EMA/459475/2019
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Brilique

International non-proprietary name: ticagrelor

Procedure No. EMEA/H/C/001241/II/0047/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure:	17 August 2019	17 August 2019	☐
☐	CHMP Co-Rapporteur Assessment Report	11 October 2019	18 October 2019	☐
☐	CHMP Rapporteur Assessment Report	11 October 2019	11 October 2019	☐
☐	PRAC Rapporteur Assessment Report	18 October 2019	11 October 2019	☐
☐	PRAC members comments	23 October 2019	23 October 2019	☐
☐	Updated PRAC Rapporteur Assessment Report	24 October 2019	N/A	☐
☐	PRAC endorsed relevant sections of the assessment report [3]	31 October 2019	31 October 2019	☐
☐	CHMP members comments	04 November 2019	04 November 2019	☐
☐	Request for supplementary information	14 November 2019	14 November 2019	☐
☐	MAH's responses	27 March 2020	25 March 2020	☐
☐	Re-start	30 March 2020	30 March 2020	☐
☐	CHMP Rapporteurs (Joint) Assessment Report	04 May 2020	06 May 2020	☐
☐	CHMP members comments	18 May 2020	18 May 2020	☐
☐	Updated CHMP Rapporteurs (Joint) Assessment Report	20 May 2020	20 May 2020	☐
☐	2nd Request for supplementary information	28 May 2020	28 May 2020	☐
☐	MAH's responses	11 Sep 2020	11 Sep 2020	☐
☐	Re-start	14 Sep 2020	14 Sep 2020	☐
☐	CHMP Rapporteurs (Joint) Assessment Report	19 Oct 2020	20 Oct 2020	☐
☐	CHMP members comments	03 Nov 2020	03 Nov 2020	☐
☐	Updated CHMP Rapporteurs (Joint) Assessment Report	05 Nov 2020	06 Nov 2020	☐
☐	3rd request for Supplementary information	12 Nov 2020	12 Nov 2020	☐

Status of this report and steps taken for the assessment				
☐	MAH's responses	22 Jan 2021	20 Jan 2021	☐
☐	Re-start	25 Jan 2021	25 Jan 2021	☐
☐	CHMP Rapporteurs (Joint) Assessment Report	01 March 2021	02 March 2021	☐
☒	Notification of withdrawal (C.I.6 only)	n/a	05 March 2021	
☐	CHMP members comments	15 March 2021	n/a	☐
☐	Updated CHMP Rapporteurs (Joint) Assessment Report	18 March 2021	19 March 2021	☐
☐	Opinion (C.I.4 only)	25 March 2021	25 March 2021	☐

Procedure resources	
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List of abbreviations

AE	adverse event
ACS	acute coronary syndrome
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
bd	twice daily
CABG	coronary artery bypass grafting
CI	confidence interval
CV	cardiovascular
DAE	premature permanent discontinuation of investigational product due to adverse event
DAPT	dual antiplatelet therapy
HR	hazard ratio
ICH	intracranial haemorrhage
IP	investigational product (ticagrelor and placebo)
KM	Kaplan-Meier
Max	maximum
MI	myocardial infarction
Min	minimum
N	number of patients in treatment group
n	number of patients included in analysis
NNH	number needed to harm
NNT	number needed to treat
P	placebo
PCI	percutaneous coronary intervention
R	randomisation
SAE	serious adverse event
TIA	transient ischaemic attack
ULN	Upper Limits of Normal

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 26 July 2019 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Extension of indication to include, in co-administration with acetylsalicylic acid (ASA), the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) without a history of myocardial infarction who have undergone percutaneous coronary intervention (PCI) based on the final results of study D513BC00001 (THEMIS), a phase III multinational, randomised, double-blind, placebo-controlled study to evaluate the effect of ticagrelor twice daily on the incidence of cardiovascular death, myocardial infarction or stroke in patients with CAD and T2DM; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated.

Update of section 4.8 of the SmPC regarding new safety information on traumatic haemorrhages based on the results of study D513BC00001 (THEMIS) and data from the ticagrelor clinical development programme and post-marketing data. The Package Leaflet is updated in accordance. The RMP version 12 has also been submitted.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0205/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0205/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Scientific discussion

2.1. Introduction

Medicinal product

Ticagrelor is an oral, direct-acting, selective, and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation.

Ticagrelor co-administered with acetylsalicylic acid/aspirin (ASA) is currently indicated for patients with coronary artery disease (CAD) manifested as acute coronary syndromes (ACS) or in patients with a history of myocardial infarction (MI). Ticagrelor 90 mg twice daily (bd) is currently approved in over 100 countries for the prevention of cardiovascular (CV) events (CV death, MI, or stroke) in patients with ACS. Approval was granted by the European Union (EU) in December 2010, and by the Food and Drug Administration (FDA) in the United States (US) in July 2011, based on the results of the Phase III PLATO study (D5130C05262). An expanded indication for ticagrelor (60 mg bd) in patients with a history of MI was approved in the US in September 2015, and the EU in February 2016, based on the results of the Phase III PEGASUS TIMI-54 study (D5132C00001), hereafter referred to as PEGASUS. Ticagrelor 60 mg bd for treatment of patients with a history of MI is currently approved in over 70 countries, and applications are under review in a number of other countries.

Problem statement

The clinical presentations of CAD range from ACS due to a coronary artery thrombosis to a more stable phase with or without transient symptoms of reversible coronary ischaemia (angina pectoris). The prevalence of stable CAD increases with age and in the US, for example, has been estimated to be in the range from 4% to 7% among people aged 45 to 64 years, and 12% to 13% in the age group 75 years and older. Patients with CAD are at increased risk for CV morbidity and mortality, with an estimated annual incidence of non-fatal MI, ranging between approximately 0.6% and 3.2%. When considering the broader term 'CV event' (including MI, stroke, unstable angina, heart failure, emergency revascularisation and CV death) the estimated annual incidence is as high as 22% in patients with angiographically confirmed CAD.

In addition to medical treatment of CAD, coronary revascularisation is a well-established treatment for relieving ischaemic symptoms and improving prognosis under specific clinical scenarios; however, even after a PCI or CABG, patients remain at high risk for CV events. Atherosclerosis is a progressive disease, and coronary revascularisation does not remove residual risks arising from non-target coronary laesions or laesions in other vascular beds. Importantly, patients with diabetes remain at particularly high risk for CV events after PCI and CABG compared with patients without diabetes. Analysis of the Swedish Coronary Angiography Angioplasty Registry found that among patients with their first PCI between 2006 and 2010, those with diabetes had substantially higher 3-year mortality rates (16% vs 9%) and acute MI rates (16% vs 11%) compared with those without diabetes.

In patients with CAD, concomitant diabetes increases the CV related risks. Globally, about one-third of patients with T2DM have CVD, and the most common type is CAD, with a prevalence of about 20%. Type 2 diabetes mellitus is commonly associated with macrovascular complications resulting in premature coronary heart disease and increased risk of cerebrovascular disease. Diabetes doubles the risk of death and MI in patients with CAD. A two-fold increase in rates of CV death, MI, or stroke is seen in patients with diabetes mellitus and known atherothrombosis compared to the group with diabetes and CV risk factors only. Most patients with diabetes die of CV diseases, predominantly ischaemic heart disease, thus justifying the need for intensified antiplatelet therapy. In THEMIS, the population is at high risk for CV events since the combination of CAD and T2DM is associated with a risk for thrombotic events similar to a history of MI and no diabetes.

Few population-based studies have evaluated T2DM patients without a previous MI or stroke but at high risk of CV events, ie, with characteristics similar to the selection criteria for THEMIS. As part of the AstraZeneca-sponsored ATHENA programme of epidemiology studies in several countries, the results from 260000 Swedish patients and 110175 patients in the US with T2DM with or without CAD showed that in both countries about two-thirds of patients with CAD did not have a history of MI. In the Swedish study, while the 3-year cumulative incidence of CV events was highest among those with CAD and a previous MI (18.8%), the risk in patients with CAD without a history of MI was still higher (13.1%) than the risk in diabetic patients without CAD (5.7%). This difference in risk was observed despite a high proportion of patients with CAD but no prior MI or stroke being treated with statins, antihypertensives and antiplatelets. In the US, there are two parts of the ATHENA programme, both showing high CV event rates in patients with CAD and T2DM. In a cohort of commercially insured subjects with mean age 67 years, the major adverse CV event (MACE) rate was 11.5% during a median 3-year follow-up period. In an older population (mean age 74 years) from the Diabetes Collaborative Registry, the MACE rate was 16.3% during a mean 1.2-year follow-up period.

Similar patterns as in the Swedish part of ATHENA were observed in the international REACH registry, including patients at high risk of atherothrombosis or with established atherothrombosis. The 4-year cumulative incidence of a major CV event (CV death, MI or stroke) was highest among patients with diabetes and a prior history of MI or stroke (approximately 23%). The corresponding risk among patients with diabetes and established atherothrombosis, but no prior MI was approximately 17%, while the risk was approximately 8% among those with diabetes but no established atherothrombotic disease.

Antiplatelet agents are recommended in patients with documented CAD whether or not T2DM is present and should be used unless contraindicated or not tolerated. Acetylsalicylic acid/aspirin is the current standard of care, with clopidogrel being an alternative if ASA is not tolerated. Use of DAPT in stable CAD has been documented for ticagrelor in patients with a history of MI, but otherwise, DAPT in stable CAD is currently reserved for situations such as in patients undergoing elective PCI. The benefit-risk of DAPT beyond the immediate period after revascularisation or in patients not yet having experienced an MI remains to be clarified.

The high residual CV risk in patients with T2DM and CAD described above combined with the limited efficacy of ASA or clopidogrel demonstrates a medical need for intensified antiplatelet therapy to prevent thrombotic events occurring in this group of patients.

The THEMIS study (D513BC00001) tested the hypothesis that ticagrelor on a background of low-dose ASA can reduce the risk for CV events in patients with CAD and type 2 diabetes mellitus (T2DM) at high risk for a thrombotic event but with no history of MI or stroke, compared to ASA alone. Coronary artery disease was defined by key inclusion criteria as a history of percutaneous coronary intervention [PCI], or history of coronary artery bypass grafting surgery [CABG]) or if no coronary revascularisation, having angiographic evidence of at least 50% lumen stenosis in at least one coronary artery. In THEMIS, patients were neither in an acute nor in a post-MI period of CAD and therefore were not considered to be covered by the currently approved ticagrelor indications. They were still at high risk for adverse CV events because of CAD, the important T2DM comorbidity (patients had received treatment with antidiabetic agents for at least 6 months) and being at least 50 years of age. The population studied is hereafter referred to as 'patients with CAD and T2DM'.

Patients with a history of haemorrhagic stroke have been excluded from all studies with ticagrelor, and those with a history of ischaemic stroke were excluded in studies with long-term dual antiplatelet treatment (DAPT), ie, THEMIS and PEGASUS.

Based on a thorough analysis of the available data, AstraZeneca concludes that ticagrelor has demonstrated significant efficacy and favourable benefit-risk balance in THEMIS PCI patients and now

seeks marketing approval for ticagrelor 60 mg bd in patients with CAD and T2DM who have undergone PCI. Patients with a history of PCI were considered to have a more favourable benefit-risk profile than patients with a history of CABG or those with no history of a coronary revascularisation. According to the applicant, patients with CAD who have undergone PCI are an easily identifiable patient population clinically and a logical group in whom to consider long-term treatment with DAPT. A clinically plausible explanation for the more favourable benefit-risk profile in patients with a history of PCI than in patients with no history of PCI is that most of the PCI patients would have been previously exposed to DAPT.

The additional indication proposed is: "*Brilique 60 mg is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with coronary artery disease (CAD) and Type 2 Diabetes Mellitus (T2DM) who have undergone percutaneous coronary intervention*."

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The MAH has notified that there was GCP non-compliance with unreported serious adverse events at THEMIS site 7605.

During the AstraZeneca visit at site 7605, it was found that a total of 52 serious adverse events (SAEs) had not been reported during the conduct of the study. These SAEs have now been reported to AstraZeneca and included in the safety database. The SAEs have been reported to local authorities and ethics committees according to local regulations. The Principal Investigator has confirmed that from the list of previously unreported SAEs, there are no study endpoints.

A root cause analysis of this quality issue showed that both the Principal Investigator and the local monitor had an insufficient awareness and understanding of SAE definitions. Also, the monitor failed to review relevant source documents since the site did not provide the complete electronic medical records for patients, and the unreported SAEs were not evident in the source data that was reviewed by the monitor. After the root cause analysis, preventive actions of additional training in SAE handling and requirements were provided to AstraZeneca monitors in Turkey, and a 'Source Data Agreement' was put in place in ongoing studies and will be included in future studies to secure access for monitors to all source data. Apart from THEMIS, the Investigator was not involved in any other AstraZeneca study between 2014 and today.

See further efficacy section (ancillary analyses) and safety (serious events).

2.3.2. Pharmacokinetics

N/A

2.3.3. Pharmacodynamics

Appropriate clinical pharmacology study packages were provided as part of the initial submission for registration of the ticagrelor 90 mg bd for the ACS indication, and the subsequent submission for registration of the ticagrelor 60 mg tablets for the post-MI indication. There are no new clinical pharmacology data relevant to the current application. AstraZeneca considers that the previously provided clinical pharmacology data also support the current application.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

N/A

2.4.2. Main study

Table 1 Description of the THEMIS study - Study D513BC00001

Study ID	Number of centres Locations	Study start / completion Total enrolled/ randomised	Design and duration	Study and control drugs	Patients by treatment (randomised / completed)	Sex Median age (range)	Diagnosis	Primary endpoint
D513BC00001 (THEMIS)	1315 Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Japan, Mexico, The Netherlands, Norway, Peru, Philippines, Poland, South Korea, Romania, Russia, Saudi Arabia, Slovakia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom (UK), Ukraine, United States (US) and Vietnam	10 February 2014 / 25 January 2019 20108 / 19220	Randomised, double-blind, placebo-controlled, parallel-group Event driven	Ticagrelor 90/60 mg, 1 tablet bd given orally Ticagrelor 90/60 mg placebo, 1 tablet bd given orally	Ticagrelor: 9619/6258 Placebo: 9601/7106	31.4% F 68.6% M 66 years (46 to 95 years)	Patients aged ≥50 years with CAD, diagnosed with T2DM and treated with antidiabetic medications for at least 6 months, without a history of MI or stroke	Time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke (ischaemic, haemorrhagic or unknown aetiology)

A Multinational, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Ticagrelor Twice Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Stroke in Patients with Type 2 Diabetes Mellitus [THEMIS - Effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study]

Methods

Study participants

The study inclusion and exclusion criteria were selected to ensure enrolment of a population of patients who were at high risk of a thrombotic event and would thus be more likely to benefit from intensified platelet inhibition therapy.

The patient population was defined by a history of a PCI, or having undergone CABG surgery, or angiographic evidence of at least 50% lumen stenosis of at least 1 coronary artery, having a diagnosis of T2DM treated with anti-diabetic medications for at least 6 months, and being at least 50 years old. Participants had no medical history of MI or stroke. All patients were treated with low-dose ASA (75 to 150 mg once daily [od]), unless contraindicated or not tolerated.

THEMIS participants were patients with CAD as defined by either a history of PCI or a history of CABG surgery, or angiographic evidence of at least 50% lumen stenosis of at least 1 coronary artery. This definition of CAD ensured all participants had angiographically verified CAD.

In addition to CAD being a CV risk factor in itself, the requirements to have a T2DM diagnosis and to be at least 50 years of age increase the risk for a CV event further in this population, i.e., a prognostic risk enrichment was applied.

History of stroke and history of MI were exclusion criteria in THEMIS in order to study the prevention of the first occurrence of CV endpoints in a high-risk population without prior CV events. The PARTHENON programme (Held et al. 2016, Dobesh and Patel 2017, Johnston et al. 2019) evaluates ticagrelor in patient populations with different manifestations of atherosclerotic CVD. Ticagrelor has already been documented in patients with ACS in the PLATO study and in patients with a history of MI in the PEGASUS study. THEMIS investigated ticagrelor in patients not covered by the PLATO or PEGASUS studies, ie, patients with known CAD but with no history of MI. Decisions on the patient population in the PEGASUS study, which was ongoing at the time of starting THEMIS, contributed to the exclusion of patients with a prior ischaemic stroke in the THEMIS study. Patients with a history of stroke were excluded from PEGASUS because reports from studies of another class of antiplatelet drugs suggested a potential increased risk of ICH in such patients during more intensive antiplatelet therapy (Morrow et al. 2012, Tricoci et al. 2012).

Although patients with a history of MI or stroke were not eligible, patients with a history of a transient ischaemic attack or definite secondary MI (due to e.g. revascularisation procedure or hypertensive emergency) could be considered for participation. Since the THEMIS study included a comparison versus placebo, there was an exclusion criterion specifying that patients for whom the use of ADP receptor antagonists (such as clopidogrel, ticagrelor or prasugrel) was planned could not be enrolled. Other clinical, non-administrative exclusion criteria representing potential contraindications to DAPT were also applied, such as the exclusion of patients with a need for chronic anticoagulant therapy, or patients with a history of ICH, major surgery within last 30 days, or patients with known bleeding diathesis or coagulation disorder.

Inclusion criteria

For inclusion in the study patients had to fulfil all of the following criteria;

1 Provision of informed consent prior to any study-specific procedures

2 Men or women ≥50 years of age

3 Diagnosed with T2DM defined by ongoing glucose lowering drug treatment prescribed by a physician for treatment of T2DM since at least 6 months prior to Visit 1

4 At high risk of CV events, defined as a history of percutaneous coronary intervention or coronary artery bypass graft or angiographic evidence of ≥50% lumen stenosis of at least 1 coronary artery.

Relevant exclusion criteria

Patients were not allowed to enter the study if any of the following exclusion criteria were fulfilled:

1 Previous MI (with the exception of definite secondary MI [e.g., due to coronary revascularisation procedure, profound hypotension, hypertensive emergency, tachycardia, or profound anaemia]) - Previous MI herein refers to a documented hospitalisation with a final diagnosis of spontaneous MI

2 Previous stroke (transient ischaemic attack [TIA] is not included in the stroke definition)

3 Planned use of ADP receptor antagonists (eg, clopidogrel, ticlopidine, prasugrel), dipyridamole, or cilostazol. Planned use of ASA treatment at doses >150 mg od

4 Planned coronary, cerebrovascular, or peripheral arterial revascularization.

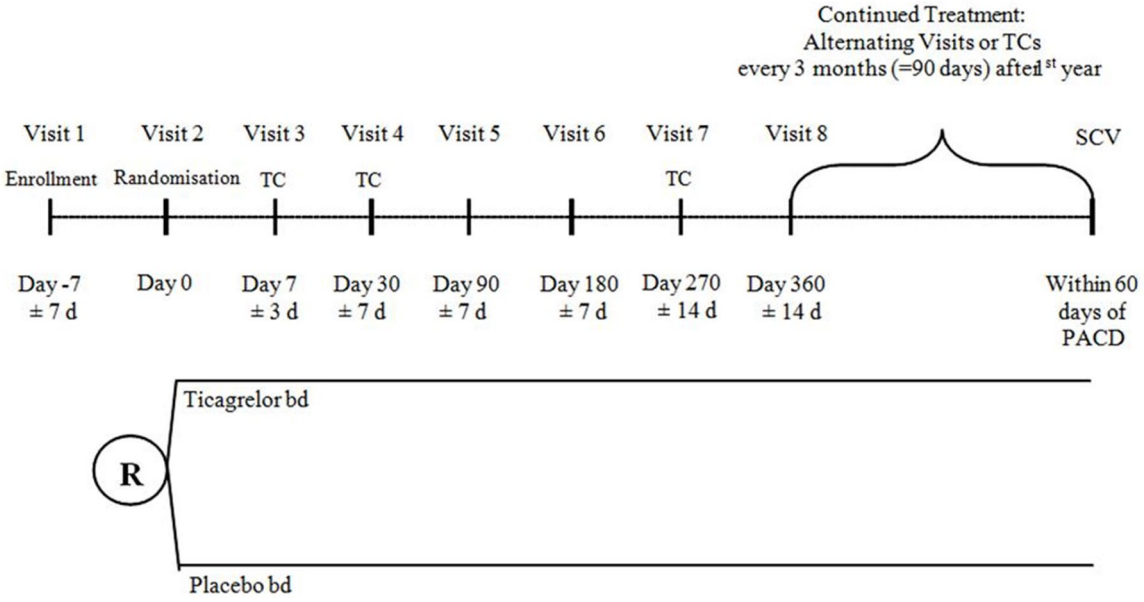
5 increased risk for bleeding or trauma (known bleeding diathesis or coagulation disorder, history of previous intracerebral bleed, recent GI bleed, or recent major surgery).

Treatments

General study design

The general design is outlined in the figure below.

Figure 1 THEMIS study design



bd twice daily; d day; PACD Primary analysis censoring date (eg, date when the predetermined number of adjudicated primary events were anticipated); R Randomisation; SCV Study closure visit; TC Telephone contact.

Study treatment and study dose

The dose of ticagrelor selected for THEMIS when the study started was 90 mg bd. Approximately a year after the initiation of THEMIS, the PEGASUS study showed a better benefit-risk profile of the 60 mg dose than the 90 mg dose, both in diabetes and non-diabetic patients. Therefore, the dose of ticagrelor in the ongoing THEMIS trial was changed to 60 mg bd.

Objectives

Primary objective: To compare the effect of long-term treatment with ticagrelor bd vs. placebo for the prevention of major CV events (composite of CV death, MI or stroke) in patients with T2DM at high risk of CV events, but without a medical history of previous MI or stroke.

Secondary objectives: To compare the effect of long-term treatment with ticagrelor vs. placebo for: 1) prevention of CV death, 2) prevention of MI, 3) prevention of ischaemic stroke, 4) prevention of all-cause death.

Other objectives were to explore other long-term treatment effects of ticagrelor versus placebo on:

- Prevention of the composite of all-cause death, MI or stroke. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause death, MI or stroke
- Prevention of stroke. The efficacy variable is time from randomisation to first occurrence of stroke
- Effect on irreversible harm events, the composite of all-cause mortality, MI, stroke, intracranial haemorrhage (ICH) and fatal bleeding. The efficacy variable is time from randomisation to first occurrence of any event from the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding
- Health care resource utilisation and utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire to support health technology assessment and health economic modelling.

Outcomes/endpoints

The **primary efficacy variable** was time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke (ischaemic, haemorrhagic or unknown aetiology).

Secondary endpoints included time from randomisation to first occurrence of 1) prevention of CV death, 2) prevention of MI, 3) prevention of ischaemic stroke, 4) prevention of all-cause death.

The composite primary endpoint and 4 secondary endpoints were part of the hierarchical confirmatory statistical testing under type I error control in the order mentioned.

Sample size

The event rate for the composite of CV death, MI or stroke was estimated to be 2.5% annually in a population consisting of patients with T2DM at high risk of CV events, but without a history of MI or stroke. Assuming a true hazard ratio of 0.84 between ticagrelor and placebo, 1385 primary endpoint events were to provide a power of 90%. It was estimated that with an annual event rate of 2.5% in the placebo group, 19000 patients randomised in a 1:1 ratio, with an average follow-up period of 40 months, would provide the required number of events. The expected maximum follow-up period was 58 months, and the enrolment period of 28 months. The final primary treatment comparison was made at a significance level of 4.96%, estimated using a Haybittle-Peto procedure (Haybittle 1971, Peto et al. 1976) to control the family-wise error rate at 5.00%, when adjusting for one planned efficacy interim analysis.

Randomisation

Randomisation and treatment pack assignment were managed via interactive voice/web response system (IVRS/IWRS) and the first dose of study drug was to be taken as soon as possible after

randomisation. Subsequent maintenance doses were to be taken in the morning and in the evening, at approximately 12-hour intervals, during the treatment period.

As a result of data from the PEGASUS study in Q1 2015, the ticagrelor dose was reduced from 90 mg bd to 60 mg bd in CSP amendment 1 in May 2015. When ticagrelor 60 mg and matching placebo tablets became available, patients already randomised to ticagrelor 90 mg bd or matching placebo were transferred to ticagrelor 60 mg or matching placebo tablets in accordance with their previous randomisation to either ticagrelor or placebo at the next planned visit or at an extra visit (any TC visit was rescheduled to an on-site visit).

Blinding (masking)

The active and placebo tablets were equal in appearance.

AstraZeneca Research and Development generated the randomisation codes using. AstraZeneca Global Randomisation (GRand) computerised system and loaded them into the IVRS/IWRS database. Randomisation codes were generated in blocks to ensure approximate balance (1:1) between the two treatment arms. The IVRS/IWRS allocated randomisation codes sequentially within each centre as patients became eligible for randomisation.

Statistical methods

Statistical analyses of the efficacy data were pre-specified in the CSP and detailed in the Statistical Analysis Plan (SAP). The original SAP was finalised on 13 January 2014, before the start of patient recruitment. The SAP was amended on 27 March 2017.

All randomised patients were included in the full analysis set (FAS) according to the intention-to-treat principle, ie, irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomised study drug (ie, ticagrelor or placebo) irrespective of whether the event occurred before, during treatment with, or following discontinuation of study drug. Patients who withdrew consent to participate in the study were included up to the date of their study termination except for vital status known through public records (for use in the analysis of all-cause mortality). All efficacy variables were analysed using the FAS (see THEMIS CSR Section 5.7.2.1).

The primary endpoint, time to first occurrence of any event from the composite of CV death, MI, and stroke, was analysed using the Cox proportional hazards model with a factor for treatment group. Event-free patients were censored as described in the CSR (see THEMIS CSR Section 5.7.1.2).

Kaplan-Meier (KM) estimates of the cumulative proportion of patients with events were calculated and plotted. The p-value, HR and 95% CI are also reported. Model checking and sensitivity analyses were performed as detailed in the SAP. Exploratory analyses to evaluate the consistency of the observed effects in relevant, predefined patient subgroups were performed as described in the SAP.

To explore the consistency between the treatment effect of ticagrelor 60 mg bd and the overall treatment effect of ticagrelor, a sensitivity analysis of the primary efficacy variable with a Cox proportional hazards model with time-dependent covariates was performed. This model included a factor for treatment group and a time-dependent indicator of the dose of study drug for patients treated with ticagrelor as covariates. Additional sensitivity analyses for the primary endpoint assessed the treatment effect in patients randomised to ticagrelor 60 mg bd compared to those randomised to matching placebo, on-treatment in patients randomised to ticagrelor 60 mg bd or matching placebo, and on-treatment in patients randomised to ticagrelor 90 mg bd or matching placebo, respectively. These analyses used a Cox proportional hazards model with treatment as the only covariate.

The analysis method used for the composite primary variable was also used for the secondary efficacy variables. The primary and secondary endpoints were included in a confirmatory testing procedure with hierarchical testing. Hypothesis testing continued at the 2-sided 4.96% significance level until the first statistically non-significant treatment difference ($p \geq 0.0496$) was observed. Secondary endpoints were tested in an exploratory manner if there had been at least one non-significant test earlier in the sequence. For further details, see THEMIS CSR Section 5.7.1.4.

The same statistical methods were used for the additional analyses as for the prespecified analyses described in Section 5.7 of the CSR and associated SAP (see THEMIS CSR Appendix 12.1.9).

The primary and secondary efficacy variables were included in a confirmatory testing procedure described in Section 5.7.1.4. No further multiplicity adjustment was made to confidence intervals or p-values. Analyses of efficacy or safety variables that were not part of the confirmatory analyses are considered exploratory, and any p-values and CIs that have been quoted are used as measures of precision only. Because the dose of ticagrelor used in the study was changed from 90 mg bd to 60 mg bd while the study was ongoing (Section 5.1), an analysis to explore consistency between the treatment effect of ticagrelor 60 mg and the overall treatment effect of ticagrelor was included (Section 5.7.1.4).

Following the initial analyses of unblinded study data in accordance with the CSP and SAP, additional data-driven analyses were conducted to assist in the interpretation of the results of the THEMIS study. All tables and figures generated from these additional analyses are presented separately, in a CSR Addendum. The Addendum contains analyses such as in the prespecified subgroup of patients with a history of PCI, and also data in the full study population on duration of hospitalisations in relation to efficacy and safety endpoints.

Interim analysis

An interim analysis was planned following the accrual and confirmation by the adjudication of 517 primary events. The stopping boundary at the interim analysis was a two-sided p-value <0.001 for both primary endpoint event and for CV death (the 1st secondary efficacy variable). The interim p-value is small enough for the final analysis to be conducted at a significance level of 4.96%, with the family-wise error rate controlled at 5.00%. These boundaries were estimated using a Haybittle-Peto procedure.

The interim analysis was performed on 29 March 2017 by the DMC after observing adjudication of 555 primary events. Following the interim analysis, the DMC recommended that the study should continue as planned.

Results

Participant flow

Of the 19220 patients who were randomised and included in the analyses, 6258 (65.5%) in the ticagrelor group and 7106 (74.5%) in the placebo group completed treatment (ie, did not prematurely permanently discontinue treatment, including those patients who died prior to study closure visit). Few patients withdrew consent or were lost to follow-up, and there was complete follow-up of all first primary endpoint events in 96.4% of patients in the ticagrelor group and 97.3% of patients in the placebo group. The rate of discontinuation of study drug was higher in the ticagrelor treatment group compared with placebo throughout the study. The most common reasons for premature permanent discontinuation of study drug were adverse event (13.6% of patients who received treatment) and withdrawal by subject (13.3%). A low number of patients had unknown vital status at the end of study (n= 21, 0.1%).

Table 2 Patient disposition (all patients)

Table 6 Patient disposition (all patients)			
	Number (%) of patients		
	Ticagrelor	Placebo	Total
Patients enrolled[a]			20108
Patients who were not randomised[b]			837 (4.2%)
Patient did not meet inclusion/exclusion criteria			454 (2.3%)
Patient decision (withdrawal of consent)			256 (1.3%)
Patients who died			1 (0.0%)
Other			131 (0.7%)
Patients randomised at site prematurely closed by sponsor[c]	26	25	51
Patients randomised[c]	9619 (100.0%)	9601 (100.0%)	19220 (100.0%)
Patients randomised to ticagrelor 90 mg or matching placebo	7127 (74.1%)	7069 (73.6%)	14196 (73.9%)
Patients randomised to ticagrelor 60 mg or matching placebo	2492 (25.9%)	2532 (26.4%)	5024 (26.1%)
Patients who did not receive treatment	58 (0.6%)	69 (0.7%)	127 (0.7%)
Withdrawal by subject	35 (0.4%)	40 (0.4%)	75 (0.4%)
Adverse event	3 (0.0%)	1 (0.0%)	4 (0.0%)
Protocol violation	7 (0.1%)	7 (0.1%)	14 (0.1%)
Other	11 (0.1%)	13 (0.1%)	24 (0.1%)
Patients who received treatment	9561 (99.4%)	9532 (99.3%)	19093 (99.3%)
Patients who completed treatment[d,e]	6258 (65.5%)	7106 (74.5%)	13364 (70.0%)
Patients who prematurely permanently discontinued treatment[d]	3303 (34.5%)	2426 (25.5%)	5729 (30.0%)
Withdrawal by subject	1425 (14.9%)	1122 (11.8%)	2547 (13.3%)
Adverse event	1618 (16.9%)	986 (10.3%)	2604 (13.6%)
Protocol violation	30 (0.3%)	44 (0.5%)	74 (0.4%)
Other	227 (2.4%)	269 (2.8%)	496 (2.6%)
Not specified	3 (0.0%)	5 (0.1%)	8 (0.0%)
Patients who withdrew consent at any time during study	117 (1.2%)	94 (1.0%)	211 (1.1%)
Dead[f]	13 (0.1%)	12 (0.1%)	25 (0.1%)
Alive[g]	97 (1.0%)	78 (0.8%)	175 (0.9%)

Table 6 Patient disposition (all patients)			
	Number (%) of patients		
	Ticagrelor	Placebo	Total
Vital status unknown	7 (0.1%)	4 (0.0%)	11 (0.1%)
Patients who did not withdraw consent	9502 (98.8%)	9507 (99.0%)	19009 (98.9%)
Dead[f]	576 (6.0%)	590 (6.1%)	1166 (6.1%)
Alive[g]	8920 (92.7%)	8913 (92.8%)	17833 (92.8%)
Vital status unknown	6 (0.1%)	4 (0.0%)	10 (0.1%)
Total vital status unknown	13 (0.1%)	8 (0.1%)	21 (0.1%)

Source: Table 11.1.1.1

[a] Informed consent received. Patients that were enrolled but not randomised within 14 days could be re-enrolled in the trial. Re-enrolled patients are included more than once.

[b] A patient can have more than one reason for not being randomised.

[c] Patients randomised at site prematurely closed by AstraZeneca due to potential GCP breach in another AstraZeneca-sponsored study are excluded from all statistical analyses, and are not included in the row 'Patients randomised'.

[d] Percentages are calculated from number of patients who received treatment. All other percentages are calculated with the number of randomised patients as denominator.

[e] Includes all patients who did not prematurely permanently discontinue treatment, including those who died prior to study closure visit.

[f] Patients who were dead at end of study.

[g] Patients who were known to be alive at primary analysis censoring date and not known to have died prior to study closure visit.

In patients with a history of PCI a similar pattern with a higher rate of study drug discontinuation on ticagrelor was seen as in the full population.

Recruitment

The THEMIS study was conducted at 1315 sites across 42 countries and provided results that are representative of the worldwide target population. Several countries in South America, North America, Australia, Europe, Eastern Europe, Russia, Japan, and Asia have recruited patients. In total, 20108 patients were enrolled in THEMIS, and 19220 patients were randomised and included in the analyses. There were 51 patients randomised at a site prematurely closed by the sponsor who were excluded from the analyses.

The first patient enrolled on 10 February 2014, and the last visit of the last patient (the end of study, as defined by the CSP) took place on 25 January 2019. PACD, i.e., the primary analysis censoring date for efficacy analyses (including events occurring on or prior to that date) was 29 October 2018. The THEMIS study randomised 95.6% of enrolled patients. Of the 837 patients who were enrolled but not randomised the primary reasons for not randomising patients were 'patient did not meet inclusion/exclusion criteria' (454 patients) and 'patient decision (withdrawal of consent)' (256 patients).

One site was closed by AstraZeneca due to a suspected GCP breach (unexplained findings of anomalous PK data) in another AstraZeneca-sponsored study not involving ticagrelor. A decision was made by AstraZeneca and the THEMIS Executive Committee before unblinding of the study data to exclude the 51 patients randomised at this site from all study report analyses.

Conduct of the study

Time until primary analysis censoring date

Median patient time in the study until PACD in THEMIS was 39.9 months (39.8 months for ticagrelor patients and 39.9 months for placebo patients), with a maximum follow-up time of 57 months. Most patients had a follow-up of at least 36 months.

Table 3: Time (months) in study until primary analysis censoring data (full analysis set).

Table 7 Time (months) in study until primary analysis censoring date (full analysis set)			
Statistic or category	Ticagrelor (N=9619)	Placebo (N=9601)	Total (N=19220)
n	9619	9601	19220
Mean	39.5	39.5	39.5
SD	9.05	8.90	8.97
Minimum	0	0	0
Median	39.8	39.9	39.9
Maximum	57	57	57
< 12 months	185 (1.9%)	159 (1.7%)	344 (1.8%)
12 to < 24 months	182 (1.9%)	188 (2.0%)	370 (1.9%)
24 to < 36 months	2934 (30.5%)	2958 (30.8%)	5892 (30.7%)
36 to < 48 months	4499 (46.8%)	4484 (46.7%)	8983 (46.7%)
≥ 48 months	1819 (18.9%)	1812 (18.9%)	3631 (18.9%)

Protocol deviations

Overall, 2480 (12.9%) patients had at least 1 important protocol deviation: 1247 (13.0%) patients in the ticagrelor group and 1233 (12.8%) patients in the placebo group. The treatment groups were similar with respect to the type of important protocol deviations. There were no concerns regarding protocol deviations in terms of study conduct or the safety of patients.

Treatment compliance

Compliance with randomised study drug was high; greater than 80% tablet compliance was seen in 78.0% of the patients. Median tablet compliance was 94.8% and similar between the treatment groups.

Protocol amendments

The most important amendments were the following:

- Amendment 1; 11 May 2015
  - Ticagrelor dose changed from 90 mg bd to 60 mg bd
  - Changes in secondary objectives from 1 Prevention of the composite of all-cause death, MI or stroke; 2 Prevention of CV death.; 3 Prevention of all-cause death. - To: The secondary objectives of the study (presented in hierarchical order) 1 Prevention of CV death. The efficacy variable is time from randomisation to death of CV cause 2 Prevention of MI. ; 3 Prevention of ischaemic stroke 4 Prevention of all-cause death.
- Amendment 2; 23 September 2015
  - An increase in the number of patients to be enrolled in the study, and a change in the anticipated length of the study.
- Amendment 3; 7 February 2017
  - A change in the anticipated length of the study to increase the number of primary endpoint events collected from 1034 to 1385 by prolonging study duration with approximately 10 months.

Baseline data

The demographic and baseline characteristics of the patients in the overall study population, including characteristics of both CAD and T2DM were generally balanced between the 2 randomised treatment groups. The population was predominantly White (71.3%), the median age was 66 years, and most

patients (68.6%) were male. A majority of patients (79.8%) had a history of coronary artery revascularization, 58.0% of patients had a history of PCI, and 28.8% had undergone a CABG. Patients had been diagnosed with diabetes a median of 10 years before study entry.

Regarding the exclusion criteria for randomisation, few patients had a history of MI (72 (0.7%) vs 81 (0.8%)) or ischemic stroke (13 (0.1%) vs 19 (0.2%)). Note that this number does not differentiate between diagnosis of spontaneous MI or secondary MI, and only the former was an exclusion criterion. There was also a low number of patients with a history of ischaemic stroke (32 patients [0.2%]), and there were no notable differences between the 2 treatment groups in numbers of patients reporting a history of either MI or ischaemic stroke. No patient entered the study with a history of haemorrhagic stroke. Additionally, the study population included a large percentage of patients with hypertension (92.5%) and dyslipidaemia (87.2%), and 99.9% of patients had CAD, including 62.1% with multivessel CAD and 37.6% with single-vessel CAD. A total of 2094 (10.9%) patients were recorded as current smokers.

Table 4 Demographic characteristics (full analysis set)

		Number (%) of patients		
Demographic characteristic		**Ticagrelor (N=9619)**	**Placebo (N=9601)**	**Total (N=19220)**
Age (years)	n	9619	9601	19220
	Mean	66.3	66.3	66.3
	SD	7.77	7.75	7.76
	Minimum	46	50	46
	Median	66.0	66.0	66.0
	Maximum	92	95	95
Sex n (%)	Male	6576 (68.4%)	6613 (68.9%)	13189 (68.6%)
	Female	3043 (31.6%)	2988 (31.1%)	6031 (31.4%)
	Total	9619 (100.0%)	9601 (100.0%)	19220 (100.0%)
Race n (%)	White	6838 (71.1%)	6858 (71.4%)	13696 (71.3%)
	Black or african american	205 (2.1%)	198 (2.1%)	403 (2.1%)
	Asian	2211 (23.0%)	2195 (22.9%)	4406 (22.9%)
	Native hawaiian or other pacific islander	7 (0.1%)	7 (0.1%)	14 (0.1%)
	American indian or alaska native	161 (1.7%)	152 (1.6%)	313 (1.6%)
	Other	197 (2.0%)	191 (2.0%)	388 (2.0%)
	Total	9619 (100.0%)	9601 (100.0%)	19220 (100.0%)
Ethnic group n (%)	Hispanic or latino	1408 (14.6%)	1368 (14.2%)	2776 (14.4%)
	Not hispanic or latino	8211 (85.4%)	8233 (85.8%)	16444 (85.6%)
	Total	9619 (100.0%)	9601 (100.0%)	19220 (100.0%)

		Ticagrelor (N=9619)	Placebo (N=9601)	Total (N=19220)
Patient characteristic				
Height (cm)	n	9611	9594	19205
	Mean	167.6	167.6	167.6
	SD	9.55	9.62	9.58
	5th percentile	152.0	151.0	151.0
	Median	168.0	168.0	168.0
	95th percentile	182.9	182.9	182.9
Weight (kg)	n	9610	9592	19202
	Mean	83.8	83.8	83.8
	SD	17.95	17.82	17.88
	5th percentile	58.0	58.0	58.0
	Median	82.0	82.0	82.0
	95th percentile	115.0	116.0	115.2
Body mass index (kg/m^2)	n	9610	9592	19202
	Mean	29.7	29.7	29.7
	SD	5.34	5.25	5.30
	5th percentile	22.4	22.3	22.4
	Median	29.0	29.1	29.0
	95th percentile	39.0	39.2	39.1

Table 5 Medical history (full analysis set)

	Number (%) of patients		
Medical history	Ticagrelor (N=9619)	Placebo (N=9601)	Total (N=19220)
Coronary artery disease	9600 (99.8%)	9592 (99.9%)	19192 (99.9%)
Single vessel CAD	3637 (37.8%)	3595 (37.4%)	7232 (37.6%)
Multi vessel CAD	5951 (61.9%)	5984 (62.3%)	11935 (62.1%)
PCI	5558 (57.8%)	5596 (58.3%)	11154 (58.0%)
CABG	2796 (29.1%)	2741 (28.5%)	5537 (28.8%)
Coronary arterial revascularisation[a]	7678 (79.8%)	7667 (79.9%)	15345 (79.8%)
Angina pectoris	5444 (56.6%)	5357 (55.8%)	10801 (56.2%)
Congestive heart failure	1543 (16.0%)	1600 (16.7%)	3143 (16.4%)
Peripheral arterial occlusive disease	827 (8.6%)	860 (9.0%)	1687 (8.8%)
Medical history	Ticagrelor (N=9619)	Placebo (N=9601)	Total (N=19220)
Hypertension	8909 (92.6%)	8867 (92.4%)	17776 (92.5%)
Dyslipidaemia	8386 (87.2%)	8367 (87.1%)	16753 (87.2%)
Family history of cardiovascular disease	2856 (29.7%)	2857 (29.8%)	5713 (29.7%)
Chronic obstructive pulmonary disease	570 (5.9%)	597 (6.2%)	1167 (6.1%)
Chronic kidney disease	853 (8.9%)	901 (9.4%)	1754 (9.1%)

Table 6 Diabetes relevant medical history (full analysis set)

	Number (%) of patients		
Medical history	Ticagrelor (N=9619)	Placebo (N=9601)	Total (N=19220)
Duration of diabetes (years)			
n	9613	9597	19210
Mean	11.8	11.7	11.7
SD	8.65	8.56	8.60
Median	10.0	10.0	10.0
Any diabetes complications at baseline	2480 (25.8%)	2430 (25.3%)	4910 (25.5%)
Retinopathy	1023 (10.6%)	976 (10.2%)	1999 (10.4%)
Neuropathy autonomic	223 (2.3%)	202 (2.1%)	425 (2.2%)
Neuropathy peripheral	1425 (14.8%)	1416 (14.7%)	2841 (14.8%)
Nephropathy	828 (8.6%)	847 (8.8%)	1675 (8.7%)

Concomitant medication

Nearly all patients (99.4%) reported using ASA at baseline. Mean dose at baseline was 92.9 mg (median dose of 100 mg). The use of ASA was similar between treatment groups. Almost all (99.7%) patients were receiving antidiabetic medication, and the types of medication were balanced between

the groups. The most common classes of antidiabetic medications were biguanides (68.3%), sulfonylureas (32.8%), insulins (28.7%) and dipeptidyl peptidase 4 (DPP-4) inhibitors (12.9%). There were low proportions of patients reporting use of GLP1 receptor agonists (2.1%) and SGLT2 inhibitors (1.8%). Use of agents acting on the renin-angiotensin system (angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], renin inhibitors), was reported by 78.7% of patients, and use of statins by 87.7% of patients, with similar proportions in the ticagrelor and placebo groups. Use of beta-blocking agents was reported in 73.8% of patients.

Demographic data in patients with a history of PCI were similar to the full population and balanced between ticagrelor and placebo. Medical history, including diabetes history, reported in patients with a history of PCI was comparable to the full population. In patients with a history of PCI, the use of concomitant medication at randomisation was similar between the 2 randomised treatment groups and comparable to the medication use described above for the full population.

Numbers analysed

The number of patients excluded from the safety analysis set was small (84 patients in the ticagrelor group and 94 patients in the placebo group). Both the FAS and the safety analysis set were well balanced between the two treatment groups.

Table 7 Analysis sets

	Ticagrelor	Placebo	Total
Patients included in full analysis set[a]	9619	9601	19220
Patients included in full analysis set and randomised to ticagrelor 60 mg or corresponding placebo	2492	2532	5024
Patients excluded from full analysis set	26	25	51
Site terminated by sponsor	26	25	51
Patients included in safety analysis set[b]	9562	9531	19093
Patients included in safety analysis set and randomised to ticagrelor 60 mg or corresponding placebo	2482	2516	4998
Patients excluded from safety analysis set	84	94	178
Patient took no study drug	58	69	127
Site terminated by sponsor	26	25	51

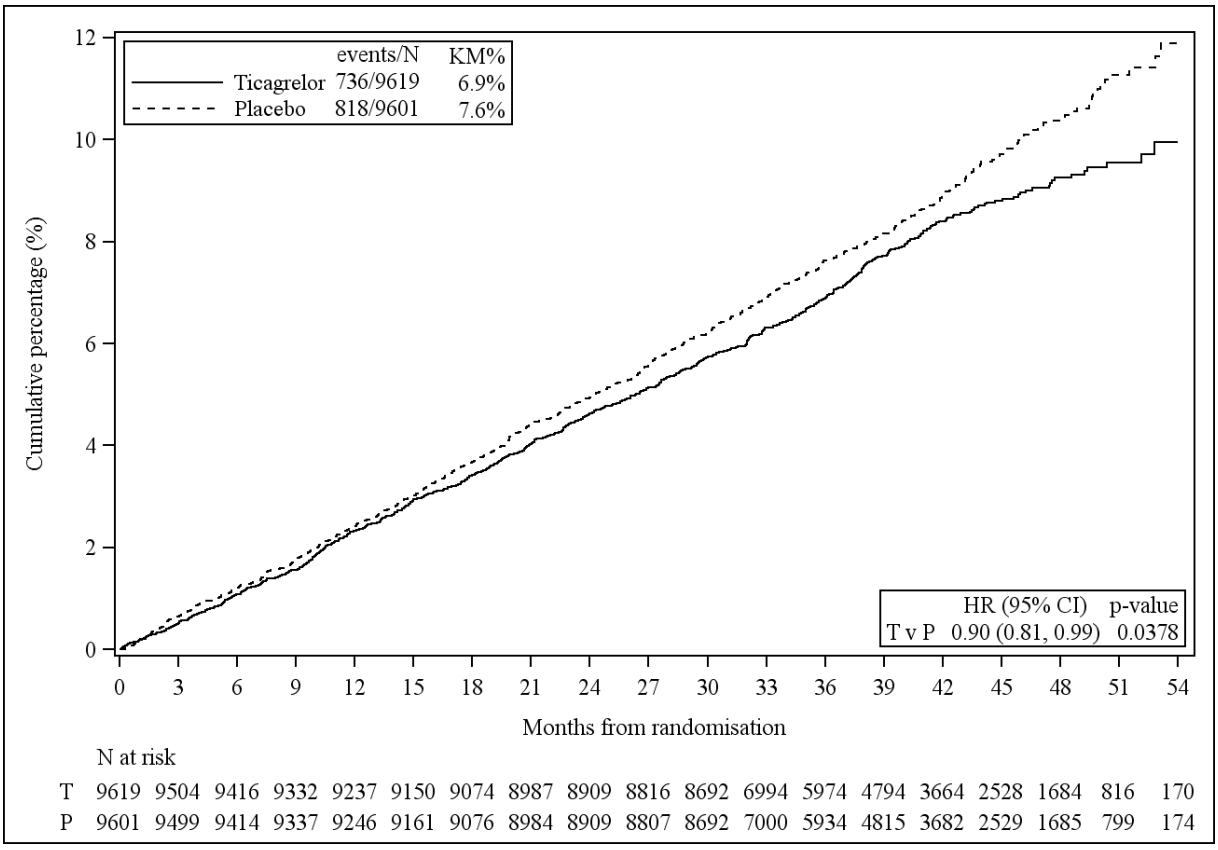
Outcomes and estimation

The primary efficacy objective was met, showing a significant reduction (10% RRR; HR 0.90 [95% CI 0.81, 0.99], p=0.0378) in the rate of primary efficacy endpoint events (CV death, MI, and stroke) for ticagrelor compared with placebo in patients with CAD and T2DM, appeared to be driven by the individual components MI (RRR 16%) and stroke (RRR 18%).

Table 8 Analysis of primary efficacy variable (composite of CV death/MI/stroke) and its components (full analysis set) - Study D513BC00001

	Ticagrelor (N=9619)		Placebo (N=9601)			
Characteristic	**Patients with events (%)**	**KM% at 36 months**	**Patients with events (%)**	**KM% at 36 months**	**Hazard ratio (95% CI)**	**p-value**
Composite of CV death/MI/stroke	736 (7.7%)	6.9%	818 (8.5%)	7.6%	0.90 (0.81, 0.99)	0.0378
CV death	364 (3.8%)	3.3%	357 (3.7%)	3.0%	1.02 (0.88, 1.18)	0.7883
MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71, 0.98)	0.0294
Stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67, 0.99)	0.0435

Figure 2 Kaplan-Meier plot of primary clinical endpoint (composite of CV death/MI/stroke) (full analysis set) - Study D513BC00001



Secondary endpoints

The table below presents the confirmatory hierarchical analyses of the primary and secondary endpoints in the overall study population.

For patients treated with ticagrelor no difference versus placebo for CV death was observed (HR 1.02 [95% CI 0.88, 1.18], p-value 0.7883), and the hierarchical statistical testing to control Type I error stopped. For all endpoints that followed, point estimates, CIs, and nominal p-values are provided to support the clinical interpretation.

Table 9 Confirmatory analysis of clinical endpoint hierarchy (full analysis set) - Study D513BC00001

	Ticagrelor (N=9619)		Placebo (N=9601)				
Characteristic	**Patients with events (%)**	**KM% at 36 months**	**Patients with events (%)**	**KM% at 36 months**	**Hazard Ratio (95% CI)**	**p-value**	**Statistically significant[a]**
Composite of CV death/MI/stroke	736 (7.7%)	6.9%	818 (8.5%)	7.6%	0.90 (0.81, 0.99)	0.0378	Yes
CV death	364 (3.8%)	3.3%	357 (3.7%)	3.0%	1.02 (0.88, 1.18)	0.7883	No
MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71, 0.98)	0.0294	-
Ischaemic stroke	152 (1.6%)	1.5%	191 (2.0%)	1.8%	0.80 (0.64, 0.99)	0.0375	-
All-cause death[b]	579 (6.0%)	5.1%	592 (6.2%)	4.9%	0.98 (0.87, 1.10)	0.6846	-

[a] Formal statistical testing is performed in the sequence presented in the table until the first non-significant result is observed. The significance level is α=0.0496, adjusted for interim analysis.

[a] Includes deaths based on publicly available vital status data in patients who have withdrawn consent.

Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable.

N Number of patients in treatment group; KM Kaplan-Meier; CI Confidence interval; CV Cardiovascular; MI Myocardial infarction.

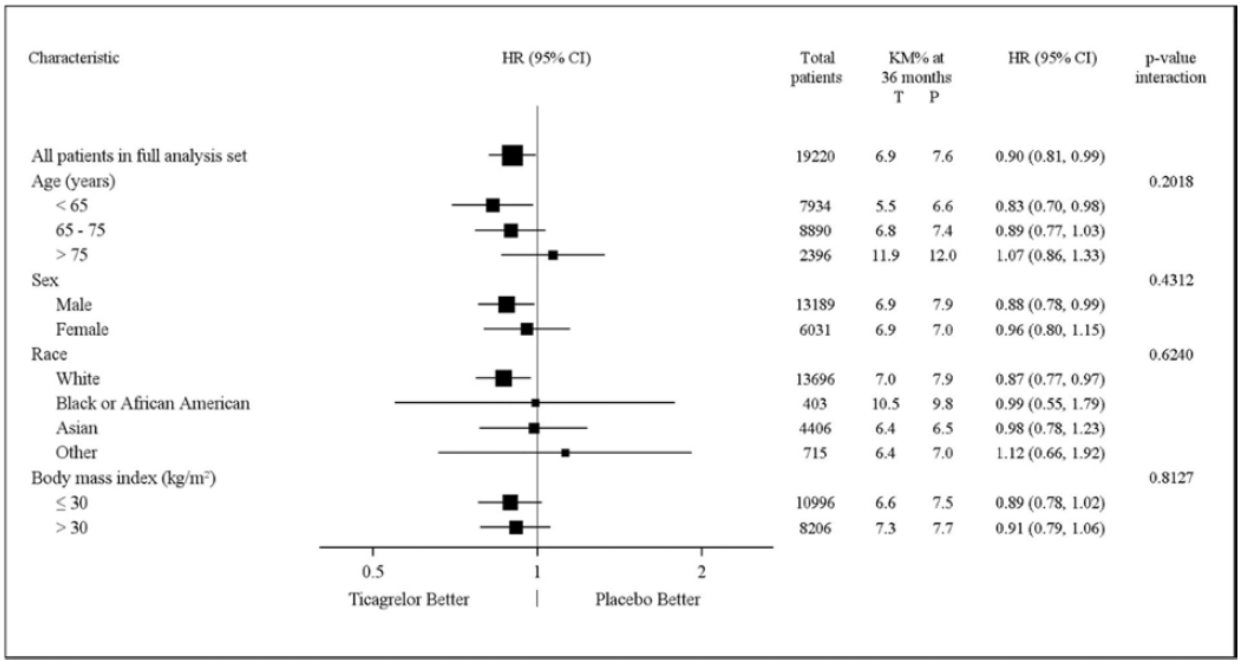
Ancillary analyses

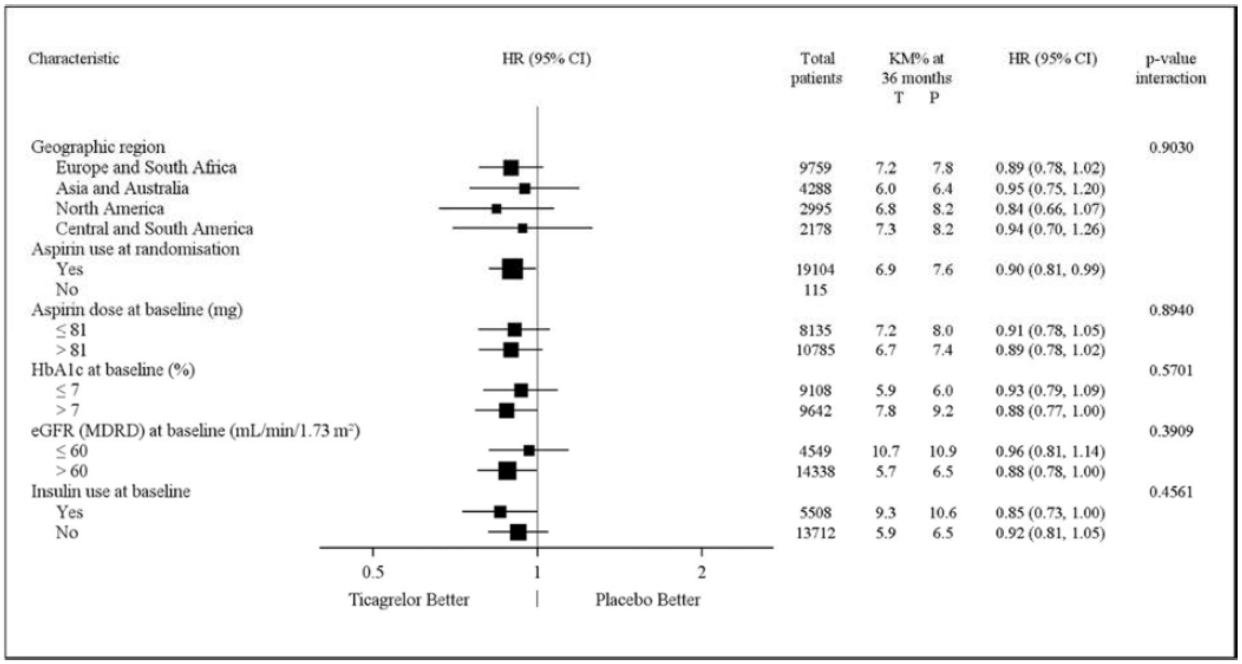
Subgroup analyses

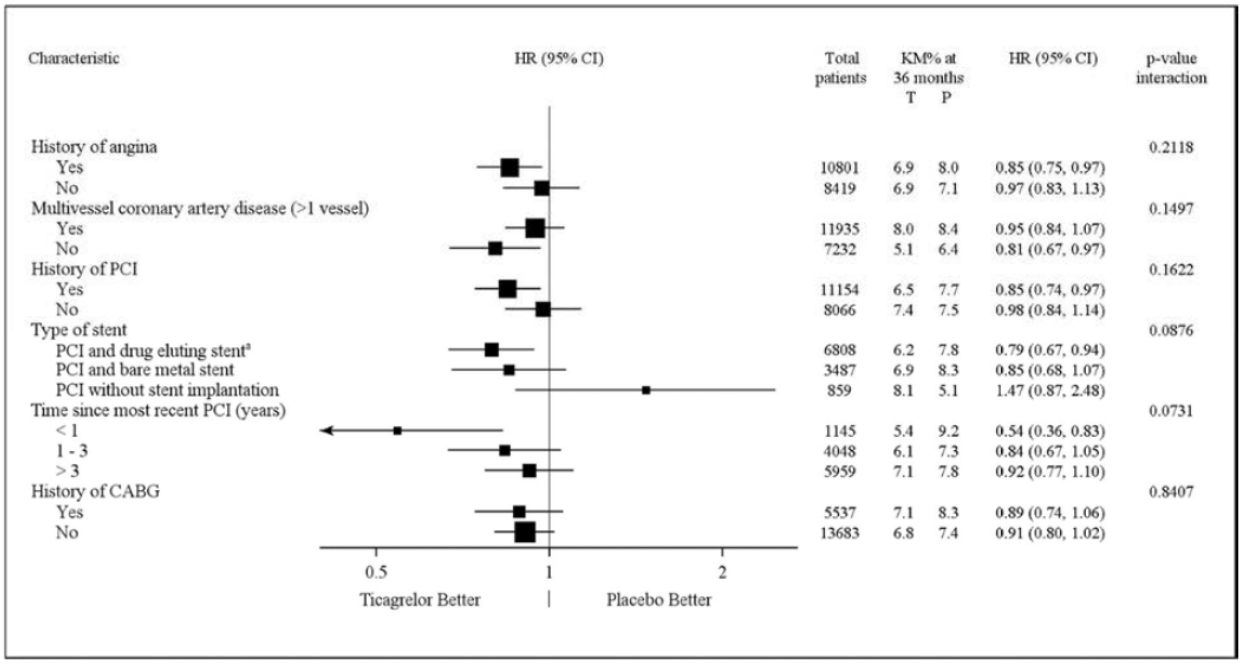
A range of pre-specified subgroup analyses was conducted to examine the influence of patient characteristics on the primary endpoint.

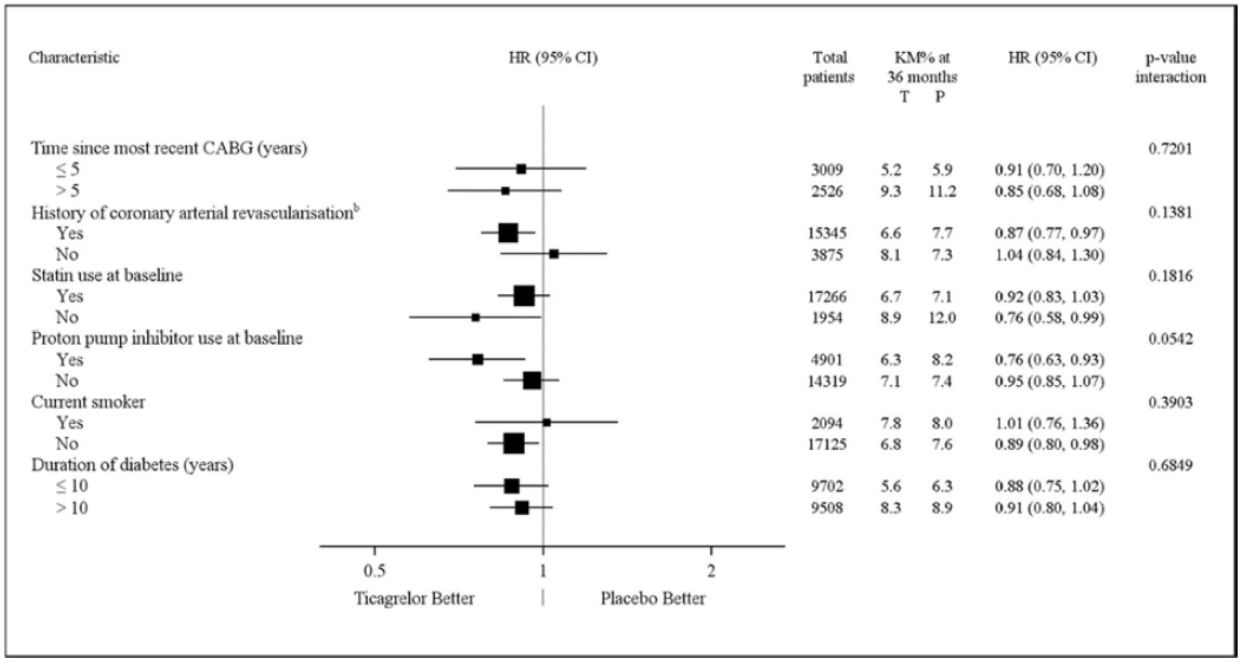
Overall the treatment effect appeared to be consistent across most predefined patient subgroups for ticagrelor compared with placebo. The p-value for interaction was below 0.05 for the subgroup "history of poly-vascular disease". The HR point estimate for each of the three CAD subgroups formed by the key inclusion criteria was 0.85 (95% CI 0.74, 0.97) for patients with a history of PCI, 0.89 (95% 0.74, 1.06) for patients with a history of CABG, and 1.04 (95% 0.84, 1.30) for patients with no history of revascularisation.

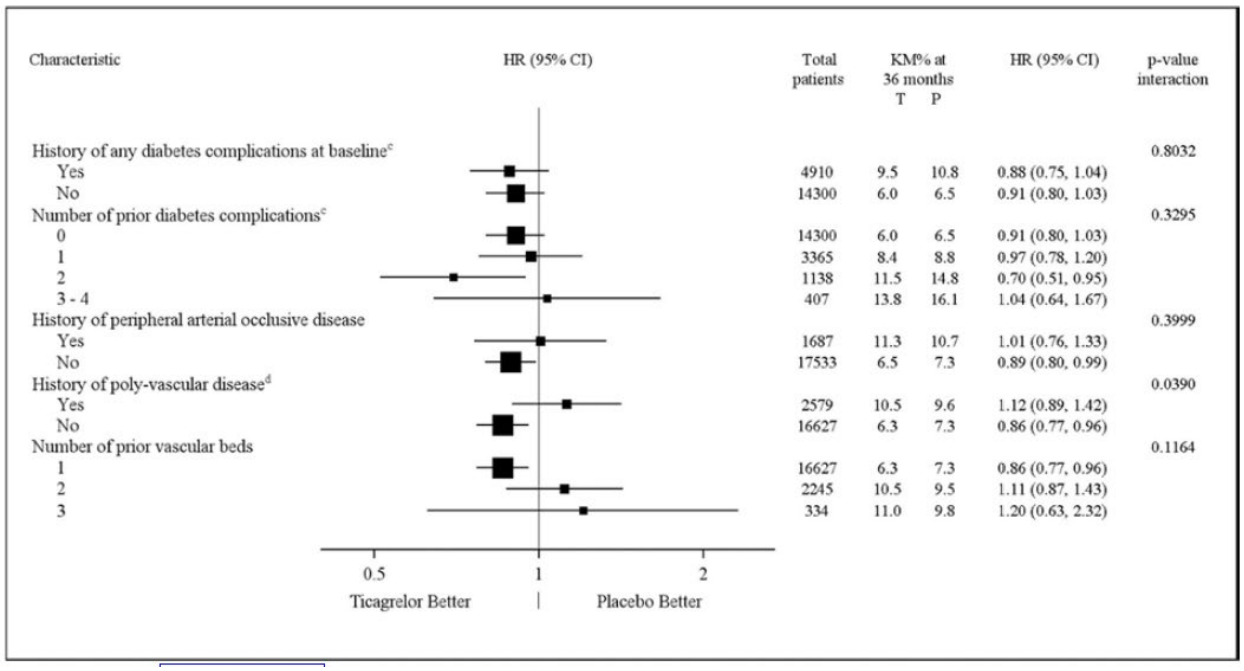
Figure 3 Hazard ratios and rates of primary efficacy variable by patient subgroup (full analysis set)






Characteristic
HR (95% CI)
Total patients
KM% at 36 months T P
HR (95% CI)
p-value interaction
History of angina 0.2118
Yes 10801 6.9 8.0 0.85 (0.75, 0.97)
No 8419 6.9 7.1 0.97 (0.83, 1.13)
Multivessel coronary artery disease (>1 vessel) 0.1497
Yes 11935 8.0 8.4 0.95 (0.84, 1.07)
No 7232 5.1 6.4 0.81 (0.67, 0.97)
History of PCI 0.1622
Yes 11154 6.5 7.7 0.85 (0.74, 0.97)
No 8066 7.4 7.5 0.98 (0.84, 1.14)
Type of stent 0.0876
PCI and drug eluting stent[a] 6808 6.2 7.8 0.79 (0.67, 0.94)
PCI and bare metal stent 3487 6.9 8.3 0.85 (0.68, 1.07)
PCI without stent implantation 859 8.1 5.1 1.47 (0.87, 2.48)
Time since most recent PCI (years) 0.0731
< 1 1145 5.4 9.2 0.54 (0.36, 0.83)
1 - 3 4048 6.1 7.3 0.84 (0.67, 1.05)
> 3 5959 7.1 7.8 0.92 (0.77, 1.10)
History of CABG 0.8407
Yes 5537 7.1 8.3 0.89 (0.74, 1.06)
No 13683 6.8 7.4 0.91 (0.80, 1.02)
0.5
1
2
Ticagrelor Better
Placebo Better


Characteristic
HR (95% CI)
Total patients
KM% at 36 months T P
HR (95% CI)
p-value interaction
Time since most recent CABG (years) 0.7201
≤ 5 3009 5.2 5.9 0.91 (0.70, 1.20)
> 5 2526 9.3 11.2 0.85 (0.68, 1.08)
History of coronary arterial revascularisation[b] 0.1381
Yes 15345 6.6 7.7 0.87 (0.77, 0.97)
No 3875 8.1 7.3 1.04 (0.84, 1.30)
Statin use at baseline 0.1816
Yes 17266 6.7 7.1 0.92 (0.83, 1.03)
No 1954 8.9 12.0 0.76 (0.58, 0.99)
Proton pump inhibitor use at baseline 0.0542
Yes 4901 6.3 8.2 0.76 (0.63, 0.93)
No 14319 7.1 7.4 0.95 (0.85, 1.07)
Current smoker 0.3903
Yes 2094 7.8 8.0 1.01 (0.76, 1.36)
No 17125 6.8 7.6 0.89 (0.80, 0.98)
Duration of diabetes (years) 0.6849
≤ 10 9702 5.6 6.3 0.88 (0.75, 1.02)
> 10 9508 8.3 8.9 0.91 (0.80, 1.04)
0.5
1
2
Ticagrelor Better
Placebo Better



a Includes any patient with drug eluting stent, or both drug eluting stent and bare metal stent.
b Defined as PCI or CABG.
c History of any of the complications Retinopathy, Neuropathy autonomic, Neuropathy peripheral and Nephropathy.
d Defined as arterial obstructive disease involving at least 2 vascular beds where vascular bed involvement is characterised by either 1) CAD, PCI or CABG, 2) PAD, 3) carotid artery stenosis or cerebral revascularisation.

Effects in patients with a history of PCI

The consistency of the treatment effect on the primary composite endpoint was explored for a wide range of pre-defined patient subgroups, and the treatment differences observed in HR point estimates across subgroups were consistent with the overall results, including the reduction of the primary composite endpoint seen in patients with a history of PCI, one of the key subgroups also defined by the CAD inclusion criterion. Although the p-value for interaction between treatment and subgroup was >0.05 in the patients who had undergone a PCI on both the primary efficacy and safety endpoint, the further analyses of benefits versus bleeding risks across the CAD subgroups suggest a more favourable benefit-risk profile in this group than in the other CAD subgroups defined by the key inclusion criteria (patients who had undergone a CABG surgery, and patients with no coronary revascularisation but angiographically verified lumen stenosis) and compared with the full study population.

In THEMIS patients with a history of PCI, there was a numerical reduction in the rate of primary efficacy endpoint events for patients treated with ticagrelor compared with placebo (15% RRR; HR 0.85 [95% CI 0.74, 0.97], nominal p=0.0133). A KM plot of the primary efficacy endpoint is provided in the figure below. The results for all individual components of the primary efficacy composite were numerically in favour of ticagrelor with nominally significant reductions in MI and stroke.

Table 10 **Analysis of primary efficacy variable (composite of CV death/MI/stroke) and its components, in patients with a history of PCI (full analysis set) - Study D513BC00001**

	Ticagrelor (N=5558)		Placebo (N=5596)			
Characteristic	**Patients with events (%)**	**KM% at 36 months**	**Patients with events (%)**	**KM% at 36 months**	**Hazard ratio (95% CI)**	**p-value**
Composite of CV death/MI/stroke	404 (7.3%)	6.5%	480 (8.6%)	7.7%	0.85 (0.74, 0.97)	0.0133
CV death	174 (3.1%)	2.7%	183 (3.3%)	2.6%	0.96 (0.78, 1.18)	0.6803
MI	171 (3.1%)	2.8%	216 (3.9%)	3.8%	0.80 (0.65, 0.97)	0.0266
Stroke	96 (1.7%)	1.6%	131 (2.3%)	2.1%	0.74 (0.57, 0.96)	0.0243

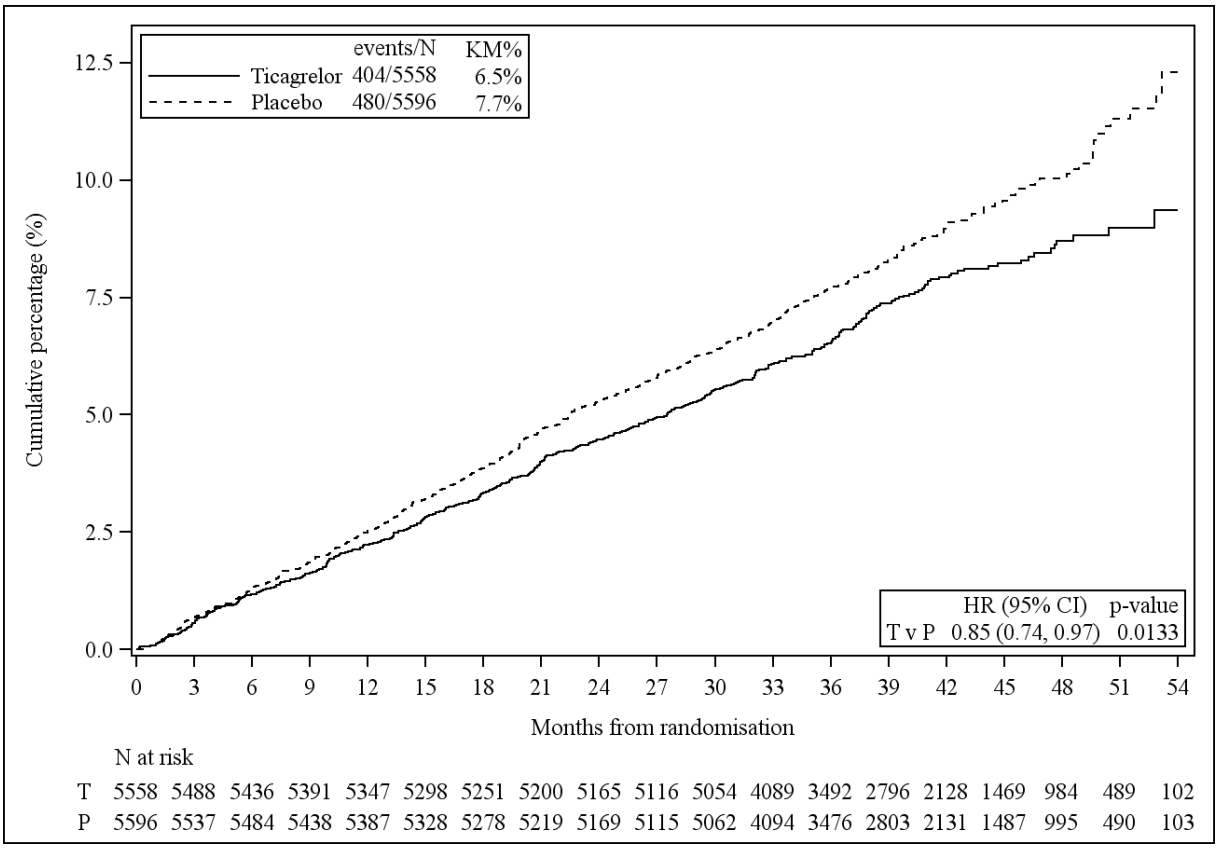
Source: THEMIS CSR Addendum Table A1.2.1.

Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable.

The number of first events for the components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

N Number of patients in treatment group; KM Kaplan-Meier; CI Confidence interval; CV Cardiovascular; MI Myocardial infarction; PCI Percutaneous coronary intervention.

Figure 4 **Kaplan-Meier plot of primary efficacy variable (composite of CV death/MI/stroke), in patients with a history of PCI (full analysis set) - Study D513BC00001**



Source: THEMIS CSR Addendum Figure A1.2.1.

Kaplan-Meier percentages are calculated at 36 months.

N Number of patients in treatment group; KM Kaplan-Meier; HR Hazard ratio; CI Confidence interval; CV Cardiovascular; MI Myocardial infarction; T Ticagrelor; P Placebo; PCI Percutaneous coronary intervention.

Effect in the 60 mg bd population

In the overall study population, the comparison of the treatment effect in the subset of patients who were randomised exclusively to ticagrelor 60 mg or matching placebo, and the overall effect of ticagrelor for the primary endpoint is provided in the table below. The treatment effect of ticagrelor 60 mg versus placebo from a time-dependent Cox proportional hazards model is presented in the same table. These sensitivity analyses showed that the treatment effect of ticagrelor 60 mg, as assessed by the reduced risk of the composite endpoint of CV death/MI/stroke, was consistent with that of ticagrelor overall.

Table 11 Sensitivity analysis of consistency between treatment effect of ticagrelor 60 mg bd and overall effect of ticagrelor for primary endpoint (full analysis set) - Study D513BC00001

		Ticagrelor (N=9619)			Placebo (N=9601)				
Characteristic	**Estimate**	**Number of patients**	**Patients with events(%)**	**KM% at 24 months**	**Number of patients**	**Patients with events(%)**	**KM% at 24 months**	**Hazard Ratio (95% CI)**	**p-value**
Composite of CV death/MI/stroke, using treatment as only explanatory variable	Ticagrelor vs placebo	9619	736 (7.7%)	4.6%	9601	818 (8.5%)	4.9%	0.90 (0.81, 0.99)	0.0378
Composite of CV death/MI/stroke, using treatment as only explanatory variable, including only patients randomised to ticagrelor 60 mg or matching placebo	Ticagrelor 60 mg bd vs matching placebo	2492	127 (5.1%)	3.5%	2532	147 (5.8%)	4.2%	0.87 (0.69, 1.11)	0.2593
Composite of CV death/MI/stroke, using treatment and time-dependent indicator for ticagrelor dose as explanatory variable[a]	Ticagrelor 60 mg bd vs placebo	9619	736 (7.7%)		9601	818 (8.5%)		0.83 (0.74, 0.93)	0.0018

For the composite of CV death/MI/stroke using treatment as the only explanatory variable (the primary analysis), the HR was 0.90 (95% CI 0.81, 0.99). Conducting the same analysis, including only patients randomised to ticagrelor 60 mg bd or matching placebo, the HR was 0.87 (95% CI 0.69, 1.11),

showing consistency with the primary analysis. For the sensitivity analysis of the composite of CV death/MI/stroke using both treatment and time-dependent indicator for ticagrelor dose as explanatory variables (ITT) the HR for ticagrelor 60 mg bd compared with placebo was 0.83 (95% CI 0.74, 0.93), which is consistent with the primary analysis.

The on-treatment analysis of the composite of CV death/MI/stroke using treatment as the only explanatory variable resulted in an HR of 0.83 (95% CI 0.73, 0.94). The on-treatment analysis, including only patients randomised to ticagrelor 60 mg bd or matching placebo resulted in an HR of 0.72 (95% CI 0.53, 0.97). An analysis of the primary composite endpoint including only patients randomised to ticagrelor 90 mg bd or matching placebo, where the patients were censored 7 days after the last 90 mg dose, resulted in an HR of 0.99 (95% CI 0.77, 1.27). An analysis during treatment with ticagrelor 60 mg, including patients who were randomised to ticagrelor 60 mg or matching placebo, or patients who had been randomised to ticagrelor 90 mg or matching placebo and were event-free up to the day they reduced dose to 60 mg, resulted in an HR of 0.78 (95% CI 0.68, 0.90).

These sensitivity analyses were repeated in patients with a history of PCI and showed consistency with the results of the primary analysis in the full group of patients with a history of PCI (see table below). The hazard ratios for all the secondary efficacy variables (CV death, MI, ischaemic stroke, and all-cause death) were numerically in favour of ticagrelor, with a nominally significant difference for MI.

Table 12 Sensitivity analysis of consistency between treatment effect of ticagrelor 60 mg and overall effect of ticagrelor for primary endpoint, in patients with a history of PCI (full analysis set)

		Ticagrelor (N=5558)			Placebo (N=5596)				
Characteristic	Estimate	Number of patients	Patients with events (%)	KM% at 24 months	Number of patients	Patients with events (%)	KM% at 24 months	Hazard Ratio (95% CI)	p-value
Composite of CV death/MI/stroke, using treatment as only explanatory variable	Ticagrelor vs placebo	5558	404 (7.3%)	4.5%	5596	480 (8.6%)	5.3%	0.85 (0.74, 0.97)	0.0133
Composite of CV death/MI/stroke, using treatment as only explanatory variable, including only patients randomised to ticagrelor 60 mg or matching placebo	Ticagrelor 60 mg bd vs matching placebo	1469	72 (4.9%)	3.4%	1490	87 (5.8%)	4.2%	0.83 (0.61, 1.14)	0.2538
Composite of CV death/MI/stroke, using treatment and time dependent indicator for ticagrelor dose as explanatory variable[a]	Ticagrelor 60 mg bd vs placebo	5558	404 (7.3%)		5596	480 (8.6%)		0.80 (0.68, 0.93)	0.0031

Exploratory outcomes

a) In the overall THEMIS study population

Exploratory efficacy endpoints in the overall THEMIS study population are summarised in Table 11.2.5.1. These endpoints were considered exploratory and were not part of the hierarchical (confirmatory) testing procedure. There were numerically fewer patients with "irreversible harm events" (composite of all-cause death, MI, stroke, ICH, and fatal bleeding) in the ticagrelor group compared with placebo: 968 patients treated with ticagrelor had events compared with 1039 patients treated with placebo, HR 0.93 (95% CI 0.86, 1.02; see Table 12.2.5.1).

Table 12.2.5.1 Analyses of exploratory objectives in the overall THEMIS study population (full analysis set)

	Ticagrelor (N=9619)		Placebo (N=9601)			
Characteristic	Patients with events (%)	KM% at 36 months	Patients with events (%)	KM% at 36 months	Hazard Ratio (95% CI)	p-value
Composite of all-cause death/MI/stroke[a]	919 (9.6%)	8.5%	1018 (10.6%)	9.2%	0.90 (0.83, 0.99)	0.0252
All-cause death	579 (6.0%)	5.1%	592 (6.2%)	4.9%	0.98 (0.87, 1.10)	0.6846
MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71, 0.98)	0.0294
Stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67, 0.99)	0.0435
Stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67, 0.99)	0.0435
Composite of all-cause death/MI/stroke/intracranial haemorrhage/fatal bleeding[a]	968 (10.1%)	8.9%	1039 (10.8%)	9.5%	0.93 (0.86, 1.02)	0.1248
All-cause death	579 (6.0%)	5.1%	592 (6.2%)	4.9%	0.98 (0.87, 1.10)	0.6846
MI	274 (2.8%)	2.6%	328 (3.4%)	3.3%	0.84 (0.71, 0.98)	0.0294
Stroke	180 (1.9%)	1.7%	221 (2.3%)	2.1%	0.82 (0.67, 0.99)	0.0435
Intracranial haemorrhage	91 (0.9%)	0.9%	63 (0.7%)	0.6%	1.45 (1.05, 2.00)	0.0228
Fatal bleeding	25 (0.3%)	0.3%	17 (0.2%)	0.1%	1.48 (0.80, 2.74)	0.2147
Composite of arterial and venous thrombotic events that fulfills any serious adverse event criteria[b]	183 (1.9%)	1.8%	186 (1.9%)	1.8%	0.99 (0.80, 1.21)	0.9007
Coronary arterial revascularisation[c]	828 (8.6%)	8.2%	879 (9.2%)	8.9%	0.94 (0.86, 1.04)	0.2116
Composite of ALI and major amputation of vascular aetiology	13 (0.1%)	0.1%	29 (0.3%)	0.3%	0.45 (0.23, 0.86)	0.0166

Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable.
[a] The number of first events for the components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.
[b] A venous or arterial serious adverse event is a serious adverse event documented by the investigator in the eCRF including preferred terms in Table 11.3.8.1.
[c] Coronary arterial revascularisation is defined as percutaneous coronary intervention or coronary artery bypass graft documented by the investigator in the eCRF.
N Number of patients in treatment group; KM Kaplan-Meier; CI Confidence interval; MI Myocardial infarction; eCRF Electronic case report form; ALI Acute limb ischaemia.

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Source: root/cdar/d513/d513bc00001/ar/csr/tlf/dev/program/s1102p024.sas

b) In the PCI subgroup

There were fewer patients with irreversible harm events (composite of all-cause death, MI, stroke, ICH, and fatal bleeding) in the ticagrelor group than in the placebo group in the PCI subgroup (HR 0.85; 95% CI 0.75, 0.95) (see Table A1.2.10).

Table A1.2.10 Analyses of exploratory objectives, in patients with a history of PCI (full analysis set)

Characteristic	Ticagrelor (N=5558) Patients with events (%)	KM% at 36 months	Placebo (N=5596) Patients with events (%)	KM% at 36 months	Hazard Ratio (95% CI)	p-value
Composite of all-cause death/MI/stroke[a]	494 (8.9%)	7.8%	603 (10.8%)	9.4%	0.82 (0.73, 0.93)	0.0014
All-cause death	282 (5.1%)	4.2%	323 (5.8%)	4.5%	0.88 (0.75, 1.03)	0.1067
MI	171 (3.1%)	2.8%	216 (3.9%)	3.8%	0.80 (0.65, 0.97)	0.0266
Stroke	96 (1.7%)	1.6%	131 (2.3%)	2.1%	0.74 (0.57, 0.96)	0.0243
Stroke	96 (1.7%)	1.6%	131 (2.3%)	2.1%	0.74 (0.57, 0.96)	0.0243
Composite of all-cause death/MI/stroke/intracranial haemorrhage/fatal bleeding[a]	519 (9.3%)	8.2%	617 (11.0%)	9.7%	0.85 (0.75, 0.95)	0.0052
All-cause death	282 (5.1%)	4.2%	323 (5.8%)	4.5%	0.88 (0.75, 1.03)	0.1067
MI	171 (3.1%)	2.8%	216 (3.9%)	3.8%	0.80 (0.65, 0.97)	0.0266
Stroke	96 (1.7%)	1.6%	131 (2.3%)	2.1%	0.74 (0.57, 0.96)	0.0243
Intracranial haemorrhage	42 (0.8%)	0.6%	41 (0.7%)	0.7%	1.04 (0.67, 1.59)	0.8738
Fatal bleeding	10 (0.2%)	0.2%	10 (0.2%)	0.1%	1.01 (0.42, 2.43)	0.9784
Composite of arterial and venous thrombotic events that fulfills any serious adverse event criteria[b]	93 (1.7%)	1.5%	115 (2.1%)	1.9%	0.81 (0.62, 1.07)	0.1411
Coronary arterial revascularisation[c]	599 (10.8%)	10.4%	645 (11.5%)	11.2%	0.93 (0.84, 1.04)	0.2238

Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable.
[a] The number of first events for the components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.
[b] A venous or arterial serious adverse event is a serious adverse event documented by the investigator in the eCRF including preferred terms in Table 11.3.8.1.
[c] Coronary arterial revascularisation is defined as percutaneous coronary intervention or coronary artery bypass graft documented by the investigator in the eCRF.
N Number of patients in treatment group; KM Kaplan-Meier; CI Confidence interval; MI Myocardial infarction; eCRF Electronic case report form; ALI Acute limb ischaemia; PCI Percutaneous coronary intervention.

GCP noncompliance at study site 7605

As part of AstraZeneca's routine GCP inspection procedures, site 7605 was identified as the highest recruiting site in Turkey, randomising in total 87 patients (0.5 % of total study population), and was therefore selected for an AstraZeneca visit to monitor quality compliance.

To investigate a potential impact by the data from site 7605 on the primary efficacy results in the THEMIS study, sensitivity analyses have been conducted where data from this site were excluded.

The clinical efficacy endpoint analyses (the composite primary endpoint of cardiovascular death, myocardial infarction and stroke, and secondary endpoints) were repeated with 87 patients in site 7605 excluded (Table 13), and the results were consistent with results in the full study population. In patients with a history of PCI, i.e., the patient group proposed in the THEMIS dossier for an expanded indication with ticagrelor, the analysis of efficacy endpoints was repeated with 19 patients with a history of PCI from site 7605 excluded, and the results of this analysis (Table 14) were consistent with results in the overall studied population with a history of PCI.

Table 13 : Analysis of clinical endpoint hierarchy, excluding site 7605 (full analysis set)

	Ticagrelor (N=9575)		Placebo (N=9558)			
Characteristic	Patients with events (%)	KM% at 36 months	Patients with events (%)	KM% at 36 months	Hazard Ratio (95% CI)	p-value
Composite of CV death/MI/stroke	733 (7.7%)	6.9%	811 (8.5%)	7.6%	0.90 (0.82, 1.00)	0.0481
CV death	361 (3.8%)	3.3%	352 (3.7%)	3.0%	1.03 (0.89, 1.19)	0.7294
MI	274 (2.9%)	2.6%	326 (3.4%)	3.3%	0.84 (0.72, 0.99)	0.0359
Ischaemic stroke	152 (1.6%)	1.5%	191 (2.0%)	1.8%	0.80 (0.64, 0.99)	0.0376
All-cause death[a]	575 (6.0%)	5.1%	586 (6.1%)	4.9%	0.98 (0.87, 1.10)	0.7281

[a] Includes deaths based on publically available vital status data in patients who have withdrawn consent.
Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable.
All patients randomised at site 7605 are excluded from the analysis.
N Number of patients in treatment group; KM Kaplan-Meier; CI Confidence interval; CV Cardiovascular; MI Myocardial infarction.

Table 14: Analysis of clinical endpoint hierarchy in patients with a history of PCI, excluding site 7605 (full analysis set)

	Ticagrelor (N=5551)		Placebo (N=5584)			
Characteristic	Patients with events (%)	KM% at 36 months	Patients with events (%)	KM% at 36 months	Hazard Ratio (95% CI)	p-value
Composite of CV death/MI/stroke	404 (7.3%)	6.6%	476 (8.5%)	7.7%	0.85 (0.75, 0.97)	0.0184
CV death	174 (3.1%)	2.7%	181 (3.2%)	2.6%	0.97 (0.79, 1.19)	0.7524
MI	171 (3.1%)	2.8%	214 (3.8%)	3.8%	0.80 (0.66, 0.98)	0.0333
Ischaemic stroke	88 (1.6%)	1.4%	113 (2.0%)	1.8%	0.78 (0.59, 1.04)	0.0878
All-cause death[a]	282 (5.1%)	4.2%	321 (5.7%)	4.5%	0.88 (0.75, 1.03)	0.1222

[a] Includes deaths based on publically available vital status data in patients who have withdrawn consent.
Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as only explanatory variable.
All patients randomised at site 7605 are excluded from the analysis.
N Number of patients in treatment group; KM Kaplan-Meier; CI Confidence interval; CV Cardiovascular; MI Myocardial infarction; PCI Percontaneous coronary revascularisation.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Table 15 Summary of Efficacy for THEMIS trial (D513BC00001)

Title: A Multinational, Randomised, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Ticagrelor Twice Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Stroke in Patients with Type 2 Diabetes Mellitus [THEMIS - Effect of Ticagrelor on Health outcomes in diabEtes Mellitus patients Intervention Study]		
Study identifier	D513BC00001	
Design	Randomised, double-blind, placebo-controlled, 2-arm parallel group, multinational trial.	
	Duration of main phase: Duration of Run-in phase:	Average 40 months (58 months maximum) 7 days to randomisation (28 months enrolment)

	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Ticagrelor 60 mg		N= 9601 randomised, N= 9562 received study drug
	Placebo (ASA)		N= 9601 randomised, N=9531 received study drug
Endpoints and definitions	Primary endpoint	MACE	Composite of CV death, MI, stroke
	Secondary endpoints	Single component CHD	CV death (first), MI (second), ischemic stroke (third), all-cause mortality (fourth), hierarchical testing
Database lock	16 February 2019		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Ticagrelor 60 mg	Placebo (ASA)	HR (95% CI), p value
	Number of subject	9619	9601	19220
	Composite of CV death, MI, stroke	736 (7.7%)	818 (8.5%)	KM% at 36 months: 6.9% vs 7.6%; HR 0.90 (0.81-0.99), p=0.0378
Analysis description	**Secondary analyses**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Ticagrelor 60 mg	Placebo (ASA)	HR (95% CI), p value
	Number of subject	9619	9601	19220
	CV death	364 (3.8%)	357 (3.7%)	KM% at 36 months: 3.3% vs 3.0%; HR 1.02 (0.88-1.18), p=0.7883
	MI	274 (2.8%)	328 (3.4%)	KM% at 36 months: 2.6% vs 3.3%; *HR 0.84 (0.71-0.98), p=0.0294*
	Ischaemic stroke	152 (1.6%)	191 (2.0%)	KM% at 36 months: 1.5% vs 1.8%; *HR 0.80 (0.64-0.99), p=0.0375*
Notes	The secondary endpoints were performed according to a hierarchical testing which was violated at the CH death endpoint.			

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The study is a randomised, double-blind, placebo-controlled, 2-arm parallel-group study and is considered appropriate to evaluate its primary objective. This primary objective was to compare the effect of long-term treatment with ticagrelor 60 mg bd vs placebo on a background of ASA (75 to 150 mg daily) on the event rate of the composite of CV death, non-fatal MI, or non-fatal stroke in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) at high risk of CV events, but without a medical history of MI or stroke. A background therapy of ASA (75-150 mg) is considered in line with current common practice of primary prevention of CV risk in patients with increased CV risk. Patients with a history of PCI are very likely to have already been treated with DAPT previously in accordance with clinical practice guidance before study inclusion and thus would be reinitiated with DAPT. However, such data have not been captured.

Coronary artery disease is angiographically confirmed in these patients by the applied inclusion criteria of history of percutaneous coronary intervention or coronary artery bypass graft or angiographic evidence of ≥50% lumen stenosis of at least 1 coronary artery and is considered appropriate to identify a population at increased risk of atherosclerotic disease. Patients were further enriched by an age cut-off of 50 years and by only including patients with T2DM (at least 6 months prior to inclusion). These selection criteria result in a very restricted part of the primary prevention CAD population likely at the higher end of the CV risk estimation. Although, the specific exclusion criteria of patients with previous MI (documented hospitalisation with a final diagnosis of spontaneous MI) discriminates the current population to a population at lower CV risk in comparison to those already covered by current ticagrelor secondary prevention indications.

The primary composite endpoint of CV death, MI and stroke is clinically relevant. Although overall mortality is preferred in the composite of the primary endpoint, inclusion of CV death in the composite is also considered acceptable as per *EMA Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMEA/CHMP/EWP/311890/2007)*. Key secondary endpoints, to compare the event rate of the individual components of the composite primary endpoint, is considered of relevance as well. These endpoints were hierarchically tested under type 1 error, respectively.

Sample size calculation is considered appropriate. The statistical analysis and the populations used are standard and considered acceptable.

The method of randomisation is acceptable. The blinding method for investigators and patients is appropriate. Central adjudication also ensures proper blinding of the adjudication of the endpoints and bleeding events.

Efficacy data and additional analyses

A large proportion of patients who received informed consent could be followed-up, with only 4.2% of patients who were not randomised. One study site was prematurely closed, but this concerns only 51 patients unlikely to impact the overall findings. As previously observed in the PEGASUS, a large proportion of patients discontinued study drug (34.5%), which was substantially larger than in the placebo group (25.5%). This could be of concern and could impact study outcome depending on the analyses methods chosen. This was largely due to drug-related AEs (16.9% vs 10.3%) and patients' decision to withdraw (14.9% vs 11.8%).

Randomisation was successful, with only slight differences between treatment groups. A large proportion of patients comply with the inclusion criteria of history of PCI (58%) and a history of CABG (29%) with 20% without previous coronary arterial revascularisation. From the subgroup analyses, it can be

retrieved that only 12% of patients > 75 years of age were included. Almost all patients were Caucasian (71%) or Asian (23%), consequently, other races were underrepresented. Approximately half of the patients were recruited in Europe, and thus the study can be considered representative for the European situation. The mean time of diabetes was 11.7 years. Concomitant medication was in line with current treatment standards including oral antidiabetics, ACE/ARB, BBs, statins, although the use of newer oral antidiabetics was still limited. Regarding medications at baseline, the sum of all active ingredients related to different clopidogrel salts, prasugrel and ticagrelor indicate that about 4% (n=762 patients) of the THEMIS study population were on a second antiplatelet agent (plus ASA) at baseline (i.e., DAPT).

Only a small proportion had a previous MI (0.8%), which is considered sufficiently limited and meeting this exclusion criterion. However, only patients with a history of spontaneous MI were excluded, while, on the contrary, patients with history of secondary MI (e.g.: due to revascularisation/stent thrombosis, hypotension, etc.) and silent MIs detected at baseline screening, were included. These patients overlap with the target population included in the currently approved indication: "*a history of MI and a high risk of developing an atherothrombotic event*". A total of 153 patients had a history of MI, 99 (45 randomised to ticagrelor and 54 randomised to placebo) had a history of spontaneous MI (which was an exclusion criterion). It is not understood why these 99 patients with spontaneous MI were not excluded from the analysis, despite spontaneous MI was an exclusion criterion.

Assessment based on the Full Analysis Set is acceptable. However, considering the large proportion of patients prematurely discontinuing treatment, other analyses may also offer valuable information on the benefit-risk balance of ticagrelor and were assessed. The proportion of 25% patients randomised to the 60 mg dose was only a limited proportion of the entire study population, although these data provide the cleanest output to support the proposed 60 mg dose.

During a median treatment period of 35 months (33.2 and 36.1 months for the ticagrelor and placebo), a statistically significant treatment effect for ticagrelor in comparison to placebo on a background of ASA therapy has been shown, however, with 82 less first events (736 vs 818) and a Kaplan-Meier percentages at 36 months of 6.9% and 7.6% resulting in a 10% relative risk reduction (RRR), HR 0.90 (95% CI 0.81, 0.99), p=0.0378, the treatment effect is considered small and may be of limited clinical relevance. The effect seemed to be generally consistent throughout the study period.

The effects on the individual components of the primary endpoint were consistent with the composite, although the hierarchical testing was terminated due to a non-significant (increased) effect on CV death (HR 1.02 [95% CI 0.88, 1.18], p-value 0.7883). CV death showed the highest event rate with slightly more events in the ticagrelor group; however, no increase was found for all-cause mortality (579 (6.0%) vs 592 events (6.2%)), which is reassuring. MI seems to contribute the most to the overall treatment effect (54 less events from 602 events (2.8% vs 3.4%)), followed by stroke (41 less events from 401 events (1.9% vs 2.3%)). There were 184 patients with at least a stroke in the ticagrelor group, with 180 events in the analysis in accordance with censoring rules.

The data on placebo are consistent (221 patients with at least a stroke). CV death numerically tended to favour placebo, while non-CV tended to be lower in the ticagrelor arm, mainly to less cases of death due to infection/sepsis. This finding is consistent with lower rate of SAEs related to Infections and infestations (TIC: 4.8% vs PBO: 5.1%; safety section), but anyway, the results did not show statistically significant differences between groups.

Some differences appear in the subgroup analyses. A counter-intuitive difference can be observed for the subgroup of history of poly-vascular disease with a p-value for interaction below 0.05. Further, most noticeable trend differences appear in age, race, history of coronary arterial revascularisation, smoking status, history of peripheral arterial occlusive disease, and number of prior vascular beds due to increased treatment HR with ticagrelor in one of the categories within these subgroups with some showing counter-intuitive results according to risk status (including age, smoking status, history of

peripheral arterial occlusive disease , number of prior vascular beds). Similar counter-intuitive findings although less outspoken were observed for eGFR status, and multivessel coronary artery disease. Although, most of these subgroups differences are likely due to chance finding.

Taken the small overall treatment effect, additional analyses were provided for the subgroup of patients with a history of PCI, identified by the applicant as an important subgroup where treatment with ticagrelor may be more beneficial. Greater benefit appears to be observed with shorter time to most recent PCI, and it seems that these data have driven the apparently greater benefit, but this is a subgroup within a subgroup analysis, and thus these results should be interpreted with great caution. However, the relevance and robustness of the PCI subgroup data are questionable to support any proposed restriction of the originally intended indication extension to this subgroup. Apart from the fact that history of PCI was one of the qualifying inclusion criteria, selection of this subgroup appears not well-founded as it was not specifically defined a-priori as an important subgroup, and any p-value for interaction was not significant. Moreover, a retrospectively compelling explanation for (biological) plausibility for subgroup differences cannot be sufficiently justified. In this respect, the speculation of a potentially lower risk of bleeding due to assumed previous treatment with DAPT (data not provided) for patients with a history of PCI (and thus an apparently improved BR based on improved safety) in comparison to patients without a history of PCI cannot be clearly supported by any data; including study baseline data and/or exclusion criteria applied, data from other ticagrelor studies, or any other studies. Also, any clinical and statistically extreme evidence replication is not evident from other available data. Differences in baseline (mainly history of MI, history of DM2, and time since PCI) make any comparison to other ticagrelor studies difficult. Moreover, any differentiation according to PCI subgroup in PEGASUS is not useful as likely all patients in PEGASUS have been treated with DAPT. For PLATO, similar issues apply, most notable that patients were included based on recent ACS (very small proportion without MI) and comparison was made to clopidogrel treatment).. For further consideration with respect to the PCI subgroup see further below. If any subgroup (with increased CV risk and) with increased benefit could be identified, this should be based on a more robust argumentation and analysis of the available results.

During the study the dose was amended from 90 mg to 60 mg bd. Although approximately only 25% of the total study population was initially randomized to the 60 mg, such data provide the cleanest output to support such a dose for the intended target population. The overall primary endpoint was consistent with the overall findings, although not significant (HR was 0.87 (95% CI 0.69, 1.11)). When a time dependency analysis was performed, knowing that patients were overall treated to al large extent on the 60 mg dose (median time 32 vs 7.7 months), a consistent HR of 0.83 (95% CI 0.74, 0.93) was shown. Moreover, on-treatment data also demonstrated a consistent HR for the 60 mg dose (HR of 0.72 (95% CI 0.53, 0.97)). The on-treatment effect of HR of 0.99 (95% CI 0.77, 1.27) for the 90 mg dose is likely due to the fact that patients were shortly treated with this dose not already sufficient to result in any treatment effect.

Further considerations with respect to the subgroup of patients with a history of PCI

Within the PCI subgroup, there is suggestion of significant interaction depending on the time since PCI (interaction p=0.0731). The effect seems to be driven by patients with a PCI < 1 year before enrolment (HR: 0.54; 95%CI: 0.36 to 0.83; n=1145), Since clinical guidelines suggest that these high-risk patients have to be on DAPT at least for 6 months, it remains uncertain how these patients have actually been treated. Moreover, these data complicate interpretation if the PLATO study would be taken into account, as patients with ACS, but without MI, should be treated with ticagrelor 90 mg according to this PLATO study instead of 60 mg. Since history of DAPT therapy has not been captured, such issues remain uncertain.

2.5. Clinical safety

Introduction

There is a large safety database available from the extensive ticagrelor development programme comprising more than 53000 patients exposed to ticagrelor in completed clinical studies, and post-marketing experience from more than 4.6 million patient-years of treatment.

The safety data from THEMIS provide information related to use of the drug in patients with CAD and T2DM additional to the current approved ACS and history of MI indications of ticagrelor.

Patient exposure

A total of 19093 patients (99.3% of randomised patients) received at least 1 dose of randomised study drug: 9562 patients received ticagrelor, and 9531 patients received placebo. The maximum total duration of exposure to study drug (from first dose to last dose) was 59 months. The median total duration of exposure was 33.2 and 36.1 months for the ticagrelor and placebo treatment groups, respectively. The median duration of exposure on ticagrelor 60 mg bd was 32.1 months and on ticagrelor 90 mg bd 7.7 months. The total number of treatment years in the ticagrelor group was 23240, of which 17779 (76.5%) were on ticagrelor 60 mg bd.

At baseline the study patients were on a background of low-dose ASA (75 to 150 mg daily), unless contraindicated or not tolerated. Nearly all patients (99.4%) reported using ASA at baseline.

Adverse events

The table below presents an overview of SAEs, DAEs, and AEs of interest in the full THEMIS population.

Table 16 Adverse events in any category - on treatment (safety analysis set) - Study D513BC00001

	Ticagrelor (N=9562)		Placebo (N=9531)	
AE category	**Number (%) of patients with event**	**Event rate per 100 patient years[a]**	**Number (%) of patients with event**	**Event rate per 100 patient years[a]**
Patients with any bleeding event[b]	1446 (15.1%)	6.22	595 (6.2%)	2.26
Patients with any adverse event of interest	2562 (26.8%)	11.02	1302 (13.7%)	4.96
Patients with any dyspnoea	2049 (21.4%)	8.82	700 (7.3%)	2.66
Patients with any renal impairment	225 (2.4%)	0.97	220 (2.3%)	0.84
Patients with any bradyarrhythmia	137 (1.4%)	0.59	120 (1.3%)	0.46
Patients with any gout	190 (2.0%)	0.82	159 (1.7%)	0.61
Patients with any pneumonia	252 (2.6%)	1.08	263 (2.8%)	1.00
Patients with any AE with outcome = death	256 (2.7%)	1.10	309 (3.2%)	1.18
Patients with any SAE (including events with outcome = death)	3049 (31.9%)	13.12	3210 (33.7%)	12.22
Patients with any AE leading to discontinuation of study drug	1987 (20.8%)	8.55	1167 (12.2%)	4.44

Dyspnoea

In the full THEMIS population, there were 2049 patients (21.4%) in the ticagrelor group and 700 patients (7.3%) in the placebo group with Dyspnoea AEs.

Dyspnoea was mostly mild to moderate in intensity, and SAEs of Dyspnoea were rare (40 [0.4%] patients in the ticagrelor group and 37 [0.4%] in the placebo group). A higher incidence of discontinuations of study drug due to Dyspnoea was seen on ticagrelor compared with placebo (6.9% in the ticagrelor group versus 0.8% in the placebo group).

Renal impairment

Renal impairment AEs were reported in 225 (2.4%) patients in the ticagrelor group and 220 (2.3%) in the placebo group. Renal impairment SAEs were reported by 82 (0.9%) and 66 (0.7%) patients and Renal impairment DAEs by 11 (0.1%) and 10 (0.1%) patients in the ticagrelor and placebo groups, respectively.

Bradyarrhythmia

Bradyarrhythmia AEs were reported in 137 (1.4%) patients in the ticagrelor group and 120 (1.3%) patients in the placebo group. Bradyarrhythmia SAEs were reported by 63 (0.7%) and 45 (0.5%) patients and Bradyarrhythmia DAEs by 8 (0.1%) and 7 (0.1%) patients in the ticagrelor and placebo groups, respectively.

Gout

Gout AEs were reported in 190 (2.0%) patients in the ticagrelor group and 159 (1.7%) patients in the placebo group. Gout SAEs were reported by 9 (0.1%) and 11 (0.1%) patients and Gout DAEs by 6 (0.1%) and 6 (0.1%) patients in the ticagrelor and placebo groups, respectively.

Pneumonia

Pneumonia AEs were reported in 252 (2.6%) patients in the ticagrelor group and 263 (2.8%) patients in the placebo group. Pneumonia SAEs were reported by 142 (1.5%) and 155 (1.6%) patients and Pneumonia DAEs by 13 (0.1%) and 6 (0.1%) patients in the ticagrelor and placebo groups, respectively.

Serious adverse event/deaths/other significant events

Serious adverse events

In the full THEMIS population, there were similar proportions of patients with SAEs in the ticagrelor and placebo groups: 31.9% and 33.7% respectively. The most commonly reported SAEs by SOC were Cardiac disorders (11.9% and 14.1%, respectively), Infections and infestations (4.8% and 5.1%, respectively) and Nervous system disorders (3.3% and 4.3%, respectively).

The most commonly reported SAEs by PT were Angina unstable (3.7% and 4.2%, respectively), Angina pectoris (2.1% and 2.6%, respectively), and Acute MI (1.3% and 2.1%, respectively), reflecting reported endpoints and potential endpoints. These were reported at numerically lower frequencies in the ticagrelor group compared with the placebo group.

Table 17 Serious adverse events, by SOC - on treatment (safety analysis set)

	Number (%) of patients[a]	
System organ class	Ticagrelor (N=9562)	Placebo (N=9531)
Patients with any serious adverse event[b]	3049 (31.9%)	3210 (33.7%)
Cardiac disorders	1140 (11.9%)	1344 (14.1%)
Infections and infestations	462 (4.8%)	489 (5.1%)
Nervous system disorders	320 (3.3%)	410 (4.3%)
Gastrointestinal disorders	355 (3.7%)	253 (2.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	285 (3.0%)	296 (3.1%)
Injury, poisoning and procedural complications	229 (2.4%)	212 (2.2%)
Vascular disorders	185 (1.9%)	226 (2.4%)
Metabolism and nutrition disorders	178 (1.9%)	213 (2.2%)
Musculoskeletal and connective tissue disorders	182 (1.9%)	199 (2.1%)
Renal and urinary disorders	199 (2.1%)	169 (1.8%)
Respiratory, thoracic and mediastinal disorders	194 (2.0%)	172 (1.8%)
General disorders and administration site conditions	170 (1.8%)	175 (1.8%)
Hepatobiliary disorders	78 (0.8%)	100 (1.0%)
Blood and lymphatic system disorders	82 (0.9%)	41 (0.4%)
Eye disorders	56 (0.6%)	61 (0.6%)
Reproductive system and breast disorders	57 (0.6%)	43 (0.5%)
Skin and subcutaneous tissue disorders	50 (0.5%)	48 (0.5%)
Ear and labyrinth disorders	33 (0.3%)	20 (0.2%)
Investigations	27 (0.3%)	21 (0.2%)
Psychiatric disorders	23 (0.2%)	18 (0.2%)
Immune system disorders	5 (0.1%)	11 (0.1%)
Endocrine disorders	9 (0.1%)	6 (0.1%)
Product issues	5 (0.1%)	6 (0.1%)
Congenital, familial and genetic disorders	3 (0.0%)	0 (0.0%)

Preferred term	Ticagrelor (N=9562)	Placebo (N=9531)
Patients with any serious adverse event[b]	3049 (31.9%)	3210 (33.7%)
Angina unstable	354 (3.7%)	405 (4.2%)
Angina pectoris	200 (2.1%)	251 (2.6%)
Acute myocardial infarction	126 (1.3%)	197 (2.1%)
Pneumonia	130 (1.4%)	147 (1.5%)
Ischaemic stroke	85 (0.9%)	119 (1.2%)
Coronary artery disease	85 (0.9%)	90 (0.9%)
Atrial fibrillation	82 (0.9%)	76 (0.8%)
Cardiac failure	64 (0.7%)	87 (0.9%)
Non-cardiac chest pain	54 (0.6%)	66 (0.7%)
Death	52 (0.5%)	60 (0.6%)
Diabetes mellitus inadequate control	50 (0.5%)	60 (0.6%)
Cardiac failure congestive	60 (0.6%)	47 (0.5%)
Acute kidney injury	56 (0.6%)	39 (0.4%)

Unreported SAEs at THEMIS site 7605

There were 19093 patients in the safety analysis set in THEMIS. In the on-treatment analysis, 10323 SAEs were reported. AstraZeneca has reviewed the additional 52 SAE reports in 23 patients at site 7605 and concludes that the addition of these SAEs does not change the overall safety conclusion from the THEMIS study.

Based on inclusion of these serious adverse events, 3054 (31.9%) and 3216 (33.7%) patients reporting at least 1 serious adverse events were identified for respectively ticagrelor and placebo.

Deaths

A summary of deaths in the study in the full THEMIS population is given in the table below.

Death was an efficacy endpoint in this study, and all deaths that occurred prior to withdrawal of consent were adjudicated. The safety analysis set includes the 1151 deaths occurring in randomised patients who took at least one dose of study drug (15 deaths occurred in patients who were excluded from the safety analysis set due to no intake of study drug).

For adjudicated death classification of on-treatment deaths, see table below. Analyses of all deaths, including those occurring after withdrawal of consent (13 and 12 in the ticagrelor and placebo groups, respectively). In the full THEMIS population, there were fewer deaths on-treatment in the ticagrelor group compared to the placebo group. Adjudicated deaths on- and off-treatment, showed that there were 366 (3.8%) vs 359 (3.8%) CV death events and 202 (2.1%) vs 224 (2.4%) non-CV death events (total 568 vs 583). The distribution of causes of death between ticagrelor and placebo on-treatment was generally consistent with that on- and off-treatment.

Table 18 Summary of deaths (full analysis set) - Study D513BC00001

	Number of patients	
Characteristic	Ticagrelor (N=9619)	Placebo (N=9601)
Total deaths	589	602

Table 18 Summary of deaths (full analysis set) - Study D513BC00001

	Number of patients	
Characteristic	**Ticagrelor (N=9619)**	**Placebo (N=9601)**
Before or on PACD for efficacy	579	592
After PACD for efficacy	10	10
Deaths that occurred after withdrawal of consent	13	12
Before or on PACD for efficacy[a]	12	12
After PACD for efficacy	1	0
All adjudicated deaths	576	590
Before or on PACD for efficacy	567	580
After PACD for efficacy	9	10
CV death	372	364
Before or on PACD for efficacy	364	357
After PACD for efficacy	8	7
Adjudicated deaths for patients included in safety analysis set	568	583
Included in on-treatment analysis	187	223
Fatal bleeding	23	17
Included in on-treatment analysis	17	10

Table 19 Adjudicated death classification - on treatment (safety analysis set) - Study D513BC00001

	Number (%) of patients	
Characteristic	**Ticagrelor (N=9562)**	**Placebo (N=9531)**
Number of adjudicated deaths	187 (2.0%)	223 (2.3%)
CV death	146 (1.5%)	172 (1.8%)
Sudden cardiac death	46 (0.5%)	50 (0.5%)
Death due to an acute MI	10 (0.1%)	15 (0.2%)
Death due to heart failure or cardiogenic shock	6 (0.1%)	11 (0.1%)
Death due to cerebrovascular event	14 (0.1%)	10 (0.1%)
Death due to other cardiovascular cause	2 (0.0%)	6 (0.1%)
Presumed cardiovascular death (unknown cause of death)	68 (0.7%)	80 (0.8%)
Non-CV death	41 (0.4%)	51 (0.5%)
Pulmonary failure	0 (0.0%)	2 (0.0%)
Renal failure	4 (0.0%)	1 (0.0%)
Gastrointestinal causes	1 (0.0%)	0 (0.0%)
Hepatobiliary	0 (0.0%)	1 (0.0%)
Pancreatic	2 (0.0%)	2 (0.0%)
Infection (includes sepsis)	14 (0.1%)	21 (0.2%)
Non-infectious systemic inflammatory response syndrome	0 (0.0%)	0 (0.0%)
Haemorrhage (not CV bleeding or stroke)	2 (0.0%)	0 (0.0%)

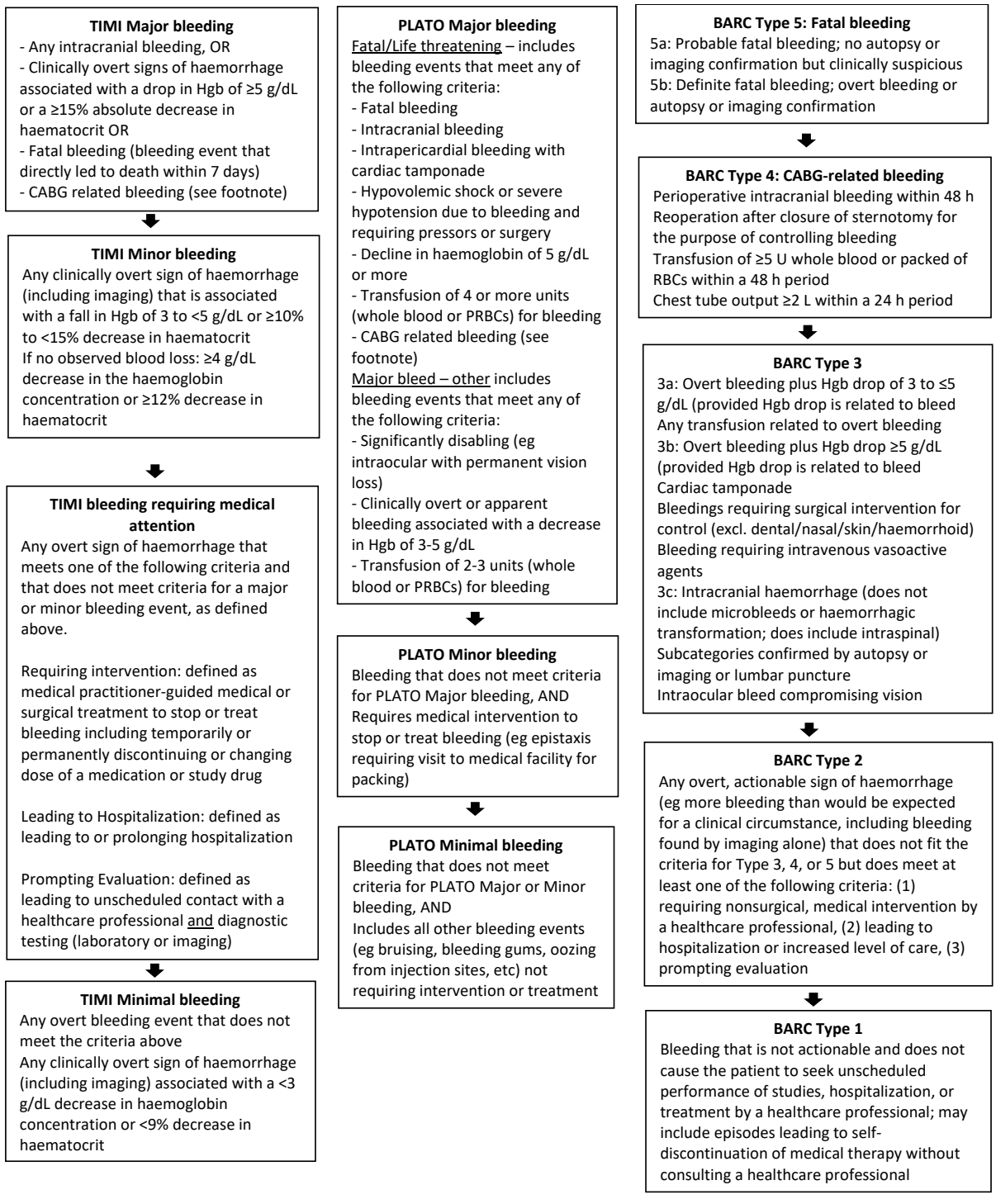
Table 19 Adjudicated death classification - on treatment (safety analysis set) - Study D513BC00001

	Number (%) of patients	
Characteristic	**Ticagrelor (N=9562)**	**Placebo (N=9531)**
Non-CV procedure or surgery	1 (0.0%)	0 (0.0%)
Trauma	5 (0.1%)	2 (0.0%)
Suicide	1 (0.0%)	1 (0.0%)
Non-prescription drug reaction or overdose	0 (0.0%)	0 (0.0%)
Prescription drug reaction or overdose	0 (0.0%)	0 (0.0%)
Neurological	0 (0.0%)	0 (0.0%)
Malignancy	9 (0.1%)	21 (0.2%)
Other	2 (0.0%)	0 (0.0%)

Bleeding events

Bleeding events were evaluated according to different bleeding definitions including TIMI, PLATO and BARC as presented in the figure below.

Figure 5 Bleeding definitions in THEMIS



Notes

CABG related bleeding: fatal bleeding or perioperative intracranial bleeding or reoperation following closure of the sternotomy incision for the purpose of controlling bleeding or transfusion of ≥5 units of whole blood or PRBCs within a 48 hour period or chest tube input >2 L within a 24 hour period.
TIMI and PLATO intracranial bleeding definitions excluded microhaemorrhages <10 mm evident only on gradient-echo MRI

For bleeding events by PT, the most common bleeding events were Epistaxis (285 patients in the ticagrelor group and 105 in the placebo group), Haematuria (108 and 55, respectively), and Ecchymosis (108 and 18, respectively).

Table 20 Bleeding events by location - on treatment (safety analysis set)

	Total number of bleeding events		Number (%) of patients	
Bleed location[a]	**Ticagrelor**	**Placebo**	**Ticagrelor (N=9562)**	**Placebo (N=9531)**
Patients with any bleeding event[b]	1771	684	1446 (15.1%)	595 (6.2%)
Subcutaneous/dermal	587	114	519 (5.4%)	106 (1.1%)
Gastrointestinal	400	182	374 (3.9%)	169 (1.8%)
Epistaxis	358	127	287 (3.0%)	107 (1.1%)
Genitourinary	189	107	173 (1.8%)	96 (1.0%)
Intracranial	70	46	70 (0.7%)	46 (0.5%)
Intraocular	69	49	65 (0.7%)	45 (0.5%)
Other	55	29	54 (0.6%)	29 (0.3%)
Hemoptysis	29	19	26 (0.3%)	19 (0.2%)
Cardiac cath/PCI access site	3	4	3 (0.0%)	4 (0.0%)
Intra-articular	2	2	2 (0.0%)	2 (0.0%)
Pericardial	1	3	1 (0.0%)	3 (0.0%)
Intramuscular causing compartment syndrome	2	1	2 (0.0%)	1 (0.0%)
Retroperitoneal	2	1	2 (0.0%)	1 (0.0%)
Intraspinal	0	0	0 (0.0%)	0 (0.0%)

TIMI major bleeding events

- TIMI Major bleeding events were reported for 206 patients on ticagrelor and 100 patients on placebo, corresponding to KM percentages at 36 months of 2.7% and 1.2%, respectively.
- The KM curves show that bleeding risk appeared constant over time, with proportionally higher risk on ticagrelor throughout the study.
- The relative risk of TIMI major bleeding events with ticagrelor versus placebo appeared consistent across most pre-defined subgroups based on demographics, medical history, or medications at baseline.
  - The relative risk increase of TIMI Major bleeding appeared smaller in subgroups related to coronary interventions compared with patients without a history of coronary interventions.
  - The relative risk versus placebo of TIMI Major Bleeding events in patients randomised to 60 mg ticagrelor or matching placebo appeared consistent with the relative risk versus placebo in all patients in the safety analysis set

Table 21 Analysis of TIMI bleeding events - on treatment (safety analysis set)

	Ticagrelor (N=9562)		Placebo (N=9531)			
Characteristic	**Patients with events (%)**	**KM% at 36 months**	**Patients with events (%)**	**KM% at 36 months**	**Hazard Ratio (95% CI)**	**p-value**
TIMI major bleeding	206 (2.2%)	2.7%	100 (1.0%)	1.2%	2.32 (1.82, 2.94)	<.0001
TIMI major or minor bleeding	285 (3.0%)	3.6%	129 (1.4%)	1.6%	2.49 (2.02, 3.07)	<.0001
TIMI major, minor or requiring medical attention bleeding	1072 (11.2%)	13.0%	485 (5.1%)	5.6%	2.51 (2.26, 2.80)	<.0001

Figure 6 Kaplan-Meier plot of TIMI Major bleeding events – on treatment (safety analysis set)

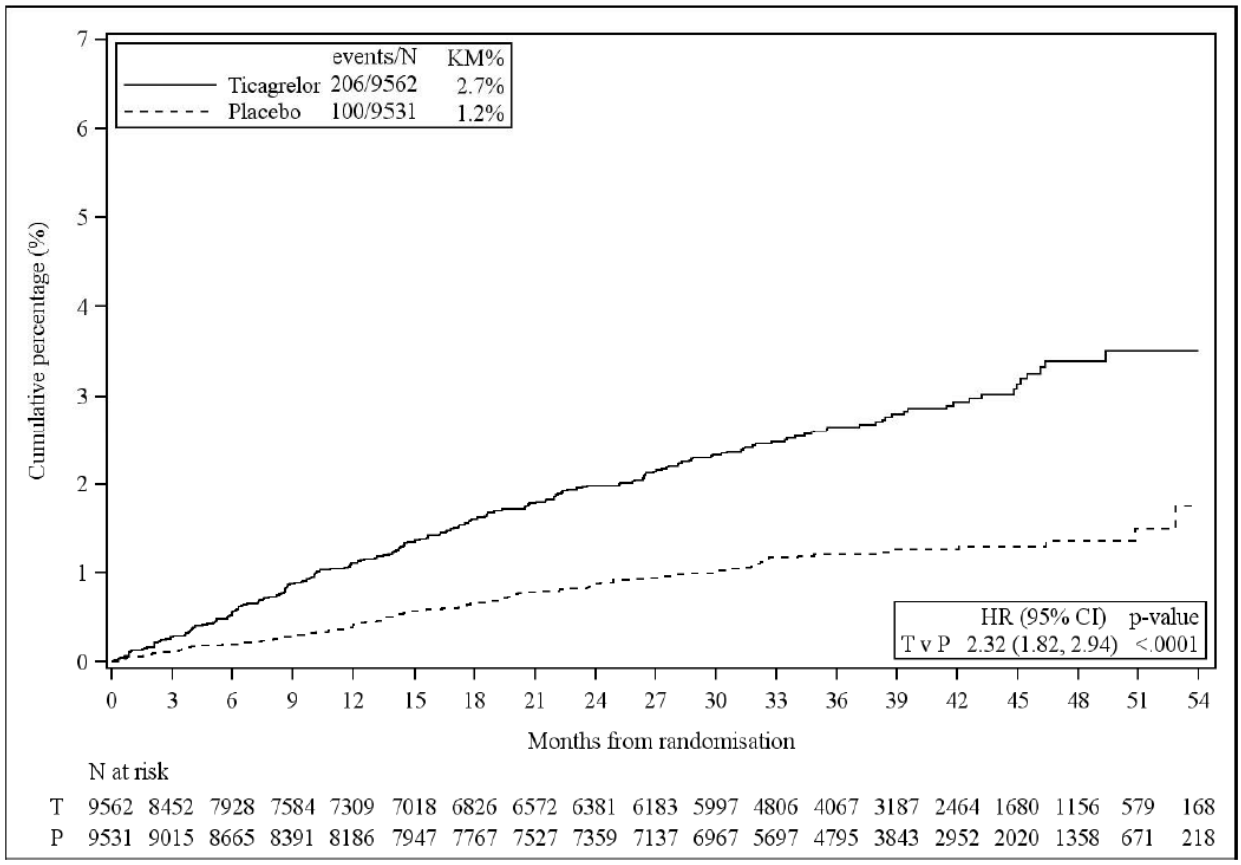
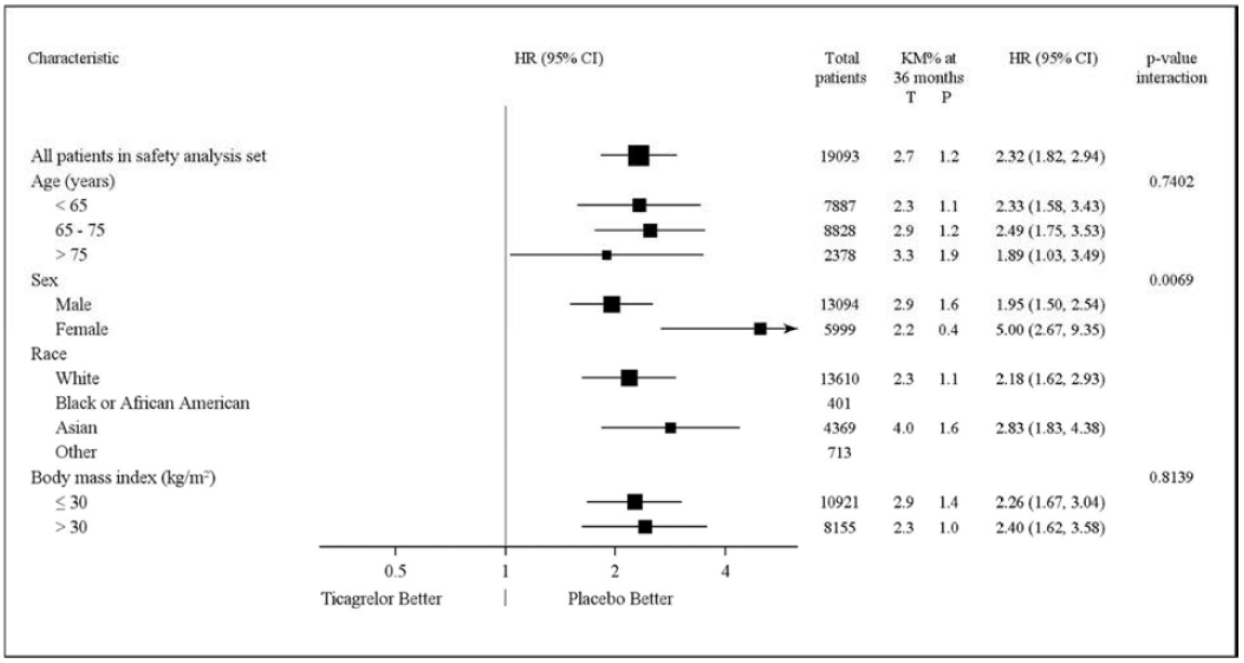
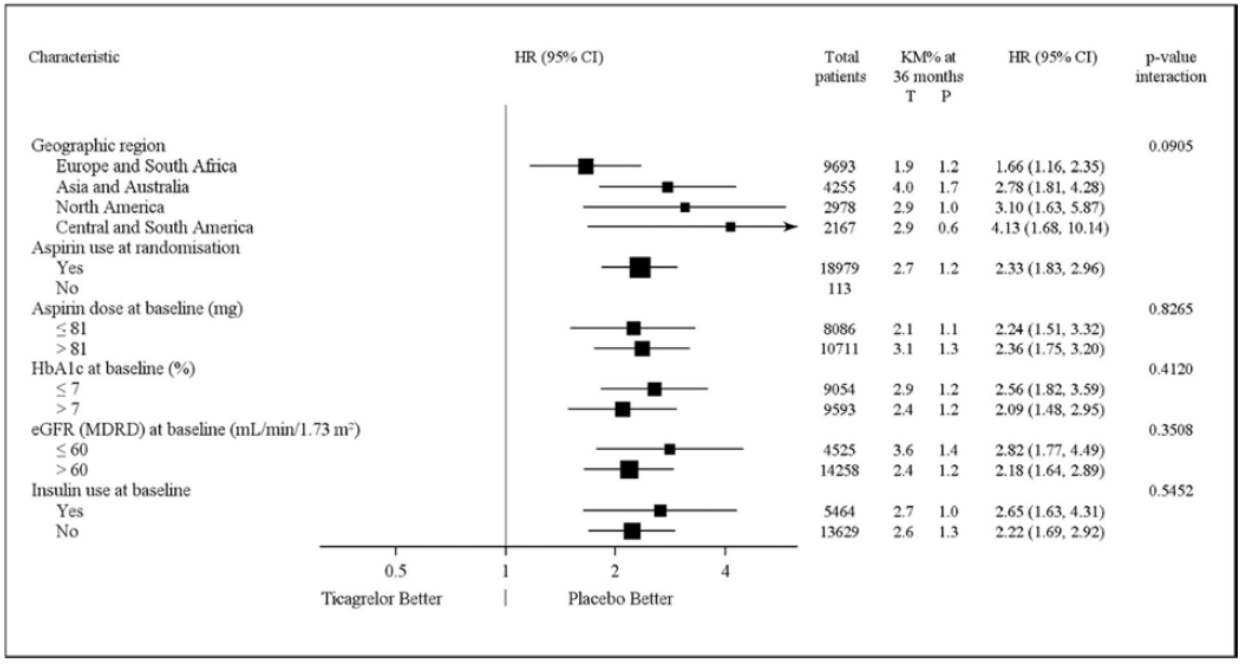
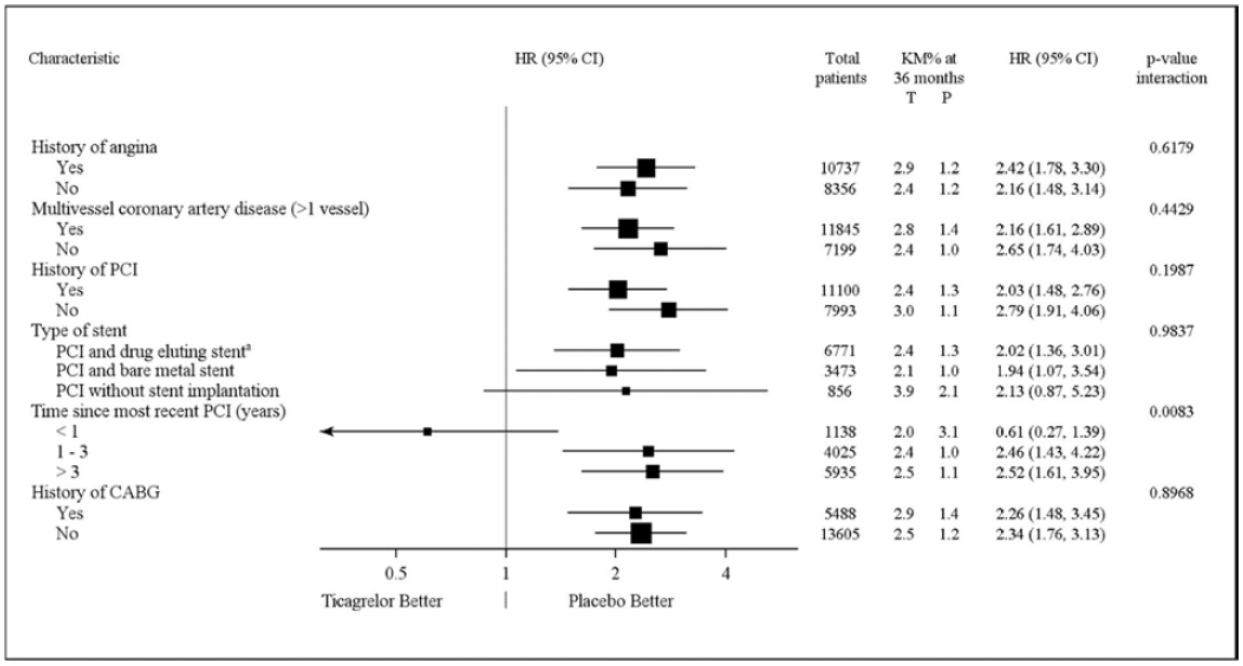
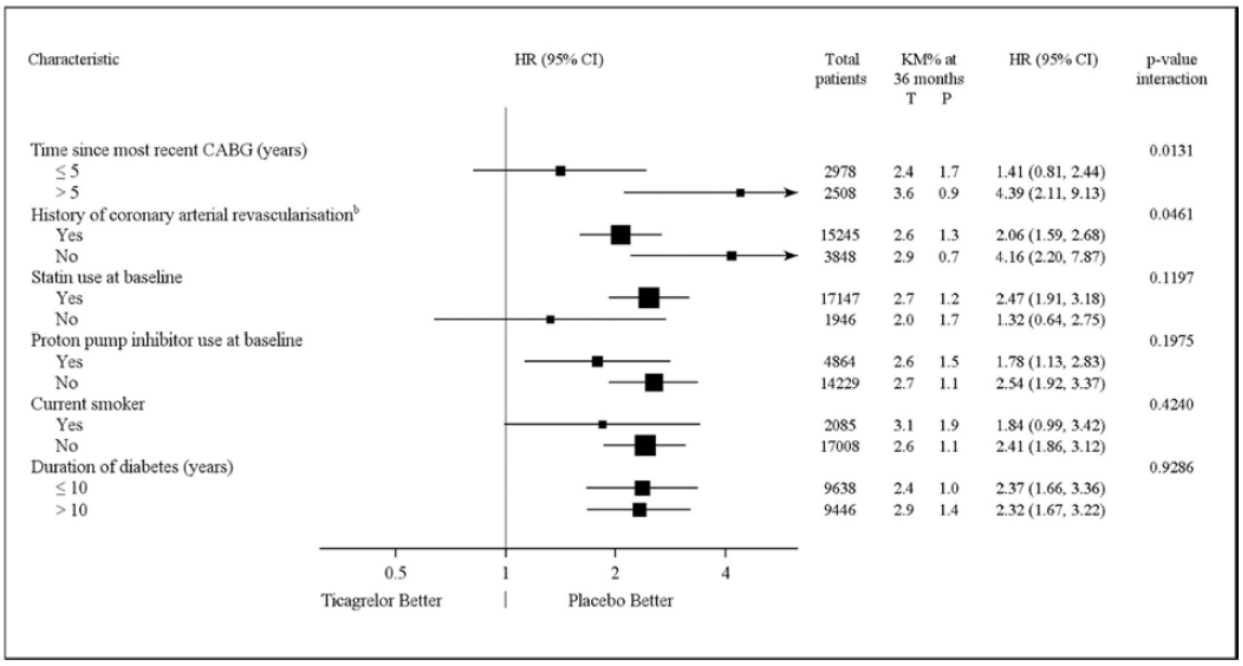


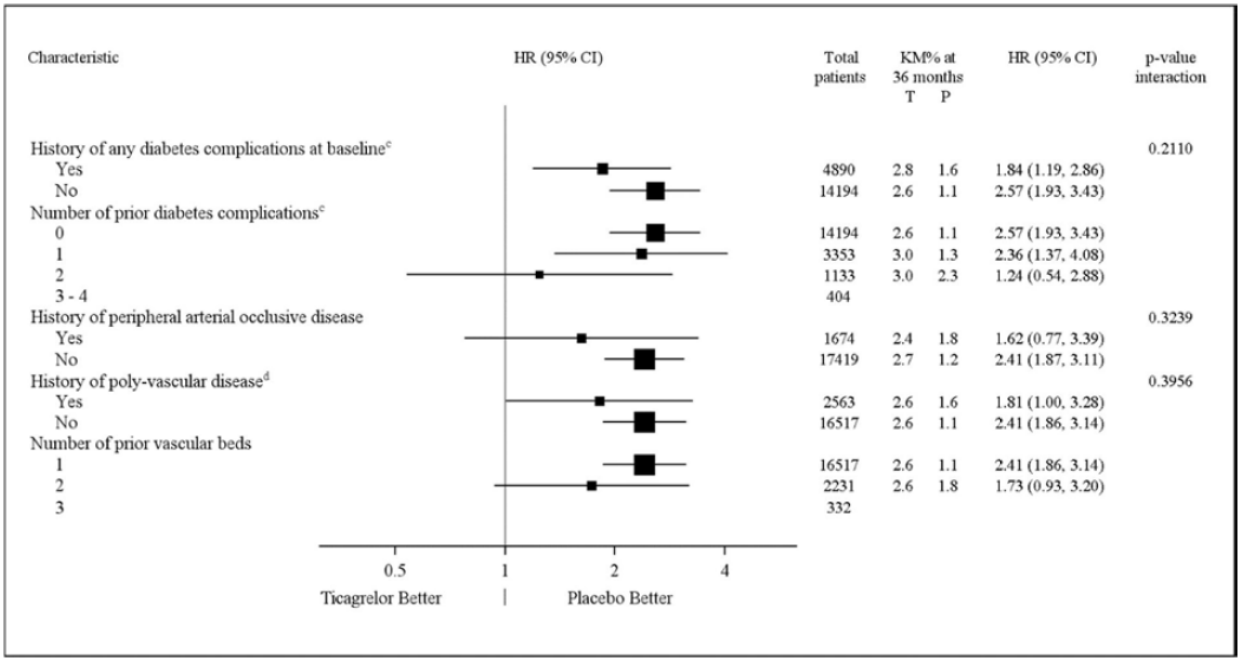
Figure 7 Hazard ratios and rates of TIMI major bleeding events by patient subgroup - on treatment (safety analysis set)






Characteristic
HR (95% CI)
Total patients
KM% at 36 months T P
HR (95% CI)
p-value interaction
History of angina 0.6179
Yes 10737 2.9 1.2 2.42 (1.78, 3.30)
No 8356 2.4 1.2 2.16 (1.48, 3.14)
Multivessel coronary artery disease (>1 vessel) 0.4429
Yes 11845 2.8 1.4 2.16 (1.61, 2.89)
No 7199 2.4 1.0 2.65 (1.74, 4.03)
History of PCI 0.1987
Yes 11100 2.4 1.3 2.03 (1.48, 2.76)
No 7993 3.0 1.1 2.79 (1.91, 4.06)
Type of stent 0.9837
PCI and drug eluting stent[a] 6771 2.4 1.3 2.02 (1.36, 3.01)
PCI and bare metal stent 3473 2.1 1.0 1.94 (1.07, 3.54)
PCI without stent implantation 856 3.9 2.1 2.13 (0.87, 5.23)
Time since most recent PCI (years) 0.0083
< 1 1138 2.0 3.1 0.61 (0.27, 1.39)
1 - 3 4025 2.4 1.0 2.46 (1.43, 4.22)
> 3 5935 2.5 1.1 2.52 (1.61, 3.95)
History of CABG 0.8968
Yes 5488 2.9 1.4 2.26 (1.48, 3.45)
No 13605 2.5 1.2 2.34 (1.76, 3.13)
0.5
1
2
4
Ticagrelor Better
Placebo Better


Characteristic
HR (95% CI)
Total patients
KM% at 36 months T P
HR (95% CI)
p-value interaction
Time since most recent CABG (years) 0.0131
≤ 5 2978 2.4 1.7 1.41 (0.81, 2.44)
> 5 2508 3.6 0.9 4.39 (2.11, 9.13)
History of coronary arterial revascularisation[b] 0.0461
Yes 15245 2.6 1.3 2.06 (1.59, 2.68)
No 3848 2.9 0.7 4.16 (2.20, 7.87)
Statin use at baseline 0.1197
Yes 17147 2.7 1.2 2.47 (1.91, 3.18)
No 1946 2.0 1.7 1.32 (0.64, 2.75)
Proton pump inhibitor use at baseline 0.1975
Yes 4864 2.6 1.5 1.78 (1.13, 2.83)
No 14229 2.7 1.1 2.54 (1.92, 3.37)
Current smoker 0.4240
Yes 2085 3.1 1.9 1.84 (0.99, 3.42)
No 17008 2.6 1.1 2.41 (1.86, 3.12)
Duration of diabetes (years) 0.9286
≤ 10 9638 2.4 1.0 2.37 (1.66, 3.36)
> 10 9446 2.9 1.4 2.32 (1.67, 3.22)
0.5
1
2
4
Ticagrelor Better
Placebo Better



TIMI Major or Minor bleeding events

- In the full study population, TIMI Major or Minor bleeding events were reported for 285 patients on ticagrelor and 129 patients on placebo, corresponding to KM percentages at 36 months of 3.6% and 1.6%, respectively.
- The KM curves showed that the risk of TIMI Major or Minor bleeding events appeared constant over time, with proportionally higher risk on ticagrelor throughout the study.

PLATO major bleeding events

- In the full study population, PLATO Major bleeding events were reported for 310 patients on ticagrelor and 145 patients on placebo, corresponding to KM percentages at 36 months of 4.0% and 1.7%, respectively.
- The KM curves show that the risk of PLATO Major bleeding appeared constant over time, with proportionally higher risk on ticagrelor throughout the study.

Table 22 Analysis of PLATO major bleeding event - on treatment (safety analysis set)

	Ticagrelor (N=9562)		Placebo (N=9531)			
Characteristic	**Patients with events (%)**	**KM% at 36 months**	**Patients with events (%)**	**KM% at 36 months**	**Hazard Ratio (95% CI)**	**p-value**
PLATO major bleeding	310 (3.2%)	4.0%	145 (1.5%)	1.7%	2.41 (1.98, 2.93)	<.0001
Fatal/Life threatening	206 (2.2%)	2.6%	99 (1.0%)	1.2%	2.34 (1.84, 2.97)	<.0001
Other PLATO major bleeding	108 (1.1%)	1.4%	46 (0.5%)	0.6%	2.64 (1.87, 3.72)	<.0001

BARC bleeding events

Consistent with results of TIMI and PLATO bleeding classifications, BARC bleeding events were reported in more patients in the ticagrelor group than in the placebo group.

Fatal bleeding events

In the full study population, there were 17 patients in the ticagrelor group (0.2%, 0.07 events/100 patient-years) and 10 patients in the placebo group (0.1%, 0.04 events/100 patient-years) with fatal bleeding events. The most common fatal bleeding events (based on the total number of events) by SOC were Nervous system disorders (8 patients in the ticagrelor group and 6 patients in the placebo group) and Injury, poisoning and procedural complications (7 patients and 2 patients, respectively).

The most common fatal bleeding events (based on the total number of events) by PT were Haemorrhagic stroke (3 patients in the ticagrelor group and 2 patients in the placebo group) and Cerebral haemorrhage (2 and 2, respectively).

Table 23 Fatal bleeding events by SOC and PT - on treatment (safety analysis set)

	Ticagrelor (N=9562)		Placebo (N=9531)	
Characteristic (SOC/PT)	Number (%) of patients[a]	Event rate (per 100 patient years)[b]	Number (%) of patients[a]	Event rate (per 100 patient years)[b]
Patients with a fatal bleeding	17 (0.2%)	0.07	10 (0.1%)	0.04
Nervous system disorders	8 (0.1%)	0.03	6 (0.1%)	0.02
Brain stem haemorrhage	2 (0.0%)	0.01	0 (0.0%)	0.00
Cerebral haematoma	0 (0.0%)	0.00	1 (0.0%)	0.00
Cerebral haemorrhage	2 (0.0%)	0.01	2 (0.0%)	0.01
Haemorrhage intracranial	1 (0.0%)	0.00	1 (0.0%)	0.00
Haemorrhagic stroke	3 (0.0%)	0.01	2 (0.0%)	0.01
Cardiac disorders	0 (0.0%)	0.00	1 (0.0%)	0.00
Cardiac tamponade	0 (0.0%)	0.00	1 (0.0%)	0.00
Gastrointestinal disorders	1 (0.0%)	0.00	0 (0.0%)	0.00
Gastrointestinal ulcer haemorrhage	1 (0.0%)	0.00	0 (0.0%)	0.00
Hepatobiliary disorders	0 (0.0%)	0.00	1 (0.0%)	0.00
Cirrhosis alcoholic	0 (0.0%)	0.00	1 (0.0%)	0.00
General disorders and administration site conditions	1 (0.0%)	0.00	0 (0.0%)	0.00
Medical device site haemorrhage	1 (0.0%)	0.00	0 (0.0%)	0.00
Injury, poisoning and procedural complications	7 (0.1%)	0.03	2 (0.0%)	0.01
Post procedural haematoma	1 (0.0%)	0.00	0 (0.0%)	0.00
Subdural haematoma	3 (0.0%)	0.01	0 (0.0%)	0.00
Subdural haemorrhage	0 (0.0%)	0.00	2 (0.0%)	0.01
Traumatic haemorrhage	1 (0.0%)	0.00	0 (0.0%)	0.00
Traumatic intracranial haemorrhage	2 (0.0%)	0.01	0 (0.0%)	0.00

Intracranial haemorrhage events

In the full study population, there were 70 patients with ICH in the ticagrelor group (0.7%, 0.30 events/100 patient years) and 46 (0.5%, 0.18 events/100 patient years) in the placebo group, corresponding to KM percentages at 36 months of 0.9% and 0.5%, respectively (HR 1.71 [95% CI 1.18, 2.48]).

The difference in ICH events was due to an imbalance in traumatic bleeding events across groups: 41 (0.4%) and 16 (0.2%) in the ticagrelor and placebo groups, respectively. The most commonly reported location of traumatic ICH was subdural. Spontaneous ICH events occurred in 28 (0.3%) and 27 (0.3%) patients in the ticagrelor and placebo groups, respectively. Procedure-related ICH events occurred in 1 patient on ticagrelor and in 3 patients on placebo.

There were 13 fatal ICH events (9 spontaneous and 4 traumatic) on ticagrelor and 8 (5 spontaneous, 2 procedural and 1 traumatic) on placebo.

Intracranial haemorrhages were seen on both 60 mg bd and 90 mg bd doses. For a sensitivity analysis of consistency between doses.

Table 24 Sensitivity analysis of consistency between treatment effect of ticagrelor 60 mg and effect of ticagrelor 90 mg for ICH - on treatment (safety analysis set)

	Ticagrelor			Placebo				
Characteristic	Number of patients	Patients with events (%)	KM% at 24 months	Number of patients	Patients with events (%)	KM% at 24 months	Hazard Ratio (95% CI)	p-value
Intracranial haemorrhage bleeding, including only patients randomised to ticagrelor 60 mg or matching placebo[a]	2482	11 (0.4%)	0.4%	2516	10 (0.4%)	0.3%	1.21 (0.52, 2.86)	0.6569
Intracranial haemorrhage bleeding, including only patients randomised to ticagrelor 90 mg or matching placebo[b]	7080	19 (0.3%)	1.1%	7015	10 (0.1%)	0.3%	2.10 (0.98, 4.52)	0.0573
Intracranial haemorrhage bleeding, including patients on treatment with ticagrelor 60 mg or matching placebo[c]	7947	50 (0.6%)	0.6%	8557	37 (0.4%)	0.4%	1.54 (1.01, 2.35)	0.0469

[a] Includes events with an onset date on or after randomisation and up to and including 7 days after last dose of ticagrelor 60 mg or matching placebo.
[b] Includes events with an onset date on or after randomisation and up to and including 7 days after last dose of ticagrelor 90 mg or matching placebo.

[c] Only patients who were randomised to ticagrelor.

Laboratory findings

Clinical laboratory variables were analysed at local laboratories for all patients at baseline (Visit 1) only. No laboratory monitoring was included in the protocol after baseline. One patient in the placebo group had combined alanine aminotransferase or aspartate aminotransferase (>3 x upper limit of normal [ULN]), and bilirubin (>2 x ULN) elevations during the study.

The effects of ticagrelor on laboratory variables have been extensively studied in previous large CV outcome studies in patients with CAD (PLATO and PEGASUS-TIMI54 studies).

Safety in special populations

Patients with a history of PCI

In the 11100 patients with a history of PCI, 5536 patients received ticagrelor, and 5564 received placebo. The median total duration of exposure was 33.3 and 36.0 months for the ticagrelor and placebo treatment groups, respectively. The median exposure on ticagrelor 60 mg bd was 32.4 months, and on ticagrelor 90 mg bd 7.3 months. The total number of treatment years for the total duration of exposure in the ticagrelor group was 13449, of which 10351 (77.0%) were on ticagrelor 60 mg bd.

For THEMIS PCI patients, there were 1219 (22.0%) and 418 (7.5%) patients with Dyspnoea AEs in the ticagrelor and placebo groups, respectively. Dyspnoea SAEs were reported by 26 (0.5%) patients in the ticagrelor group and 26 (0.5%) patients in the placebo group.

The proportions of patients with SAEs in the THEMIS PCI patients were 32.2% in the ticagrelor group and 35.7% in the placebo group. The distribution by SOC of the most commonly reported SAEs was similar to those in the total patient population. The most commonly reported SAEs by PT were the same in the THEMIS PCI patients as in the total population.

In THEMIS PCI patients, there were fewer deaths on ticagrelor compared to the placebo group both on-treatment and on- and off-treatment. There were 195 adjudicated deaths (77 on ticagrelor and 118 on placebo) on-treatment included in the safety analysis set. The corresponding number of deaths on- and off-treatment was 275 in the ticagrelor group and 317 in the placebo group. The pattern of causes of deaths was similar in the PCI group as compared to the full study population.

In the THEMIS PCI patients, TIMI Major bleeding events were reported for 111 patients on ticagrelor and 62 patients on placebo, corresponding to KM percentages at 36 months of 2.4% and 1.3%, respectively. TIMI Major or Minor bleeding events were reported for 157 patients on ticagrelor and 80 patients on placebo, corresponding to KM percentages at 36 months of 3.4% and 1.7%, respectively. PLATO Major bleeding events were reported for 176 patients on ticagrelor and 90 patients on placebo, corresponding to KM percentages at 36 months of 3.8% and 1.9%, respectively. The fatal bleeding events were balanced between the treatment groups; 6 patients in the ticagrelor group (0.1%, 0.04 events/100 patient-years) and 6 patients in the placebo group (0.1%, 0.04 events/100 patient-years). The most common fatal bleeding events (based on total number of events) by SOC were Nervous system disorders (2 patients in the ticagrelor group and 3 patients in the placebo group) and Injury, poisoning and procedural complications (3 and 1, respectively). There were 33 patients with ICH in the ticagrelor group (0.6%, 0.25 events/100 patient-years) and 31 (0.6%, 0.20 events/100 patient-years) in the placebo group.

In the THEMIS PCI patients, discontinuation due to AE was 21.3% vs 13.0%. The most commonly reported DAEs by PT were the same as for the total population. There were more Dyspnoea DAEs (7.3%) in the ticagrelor group than in the placebo group (0.8%). Discontinuation due to a bleeding event was reported for 261 patients on ticagrelor and 71 on placebo, corresponding to KM percentages at 36 months of 5.3% and 1.4%, respectively (HR 4.01 [95% CI 3.08, 5.21]).

Safety related to drug-drug interactions and other interactions

Discontinuation due to adverse events

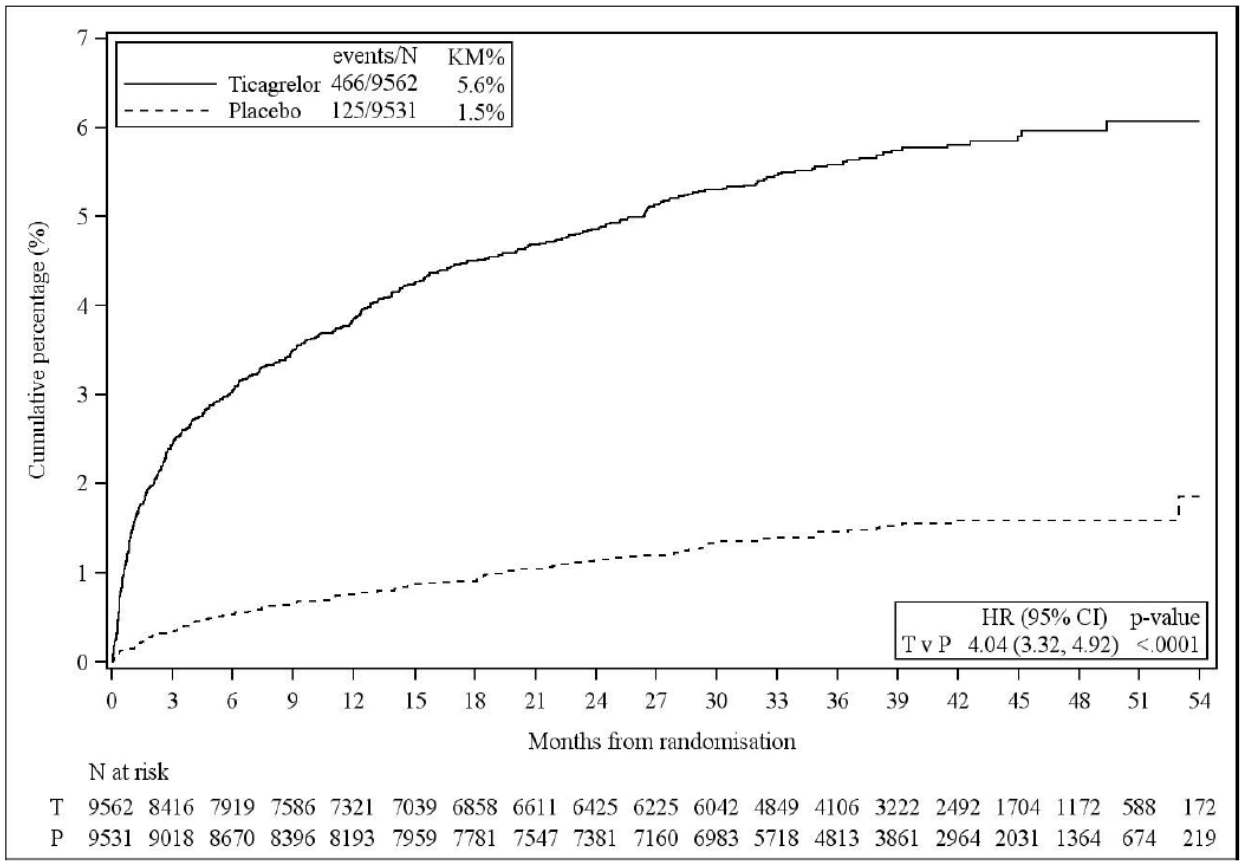
In the full THEMIS population, there was a higher proportion of patients with DAEs in the ticagrelor group than in the placebo group: 20.8% and 12.2%, respectively. The most commonly reported DAEs by PT were Dyspnoea (6.9% vs 0.8%), Atrial fibrillation (1.1% vs 1.3%), and Angina unstable (0.7% vs 1.0%), with Dyspnoea being a more common reason for discontinuing the study in the ticagrelor group compared with placebo.

Bleeding events leading to premature permanent discontinuation of study drug

In the THEMIS full population, discontinuation due to a bleeding event was reported for 466 patients on ticagrelor and 125 patients on placebo, corresponding to KM percentages at 36 months of 5.6% and 1.5%, respectively (HR 4.04 [95% CI 3.32, 4.92]).

The most common PTs for bleeding events leading to premature permanent discontinuation of study drug were Epistaxis (74 [0.8%] patients in the ticagrelor group and 20 [0.2%] in the placebo group), Increased tendency to bruise (51 [0.5%] and 4 [0.0%], respectively), and Ecchymosis (41 [0.4%] and 5 [0.1%], respectively).

Figure 8 Kaplan-Meier plot of premature permanent discontinuation due to any bleeding event – on treatment (safety analysis set)



2.5.1. Discussion on clinical safety

More than 9500 patients have been included in each treatment group to be able to demonstrate a difference in treatment effect. A total of 19093 patients (99% of randomised patients) received at least 1 dose of randomised study drug (ticagrelor or placebo). The large number of patients provided substantial placebo-controlled information on the safety of ticagrelor in addition to existing safety information of ticagrelor based on previous studies in different patient populations and post-marketing data.

The most commonly reported AEs on ticagrelor and reported at a higher frequency were dyspnoea (21.4% vs 7.3%) and bleeding events (15.1% vs 6.2%). No general overview of AEs according to SOC or overall frequencies of individual AEs has been presented as only serious AEs, and AEs of special interest have been captured considering the known safety profile from other studies.

The definition used to identify and define bleeding events was in accordance with general and accepted definition categories (TIMI, PLATO. BARC) and therefore appropriate, in particular, the TIMI scale as the main analysis method for bleeding events. As can be expected a higher AE risk for bleeding was reported (15.1% vs 6.2%). Bleeding risk was consistently increased across all bleeding scales used and constantly increased over time. TIMI major bleedings were reported at a significantly higher frequency after 36 months of treatment (2.2% vs 1.0%, HR 2.32 (95% CI 1.92-2.94), p<0.001). In line, PLATO major bleeding were reported with a significantly higher frequency (3.2% vs 1.5%, HR 2.41 (95% CI 1.98-2.93), p<0.001). The higher bleeding risk was mainly attributed to a higher frequency in subcutaneous bleedings (5.4%, 1.1%), gastrointestinal bleedings (3.9% vs 1.8%) and

epistaxis (3.0% vs 1.1%), which are known bleeding types with ticagrelor. Fatal bleedings were rare but slightly higher for ticagrelor (0.2%, 0.07 events/100 patient-years vs (0.1%, 0.04 events/100 patient-years) the most common fatal events (based on number of events) by PT were haemorrhagic stroke (3 vs 2) and cerebral haemorrhage (2 vs 2, respectively). The number of intracranial bleedings was limited, but higher for ticagrelor, 70 (0.7%, 0.30 events/100 patient-years) vs 46 (0.5%, 0.18 events/100 patient-years). This was mainly attributed to an imbalance in traumatic bleeding events across groups (41 (0.4%) and 16 (0.2%)), while spontaneous and procedure-related ICHs were similar. Somewhat reassuring is that for those patients initially randomised to the 60 mg dose ICH was similar (11 (0.4%) vs 10 (0.4%)), although this is only a subset of the total population. Increased risk of ICH was previously seen in the PLATO, while PEGASUS showed approximately similar risk across treatment groups.

In general, the observed higher bleeding risk of ticagrelor-treated patients was consistent across subgroups. Except that a significantly higher risk for bleeding was observed for female compared to male sex (HR 1.95 (1.50-2.54) vs 5.00 (2.67, 9.35); p for interaction =0.0069) likely driven by the lower background rate in the placebo group in females. Also, for patients with a history of coronary arterial revascularisation, there appears a lower bleeding risk ((HR 2.09 (1.59-2.68) vs 4.16 (2.20, 7.87); p for interaction =0.0461). Moreover, a trend for lower bleeding risk was observed for the European population (p for interaction 0.0905). Stroke, but not TIA, was an exclusion criterion. A total of 336 patients (1.8%) had a history of ischemic stroke/TIA at baseline, and 710 patients (3.7%) had a history of malignant neoplasms.

Dyspnoea is a known adverse event of ticagrelor, which has been specifically followed within the clinical program. Dyspnoea was reported at a higher frequency than previous studies of PEGASUS and PLATO (both ticagrelor and placebo (21.4%, 7.3%)). As known from previous evaluation, dyspnoea did not impact pulmonary or cardiac function (DISPERSE II and PLATO).

Specific attention has been given to bradyarrhythmic AEs, with only slightly increased frequency of these adverse events for ticagrelor (1.4% vs 1.3%) and bradyarrhythmia SAEs (0.7% vs 0.5%). Dizziness, hypotension and syncope could be associated with bradyarrhythmic AEs; however, no substantial imbalances could be reported, especially due to the very limited number of these events.

Specific attention was given to renal related AEs. However, there seemed no clear evidence of any impact of ticagrelor on AEs-related to renal function or the kidney (2.4% vs 2.3%; SAEs (0.9% vs 0.7%)). Any impact on creatinine has not been evaluated as any clinical laboratory variables have not been evaluated during the study, considering that these have been extensively evaluated in previous studies.

A known effect of ticagrelor is the reversible increase in uric acid. Therefore, gout was evaluated as a AE of interest. As can be expected, slightly more AEs of gout were reported with ticagrelor than for placebo (2.0% vs 1.7%).

For pneumonia no difference in AEs (2.6% vs 2.8%) and SAEs was reported (1.5% vs 1.6%).

Hepatic related events were not specifically evaluated, no laboratory evaluation on hepatic enzymes was performed.

Despite that SAEs were frequently reported, these were reported at a lower frequency for ticagrelor (31.9% vs 33.7%). Cardiac disorders (11.9% vs 14.1%), infections and infestations (4.8% vs 5.1%) and nervous system disorders (3.3% vs 4.3%) were mostly reported, all with a lower frequency for ticagrelor. After inspection of site 7605, it was identified that there was an underreporting of SAEs. After this inspection, an additional 52 SAEs from this site was reported. This GCP noncompliance requests for further details on the monitoring and conduct according to GCP of the trial, although the

frequency of SAEs (31.9%-33.7%) in comparison to previous studies (approximately 21% PLATO and PEGASUS) does not suggest an underreporting of SAEs in the overall study conduct.

Death was an efficacy endpoint in this study, and all deaths that occurred prior to withdrawal of consent were adjudicated. Ticagrelor treatment did not lead to a higher frequency of death, as well as for the 'on-treatment' frequency. Based on the efficacy endpoint, the HR for overall mortality was estimated at HR 0.98 (95% CI: 0.87-1.10). There were no clear imbalances in types of deaths that would raise any concern. Reassuringly, no imbalance in death due to malignancies was found as previously subject to discussion in the PEGASUS study (9(0.1%) vs 21 (0.2%) on treatment; 88 (0.9%) vs 112 (1.2%) on and off treatment). A large proportion of patients discontinued treatment with ticagrelor due to adverse events, which subside the usability for long term treatment in clinical practice (20.8% vs 12.2%).

The principal reason for discontinuation was because patients experienced adverse events, mainly bleedings and dyspnoea. As previously observed, discontinuation due to bleedings was mainly observed with the first months of treatment, with additional wearing off of the discontinuation rate. The reported discontinuation rates due to AEs with ticagrelor varied considerably in previous studies, from 7.4% (vs clopidogrel 5.4%) in PLATO, to 16.1% (vs. 8.5% ASA alone) in PEGASUS, and up to 14.3%-17% per year in cohort studies [Lee M, et al. *N Z Med J*. 2015;128:110-1] [Zanchin T, et al. *Circ Cardiovasc Interv*. 2018;11:e006132]. From prior and current studies, it is apparent that the ticagrelor efficacy depends on the patient's ability to tolerate ticagrelor adverse effects (mainly dyspnoea and bleeding) and to keep on treatment. It should be noted that if discontinuation rates with ticagrelor would increase by only ≥0.7%, the study would become negative.

No indirect data of blood loss (change in haemoglobin, hematocrit) is available, as laboratory measurements were not conducted. The only data related to blood loss derives from the assessment of bleeding leading to blood transfusion. A total of 195 patients (2.0%) in the ticagrelor group and 88 patients (0.9%) in the placebo group had a blood transfusion-related to a bleeding event.

Further considerations to the subgroup of patients with a history of PCI

Similarly, than for efficacy, the PCI < 1 year subgroup is conflicting also for safety. It is the only subgroup were the point estimate for major bleeding favors ticagrelor versus placebo (HR: 0.61; 95%CI: 0.27 to 1.39).

3. Risk management plan

The MAH submitted an updated RMP version (version 12, signed on 08 July 2019) with this application. The (main) proposed RMP changes were the following:

The RMP was updated to include the new target indication, including dose recommendations, supported by data from Phase III trial D513BC00001 (THEMIS - Effect of Ticagrelor on Health outcomes in diabetes Mellitus patients Intervention Study) in patients with coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM). Additionally, the status of non-interventional database study D5130R00027 has been changed from ongoing to completed.

Summary of significant changes in this RMP:

Part I Product Overview
Addition of BRILINTA indication in patients with CAD and T2DM who have undergone percutaneous coronary intervention (PCI) and proposed dosing regimen for these patients.

Proposed indication(s) in the EEA:
BRILIQUE, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with

- coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) without a history of myocardial infarction who have undergone percutaneous coronary intervention (PCI) or
- acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

Proposed dosage in the EEA:
In adult patients with CAD and T2DM who have undergone PCI (for patients with ACS see ACS below): 60 mg twice daily (bd), orally.

In patients with an ACS event: 180 mg loading dose (2 tablets of 90 mg) followed by 90 mg twice daily (bd), orally.

In patients with a history of MI:60 mg bd, orally.

Part II SI
Addition of new section Part II: 1.4 for CAD and T2DM epidemiology.

PRAC Rapporteurs assessment comment:
The MAH updated the RMP with information on the newly proposed indication, dosages and CAD and T2DM epidemiology. These changes can be accepted for now. However, as the approval of the extension of the indication is pending on the assessment of the LoQ and the assessment of the CHMP rapporteur, information in these sections might be subject to change.

Part II SIII
Clinical trial exposure data updated.

PRAC Rapporteurs assessment comment:
The MAH updated the clinical trial exposure with data from the THEMIS study. This is accepted.

Part II SV
Cumulative marketed exposure data updated.

PRAC Rapporteurs assessment comment:
The MAH updated this section to include the cumulative post-marketing exposure until 31 December 2017. This is accepted.

Part II SVII
Removal of text describing safety concerns reclassified based on the update to the Good Pharmacovigilance Practices (GVP) Module V – Risk management systems (Revision 2), implemented in the previous update (to Version 11).

PRAC Rapporteurs assessment comment:
The MAH updated this section to include the cumulative post-marketing exposure until 31 December 2017. This is accepted.

Part II SVIII
No changes were proposed to the summary of safety concerns:

Table II-1 Summary of safety concerns

Important identified risks	Increased risk of bleeding
Important potential risks	None
Missing information	Long-term use in patients with prior ischaemic stroke

PRAC Rapporteurs assessment comment:
The summary of safety concerns remains unchanged. No new safety information is identified in the THEMIS study that is relevant for the Risk management plan. Furthermore, no new important risks or missing information could be identified for the population to which the indication is proposed to be extended. It is accepted that the summary of safety concerns remains unchanged.

Part V: 1 and 3
Addition of 'Long-term use in patients with prior ischaemic stroke' to Tables V-1 and V-2, which was inadvertently left out of the tables upon resolution of the last approval procedure (EMEA/H/C/001241/II/0042), approval date 15 November 2018.

PRAC Rapporteurs assessment comment:
The update of part V is accepted.

Part VI: 1
Addition of Brilique indication in patients with CAD and T2DM who have undergone PCI.

Annex 2
Change of non-interventional database study D5130R00027 from ongoing to completed and addition of completed study D5130L00067, which provided missing information on use in renal failure/dialysis.

PRAC Rapporteurs assessment comment:
The studies described above were not included as additional pharmacovigilance studies or post authorization efficacy studies in the RMP. The changes to Annex 2 are accepted.

Annex 8
Update of summary of changes to RMP over time to reflect this update.

PRAC Rapporteurs assessment comment:
The changes to Annex 8 are accepted.

3.1. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

4. Changes to the Product Information

As a result of this group of variations, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated to include the data from the THEMIS study.

4.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Overall, the wording in the PL is consistent with the style tested previously during the MA applications.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

Patients with coronary artery disease (CAD) are at increased risk for CV morbidity and mortality. Even after a PCI or CABG, patients remain at high risk for CV events. ESC guideline on cardiovascular prevention classifies these patients at very high CV risk. Diabetes (T2DM) is an established risk factor for CV disease.

5.1.2. Available therapies and unmet medical need

Antiplatelet agents are recommended in patients with documented CAD whether or not T2DM is present and should be used unless contraindicated or not tolerated. Acetylsalicylic acid/aspirin is the current standard of care, with clopidogrel being an alternative if ASA is not tolerated. Use of DAPT (dual antiplatelet therapy) in CAD has been documented for ticagrelor in patients with a history of MI as investigated in the PLATO (ACS) and PEGASUS studies (history of MI 1 to 3 years). DAPT in stable CAD is currently reserved for the immediate period after patients have undergone elective PCI. The benefit-risk of DAPT beyond the immediate period after revascularisation or in patients not yet having experienced an MI remains to be clarified.

5.1.3. Main clinical studies

The THEMIS study (D513BC00001) tested the hypothesis that ticagrelor on a background of low-dose ASA can reduce the risk for CV events in patients with (stable) CAD and type 2 diabetes mellitus (T2DM) at high risk for a thrombotic event but with no history of MI or stroke, compared to ASA alone. Coronary artery disease was defined by key inclusion criteria as a history of a percutaneous coronary intervention [PCI], or a history of coronary artery bypass grafting surgery [CABG]) or if no coronary revascularisation, having angiographic evidence of at least 50% lumen stenosis in at least one coronary artery.

5.2. Favourable effects

Ticagrelor, an oral, reversible, antiplatelet agent, was previously approved for the 90 mg BID dose for the prevention of atherothrombotic events in patients with acute coronary syndrome (unstable angina, NSTEMI or STEMI) including patients managed medically, and those who are managed with a percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG). This indication recommends a treatment period for up to 12 months unless earlier discontinuation of ticagrelor is clinically indicated. Moreover, the 60 mg BID dose ticagrelor is approved for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago to 3 years), and a high risk of developing a thrombotic event. This is based on the results of the PLATO and PEAGSUS studies, respectively.

A limited beneficial effect on the composite primary endpoint of CV death, MI and stroke was demonstrated. The Kaplan–Meier rates at 36 months were 6.9% and 7.6% for the ticagrelor and placebo groups, respectively. This translated in hazard rate of (HR) of 0.90 (95% CI 0.81, 0.99), p=0.0378. The effect was largely consistent throughout the treatment period. MI seems to contribute the most to the overall treatment effect (54 less events from 602 events (2.8% vs 3.4%)), followed by stroke (41 less events from 401 events (1.9% vs 2.3%)).

5.3. Uncertainties and limitations about favourable effects

The treatment effect was not consistent for the individual components of the primary endpoint, as slightly more CV death events occurred in the ticagrelor group (HR 1.02 [95% CI 0.88, 1.18], p-value 0.7883), with the hierarchical testing being terminated. However, no increased risk was found for all-cause mortality (579 (6.0%) vs 592 events (6.2%)).

Some differences appear in the subgroup analyses. A counter-intuitive difference can be observed for the subgroup of history of poly-vascular disease with a p-value for interaction below 0.05. Further, most noticeable trend differences appear in age, race, history of coronary arterial revascularisation, smoking status, history of peripheral arterial occlusive disease, and number of prior vascular beds due to increased treatment HR with ticagrelor in one of the categories within these subgroups with some showing counter-intuitive results according to risk status (including age, smoking status, history of peripheral arterial occlusive disease, number of prior vascular beds). Similar counter-intuitive findings, although less outspoken were observed for eGFR status, and multivessel coronary artery disease. Although, apparent subgroups differences are subject to multiplicity issues and likely due to chance finding. Therefore, any selection of a subgroup in whom the benefit-risk balance may be improved should be robustly justified and supported, see further discussion in section 7.7.1.

During the study, the dose was amended from 90 mg to 60 mg bd. For the proposed 60 mg dose, several analyses were performed and demonstrated to be consistent with the overall findings. The primary endpoint for those patients initially randomized to the proposed 60 mg dose was not significant (HR was 0.87 (95% CI 0.69, 1.11)) and only comprised 25% of the overall population. Nevertheless, on-treatment data demonstrated a consistent HR for the 60 mg dose (HR of 0.72 (95% CI 0.53, 0.97)). The on-treatment effect of the 90 mg dose was HR of 0.99 (95% CI 0.77, 1.27) likely due to the fact that patients were shortly treated with this dose not already sufficient to result in any treatment effect.

Whether patients who had undergone PCI were previously on DAPT therapy has not been captured.

A limited proportion of patients > 75 years of age was presented (12%), and apart from Caucasians and Asians other races were underrepresented.

5.4. Unfavourable effects

From a total of 19220 patients, who received at least one dose of study drug, the most commonly reported AEs on ticagrelor and reported at a higher frequency than placebo were dyspnoea (21.4% vs 7.3%) and bleeding events (15.1% vs 6.2%). SAEs were reported at a lower frequency for ticagrelor (31.9% vs 33.7%) with cardiac disorders (11.9% vs 14.1%), infections and infestations (4.8% vs 5.1%) and nervous system disorders (3.3% vs 4.3%) mostly reported.

As can be expected a higher AE risk for bleeding was reported (15.1% vs 6.2%). Bleeding risk was consistently increased across all bleeding scales (TIMI major bleedings 2.2% vs 1.0%, HR 2.32 (95% CI 1.92-2.94 at 36 months, p<0.001; PLATO major bleeding 3.2% vs 1.5%, HR 2.41 (95% CI 1.98-2.93), p<0.001)) and increased over time. The higher bleeding risk was mainly attributed to a higher frequency in subcutaneous bleedings (5.4%, 1.1%), gastrointestinal bleedings (3.9% vs 1.8%) and

epistaxis (3.0% vs 1.1%), which are known bleeding types with ticagrelor.

A large proportion of patients discontinued treatment with ticagrelor due to adverse events, which subside the usability for long term treatment in clinical practice (20.8% vs 12.2%). The principal reason for discontinuation was because patients experienced adverse events, mainly bleedings and dyspnoea. For bleedings, discontinuations were mostly observed within the first months of treatment. A wearing off of the discontinuation rate mirrored this observation.

Death was an efficacy endpoint in this study, and all deaths that occurred prior to the withdrawal of consent were adjudicated. Ticagrelor treatment did not lead to a higher frequency of death, as well as for the 'on-treatment' frequency. Based on the efficacy endpoint, the HR for overall mortality was estimated at HR 0.98 (95% CI: 0.87-1.10). There were no clear imbalances in types of deaths. No imbalance in death due to malignancies was found as previously subject to discussion in the PEGASUS study (9(0.1%) vs 21 (0.2%) on treatment; 88 (0.9%) vs 112 (1.2%) on and off treatment).

5.5. Uncertainties and limitations about unfavourable effects

Fatal bleedings were rare but slightly higher for ticagrelor (0.2%, 0.07 events/100 patient-years vs (0.1%, 0.04 events/100 patient-years) the most common fatal events (based on number of events) by PT were haemorrhagic stroke (3 vs 2) and cerebral haemorrhage (2 vs 2, respectively). The number of intracranial bleedings was limited, but higher for ticagrelor, 70 (0.7%, 0.30 events/100 patient-years) vs 46 (0.5%, 0.18 events/100 patient-years). This was mainly attributed to an imbalance in traumatic bleeding events across groups (41 (0.4%) and 16 (0.2%)), while spontaneous (28 (0.3%) vs 27 (0.3%)) and procedure-related ICHs (1 vs 3) were similar. Somewhat reassuring is that for those patients initially randomised to the 60 mg dose ICH was similar (11 (0.4%) vs 10 (0.4%)), although this is only a subset of the total population.

For bleeding risk across subgroups, a significantly higher risk for bleeding was observed for female compared to male sex (HR 1.95 (1.50-2.54) vs 5.00 (2.67, 9.35); p for interaction =0.0069) likely driven by the lower background rate in the placebo group of females. Also, for patients with a history of coronary arterial revascularisation, there appears a lower bleeding risk ((HR 2.09 (1.59-2.68) vs 4.16 (2.20, 7.87); p for interaction =0.0461). Moreover, a trend for lower bleeding risk was observed for the European population (p for interaction 0.0905).

Bradyarrhythmic AEs and SAEs were only slightly increased for ticagrelor (1.4% vs 1.3% and 0.7% vs 0.5%, respectively). Dizziness, hypotension and syncope could be associated with bradyarrhythmic AEs; however, no substantial imbalances could be reported, especially due to the very limited number of these events.

No clear evidence of any impact of ticagrelor on AEs-related to renal function or the kidney (2.4% vs 2.3%; SAEs (0.9% vs 0.7%)) was observed. Any impact on creatinine has not been evaluated as any clinical laboratory variables have not been evaluated during the study, considering that these have been extensively evaluated in previous studies.

Slightly more AEs of gout were reported with ticagrelor than for placebo (2.0% vs 1.7%), likely due to the known reversible effect of ticagrelor of increase in uric acid.

Hepatic related events were not specifically evaluated, no laboratory evaluation on hepatic enzymes was performed.

After routine inspection of site 7605 by the Sponsor, an underreporting of 52 SAEs was identified. Further details on the monitoring and conduct according to GCP of the trial have been provided. The frequency of SAEs (31.9%-33.7%) in comparison to previous studies (approximately 21% PLATO and PEGASUS) does not suggest an underreporting of SAEs in the overall study conduct.

5.6. Effects Table

Table 1. Effects Table for ticagrelor for CAD without prior MI (data cut-off: 1 July 2019)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	Ref
Favourable Effects						
CV outcome	Composite CV death, MI, stroke	36 months KM % (FAS)	6.9	7.6	HR 0.90 (95% CI 0.81-0.99), p=0.0378 Inconsistent effect across individual components; CV death 3.3% vs 3.0%; MI 2.6% vs 3.3%, stroke 1.7% vs 2.1%. Hierarchical testing was violated at the CV death secondary endpoint HR 1.02 (95% CI 0.88, 1.18), p=0.7883	
Overall death		36 months KM % (FAS)	5.1	4.9	For the overall treatment period this was 6.0% vs 6.2%.	
Unfavourable Effects						
Bleeding	Major bleeding (TIMI)	36 months KM %	2.7	1.2	HR 2.32 (95% CI 1.82-2.94), p<0.001	
	ICH	36 months KM %	0.9	0.5	HR 1.71 (95% CI 1.18 – 2.48)	
	Fatal	N of patients (%)	0.2	0.1		
	Discontinuations	36 months KM %	5.6	1.5	HR 4.04 (95% CI 3.32, 4.92)	
Dyspnoea		% - on treatment	21.4	7.3		
	Discontinuations	% - on treatment	6.9	0.8		
Brady arrhythmias		% - on treatment	1.4	1.3		
Renal related AEs		% - on treatment	2.4	2.3		
Gout		% - on treatment	2.0	1.7		

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

In addition to the approved indication of treatment of ACS (90 mg bid) and history of MI (60 mg bid) with ticagrelor, co-administered with low dose acetylsalicylic acid (dual antiplatelet therapy), ticagrelor has currently been evaluated on a background of low-dose ASA for the reduction of CV risk as identified based on (stable) CAD and type 2 diabetes mellitus (T2DM) at high risk for a thrombotic event but with no history of MI or stroke. These patients generally have a lower risk profile than for the secondary prevention indications. Stable CAD was limited to those patients at the higher end of the primary prevention spectrum with evidence of coronary disease, by a history of PCI, CABG or > 50% coronary artery stenosis, and T2DM as enriching inclusion criteria. Such patients are currently not commonly indicated for dual antiplatelet therapy in accord with clinical practice guidelines (e.g. ESC), as (long term) dual antiplatelet therapy in such patients has not been sufficiently established.

Only a small beneficial effect has been demonstrated for ticagrelor, mainly based on reduction in MI and stroke events while any advantage on CV death could not be obtained. The beneficial effects come

at the cost of a substantially increased risk of bleeding, roughly neutralising any clinical relevant absolute overall benefit. This absence of a clear benefit is also confirmed in the recent NEJM publication indicating only a negligible benefit in the composite outcome of irreversible harm, which can be defined as death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial hemorrhage (10.1% vs. 10.8%; hazard ratio,0.93; 95% CI, 0.86 to 1.02) (Steg, NEJM 2019; Bhatt, NEJM, 2019). Particularly, the increase in major bleedings risk is considered of importance, as this could lead to the risk of morbidity, or even death. Moreover, although limited, an increased risk of intracranial bleedings is observed, which is generally considered important due to its irreversible and high morbidity impact.

Bleeding is one of the main components to cause patients to discontinue treatment, in particular in the first months after the start of the treatment. Further, the known effect of dyspnoea importantly contributes to very early discontinuation. Other adverse events observed in the THEMIS study are expected as based on the known safety profile of ticagrelor, though some with slightly different frequencies, but do not raise additional concerns.

It is considered reasonable to propose a 60 mg dose as patients are largely treated with this dose during the study. Although, the amendment made during the study to lower the dose from 90 mg to 60 mg bid somewhat complicates the interpretation of the data.

Taken the only modest effect observed in the overall study results, the applicant has proposed to restrict the indication (with CAD and T2DM without a history of myocardial infarction) to the subpopulation of patients who have undergone percutaneous coronary intervention as they consider the benefit-risk balance to be more beneficial based on the results on the primary endpoint and TIMI major bleedings. However, this restriction has not been well justified, especially as it does not follow the criteria as outlined in the guideline on investigations of subgroups (see scenario 2 (section 5.3) EMA/CHMP/539146/2013) to consider these data to be sufficiently credible. Any observed possible beneficial effect could be a chance finding due to multiplicity of a large number of subgroup analyses, and any possible difference in effect to those without previous PCI can be questioned also considering that the p for interaction was not significant. Further, apart from the fact that history of PCI was one of the key qualifying inclusion criteria, it has not been made sufficiently clear how this subpopulation would clearly differentiate from other pre-specified subpopulations with increased CV risk. In particular (see item 3b of scenario 2 of the subgroup guideline) , a retrospectively compelling explanation for (biological) plausibility for subgroup differences cannot be sufficiently justified. In this respect, the speculation of a potentially lower risk of bleeding due to assumed previous treatment with DAPT (data not provided) for patients with a history of PCI (and thus an apparently improved BR based on improved safety) in comparison to patients without a history of PCI cannot be clearly consistently supported by external and internal data; including study baseline data and/or based on exclusion criteria applied, data from other ticagrelor studies, or any other studies. Also, any clinical and statistically extreme evidence replication is not evident from other available data. Differences in baseline (mainly history of MI, history of DM2, and time since PCI) make any comparison to other ticagrelor studies difficult. Any differentiation, according to PCI subgroup in PEGASUS is not useful as likely all patients in PEGASUS have been treated with DAPT. For PLATO, similar issues apply, most notable that patients were included based on recent ACS (very small proportion without MI) and comparison was made to clopidogrel treatment. If any subgroup (with increased CV risk and) with improved benefit-risk balance could be identified, this should be based on a more robust argumentation and analysis of the available results.

5.7.2. Balance of benefits and risks

The benefit-risk balance is currently negative for the population with CAD and T2DM without any history of MI or stroke. The substantially higher bleeding risk compromises the small CV benefit, which

roughly results in a negligible clinical relevant absolute overall benefit of ticagrelor concomitantly with a low dose of ASA during long-term use.

The proposed restriction to a subpopulation of patients who have undergone percutaneous coronary intervention is not well justified. If any subgroup (with increased CV risk and) with improved benefit could be identified, this should be based on a more robust argumentation and analysis of the available results.

5.7.3. Additional considerations on the benefit-risk balance

The extension of the indication (as was submitted under C.I.6a within this grouped variation application) was withdrawn by the MAH in the final round of the procedure. The inclusion of information on ticagrelor and traumatic haemorrhages is pertained under the C.I.4 variation and is considered approvable, based on the provided THEMIS study results and totality of data.

5.8. Conclusions

The benefit-risk balance in the new indication proposed remains currently negative for the population with CAD and T2DM without any history of MI or stroke.