater than the local MI decision limit, c) total CK greater than twice the local MI decision limit, d) presence of new or presumably new ST-segment depression ≥0.5 mm (0.05 mV), transient ST-segment elevation ≥1 mm (0.1 mV), or T-wave inversion ≥1 mm (0.1 mV) in 2 or more contiguous leads).	1.Women with childbearing potential; 2. persistent ST-segment elevation ≥20 min, more than 48 h from onset of symptoms, index event occurring as a consequence of PCI within the prior 48 h or performance of PCI within 48 h before randomization; 3. angiography showing no significant coronary stenosis; 4. increased risk of bleeding: history of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding; gastrointestinal bleeding within the prior 6 months; gastric or duodenal ulcer disease verified by endoscopy or radiographic testing within the prior 6 months, major surgical procedure or trauma within the prior 30 days; or intracranial aneurysm or vascular malformation; 5. persistent uncontrolled hypertension > 180/100 mm Hg; 6.CABG within the 3 months; 7. nonhemorrhagic stroke within the prior 30 days; 8. active cancer (excluding skin basal cell carcinoma); 9. Concomitant oral anticoagulation, nonselective nonsteroidal anti-inflammatory drugs, digoxin or strong cytochrome P450 3A4 inhibitors or cytochrome P450 3A4 substrates with a narrow therapeutic index; 10. thrombolytic therapy within the prior 7 days; 11. contraindications for aspirin treatment; 12. creatinine level > 3.0 mg/dl; 13. known active liver disease or ALT > 2 × ULN, bilirubin > 1.5 × ULN; 14. Hb < 10 g/dl or platelet count < 100 × 109/l.	9
PEGASUS TIMI 54	2015	RCT-multicentric	Ticagrelor + ASA	T: 90mgx2 or 60mgx2; A: 75–100 mg	ASA	75–150 mg	1. a spontaneous myocardial infarction 1–3 years before enrollment, 2. at least 50 years of age, 3. had one of the following: additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance of less than 60 ml per minute	1. planned use of a P2Y12 receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period; 2. bleeding disorder or a history of an ischemic stroke or intracranial bleeding, 3. a central nervous system tumor, or an intracranial vascular abnormality; 4. gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days	10

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Table 1 (*continued*)

Study	Publication	Type	Antiplatelet treatment				Inclusion	Exclusion	Quality score
			New antiplatelet strategy	Dose	Standard antiplatelet strategy	Dose			
PHILO	2015	RCT-multicentric	Ticagrelor + ASA	T: 90mgx2 (180 mg load); A: A: 75–100 mg	Clopidogrel + ASA	C: 75 mg (300 mg load); A: 75–100 mg	Similar to those from PLATO (1. ≥18 years of age: 2. Hospitalized for potential ST-segment elevation or non–STsegment elevation ACS, with onset during the previous 24 h and cardiac ischemic symptoms due to atherosclerosis of ≥10 min' duration at rest; 3. Persistent new ST-segment elevation ≥1 mm or new LBBB plus primary PCI planned or ≥2 of the following: a) ST-segment depression or transient elevation ≥1 mm in two or more 2 contiguous leads; b) Positive biomarker indicating myocardial necrosis. (Troponin I or T or CK-MB > ULN; c) One of the following: (a) ≥60 y of age (b) Previous MI or CABG (c) CAD with ≥50% stenosis in ≥2 vessels (d) Previous ischemic stroke, TIA (hospital-based diagnosis), carotid stenosis (≥50%), or cerebral revascularization (e) Diabetes mellitus (f) Peripheral artery disease (g) Chronic renal dysfunction)	1. any contraindication against the use of clopidogrel; 2. active bleeding or a history of bleeding; 3. fibrinolytic therapy within 24 h before randomization; need for oral anticoagulation therapy; 4. increased risk of bradycardia; and concomitant therapy with a strong CYP3A inhibitor or inducer.	10
PLATO	2009	RCT-multicentric	Ticagrelor + ASA	T: 90mgx2 (180 mg load); A: A: 75–100 mg	Clopidogrel + ASA	C: 75 mg (300 mg load); A: 75–100 mg[a]	1. ≥18 years of age: 2. Hospitalized for potential ST-segment elevation or non–STsegment elevation ACS, with onset during the previous 24 h and cardiac ischemic symptoms due to atherosclerosis of ≥10 min' duration at rest; 3. Persistent new ST-segment elevation ≥1 mm or new LBBB plus primary PCI planned or ≥2 of the following: a) ST-segment depression or transient elevation ≥1 mm in two or more 2 contiguous leads; b) Positive biomarker indicating myocardial necrosis. (Troponin I or T or CK-MB > ULN; c) One of the following: (a) ≥60 y of age (b) Previous MI or CABG (c) CAD with ≥50% stenosis in ≥2 vessels (d) Previous ischemic stroke, TIA (hospital-based diagnosis), carotid stenosis (≥50%), or cerebral revascularization (e) Diabetes mellitus (f) Peripheral artery disease (g) Chronic renal dysfunction	1. Contraindication to clopidogrel; 2. Oral anticoagulation therapy that cannot be stopped; 3. Fibrinolytic therapy planned or within the previous 24 h; 4. Concomitant oral or IV therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A Inducers; 5. Index event complication of PCI or index PCI before first study dose; 6. Increased risk of bradycardiac events; 7. Dialysis required; 8. Known clinically important thrombocytopenia or anemia; 9. severe hemodynamic instability; 10. active cancer; 11. Pregnancy or lactation; 12. risk for noncompliance	9
TANG et al.	2016	RCT-single centre	Ticagrelor + ASA		Clopidogrel + ASA	C: 75 mg (600 mg load); A:	1. age < 18 years; 2. chest discomfort for .20 min and no response to	1. cardiogenic shock, defined as systolic blood pressure of < 90/60 mm Hg and	8

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Table 1 (*continued*)

Study	Publication	Type	Antiplatelet treatment				Inclusion	Exclusion	Quality score
			New antiplatelet strategy	Dose	Standard antiplatelet strategy	Dose			
				T: 90mgx2 (180 mg load); A: 75–100 mg (300 mg load)		75–100 mg (300 mg load)	nitroglycerin; 3. time from the onset of symptoms to randomization < 12 h; 4. eligible for PPCI; 5. STsegment elevation of > 1 mm in 2 or more limb leads or > 2 mm in 2 or more contiguous precordial leads; 6. Killip class of ≤ 3; and 7. the provision of informed consent.	no response to fluids; 2. thrombolysis within the past 24 h; 3. oral anticoagulation therapy or current use of P2Y12 antagonists; 4. malignant or life-threatening diseases; 5.contraindications to aspirin, clopidogrel, or ticagrelor; 6.inability to provided informed consent; 7.suspected mechanical complications of STEMI; or 8.coronary artery bypass graft surgery (CABG) within the previous year	
TREAT	2018	RCT-multicentric	Ticagrelor + ASA	T: 90mgx2 (180 mg load within 24 h from event); A: 75–100 mg (300 mg load)	Clopidogrel + ASA	C: 75 mg (300–600 mg load); A: 75–100 mg	1. Patients with STEMI presenting within 24 h from symptoms onset; 2. aged < 75 years; 3. treated with fibrinolytic therapy	1. contraindication to the use of clopidogrel, 2. use of oral anticoagulation, 3. increased risk of bradycardia, 4. concomitant use of strong CYP-450 inhibitor or inducer	8
SAW et al.	2016	RCT-dual centre	Ticagrelor + ASA	T: 90mgx2 (within 72 h after CABG); A: 81 mg/day (within 12 h of surgery)	ASA	A: 81 mg/day (within 12 h of surgery)	1. aged ≥18 years and < 80 years; 2. stable coronary artery disease or ACS, 3. undergoing isolated CABG	1. combined valve or aortic surgery, 2. deemed to require oral anticoagulation or long-term DAPT post CABG; 3. known allergy or intolerance to aspirin, clopidogrel or ticagrelor; 4. patients with active bleeding or history of bleeding diathesis; 5. patients with previous intracranial haemorrhage at any time, or ischaemic stroke within 14 days; patients with severe liver disease; 6. patients with preoperative or persistent postoperative high-grade atrioventricular block without a permanent pacemaker; 7. patients with renal dysfunction with eGFR < 50 mL/min.	8
ZHAO et al.	2018	RCT-multicentric	Ticagrelor + ASA or Ticagrelor	T: 90 mgx2; if ASA: 100 mg/daily (within 24 h from CABG)	ASA	A: 100 mg daily (within 24 h from CABG)	1. aged 18–80 years; 2. indications for elective CABG surgery	1. urgent revascularization or other concomitant cardiac surgery; 2.need for DAPT or vitamin K antagonist therapy post-CABG; 3. serious bleeding risk (eg, history of intracranial hemorrhage, bleeding diathesis within 3 months, or gastrointestinal bleeding within 1 year	7
Non-coronary artery disease									
EUCLID	2017	RCT-multicentric	Ticagrelor	90mgx2	Clopidogrel	75 mg daily	One of the criteria: 1. previous revascularization of the lower limbs for symptomatic disease more than 30 days before randomization or 2. hemodynamic evidence of peripheral artery disease, as evidenced by an ankle–brachial index (ABI) of 0.80 or less at screening	1. current or planned use of dual antiplatelet therapy or aspirin, an increased risk of bleeding, 2. treatment with long-term anticoagulation, 3. poor clopidogrel metabolizer status for the cytochrome P-450 2C19 allele, defined as a genotype with two loss-of-function alleles	10
SOCRATES	2016	RCT-multicentric	Ticagrelor	90mgx2 (180 mg load)	ASA	100 mg (300 mg load)	1. Men or women aged ≥40 years; 2. Acute ischemic stroke or high-risk TIA; 3. Able to be randomized within 24 h	1: Planned use of antithrombotic therapy in addition to study medication, including antiplatelets and	10

(*continued on next page*)

Table 1 (*continued*)

Study	Publication	Type	Antiplatelet treatment				Inclusion	Exclusion	Quality score
			New antiplatelet strategy	Dose	Standard antiplatelet strategy	Dose			
							after the onset of symptoms; 4. Able to provide informed consent; 5. Head CT or MRI ruling out hemorrhage or other pathology, such as vascular malformation, tumor, or abscess that could explain symptoms or contraindicate therapy	anticoagulants; 2. requiring dual antiplatelet therapy; 3. Known hypersensitivity to ticagrelor or aspirin; 4. history of AF, ventricular aneurysm, or suspicion of cardioembolic pathology for TIA or stroke; 5. Planned carotid, cerebrovascular, or coronary revascularization; 6. any thrombolysis or mechanical thrombectomy within 24 h prior; 7. concomitant oral or IV therapy with strong CYP3A inhibitors or substrates with narrow therapeutic indices that cannot be stopped; 8. Anticipated requirement for long-term (> 7 days) NSAIDs; 9. bleeding diathesis or coagulation disorders (e.g. TTP); 10. History of previous symptomatic non-traumatic intracerebral bleeding at any time (asymptomatic microbleeds do not qualify), GI bleeding within past 6 months or major surgery within 30 days; 11. Known severe liver disease; 12. Renal failure requiring dialysis; 13. Pregnancy or lactation; 14. Participation in another clinical trial with an investigational product during the last 30 days; 15. Previous enrolment or randomization in SOCRATES; 16. Inability to understand and/or comply with study procedures	

[a] After stent placement, ASA up to 325 mg daily was allowed for up to 6 months according to ACC/AHA guidelines.

95% confidence intervals (95%CI) were used as summary statistics. The pooled odds ratio was calculated by using a fixed effect model (Mantel-Haensel). The Breslow-Day test was used to examine the statistical evidence of heterogeneity across the studies ($p < 0.1$). Potential publication bias was examined by constructing a "funnel plot", in which sample size was plotted against odds ratios (for the primary endpoint). The study quality was evaluated by the same two investigators according to a score, that was expressed on ordinal scale, allocating 1 point for the presence of each of the following: 1) statement of objectives, 2) explicit inclusion and exclusion criteria, 3) description of intervention, 4) objective means of follow-up, 5) description of adverse events, 6) power analysis, 7) description of statistical methods, 8) multicenter design, 9) discussion of withdrawals, and, 10) details on medical therapy.

A pre-specified subgroup analysis was conducted separating patients with coronary and non-coronary atherothombotic disease. In case of different ticagrelor-based strategies or dosing were present, data were considered as the pooling of the data of the ticagrelor-treated patients.

A random-effect meta-regression analysis was carried out to evaluate the relationship between the survival benefits of Ticagrelor and patients' risk profile (defined as the Log ODDS for the event in the control group) or the difference in bleeding complication (defined as the Log ODDS Ratio for major bleedings).

The study was performed in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [17].

3. Results

3.1. Eligible studies

A total of 575 studies were screened for inclusion in our meta-analysis, as shown in the flow-chart for the selection process in Fig. 1. Two trials were excluded since comparing a ticagrelor-based antiplatelet regimen with another new antiplatelet drug [18,19], and two trials since using ticagrelor also in the control arm [20,21]. Two trials were excluded since providing only in-hospital follow-up [22,23].

Finally, 10 studies [13–16,24–29] were included in our meta-analysis, with an overall population of 73,121 patients. Among them, 40,174 (54.9%) were randomized to a ticagrelor-based antiplatelet strategy, while 32,947 patients to a different antiplatelet regimen. Two trials [15,16] were performed in the setting of non-coronary atherothrombotic disease, while 8 trials included patients with CAD, of which 5 studies were conducted in the setting of ACS, while 3 studies [14,28,29] enrolled subjects with stable CAD, especially those undergoing bypass grafting (CABG) in 2 trials [28,29].

Antiplatelet agents used for the ticagrelor-based regimen were ticagrelor and acetylsalicylic acid (ASA) in 7 trials [13,14,24–28], ticagrelor alone in 2 trials [15,16] while one trial [29] allowed the use of ticagrelor both in single therapy or in association with ASA. In the control arm, antiplatelet therapy comprised DAPT with ASA and clopidogrel in 5 trials, ASA alone in 4 trials [14,15,28,29] and clopidogrel alone in one trial [16]. Ticagrelor daily dose was 180 mg, whereas 1 trial tested a reduced 120 mg-dose in one treatment arm [14].

Study characteristics of included trials are shown in Table 1. Mean follow-up was 13.4 ± 12.6 months, (median 12 months) ranging from 1 month [27] to 36 months [14,16].

Table 2 displays the characteristics of enrolled patients, with a mean age of 63.7 ± 2.4 years, 73.8% males, 29.4% diabetics and 49.5% with ACS.

3.2. Clinical outcome

3.2.1. Primary efficacy endpoint

Data on mortality were available in 73,101 patients (99.9% of total population). Two trials provided only cardiovascular mortality [28,29]. A total of 3375 patients (4.6%) had died at follow-up, with a significant lower rate of events in ticagrelor treated patients (4.4% (1781/40,164) *vs.* 4.8% (1594/32937), OR[95%CI] = 0.92[0.86,0.99], $p = 0.02$; *p*het = 0.14, Fig. 2).

However, such benefits were more evident in patients with coronary artery disease (4.1% (1085/26645) *vs.* 4.7% (901/19372), OR [95%CI] = 0.86[0.79,0.95], $p = 0.002$; *p*het = 0.31) while not in non-coronary trials (5.2% (696/13519) *vs.* 5.1% (693/13565), OR [95%CI] = 1.01[0.90,1.13], $p = 0.88$, *p*het = 0.36, *p* int = 0.03).

By the use of meta-regression analysis, the benefits of the new antiplatelet therapy were not affected by patients' risk profile (r = 0.041[-0.047,0.128], $p = 0.36$) or the differential risk of major bleeding complications between the two treatment arms (r = −0.195, [-0.99,0.61], $p = 0.63$), Fig. 3. However, larger benefits in mortality with ticagrelor were observed among younger patients ($p = 0.002$), as shown in Supplementary Table 3.

3.3. Secondary endpoints

3.3.1. Cardiovascular mortality

Data on cardiovascular mortality were available in 73,101 patients (99.9%); among them, 2277 (3.1%) experienced an event, with a lower CV mortality with the new as compared with the traditional antiplatelet regimen (2.9% (1179/40,164) *vs.* 3.3% (1098/32,937), OR [95%CI] = 0.90 [0.83,0.98], $p = 0.02$, *p*het = 0.17, Supplementary Fig. 4. Similar results were obtained in cardiovascular trials (2.9% (775/26645) *vs.* 3.7% (720/19372), OR[95%CI] = 0.72 [0.74,0.91], $p = 0.0002$, *p*het = 0.78), but not in non-coronary disease (2.99%(404/13519) *vs.* 2.8% (378/13565), OR[95%CI] = 1.08 [0.93, 1.24],

Table 2
Clinical features of patients in included studies.

Study	DISPERSE-2	PEGASUS TIMI 54	PHILO	PLATO	TANG et al.	TREAT	SAW et al.	ZHAO et al.	EUCLID	SOCRATES
Patients, n (new/standard therapy)	334/327	14095/7067	401/400	9333/9291	210/210	1913/1886	35/35	334/166	6930/6955	6589/6510
Follow-up (months)	3	36	12	12	6	1	12	12	36	4
Bleeding definition	TIMI	TIMI	non CABG related, PLATO defined	PLATO	TIMI	TIMI	PLATO	–	TIMI	PLATO
Age (mean)	64/62	65.4/65.2	67/66	62/62	64.4/64.2	59/58.8	61.7/62.5	63.4/64	66/66	65.8/65.9
Male gender (%)	63.8	76.3	76.5	71.8	72	77.1	87.2	82.7	72	58.5
Diabetes mellitus(%)	24.9	32.3	34.6	25	25	16.8	30	42.7	38.5	24.4
Hypertension (%)	–	77.5	74.3	65.5	59.5	56.4	77.2	74.6	78.2	73.7
Acute coronary syndromes (%)	53.4	52	37.6	100	100	0	0	–	–	

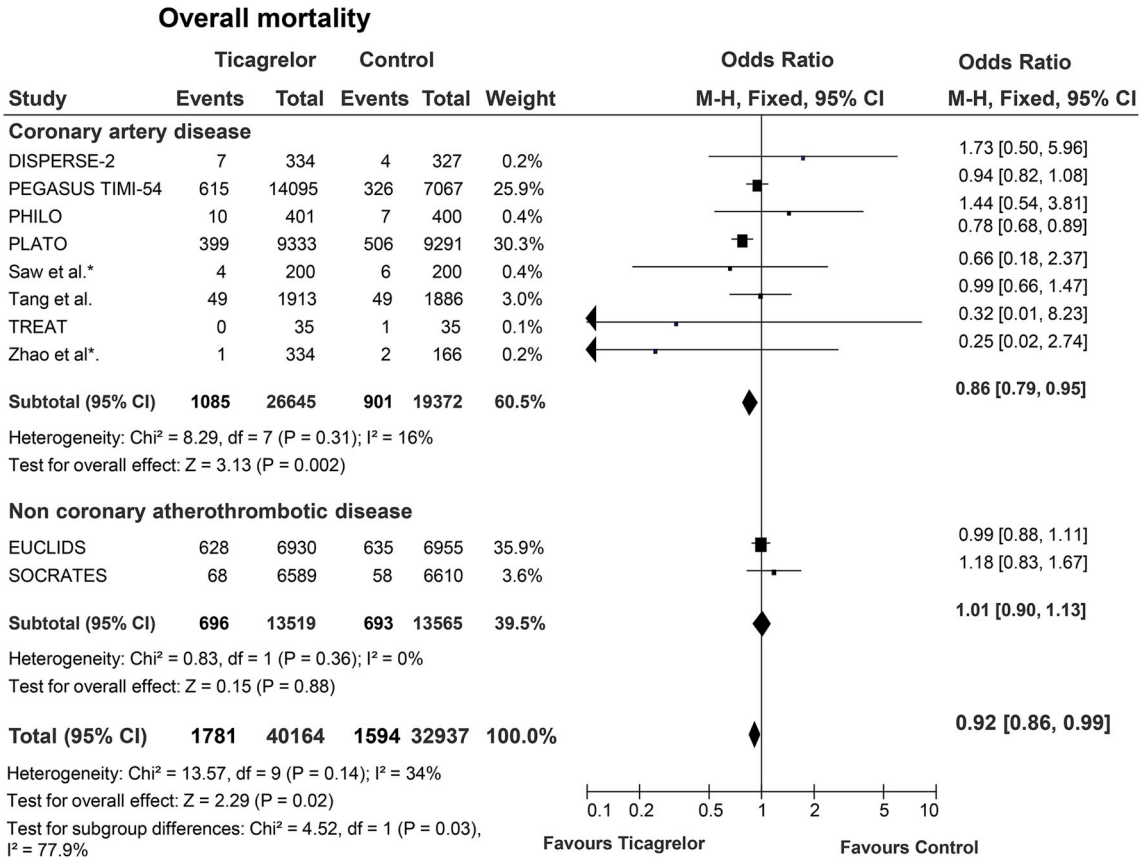


Fig. 2. Ticagrelor *versus* traditional antiplatelet agents in mortality, with odds ratios and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

$p = 0.32$, phet = 0.68, p int = 0.003).

3.3.2. Myocardial infarction

Data on recurrent myocardial infarction were available in 73,101 patients (99.9%), of whom 2015 (3.9%) experienced an event. A significant reduction in the risk of non-fatal myocardial infarction was observed in the ticagrelor as compared to the traditional antiplatelet strategy arm (3.7% (480/40,164) *vs.* 4.1% (1335/32,937), OR [95%CI] = 0.89 [0.82, 0.96], $p = 0.002$; phet = 0.21; Supplementary Fig. 5, mainly driven by trials conducted in CAD patients (4.2% (1106/26,645) *vs.* 5.1% (980/19372), OR[95%CI] = 0.83 [0.76, 0.91], $p < 0.0001$; phet = 0.80), whereas a null effect was observed in patients with peripheral or cerebrovascular disease (2.8% (374/13,519) *vs.* 2.6% (355/13,565), OR[95%CI] = 1.06 [0.91, 1.23], $p = 0.044$, phet = 0.68, p int = 0.006).

3.3.3. Stroke

Data on stroke were available in 73,101 patients (99.9%). A total of 947 (1.3%) experienced such an event. The risk of cerebrovascular events was significantly reduced with the newer antithrombotic strategy (1.2% (497/40,164) *vs.* 1.4% (450/32,937), OR [95%CI] = 0.88 [0.77, 1], $p = 0.05$; phet = 0.12; Supplementary Fig. 6. The results were mainly driven by a significant benefit in stroke in patients with a previous non-coronary atherothrombotic event (1.1% (149/13,519) *vs.* 1.3% (186/13,565), OR[95%CI] = 0.80 [0.64, 1.00], $p = 0.04$; phet = 0.38), while a similar trend was observed in CAD trials (1.3% (348/26,645) *vs.* 1.4% (264/19,372), OR[95%CI] = 0.92 [0.79, 1.09], $p = 0.34$; phet = 0.09, p int = 0.30).

3.3.4. Major bleedings

Data on major bleedings were available in 72,678 patients (99.4%). A major bleeding event was documented in 2020 patients (2.8%). TIMI (Thrombolysis in Myocardial Infarction) Major definition was used in 5 studies [11,13,19,21,24], whereas 4 studies provided data on PLATO defined major bleedings [10–12,20,25], while in one study definition was not available [29].

As shown in Supplementary Fig. 7, the newer ticagrelor-based antiplatelet regimen significantly increased the rate of major bleeding events (3.5%, (1421/39,917) *vs.* 1.6% (1194/32,761), OR [95%CI] = 1.11 [1.02, 1.20], $p = 0.01$; phet = 0.0003) mainly in trials including CAD patients (OR[95%CI] = 1.13 [1.04, 1.23], $p = 0.006$; phet = 0.0001 rather than non-coronary trials (OR[95%CI] = 0.98 [0.78, 1.24], $p = 0.88$, phet = 0.38, p int = 0.27).

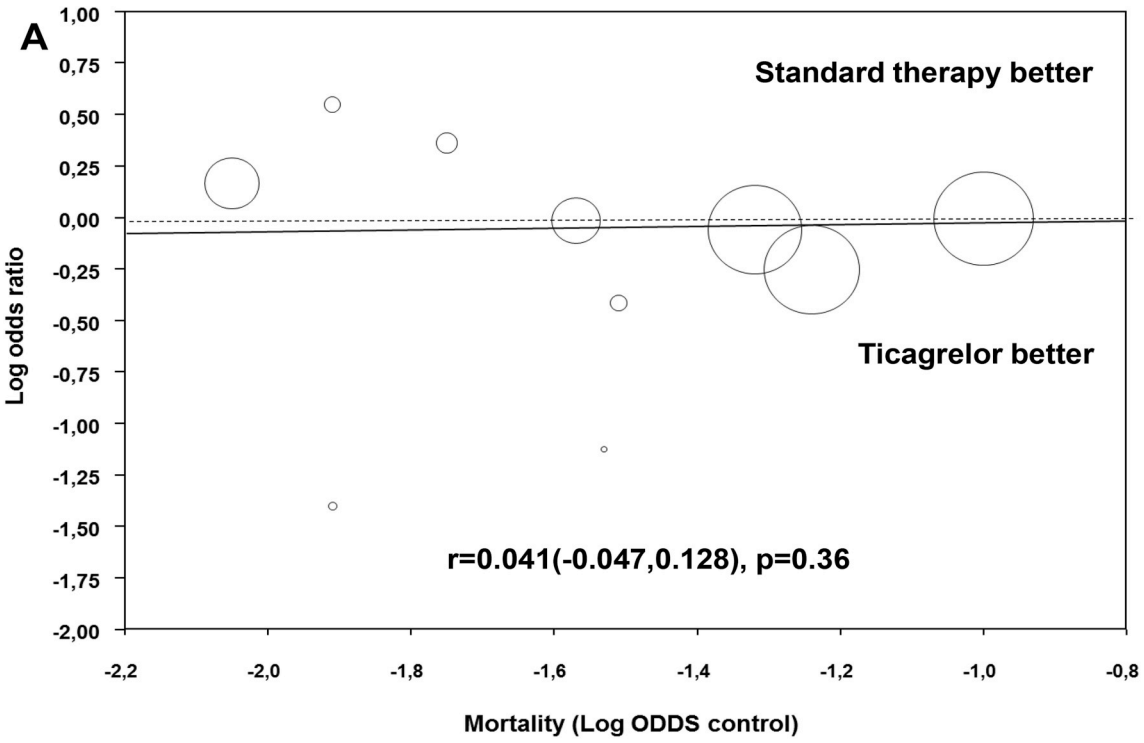
4. Discussion

The present study represents one of the most updated and comprehensive meta-analysis evaluating the prognostic impact of a newer antiplatelet therapy, based on the more potent drug ticagrelor, as compared to a standard antiplatelet treatment in patients with coronary and non-coronary atherothrombotic disease.

We demonstrated that the introduction of this new drug is associated with significant benefits in the reduction of recurrent ischemic events and, despite being weighted by an increase in major bleeding complications, the use of ticagrelor could lower mortality, ad especially among patients with coronary artery disease (CAD).

Recent advances in the field of pharmacological antithrombotic therapies, in fact, have significantly improved the outcomes of patients with atherothrombotic disease, including coronary, cerebral or peripheral vascular disorders [30–32].

Indeed, the largest trials have been conducted in the cardiovascular field, and mainly in setting of acute coronary syndromes (ACS) or



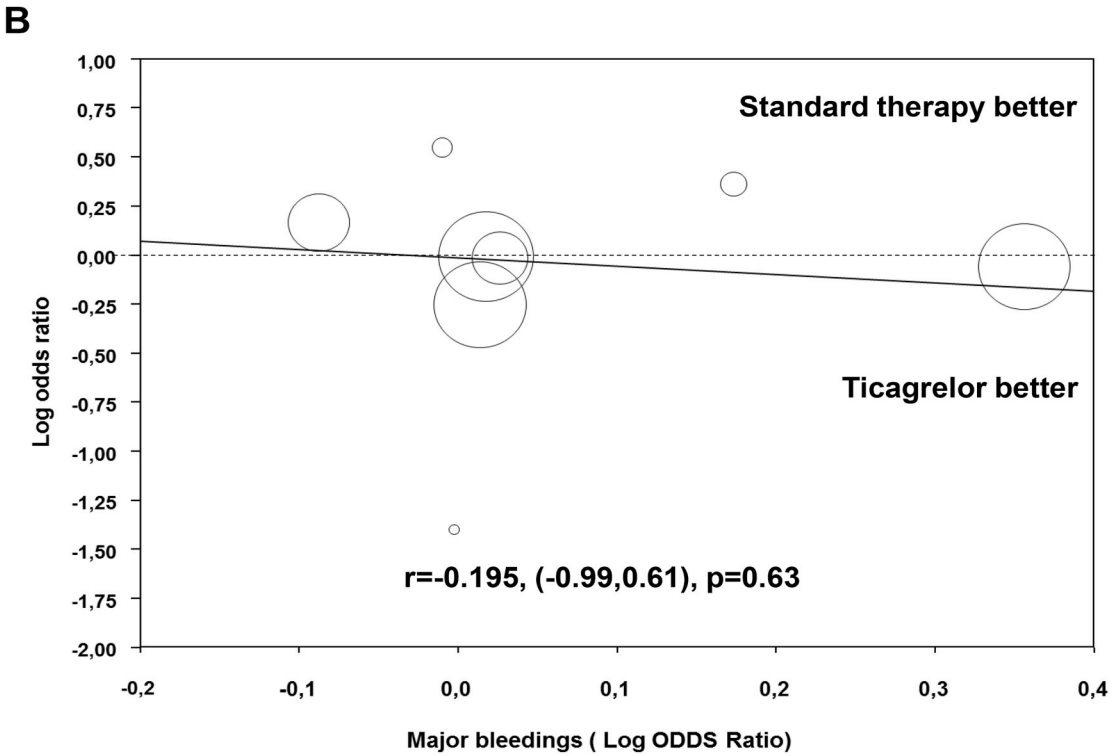


Fig. 3. Fixed-effect meta-regression analyses for the risk (OR) of mortality between new and traditional antiplatelet agents and patients' risk profile (A, upper graph) or the difference in the risk of major bleeding complications (Log Odds Ratio, B, lower graph).
The size of the circle corresponds to its statistical weight.

percutaneous coronary revascularization (PCI) [33,34,35], where a prompt and potent platelet inhibition has been shown to favor the restoration of myocardial perfusion and prevent periprocedural complications and stent thrombosis. In fact, the recent introduction of new oral antiplatelet agents, such as ticagrelor and prasugrel, allowing a faster and more predictable onset of action and a greater degree of platelet inhibition, have demonstrated large prognostic benefits in patients at high risk for thrombotic complications, such in the settings of ACS [7,35].

In the PLATO trial [10], ticagrelor decreased the incidence of major adverse cardiovascular events (MACE) and total mortality in patients with ACS, being so far the only antiplatelet ADP-antagonist to achieve such a survival benefit. Indeed, other newer oral antiplatelet agents, such as prasugrel, did not show such a prognostic impact on survival, among ACS patients, despite providing a similar degree of platelet inhibition or even a larger reduction in the relative risk of stent thrombosis (54% with prasugrel *vs.* 25% with ticagrelor). Several studies comparing head-to-head prasugrel vs ticagrelor [18,19], showed similar inhibition of platelet aggregation between the two drugs, suggesting that the largest outcome benefits offered by ticagrelor could not be dependent from its antiplatelet effect. In fact, the presence of additional pleiotropic effects, via the adenosine A2a pathway, have been suggested with ticagrelor, [36,37] improving additionally microcirculatory function and tissue perfusion, thus resulting potentially effective both in coronary circulation and peripheral districts.

In addition, the outcome benefits with ticagrelor have recently emerged even at distance after an acute coronary event. In fact, in the PEGASUS-TIMI 54 trial [14], a single antiplatelet strategy with low-dose (120 mg daily) ticagrelor was associated with a significantly reduced rate of cardiovascular death, myocardial infarction, or stroke, despite at the expense of increasing the risk of major, but not fatal or intracranial, bleeding events.

Therefore, newer antiplatelet strategies certainly pave the way to different options of antiplatelet strategies, even as a single antiplatelet regimen, and especially in selected subpopulations, as high bleeding-risk patients.

The recent GLOBAL LEADERS trial [21], in fact, randomized patients undergoing percutaneous coronary intervention for ACS od stable CAD to 1 month dual antiplatelet therapy followed by ticagrelor alone for 23 months *vs.* the traditional 12 months of standard dual antiplatelet therapy. The two strategies resulted comparable in terms of safety and anti-ischemic prevention of recurrent events.

However, a similar escalation to more potent antithrombotic strategies has been observed also for non-coronary atherothrombotic disease.

In the CHANCE trial, a combination of clopidogrel and aspirin was superior to aspirin alone in the prevention of recurrent stroke among patients with a previous transient ischemic cerebral event (TIA) or minor stroke, without increasing major bleedings. In peripheral artery disease, a subgroup analysis of the CAPRIE trial [38] showed that clopidogrel monotherapy was more effective than aspirin monotherapy in reducing cardiovascular events. Moreover, in both the PLATO and PEGASUS trials [13,14], the presence of concomitant peripheral artery disease was associated with an increased risk of ischemic events and with a consistent benefit for ticagrelor in comparisons with the overall trial populations.

However, only two trials have addressed, so far, the prognostic impact of ticagrelor in secondary prevention among patients with non-coronary atherothrombotic disease [15,16]. While cumulative data showed a significant reduction in stroke, clear benefits were only observed in the EUCLID trial, but not in the only trial strictly dedicated to the evaluation of the recurrence of stroke (SOCRATES trial, [15]). This issue certainly deserves further investigation in larger randomized trials. In addition, despite patients with peripheral artery disease are generally deemed at higher-risk as compared to coronary patients [39], no impact of mortality was observed among these patients.

The present study represents the most updated and comprehensive meta-analysis including a large population of over 70000 patients with coronary and non-coronary atherothrombotic disease. We showed that a newer ticagrelor-based antiplatelet regimen is associated with a significant reduction in mortality and major cardiovascular events, although paying the fee of increasing bleedings. The increase in bleeding complications was mainly driven by the PEGASUS trial [14], where a prolonged DAPT with ticagrelor in combination with ASA was administered for over 3 years after the acute cardiovascular event, and especially driven by the subgroup of patients randomized to a full-dose Ticagrelor. In fact, in the GLOBAL LEADERS [21], where the prolonged treatment with ticagrelor was performed as a single antiplatelet regimen, such treatment was not associated with an increase in hemorrhagic events at 2 years follow-up.

Nevertheless, the hemorrhagic complications did not affect overall survival, as confirmed by our regression analysis. On the contrary, a significant inverse association was observed between age and benefits from Ticagrelor in terms of mortality, with a trend for CV mortality, whereas such results were not affected by bleeding complications. In fact, enhanced platelet reactivity associated with advanced age could have conditioned the thrombotic risk and therefore the efficacy and advantages of ticagrelor, as previously documented by our group in a large cohort of elderly patients undergoing platelet function assessment on DAPT [40].

Indeed, the positive effect of ticagrelor in the prevention of recurrent ischemic events were mainly observed in patients with CAD, and were consistent both in patients with acute coronary syndrome and in the stable setting [14,28,29]. In effect, different pathophysiological basis of the atherothrombotic disease in coronary and non-coronary patients could have represented the mechanism for our different observation. In fact, plaque rupture and acute platelet activation, that represent the pillar determinants of ACS, are less common in peripheral artery disease. On the contrary, non-atherosclerotic causes of cerebrovascular events can also be observed, as in patients with atrial fibrillation or embolic events, therefore achieving more benefits from anticoagulation rather than potent platelet inhibition. In fact, the recent COMPASS trial showed the effectiveness of the antiXa rivaroxaban in addition to ASA in secondary cardiovascular prevention, and especially among PAD patients [41]. Moreover, in a similar meta-analysis including 13 RCTs among patients with cerebral or cardiovascular risk factors treated with ticagrelor, Malhotra et al. reported that ticagrelor reduced the risk of incident strokes (HR adjusted = 0.87; 95%CI = 0.76–0.98; $p = 0.03$) and composite stroke/MI/CVD (HR adjusted = 0.88; 95%CI = 0.78–0.98; $p = 0.02$) among patients with prior history of cerebral ischemic attack [42]. However, the present analysis certainly encloses the largest population treated with ticagrelor where cardiovascular endpoints were assessed, although reaching similar conclusions as compared with from previous studies, still resulting in smaller sample size despite the inclusion of non-randomized data or heterogeneous antithrombotic therapies [43,44].

Nevertheless, coronary and non-coronary atherosclerotic disease often coexist [45], thus requiring to attentively stratify this higher-cardiovascular risk subset of patients, and especially among those undergoing revascularization procedures, where advanced techniques and newer devices require to outstretch the knowledge for use of antiplatelet and concomitant medical therapies after revascularization, therefore pointing at the need of new dedicated studies. Therefore, until new data from larger randomized trials would become available, and mainly in non-coronary disease and with the newer combinations of ticagrelor-based regimens, a tailored approach, with case by case decision should be still advocated, allowing to balance between the thrombotic and hemorrhagic risk and improve the adherence to ticagrelor therapy. In particular, an adequate patients' information about the potential appearance of dyspnea, and reassurance about its benign features, may certainly contribute to further increase compliance to the therapy.

4.1. Study limitations

The first limitation of our study derives from the synthesis of different trials. Despite, no statistically significant heterogeneity was observed in our ischemic endpoints, the different baseline risk profile, as much as the combinations of antiplatelet regimens with single or dual therapy and the variability in drugs dosing could have contributed to the observed heterogeneity in bleedings. Indeed, despite low-dose ASA dose was applied in DAPT in the majority of studies, 300 mg ASA was allowed for up to 6 months in < 1% of the entire study population [13], however, we do not expect that such a small difference could have affected our long-term follow-up. Moreover, the definitions of major bleeding differed among trials.

In addition, the most positive effects were observed in coronary trials and were mainly driven by two larger trials, whereas the smaller study population could certainly have conditioned the more contained advantages in non-coronary patients. In addition, the modest number of non-coronary events among post-ACS patients did not certainly empower the majority of included studies to draw any conclusion on the impact of ticagrelor in the prevention of stroke. However, a similar trend of benefit was observed in most of the studies included in our meta-analysis and was consistent with the results of similar meta-analysis in literature [41].

Finally, the significant interaction between the type of atherothrombotic, coronary or non-coronary, disease, certainly points at the importance of an adequate stratification of patients' risk profile. However, since we had no access to individual patients' data, we could not identify the proportion of patients with concomitant CAD and cerebral or peripheral vascular disease in all trials and neither we could provide data on the net clinical benefit derived from the balance between thrombotic and haemorragic complications.

4.2. Conclusions

Based on the current meta-analysis, a newer antiplatelet strategy based on ticagrelor is associated with a significant reduction in mortality and recurrent cardiovascular events as compared to a traditional treatment among patients treated for coronary disease but not among those with non-coronary atherothrombotic disease. However, ticagrelor therapy was associated with a significant increase in major bleeding complications.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.02.011.

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