26 July 2018 Corr. 1[1]
EMA/556022/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xarelto

International non-proprietary name: rivaroxaban

Procedure No. EMEA/H/C/000944/II/0058

Note

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

[1] 27.07.2018

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List of abbreviations

ABI Ankle-brachial index

ACE Angiotensin-converting enzyme

ACS Acute Coronary Syndrome

AE Adverse Event

AF Atrial Fibrillation

ALI Acute Limb Ischaemia

ASA Acetylsalicylic acid

bid Twice daily

BMI Body mass index

BP Blood pressure

CABG Coronary Artery Bypass Graft

CAD Coronary artery disease

CCDS Company Core Data Sheet

CHD Coronary heart disease

CI Confidence interval

CRF Case Report Form

CSR Clinical Study Report

CV Cardiovascular

DAPT Double Antiplatelet Therapy

DOAC Direct oral anticoagulant

DVT Deep vein thrombosis

DSS Digit Symbol Substitution

ECG Electrocardiogram

EMA European Medicines Agency

EQ-5D European Quality of Life-5 Dimensions

ESC European Society of Cardiology

FAS Full analysis set

GCP Good Clinical Practice

GI Gastrointestinal

HR Hazard ratio

ICH International Conference on Harmonization

IEC Independent ethics committee

ISTH International Society on Thrombosis and Haemostasis

LEAD Lower Extremity Artery Disease

LVEF Left Ventricular Ejection Fraction

MACE Major cardiovascular events

MedDRA Medical Dictionary for Regulatory Activities

MI Myocardial infarction

MLG MedDRA Labeling Grouping

MoCA Montreal Cognitive Assessment

NYHA New York Heart Association

NVAF Non-valvular atrial fibrillation

od once daily

OS orthopedic surgery

PAD Peripheral arterial disease

PCI Percutaneous intervention

PE Pulmonary embolism

PPI Proton pump inhibitor

PV Pharmacovigilance

RMP Risk Management Plan

SAE Serious Adverse Event

SAF Safety Analysis Set

SAGE Standard Assessment of Global-Activities in the Elderly

SAPT Single Antiplatelet Therapy

SN Study Number

SOC System Organ Class according to MedDRA

SPAF Stroke prevention in atrial fibrillation

SmPC Summary of Product Characteristics

TDD Total daily dosage

UA Unstable angina

VTE Venous thromboembolism

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 3 November 2017 an application for a variation.

The following variation was requested:

Variation 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, IIIA and IIIB

Extension of Indication to include the prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischaemia and mortality in adult patients with coronary artery disease (CAD) or peripheral artery disease (PAD) for Xarelto 2.5 mg co-administered with acetylsalicylic acid; as a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.
In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data.
The updated RMP version 11.1 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling 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/0194/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0194/2017 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 received Scientific Advice from the CHMP on 17 November 2011 (EMEA/H/SA/422/7/2011/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	3 November 2017
Start of procedure:	25 November 2017
CHMP Rapporteur Assessment Report	19 January 2018
PRAC Rapporteur Assessment Report	19 January 2018
PRAC Outcome	8 February 2018
CHMP members comments	12 February 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 February 2018
Request for supplementary information (RSI)	22 February 2018
CHMP Rapporteur Assessment Report	30 April 2018
PRAC members comments	7 May 2018
Updated PRAC Rapporteur Assessment Report	9 May 2018
PRAC Outcome	17 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteur Assessment Report	24 May 2018
2nd Request for supplementary information (RSI)	31 May 2018
PRAC Rapporteur Assessment Report	29 June 2018
PRAC members comments	4 July 2018
Updated PRAC Rapporteur Assessment Report	9 July 2018
CHMP Rapporteur Assessment Report	9 July 2018
PRAC Outcome	12 July 2018
SAG experts meeting to address questions raised by the CHMP (Annex 6)	13 July 2018
CHMP members comments	16 July 2018
Updated CHMP Rapporteur Assessment Report	19 July 2018
CHMP Opinion	26 July 2018

2. Scientific discussion

2.1. Introduction

Rivaroxaban is an oral direct factor Xa inhibitor that acts by inhibiting thrombin formation and thus formation of thrombi. In the EU, rivaroxaban is approved for prevention of stroke and systemic embolism in atrial fibrillation, treatment and prevention of venous thrombosis and, in addition to acetylsalicylic acid (ASA) or ASA plus clopidogrel or ticlopidine, for prevention of atherothrombotic events after an ACS.

The Marketing Authorisation Holder proposed an extension of indication with this application to include the prevention of stroke, myocardial infarction and cardiovascular death, and the prevention of acute limb

ischaemia and mortality in adult patients with coronary artery disease (CAD) or peripheral artery disease (PAD) for rivaroxaban 2.5 mg bid co-administered with ASA.

Stable CAD is usually characterized by episodes of reversible myocardial ischaemia or hypoxia, induced by exercise, emotion or occurring spontaneously, with symptoms of angina pectoris. The pathophysiological mechanisms that cause stable CAD are traditionally described as atherosclerotic narrowings of ≥50% of the left main coronary artery and ≥70% in one or several of the major coronary arteries; however, in more recent years, other pathophysiological features such as microvascular dysfunction and coronary vasospasm have also been distinguished. CAD can also present clinically as left ventricular dysfunction caused by ischaemic cardiomyopathy. The clinical presentation and severity of CAD varies considerably between individuals. Other medical conditions that are not caused by CAD could present clinically with symptoms of angina pectoris, including valvular disease (e.g. aortic stenosis), tachyarrhythmia and severe anaemia.

Stable CAD with symptoms of angina pectoris is essentially a diagnosis based on history and the characteristics of chest pain. In most patients, however, apart from physical examination, some objective tests are performed to confirm the diagnosis, assess underlying disease and assist in risk stratification. Such testing includes biochemistry, resting ECG, echocardiography and stress testing. However, for patients in which revascularization is unlikely to be an option, investigations may be reduced to a clinically indicated minimum and appropriate therapy should be commenced although objective testing has not been performed (ESC Guidelines 2013).

The natural history of the disease varies greatly between individuals. In patients with stable angina pectoris only, the prognosis is usually favourable with a low risk of mortality (approx. 1% annually) and a low risk of MI (approx. 1-3% annually). However, the prognosis is poorer in patients with heart failure, a greater number of diseased vessels, more proximal locations of coronary stenosis, greater severity of lesions, more extensive ischaemia, more impaired functional capacity, older age, significant depression and more severe angina (ESC Guidelines 2013). Thus, risk stratification based on clinical evaluation, ventricular function, stress testing and coronary anatomy is important when deciding on the optimal therapy for a patient. Within a population with stable CAD, an individual's prognosis can vary considerably, depending on baseline clinical, functional and anatomical characteristics. This is exemplified in the Reduction of Atherothrombosis for Continued Health (REACH) registry which included very high-risk patients, many with peripheral arterial disease or previous MI and almost 50% with diabetes. Consequently, annual mortality rate was as high as 3.8% in this population, whereas patients with non-obstructive plaques within the coronary arteries have an annual mortality rate of only 0.63% (ESC Guidelines for CAD 2013).

Existing pharmacological treatments of CAD aim at relief from symptoms and to prevent CV events by reducing plaque progression, stabilize plaques, reduce inflammation and prevent thrombosis. For event prevention in stable CAD patients, lipid-lowering agents, anti-hypertensive agents and antithrombotic agents are used. For most patients, SAPT (single antiplatelet therapy) is recommended as antithrombotic treatment; DAPT (dual antiplatelet therapy) is used primarily after an ACS in the acute phase or in stable CAD after a PCI procedure. It has been convincingly demonstrated that increasing the intensity of antithrombotic therapy for secondary prevention of CV events is effective, but at the cost of an increase in bleeding. In stable CAD patients, combined antiplatelet therapy by addition of vorapaxar (a PAR-1-antagonist) in addition to standard antiplatelet therapy has been proven to significantly reduce a composite of CV death, MI or stroke, particularly in post-MI patients, but at the cost of an increased risk of moderate and severe bleeding. In the ESC Guidelines, it was concluded that combined antiplatelet therapy may be beneficial only in selected patients at high risk of ischaemic events, not to be recommended systematically in SCAD patients.

PAD (peripheral arterial disease) encompasses all arterial diseases other than coronary arteries and the aorta, and should be distinguished from peripheral artery disease, which is often used for lower extremity artery disease (LEAD). In the COMPASS trial, PAD was represented by patients with LEAD and carotid stenosis only. PAD secondary to atherosclerosis and CAD often share the same risk factors, including hypertension, hypercholesterolemia, diabetes, obesity, smoking, sedentary lifestyle and family history. Patients affected by PAD are also at risk for other atherosclerotic events. 10-year rates of coronary events, CV mortality and total mortality has been showed to be doubled in LEAD patients (Fowkes et al, 2008). ABI is considered to be a strong marker for CV events (ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, 2017). As with CAD, pharmacological treatments of PAD aim at reducing symptoms, and prevent CV events by using lipid-lowering, antihypertensive and antithrombotic drugs. In the ESC Guidelines from 2017, the antithrombotic regimens are similar to CAD. SAPT forms the basis, with low-dose aspirin for carotid artery stenosis, and clopidogrel in symptomatic LEAD or LEAD that has undergone revascularization. Anticoagulation therapy is recommended only in patients with a concomitant indication that requires anticoagulation, and could be combined with SAPT after a recent revascularization procedure.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

An updated ERA with a study on Algal (Desmodesmus subspicatus) growth inhibition (OECD 201) was submitted. The no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC) was 0.52 and 1.02 mg/L respectively.

The PECsurfacewater was revised by adding the PEC for the existing indications with the PEC of the new indication. The revised PECsurfacewater has been re-calculated to 0.12 µg/L.

2.2.2. Conclusion on the non-clinical aspects

Considering the available data, no risks were identified for rivaroxaban with regard to the various environmental compartments and no specific labelling regarding the environmental risk is required.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study number	Study Design and type of control	Rivaroxaban regimen and treatment duration	Comparator regimen and treatment duration	Number of subjects exposed to rivaroxaban	Number of subjects exposed to comparator
15786 (COMPASS)	Randomized, multicenter, double-blind, double-dummy, active-controlled, event-driven trial with a 3 x 2 partial factorial design	2.5 mg bid/ ASA 100 mg od or 5 mg bid (or matching placebo) Treatment duration: Estimated average: 3-4 yrs; Actual (mean)*: 2.5 mg bid/ ASA 100 mg od: 1.69 yrs 5 mg bid: 1.69 yrs	ASA 100 mg od (or matching placebo) Treatment duration: Estimated average: 3-4 yrs Actual (mean)*: 1.71 yrs	Rivaroxaban 2.5 mg/ASA 100 mg: 9152 ITT 9134 SAF Rivaroxaban 5 mg: 9117 ITT 9110 SAF	ASA 100 mg: 9126 ITT 9107 SAF

* Manually calculated: 1 year = 365.25 days (reflecting the study duration until the global cut-off date at 06 FEB 2017)

As part of the partial factorial design, subjects without continuous need for PPI were randomized to pantoprazole 40 mg/placebo. This part of the study is still ongoing and will be reported later.

2.3.2. Clinical pharmacology

No information relevant to the clinical pharmacology of rivaroxaban was provided in this submission.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies were provided with this application. Rivaroxaban was tested in study 15786 (COMPASS) at a dose of 2.5 mg bid plus ASA compared with ASA alone, and at a dose of 5 mg bid alone compared with ASA alone, based on data from patients with a recent ACS in the Phase II and Phase III trials (ATLAS ACS TIMI 46 and ATLAS ACS 2 TIMI 51).

2.4.2. Main study

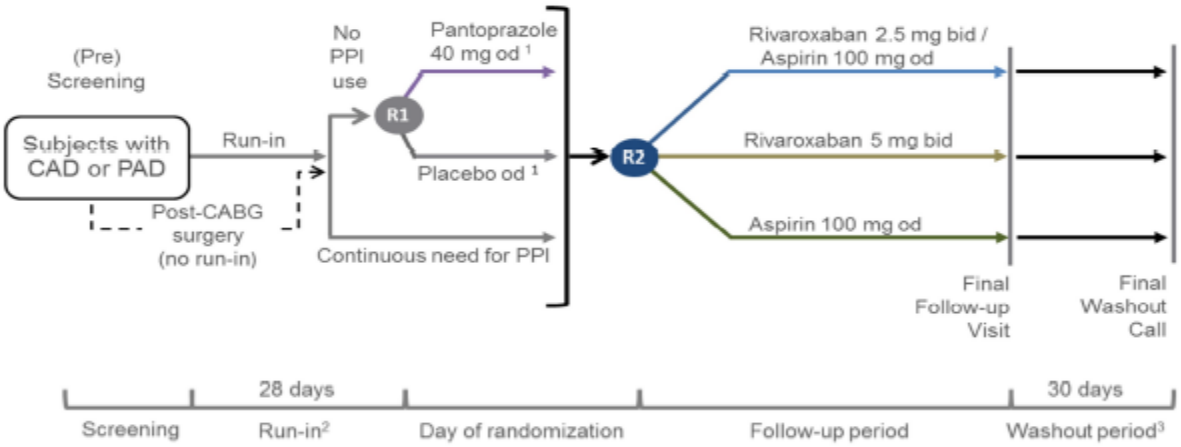
Title of Study

COMPASS (Cardiovascular OutcoMes for People using Anticoagulation StrategieS): A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease

Methods

This was a multi-centre, randomized, double-blind, double-dummy, active comparator, event-driven study. The study comprised 4 periods: screening, run-in, follow-up, and washout, depicted in **Figure 1**.

Figure 1. COMPASS study flow diagram



1 The pantoprazole/placebo arms of the trial were still ongoing at the time of submission

2 Aspirin 100 mg od and rivaroxaban placebo as run-in medication

3 Subjects treated according to local standard of care

bid = twice daily; CABG = coronary artery bypass graft; CAD = coronary artery disease; od = once daily; PAD = peripheral artery disease; PHRI = Population Health Research Institute; PPI = proton pump inhibitor; R = randomization.

Study participants

Inclusion criteria:

- Subjects willing and able to provide written informed consent
- Meet criteria for CAD* and/or PAD
- *Subjects with CAD had also to meet at least one of the following criteria:
- Age ≥ 65, or
- Age <65 and documented atherosclerosis or revascularization involving at least
- 2 vascular beds§, or at least 2 additional risk factors:

1) Current smoker (within 1 year of randomization)

2) Diabetes mellitus

3) Renal dysfunction with estimated glomerular filtration rate

<60 mL/min

4) Heart failure

5) Non-lacunar ischemic stroke ≥1 month ago

§ Because CAD involves disease in the coronary vasculature, only one additional vascular bed was required: e.g. the aorta d arterial supply to the brain, GI tract, lower limbs, upper limbs, or kidneys.

Exclusion criteria:

- High risk of bleeding
- Stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Severe heart failure with known ejection fraction <30% or New York Heart
- Association (NYHA) class III or IV symptoms
- Estimated glomerular filtration rate (eGFR) <15 mL/min
- Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy
- Known non-cardiovascular disease that was associated with poor prognosis (e.g., metastatic cancer) or that increases the risk of an adverse reaction to study interventions
- History of hypersensitivity or known contraindication for rivaroxaban, aspirin,
- pantoprazole, or excipients, if applicable
- Systemic treatment with strong inhibitors of both Cytochrome P450 3A4 (CYP3A4) and p-glycoprotein (P-gp) (e.g., systemic azole antimycotics, such as ketoconazole, and human immunodeficiency virus [HIV]-protease inhibitors, such as ritonavir), or strong inducers of CYP3A4, i.e. rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine

For Germany only:

- Systemic treatment with strong CYP 3A4 and P-gp inhibitors (e.g. systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, including the use of a booster, such as ritonavir in antiretroviral combination therapy)
- Any known hepatic disease associated with coagulopathy
- Subjects who were pregnant, breastfeeding, or were of childbearing potential, and sexually active and not practicing an effective method of birth control (e.g. surgically sterile, prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization)
- Previous assignment to treatment during this study
- Concomitant participation in another study with investigational drug
- Known contraindication to any study related procedures

Treatments

During the run-in period, Day -28 to Day -1, eligible subjects (excluding those who were randomized between Day 4-7 after CABG surgery) who had signed informed consent and stopped non-study anticoagulants and aspirin received rivaroxaban placebo bid and aspirin 100 mg od.

Subjects who had completed the run-in period with at least 80% adherence to treatment were first divided in those who had a continuous need for PPI and those who did not. The latter group was randomized to pantoprazole 40 mg od or matching placebo. Thereafter, the participants were randomized into three arms of different antithrombotic treatments:

Arm A: rivaroxaban 2.5 mg bid/aspirin 100 mg od

Arm B: rivaroxaban 5 mg bid/aspirin placebo od

Arm C: rivaroxaban placebo bid/aspirin 100 mg od

Objectives

Primary objectives for rivaroxaban randomization were

- To determine whether rivaroxaban 2.5 mg bid/aspirin 100 mg od compared with aspirin 100 mg od reduces the risk of a composite of MI, stroke, or CV death in subjects with CAD or PAD
- To determine whether rivaroxaban 5 mg bid compared with aspirin 100 mg od reduces the risk of a composite of MI, stroke, or CV death in subjects with CAD or PAD

Secondary objectives for rivaroxaban randomization were

- To determine whether each of rivaroxaban 2.5 mg bid/aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the risk of the composite of major thrombotic events: CHD death, MI, ischemic stroke, acute limb ischemia (ALI), compared with aspirin 100 mg od in subjects with CAD or PAD
- To determine whether each of rivaroxaban 2.5 mg bid/aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the risk of the composite of major thrombotic events: CV death, MI, ischemic stroke, ALI, compared with aspirin 100 mg od in subjects with CAD or PAD
- To determine whether each of rivaroxaban 2.5 mg bid/aspirin 100 mg od and rivaroxaban 5 mg bid alone reduces the risk of mortality compared with aspirin 100 mg od in subjects with CAD or PAD

Objective for pantoprazole randomization was

- To determine whether pantoprazole 40 mg od compared with placebo reduces the risk of upper GI bleeding, ulceration, or GI obstruction or perforation in subjects with CAD or PAD receiving antithrombotic study medications

Outcomes / endpoints

Primary efficacy outcome was the time (in days) from randomization to the first occurrence of the composite of the following efficacy outcome events:

- Myocardial infarction *or*
- Stroke *or*
- Cardiovascular death

Secondary efficacy outcomes were the time (in days) from randomization to the first occurrence of the following secondary efficacy outcomes – in the order as specified below:

1. The composite of outcomes – CHD death, MI, ischemic stroke or ALI
2. The composite of outcomes – CV death, MI, ischemic stroke or ALI
3. All-cause mortality

CHD death includes death due to acute MI, sudden cardiac death, or death due to a CV procedure and is only derived via adjudication. ALI is defined as limb-threatening ischemia that is confirmed by limb hemodynamics or imaging and leads to an acute vascular intervention (i.e. pharmacologic [heparin, thrombolysis], peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation) within 30 days of onset of symptoms. In the absence of confirmation by limb hemodynamics or imaging, absent pedal pulses is acceptable as hemodynamic criterion for ALI.

Tertiary efficacy outcomes included:

- The time (in days) from randomization to the first occurrence of the following tertiary efficacy outcomes:
    - Individual components of the primary and secondary outcomes, i.e., MI, stroke, ischemic stroke, CV death, CHD death, ALI, and non-CV death

Primary safety variable was the time (in days) from randomization to the first occurrence of the following primary safety outcome:

Modified International Society on Thrombosis and Haemostasis (ISTH) major bleeding, defined as:

I. fatal bleeding, or

II. symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or bleeding into the surgical site requiring reoperation, or

III. bleeding leading to hospitalization*

*Major bleeding also includes presentation to an acute care facility with discharge on the same day.

A net clinical benefit time-to-event variable was defined as the composite of the primary efficacy outcome and the primary safety outcome, excluding bleedings leading to hospitalization and bleedings into surgical site associated with re-operation (thus representing fatal or symptomatic critical organ bleeding only).

The outcome for the pantoprazole randomization is the composite of the following outcomes:

- Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography
- Overt upper gastrointestinal bleeding of unknown origin
- Bleeding of presumed occult gastrointestinal origin with documented decrease in Hb of 2 g/dL from baseline
- Symptomatic gastroduodenal ulcer
- Gastrointestinal pain with underlying multiple gastroduodenal erosions, obstruction or perforation

Sample size

Initially, approximately 19,500 eligible subjects were to be admitted to the run-in period and an additional 2000 were to be enrolled post CABG and without run-in. Approximately 10% of run-in subjects were expected to either be non-compliant with treatment or to decline further interest in participating; thus, the study was to randomise approximately 19,500 subjects, at least 6,500 subjects per antithrombotic study group.

The study was event-driven and was to continue until a minimum of 2,200 subjects had experienced an event for the primary efficacy outcome. The aim was to have at least 90% power to detect a 20% relative risk reduction for each of the two rivaroxaban treatment groups versus the aspirin control group.

The following assumptions were made for the antithrombotic treatment part of the study; a 2-sided type I error level of 2.7% for each of the two comparisons to control the overall type I error level of 5%, an annual event rate in the aspirin control group between 4.0% and 4.5%, a recruitment period of about 2.5 years, a total expected study duration of 4.5 to 5 years and, an early study drug discontinuation rate of about 6% and 4% in the 1st and 2nd 6-month periods, and 3% in the 6-month periods thereafter.

Within study protocol amendment 6 (03 July 2014) the number of subjects was increased to 21,400 randomised ((approximately 7,134 subjects per treatment group)) based on emerging data which suggested that a realistic event rate was 3.5-4.0% rather than 4.0-4.5%.

During the first 2 years after randomisation of the first patient, it was found that the actual randomisation was slower than expected and that the observed cumulated overall annual incidence was at the lower end of the projected range of 3.0 to 4.0%. This led to the decision to continue enrollment to maintain the study duration in the originally planned range of 4.5 to 5 years. Simulations were performed to justify the implied sample size increase, based on the following revised assumptions, which are partially taken from the blinded data observed within the first 2 years of the trial;

- Overall length of recruitment period about 3 to 3.5 years, where randomisation times are
    - taken as observed for the first ~18,000 subjects
    - assumed to be approximately uniform over about 10 months with some seasonal variation for the remaining ~9,400 subjects
- 2-sided overall type I error level of 5% using a truncated Hochberg test (γ = 0.9) for the testing of the two primary hypotheses
- Constant overall incidence rate of about 2.9% per year (95% CI: 2.56 – 3.22%), resulting in a constant incidence rate of about 3.3% (95% CI: 2.95 – 3.71%) per year for the aspirin control group assuming a 20% relative risk reduction for both hypotheses
- Early discontinuation of study drug: about 6% and 4.5% in the 1st and 2nd 6-month periods, and 3% in the 6-month periods thereafter
- Censoring due to non-CV death at an event rate of almost 1% per year

Based on these simulation results, the sample size was increased from 21,400 randomised subjects to 27,400 (approximately 9,134 subjects per treatment group) by protocol amendment 8 (19 Aug 2015).

Randomisation

Subjects being randomized after run-in and those who were randomized between Day 4-7 after CABG surgery and

- Who did not have a continuous need to take a PPI, were initially randomized 1:1 to receive pantoprazole 40 mg od or matching placebo od, using a block size of 6, stratified by centre. Within each of these blocks of 6, subjects were then randomized 1:1:1 to anticoagulant therapy (see below) stratified by the randomization to pantoprazole or pantoprazole placebo, resulting in blocks of 3.
- Who did have a continuous need to take a PPI, were randomized 1:1:1 to anticoagulant therapy using a block size of 6 stratified by centre as shown below.

Table 1. Randomised study treatments-COMPASS study

Study Arm	Treatment Assignments	
A	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole placebo od
B	Rivaroxaban 5 mg bid + Aspirin placebo od + Pantoprazole 40 mg od	Rivaroxaban 5 mg bid + Aspirin placebo od + Pantoprazole placebo od
C	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole placebo od

Blinding (masking)

This was a double-blind study. All doses were provided in tablet form for oral administration.

Statistical methods

Analysis sets
Analysis of the primary efficacy outcome was based on the intention-to-treat principle. The intention-to-treat analysis set included all randomised subjects. The safety analysis set included all randomised subjects who received at least one dose of study medication.

Methods
The primary efficacy variable was the time (in days) from randomisation to the first occurrence of the composite of the following events: MI, stroke or CV death. Primary statistical analyses were based on events which were unrefuted during the adjudication process (that evaluated whether events reported by investigators met the pre-specified trial definition).

Each of the rivaroxaban-based treatment groups were compared to the control group using two separate stratified log-rank tests taking into account proton pump inhibitor use (three strata levels: not randomised to a proton pump inhibitor; pantoprazole 40 mg od; pantoprazole placebo). Study center was not used as a stratification factor in the analysis.

Kaplan-Meier estimates of cumulative risk functions and Nelson-Aalen estimates of the cumulative hazard functions were provided to evaluate the timing of event occurrence in the three treatment arms and the consistency of the respective treatment effects for all time points. Hazard ratios (HRs) and corresponding 2-sided 95% confidence intervals (CIs) were estimated based on two separate stratified Cox proportional hazards models.

Analyses of the secondary efficacy outcomes and the primary safety time-to-event variable essentially used the same statistical methods as described for the primary efficacy variable.

Sensitivity analyses

Sensitivity analyses were performed to include all primary efficacy outcome events up until the minimum (earliest) of the final rivaroxaban/aspirin follow-up visit date and the subject's last contact date during the rivaroxaban/aspirin portion of the study.

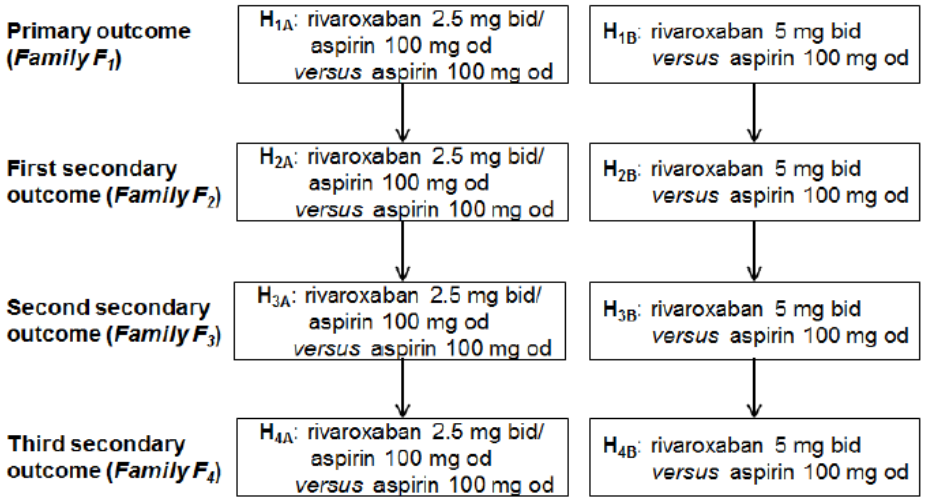
In addition, the number of primary efficacy outcome events occurring after the final rivaroxaban/aspirin follow-up visit until the rivaroxaban/aspirin washout telephone visit, included in the clean database for the rivaroxaban/aspirin comparisons, was summarized by rivaroxaban/aspirin study treatment group.

The plausibility of the proportional hazards assumption was assessed by visually examining both the plot of the log of the negative log of Kaplan-Meier estimates of the survival function versus the log of time for evidence of non-parallelism and the smoothed plot of the scaled Schoenfeld residuals to directly visualize the log hazard ratio, and by including a time*treatment interaction term in the Cox model (time log transformed). The significance of the interaction was tested at the 5% type I error level. If the interaction was significant and there was strong evidence of non-proportionality from the plots, time-dependent hazard ratios were to be estimated with the model that includes the interaction term.

Multiplicity

Each of the rivaroxaban-based treatment group was first to be compared with the aspirin control group on the primary efficacy outcome, followed by the same comparisons on the three ordered secondary efficacy outcomes (**Figure 2**). The null hypotheses of no effect corresponding to different efficacy outcomes were grouped into 4 separate families. Standard logical restrictions were imposed, i.e., the null hypotheses were split into two branches corresponding to the tests for rivaroxaban 2.5 mg bid/aspirin 100 mg od (hypotheses H1A, H2A, H3A, H4A) and to the tests for rivaroxaban 5 mg bid (hypotheses H1B, H2B, H3B, H4B). A null hypothesis within each branch could be tested if and only if the immediately preceding null hypothesis was rejected.

Figure 2. Hypothesis testing problem



Multiple hypotheses testing was to be performed according to a mixture gatekeeping procedure based on the Hochberg test with a truncation fraction of $\gamma = 0.9$, which controls the familywise error rate at the pre-assigned level of significance $\alpha = 5\%$ in the strong sense. The Hochberg-based gatekeeping procedure (based on an extension of the general mixture methodology developed in Dmitrienko and Tamhane (2011, 2013) and recently proposed in Brechenmacher et al., 2011) was to account for two sources of multiplicity at the final analysis; two arms of rivaroxaban/aspirin study treatment being compared to the active control aspirin and comparisons being performed for a primary and three

secondary outcomes. A truncation fraction γ close to 1 was chosen to ensure a high probability of success for the primary hypotheses, considering that potentially only a small fraction of α is carried forward to the next family of hypotheses. The gatekeeping procedure was to use the truncated Hochberg test in Family 1 to 3 because they were to serve as gatekeepers for the next family in the sequence. The regular Hochberg test was to be applied in Family 4 since this was the last family in the testing sequence.

A third source of multiplicity related to the planned interim analyses and was addressed for the testing of the primary outcome via the modified Haybittle-Peto rule. Given conservative monitoring boundaries, the type I error level adjustment for the final analysis was considered negligible and no adjustment was performed for the final primary efficacy analysis.

Interim analyses
Two formal interim analyses were planned when 50% (about 1,100) and 75% (about 1,650) of the expected number of accumulated primary efficacy outcome events (2200 subjects with an unrefuted event) accrued.

If the interim analyses showed clear and consistent benefit in both rivaroxaban treatment groups, the DSMB could recommend early study termination. The modified Haybittle-Peto rule was to be used to guide the decision regarding early stopping of some or all of the study treatment groups: a reduction of 4 standard deviations in the analysis of the primary efficacy outcome at the first interim analysis (one-sided p-value < 0.0001) or 3 standard deviations at the second interim analysis (one-sided p-value <0.0014). If the monitoring boundary was crossed at either of the planned interim analyses, a second analysis was to be done after at least an additional 3-6 months to confirm the boundary remained crossed and that the trend in treatment effect was not temporary.

For a lack of efficacy, a futility approach was to be utilized. Based on the conditional probability of rejecting the null hypothesis for either primary comparison, the DSMB might have considered recommending early termination of the study. If the results were clear with one intervention, but not for the second intervention, the DSMB could have decided to continue evaluation of both or one rivaroxaban treatment arms. If the study was to continue with both interventions, then the type I error levels as pre-planned were to be used in the final analysis. If one intervention was stopped early for efficacy, the multiple testing procedure for the final analysis was to be performed as pre-planned with the assumption that the p-value for the primary efficacy outcome of the arm that was stopped early for overwhelming efficacy was smaller than 0.025. For secondary outcomes, the p-values were to be obtained from log-rank tests based on all available data for the stopped arm (data from confirmation analysis 6 months after respective interim look) and the complete data from the comparator arm. If one intervention was stopped early for futility, the final analysis was to be performed when at least 1,513 subjects in the two remaining arms has experienced an event with the final analysis to be performed according to the pre-planned multiple testing strategy.

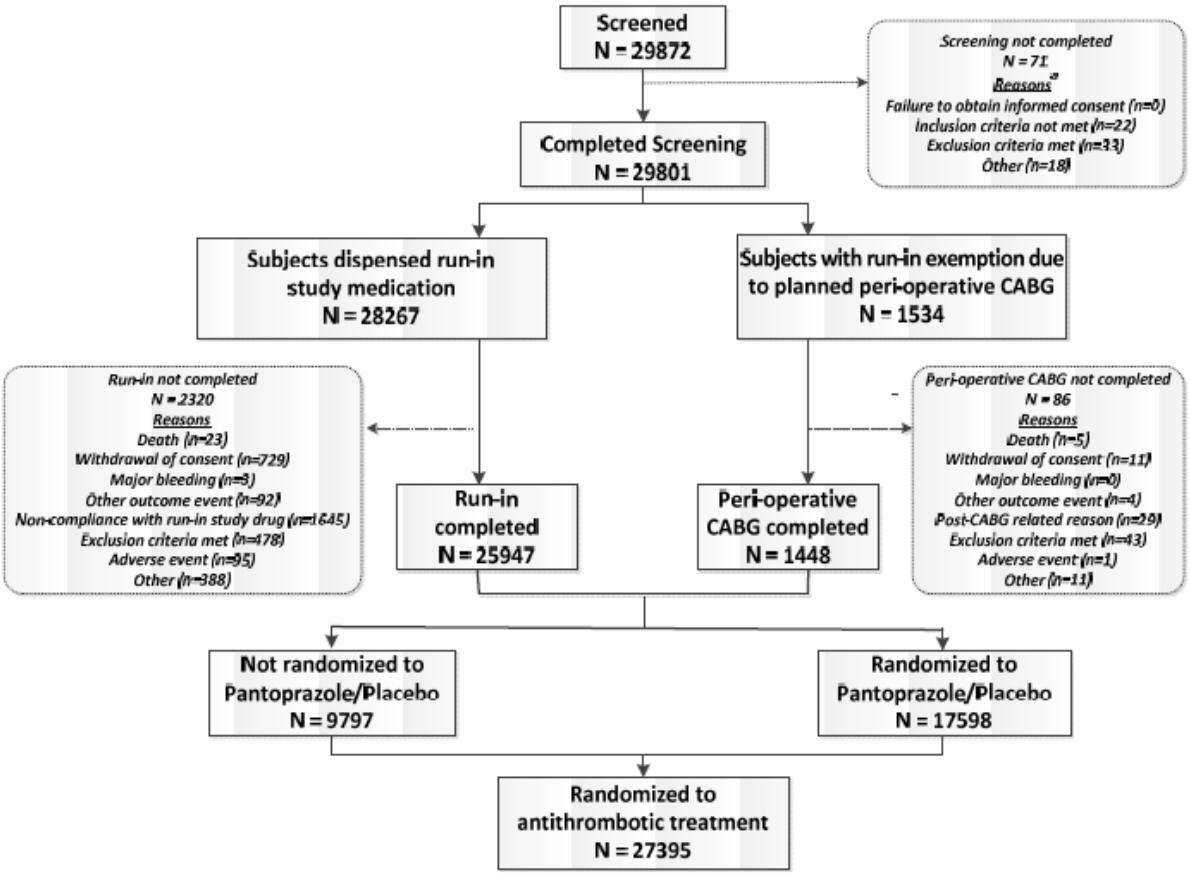
On 06 FEB 2017, the independent DSMB recommended to stop the rivaroxaban/aspirin arms early since the log-rank test statistic (z-value) for one of the primary comparisons had crossed the modified Haybittle-Peto boundary (i.e., z >4) consistently over 3 months at the first interim analysis. Considering the two comparisons, one for each rivaroxaban treatment arm, being made according to the modified Haybittle-Peto rule, the type I error level allocated at the first interim analysis is $\alpha_1 = 0.0001267$.

Results

Participant flow

Subject disposition is summarised in **Figures 3** (from screening to randomisation) and **4** (from randomisation to follow-up and wash-out).

Figure 3. Subject disposition in COMPASS study from screening to randomisation



a Multiple reasons could apply

Completed screening = either run-in medication was dispensed or the subject was planned to be randomised after peri-operative CABG surgery

Completed run-in = Subject attended randomisation visit and was randomised

Run-in not completed = Subject who did not attend the randomisation visit after he/she had run-in medication dispensed or subject who attended the randomisation visit but was not randomised to antithrombotic treatment

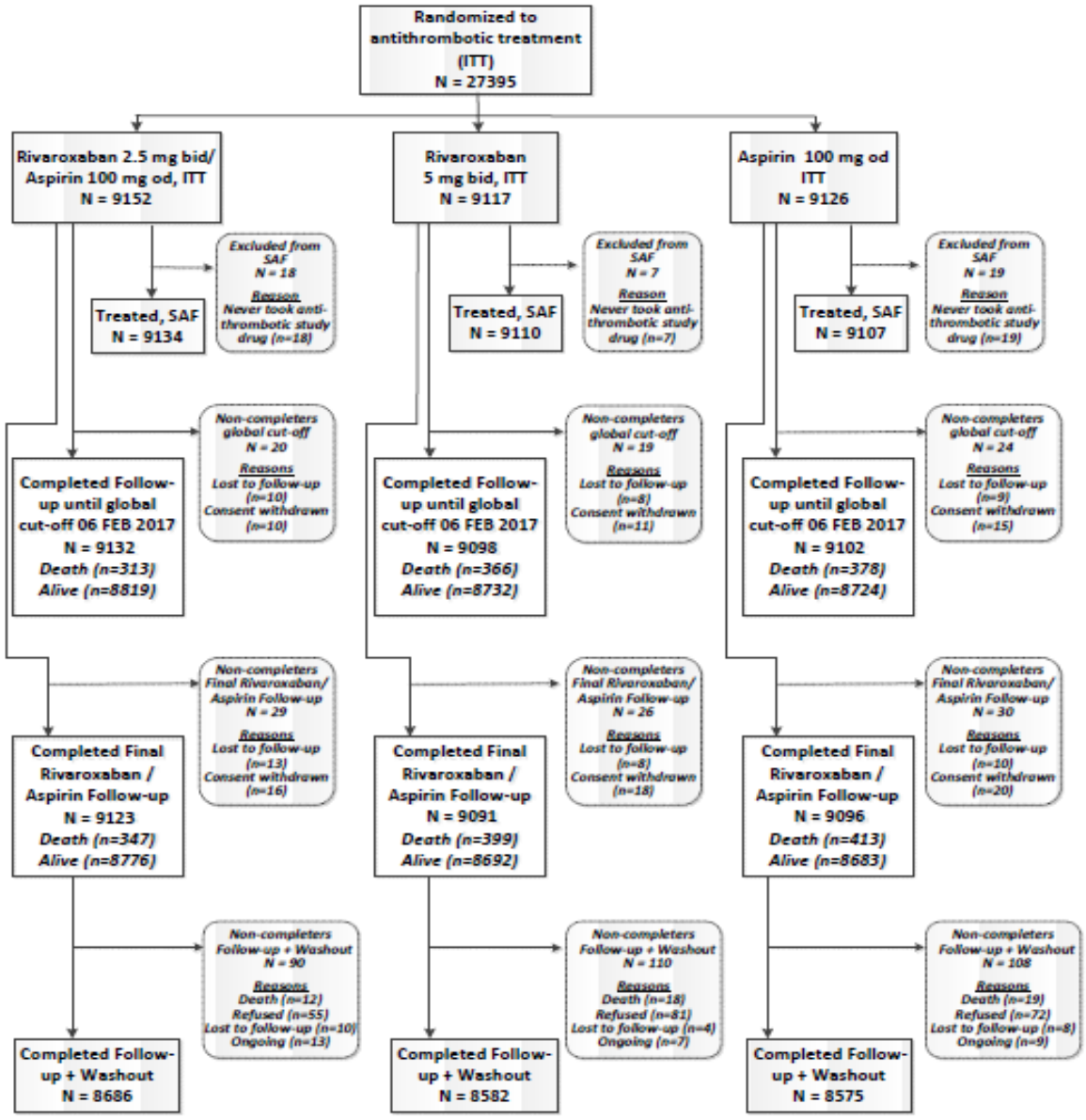
Peri-operative CABG completed = Subject attended randomisation visit and was randomised

Peri-operative CABG not completed = Subject who did not attend the randomisation visit after indicating at screening to undergo peri-operative CABG surgery or subject who attended the randomisation visit but was not randomised to antithrombotic treatment

Randomised to antithrombotic treatment = Number of unique subjects randomised

CABG = coronary artery bypass graft

Figure 4. Subject disposition in COMPASS study from randomisation to follow-up and washout



Randomised to antithrombotic treatment = Number of unique subjects randomised The reason "ongoing" regarding the antithrombotic part of the study indicates those subjects for whom the washout visit had not been performed at the date of last patient last visit.

bid = twice daily, ITT = intention-to-treat, od = once daily, SAF = safety analysis set

Recruitment

Study Start Date: 28 February 2013 (First Patient First Visit)

Study Completion Date: 20-July-2017 (Last Patient Last Visit, antithrombotic part)

Conduct of the study

The protocol and DSMB charter specified that approximately 1100 first occurrences of primary outcome events (50% of the required total 2200 subjects with a primary outcome event) would trigger the first formal interim analysis of efficacy. On 01 November 2016, a total of 1096 first occurrences of primary outcome events had been reported and analyses for the primary efficacy outcome were performed by the unblinded DSMB statistician. On 08 December 2016, a closed DSMB conference call was held based on an

analysis of best available data from 01 December 2016, and On 30 January 2017, a closed face-to-face meeting of the DSMB was held based on an analysis of best available data from 17 January 2017, when 1224 first occurrences of primary outcome events had been reported.

On 06 February 2017, the independent COMPASS DSMB issued a letter recommending stopping the rivaroxaban/aspirin arms early. The antithrombotic part of the study was completed 21 July 2017.

The DSMB also reviewed the efficacy and safety of the comparison of pantoprazole versus placebo but made no recommendation regarding early termination of this aspect of the overall study.

The study protocol was amended 10 times; the most significant amendments were Amendment 6 which formed integrated protocol version 2.0, dated 03 JUL 2014 and Amendment 8 which formed integrated protocol version 3.0, dated 19 AUG 2015. The major modifications specified in Amendment 6 were changes in the eligibility criteria for the study population with removal of the requirement for two additional risk factors or disease in at least two vascular beds for PAD subjects under the age of 65, and addition of patients with previous carotid revascularization and an increase of the sample size from 19500 to ~21400 randomized subjects. The main modification due to Amendment 8 was a change in the secondary outcomes to include 2 new composites of major thrombotic events, including new outcome components (ALI and CHD death). The multiple testing strategy was revised to ensure the control of the familywise type I error for both testing of primary and secondary efficacy variables for the final analyses based on 2200 events.

Baseline data

Demographic and other baseline characteristics of the trial population are presented in **Table 2**, and a summary of general medical history data are presented in **Table 3**.

Table 2. Summary of demographic data at baseline- ITT COMASS study

		Riva 2.5 mg bid / ASA 100 mg od	**Riva 5 mg bid**	**ASA 100 mg od**
		N = 9152 (100%)	**N = 9117 (100%)**	**N = 9126 (100%)**
Sex	Male	7093 (77.5%)	7145 (78.4%)	7137 (78.2%)
	Female	2059 (22.5%)	1972 (21.6%)	1989 (21.8%)
Age (years)	Mean ± SD	68.3 ± 7.9	68.2 ± 7.9	68.2 ± 8.0
Age group	<65	2150 (23.5%)	2183 (23.9%)	2184 (23.9%)
	65-<75	5078 (55.5%)	5060 (55.5%)	5045 (55.3%)
	≥75	1924 (21.0%)	1874 (20.6%)	1897 (20.8%)
Weight (kg)	N	9142	9113	9121
	Mean ± SD	80.72 ± 16.46	80.80 ± 16.06	81.05 ± 16.26
Weight group	<50 kg	152 (1.7%)	113 (1.2%)	126 (1.4%)
	50-90 kg	6695 (73.2%)	6691 (73.4%)	6678 (73.2%)
	>90 kg	2295 (25.1%)	2309 (25.3%)	2317 (25.4%)
Body mass index (kg/m^2)	Mean ± SD	28.31± 4.77	28.33 ± 4.64	28.38 ± 4.73
Fragile subject [a]		2308 (25.2%)	2246 (24.6%)	2284 (25.0%)
Baseline SBP	Mean ± SD	135.53 ± 17.46	135.50 ± 17.74	135.54 ± 17.50
Baseline DBP	Mean ± SD	77.45 ± 9.93	77.56 ± 10.06	77.65 ± 9.95
Baseline ABI	N	9002	8974	8973
	Mean ± SD	1.1032 ± 0.2020	1.1021 ± 0.2101	1.1014 ± 0.2074
Baseline ABI	<0.9	1190 (13.0%)	1217 (13.3%)	1233 (13.5%)
categories	≥0.9	7812 (85.4%)	7757 (85.1%)	7740 (84.8%)

		Riva 2.5 mg bid/ ASA 100 mg od	Riva 5 mg bid	ASA 100 mg od
		N = 9152 (100%)	N = 9117 (100%)	N = 9126 (100%)
History of Tobacco use	Never	2922 (31.9%)	2932 (32.2%)	2903 (31.8%)
	Former	4286 (46.8%)	4234 46.4%)	4251 (46.6%)
	Current	1944 (21.2%)	1951 (21.4%)	1972 (21.6%)
Prior CABG surgery category				
No prior CABG		6448 (70.5%)	6562 (72.0%)	6540 (71.7%)
Study baseline CABG surgery		502 (5.5%)	483 (5.3%)	463 (5.1%)
Other history of prior CABG surgery		2202 (24.1%)	2072 (22.7%)	2123 (23.3%)
Region	North America	1304 (14.2%)	1305 (14.3%)	1309 (14.3%)
	Western Europe/ AUS/ISR/ZAF	2855 (31.2%)	2845 (31.2%)	2855 (31.3%)
	Eastern Europe	1607 (17.6%)	1612 (17.7%)	1604 (17.6%)
	Asia Pacific	1332 (14.6%)	1319 (14.5%)	1304 (14.3%)
	South America	2054 (22.4%)	2036 (22.3%)	2054 (22.5%)
Baseline eGFR (mL/min) [b]	N	9148	9113	9126
	Mean ± SD	73.860 ± 17.856	73.782 ± 17.910	73.737 ± 18.121
eGFR [b]	missing	4 (<0.1%)	4 (0.1%)	0
	15 - <30 mL/min	77 (0.8%)	80 (0.9%)	86 (0.9%)
	30-<60 mL/min	1977 (21.6%)	2028 (22.2%)	2028 (22.2%)
	≥60 mL/min	7094 (77.5%)	7005 (76.8%)	7012 (76.8%)
Baseline total cholesterol (mg/dL)	N	8986	8962	8976
	Mean ± SD	167.219 ± 177.925	164.976 ± 146.521	166.971 ± 180.385
Lipid lowering agent use at randomization		8239 (90.0%)	8204 (90.0%)	8158 (89.4%)

a Fragility = yes in source table includes subjects with age >75 years or weight ≤50 kg or baseline eGFR <50 mL/min

b eGFR calculated based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

ABI = ankle-brachial index, ASA = acetylsalicylic acid; AUS/ISR/ZAF = Australia, Israel, South Africa, bid = twice daily, CABG = coronary artery bypass graft, eGFR = estimated glomerular filtration rate, ITT = intention-to-treat, od = once daily, riva = rivaroxaban, SD = standard deviation, SD = standard deviation.

Table 3. Summary of medical history at baseline- ITT COMASS study

		Riva 2.5 mg bid/ Aspirin 100 mg od	Riva 5 mg bid	Aspirin 100 mg od
		N = 9152 (100%)	N = 9117 (100%)	N = 9126 (100%)
MI	No	3498 (38.2%)	3464 (38.0%)	3405 (37.3%)
	Yes	5654 (61.8%)	5653 (62.0%)	5721 (62.7%)
Years since last MI	N	5644	5638	5710
	Mean ± SD	7.121 ± 6.468	7.105 ± 6.493	7.052±6.427
Years since last MI (categories)	<1	410 (4.5%)	403 (4.4%)	425 (4.7%)
	1 to <2	798 (8.7%)	774 (8.5%)	769 (8.4%)
	2 to ≤5	1612 (17.6%)	1614 (17.7%)	1667 (18.3%)
	>5	2824 (30.9%)	2847 (31.2%)	2849 (31.2%)
History of prior MI and age <65 years	No	7802 (85.2%)	7753 (85.0%)	7741 (84.8%)
	Yes	1350 (14.8%)	1364 (15.0%)	1385 (15.2%)
History of prior MI and eGFR <60 mL/min	No	7904 (86.4%)	7821 (85.8%)	7845 (86.0%)
	Yes	1248 (13.6%)	1296 (14.2%)	1281 (14.0%)
Presence of stable angina				
	No	6297 (68.8%)	6226 (68.3%)	6238 (68.4%)

Yes	2855 (31.2%)	2891 (31.7%)	2888 (31.6%)
Presence of unstable angina			
No	7419 (81.1%)	7332 (80.4%)	7437 (81.5%)
Yes	1733 (18.9%)	1785 (19.6%)	1689 (18.5%)
Coronary PTCA/Atherectomy/PCI			
No	4181 (45.7%)	4131 (45.3%)	4221 (46.3%)
Yes	4971 (54.3%)	4986 (54.7%)	4905 (53.7%)
CABG surgery (excluding peri-operative CABG 4-7 days before randomization), yes	2232 (24.4%)	2096 (23.0%)	2143 (23.5%)
Specified as:			
Multi-vessel	2109 (23.0%)	1982 (21.7%)	2029 (22.2%)
Post CABG recurrent angina	528 (5.8%)	513 (5.6%)	510 (5.6%)
Post CABG recurrent ischemia	335 (3.7%)	313 (3.4%)	346 (3.8%)
Presence of:			
Peripheral artery bypass surgery			
No	8893 (97.2%)	8817 (96.7%)	8860 (97.1%)
Yes	259 (2.8%)	300 (3.3%)	266 (2.9%)
Peripheral percutaneous transluminal angioplasty			
No	8682 (94.9%)	8639 (94.8%)	8640 (94.7%)
Yes	470 (5.1%)	478 (5.2%)	486 (5.3%)
Peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty			
No	8484 (92.7%)	8414 (92.3%)	8452 (92.6%)
Yes	668 (7.3%)	703 (7.7%)	674 (7.4%)
Limb or foot amputation arterial vascular disease			
No	9036 (98.7%)	9010 (98.8%)	9014 (98.8%)
Yes	116 (1.3%)	107 (1.2%)	112 (1.2%)
Intermittent claudication			
No	7854 (85.8%)	7861 (86.2%)	7851 (86.0%)
Yes	1298 (14.2%)	1256 (13.8%)	1275 (14.0%)
History of polyvascular disease and number of vascular beds affected [a]			
1 vascular bed affected	7078 (77.3%)	7069 (77.5%)	7039 (77.1%)
2 vascular beds affected	1613 (17.6%)	1598 (17.5%)	1589 (17.4%)
3 vascular beds affected	459 (5.0%)	448 (4.9%)	497 (5.4%)
History of both prior MI and poly-vascular disease or multivessel CAD[b]			
No	5773 (63.1%)	5754 (63.1%)	5791 (63.5%)
Yes	3379 (36.9%)	3363 (36.9%)	3335 (36.5%)
Diabetes			
No	5704 (62.3%)	5698 (62.5%)	5652 (61.9%)
Yes	3448 (37.7%)	3419 (37.5%)	3474 (38.1%)
Heart failure			
If Yes, NYHA	1963 (21.4%)	1960 (21.5%)	1979 (21.7%)
Class I	685 (7.5%)	738 (8.1%)	707 (7.7%)
Class II	1274 (13.9%)	1221 (13.4%)	1270 (13.9%)
Class III	3 (<0.1%)	1 (<0.1%)	2 (<0.1%)
Unknown	1 (<0.1%)	0	0
Known ejection fraction Yes, in %	5057 (55.3%)	4933 (54.1%)	5005 (54.8%)
N	5057	4928	5004
Mean ± SD	56.188 ± 10.336	55.920 ± 10.484	55.673 ± 10.387
Hypertension			
No	2245 (24.5%)	2269 (24.9%)	2249 (24.6%)
Yes	6907 (75.5%)	6848 (75.1%)	6877 (75.4%)
TIA			
No	8953 (97.8%)	8906 (97.7%)	8899 (97.5%)
Yes	199 (2.2%)	211 (2.3%)	227 (2.5%)
Any stroke			
No	8801 (96.2%)	8771 (96.2%)	8791 (96.3%)
Yes	351 (3.8%)	346 (3.8%)	335 (3.7%)
Cancer			
No	8556 (93.5%)	8536 (93.6%)	8582 (94.0%)

Yes	596 (6.5%)	581 (6.4%)	544 (6.0%)
Bleeding requiring transfusion			
No	8904 (97.3%)	8879 (97.4%)	8889 (97.4%)
Yes	248 (2.7%)	238 (2.6%)	237 (2.6%)

[b] *Polyvascular disease, vascular beds affected (CAD, PAD, cerebrovascular disease, i.e., prior stroke or asymptomatic carotid artery stenosis ≥50%/revascularization).*

[c] *Multivessel CAD =CAD and medical history of angina, PTCA, or CABG with multivessel coronary disease.*

Concomitant medication:

Only a few subjects (95 subjects, 0.3%) in the ITT analysis set had a documented anticoagulant use at screening. All subjects discontinued the use of all anticoagulants before the run-in period. For a total of 88.9% of the subjects in the ITT analysis set, antiplatelet use was documented at screening. The most commonly reported antiplatelet agent was aspirin (87% of the subjects), followed by clopidogrel (7.2% of subjects). There were no relevant differences between the treatment groups. Prior use of antiplatelet agents was slightly lower in the subgroup of subjects with PAD only (79.5%) compared to subjects with CAD only (89.7%) and subjects with CAD and PAD (90.8%) All 88.9% subjects discontinued the use of all antiplatelets before the run-in period. At least one non-study antiplatelet therapy at any visit was taken by 19.3% of all subjects. The most frequently reported concomitant non-study antiplatelet therapies at any visit were aspirin (17.5%), and clopidogrel (5.4%). There were no relevant differences between the treatment groups. Over time, use of non-study antiplatelet therapy increased, probably corresponding to the increasing number of subjects who permanently discontinued antithrombotic study treatment.

Relevant non-study drugs were taken by almost all subjects (99.6%) in all three treatment groups during the rivaroxaban/aspirin follow-up period. The most frequently reported pre-specified relevant concomitant medications were lipid lowering agents (taken by 93.9% of all subjects), ACE inhibitors or ARB (78.9%) and beta blockers (75.5%). There were no relevant differences between the treatment groups. The use of relevant concomitant medication by CAD only mirrored the overall population. For the subgroup of PAD only there was a lower use of guideline recommended therapies across all treatment groups.

A total of 33.3% of the subjects in the ITT analysis set reported a continuous need for PPI treatment at screening. The most commonly reported PPI medications were pantoprazole (11.8%) and omeprazole (11.6%). There were no relevant differences between the treatment groups.

Numbers analysed

In this trial the ITT analysis set corresponds to the full analysis set according to the ICH E9 guideline. None of the 27395 randomized subjects were excluded from the ITT analysis set.

From the ITT analysis set, 44 subjects were excluded who were not treated with study rivaroxaban/ placebo and/or study aspirin/placebo. Thus, 27351 subjects were valid for the safety analysis set (SAF). The reason for exclusion from SAF was no intake of antithrombotic study drug.

Outcomes and estimation

The results of the primary efficacy endpoint are presented in **Table 4**.

Table 4. Summary of the results for the primary efficacy outcome and its components up until global rivaroxaban/aspirin outcomes cut-off date (06 February 2017)**-** ITT COMPASS study

Primary efficacy outcome: composite of MI, stroke or CV death	**n (%)**	**n/100 p-yrs (95% CI)**

Riva 2.5 mg bid/aspirin 100 mg od	(N=9152, 100%)	379 (4.1%)	2.18 (1.97;2.41)
Riva 5 mg bid	(N=9117, 100%)	448 (4.9%)	2.60 (2.37;2.86)
Aspirin 100 mg od	(N=9126, 100%)	496 (5.4%)	2.88 (2.64;3.15)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.76 (0.66;0.86)
Log-rank p-value			0.00004
Log-rank test (z) statistic			4.1260
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.90 (0.79;1.03)
Log-rank p-value			0.11490
Log-rank test (z) statistic			1.5765

MI		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9152)	178 (1.9%)	1.02 (0.87;1.18)
Riva 5 mg bid	(N=9117)	182 (2.0%)	1.05 (0.90;1.22)
Aspirin 100 mg od	(N=9126)	205 (2.2%)	1.18 (1.03;1.36)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.86 (0.70;1.05)
Log-rank p-value			0.14458
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.89 (0.73;1.08)
Log-rank p-value			0.24392

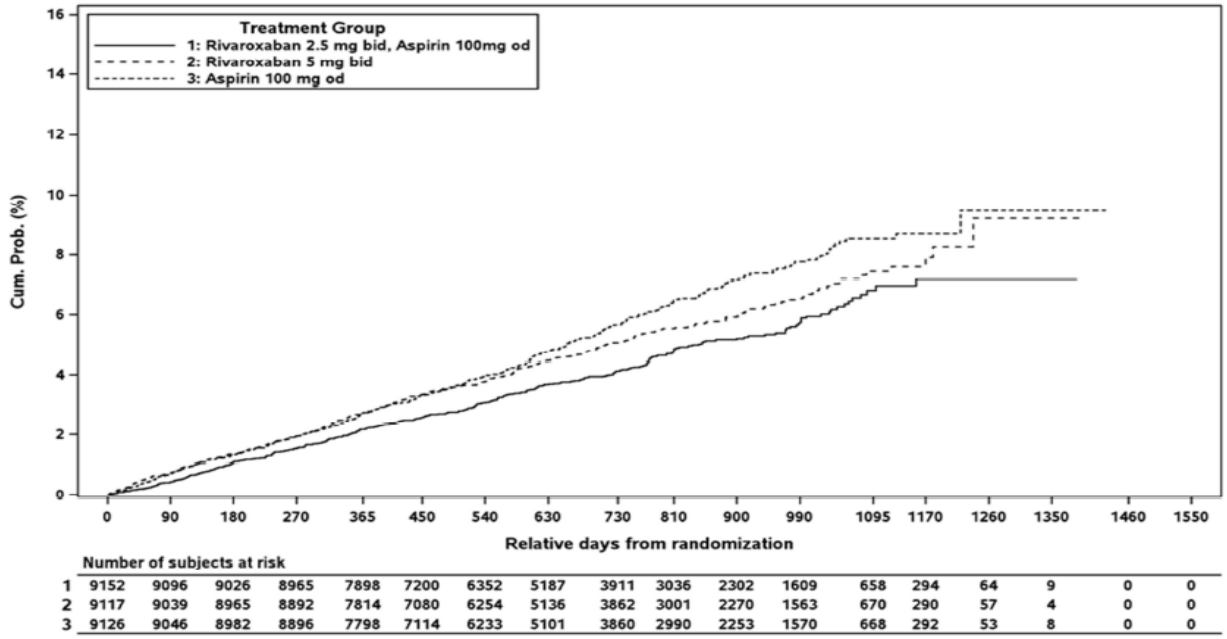
Stroke		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9152)	83 (0.9%)	0.47 (0.38;0.59)
Riva 5 mg bid	(N=9117)	117 (1.3%)	0.67 (0.56;0.81)
Aspirin 100 mg od	(N=9126)	142 (1.6%)	0.82 (0.69;0.96)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.58 (0.44;0.76)
Log-rank p-value			0.00006
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.82 (0.65;1.05)
Log-rank p-value			0.12065

CV death		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9152)	160 (1.7%)	0.91 (0.77;1.06)
Riva 5 mg bid	(N=9117)	195 (2.1%)	1.11 (0.96;1.28)
Aspirin 100 mg od	(N=9126)	203 (2.2%)	1.16 (1.00;1.33)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.78 (0.64;0.96)
Log-rank p-value			0.02053
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.96 (0.79;1.17)
Log-rank p-value			0.69006

*Table displays **unrefuted** outcomes = outcome events meeting the definition in the event adjudication plan. The primary efficacy outcome is composed of the first occurrence of MI, stroke, or CV death (includes fatal MI and stroke). For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.*
Stroke includes ischemic stroke, haemorrhagic stroke, and uncertain or unknown stroke.

The Kaplan-Meier estimates of the cumulative incidence risk for the composite primary efficacy outcome are shown in **Figure 5**.

Figure 5. Kaplan-Meier estimates of cumulative incidence risk of the composite primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date (06 February 2017)**-** ITT COMPASS study



Component of the primary efficacy outcome: MI

Hazard ratios for the incidence of MI in patients treated with rivaroxaban/aspirin or rivaroxaban alone compared to aspirin ,and corresponding p-values of the stratified log-rank tests are provided in **Table 5**.

Table 5. Rivaroxaban treatment effect for MI up until global rivaroxaban/aspirin outcomes cut-off date (06 February 2017)- ITT COMPASS study

	Riva 2.5 mg bid/ Aspirin 100 mg od versus Aspirin 100 mg od		Riva 5 mg bid versus Aspirin 100 mg od	
	HR (95% CI)	Log-rank p-value	HR (95% CI)	Log-rank p-value
MI	**0.86 (0.70;1.05)**	**0.14458**	**0.89 (0.73;1.08)**	**0.24392**
Non-procedural MI	0.84 (0.68;1.04)	0.11409	0.89 (0.73;1.10)	0.28969
Peri-procedural MI	1.28 (0.48;3.44)	0.62380	1.00 (0.35;2.85)	0.99717
associated with cardiac procedure	1.00 (0.32;3.09)	0.99456	0.84 (0.26;2.74)	0.76793
PCI-related	1.00 (0.29;3.44)	0.99432	Not calculated	
CABG, transcatheter aortic valve or mitral clip-related	Not calculated		Not calculated	
related to other cardiac procedures	Not calculated		Not calculated	
associated with non-cardiac procedures (within 48 h of procedure)	Not calculated		Not calculated	
Probable MI [a]	1.00 (0.41;2.39)	0.99358	0.90 (0.37;2.21)	0.81724

[a] *In the absence of cardiac biomarker values, the diagnosis of probable MI could be adjudicated if the following criteria were met: hospitalization for acute ischemic cardiac symptoms or ischemic ECG or imaging changes consistent with MI and narrative indicating thrombolysis or coronary revascularization within 12 hours.*

*Table displays **unrefuted** outcomes = outcome events meeting the definition in the event adjudication plan. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.*

HRs (95% CI) are based on the stratified Cox proportional hazards model. "Not calculated" is shown, if there were <5 events in a treatment group.

Log-rank p-values (two-sided) are based on the stratified log-rank test.
bid = twice daily, CABG = coronary artery bypass graft, CI = confidence interval, HR = hazard ratio, ITT = intention-to-treat, MI = myocardial infarction, PCI = percutaneous coronary intervention, od = once daily, riva = rivaroxaban.

Component of the primary efficacy outcome: Stroke

Hazard ratios for the incidence of MI in patients treated with rivaroxaban/aspirin or rivaroxaban alone compared to aspirin, and corresponding p-values of the stratified log-rank tests are provided in **Table 6**.

Table 6. Rivaroxaban treatment effect for stroke up until global rivaroxaban/aspirin outcomes cut-off date (06 February 2017)- ITT COMPASS study

	Riva 2.5 mg bid / Aspirin 100 mg od versus Aspirin 100 mg od		Riva 5 mg bid versus Aspirin 100 mg od	
	HR (95% CI)	Log-rank p-value	HR (95% CI)	Log-rank p-value
Stroke	**0.58 (0.44;0.76)**	**0.00006**	**0.82 (0.65;1.05)**	**0.12065**
Definite ischemic stroke	0.51 (0.38;0.69)	0.00001	0.66 (0.50;0.88)	0.00359
Secondary hemorrhagic transformation	0.35 (0.13;0.99)	0.03764	0.36 (0.13;0.99)	0.03876
Definite hemorrhagic stroke	1.49 (0.67;3.31)	0.32701	2.70 (1.31;5.58)	0.00515
Primary intracerebral/intraparenchymal /intraventricular brain hemorrhage	2.15 (0.82;5.66)	0.11154	3.83 (1.56;9.42)	0.00159
Subarachnoid hemorrhage	Not calculated		Not calculated	
Uncertain or unknown type of stroke [a]	Not calculated		1.14 (0.41;3.15)	0.79841

a Definite stroke that did not meet the criteria for cerebral infarction or hemorrhage (CT scan or MRI not done). The neurological deficit must have been present for 24 hours or more. NOTE: Subdural and epidural hematomas were not considered as strokes but were counted as major hemorrhages.
*Table displays **unrefuted** outcomes = outcome events meeting the definition in the event adjudication plan.*
For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.

HRs (95% CI) are based on the stratified Cox proportional hazards model.
"Not calculated" is shown, if there were <5 events in a treatment group.

Log-rank p-values (two-sided) are based on the stratified log-rank test.
Hemorrhagic transformation is considered within the category of ischemic stroke.
Table displays fatal and non-fatal strokes.
bid = twice daily, CI = confidence interval, HR = hazard ratio, ITT = intention-to-treat, od = once daily, riva =rivaroxaban.

Secondary efficacy outcomes

The numbers of subjects with secondary efficacy outcomes, crude incidences and incidence rates of the composites are presented in **Table 7**, and results from the statistical comparison in **Table 8**.

Table 7. Number of subjects with secondary efficacy outcomes- ITT, COMPASS study

	Riva 2.5 mg bid/ Aspirin 100 mg od		Riva 5 mg bid		Aspirin 100 mg od	
	N=9152 (100%)	n/100 p-yrs (95% CI)	N=9117 (100%)	n/100 p-yrs (95% CI)	N=9126 (100%)	n/100 p-yrs (95% CI)
MI, ischemic stroke, ALI, CHD death	**329 (3.6%)**	**1.89 (1.69;2.11)**	**397 (4.4%)**	**2.31 (2.09;2.54)**	**450 (4.9%)**	**2.62 (2.38;2.87)**
MI	178 (1.9%)	1.02 (0.87;1.18)	182 (2.0%)	1.05 (0.90;1.22)	205 (2.2%)	1.18 (1.03;1.36)
Ischemic stroke	64 (0.7%)	0.36 (0.28;0.47)	83 (0.9%)	0.48 (0.38;0.59)	125 (1.4%)	0.72 (0.60;0.86)
ALI	22 (0.2%)	0.12 (0.08;0.19)	24 (0.3%)	0.14 (0.09;0.20)	40 (0.4%)	0.23 (0.16;0.31)
CHD death	86 (0.9%)	0.49 (0.39;0.60)	128 (1.4%)	0.73 (0.61;0.87)	117 (1.3%)	0.67 (0.55;0.80)
MI, ischemic stroke, ALI, CV death	**389 (4.3%)**	**2.24 (2.02;2.47)**	**453 (5.0%)**	**2.63 (2.40;2.89)**	**516 (5.7%)**	**3.00 (2.75;3.27)**
CV death	160 (1.7%)	0.91 (0.77;1.06)	195 (2.1%)	1.11 (0.96;1.28)	203 (2.2%)	1.16 (1.00;1.33)
Mortality (all-cause)	**313 (3.4%)**	**1.78 (1.58;1.98)**	**366 (4.0%)**	**2.09 (1.88;2.32)**	**378 (4.1%)**	**2.16 (1.95;2.39)**
Non-CV death	153 (1.7%)	0.87 (0.74;1.02)	171 (1.9%)	0.98 (0.84;1.13)	175 (1.9%)	1.00 (0.86;1.16)

Table 8. Rivaroxaban treatment effect for secondary efficacy outcomes- ITT, COMPASS study

	Riva 2.5 mg bid/ Aspirin 100 mg od vs Aspirin 100 mg od		Riva 5 mg bid versus Aspirin 100 mg od	
	HR (95% CI)	Log-rank p-value	HR (95% CI)	Log-rank p-value
MI, ischemic stroke, ALI, CHD death	**0.72 (0.63;0.83)**	**0.00001**	**0.88 (0.77;1.01)**	**0.06437**
MI	0.86 (0.70;1.05)	0.14458	0.89 (0.73;1.08)	0.24392
Ischemic stroke	0.51 (0.38;0.69)	0.00001	0.66 (0.50;0.88)	0.00359
ALI	0.55 (0.32;0.92)	0.02093	0.60 (0.36;1.00)	0.04609
CHD death	0.73 (0.55;0.96)	0.02611	1.09 (0.85;1.41)	0.48118
MI, ischemic stroke, ALI, CV death	**0.74 (0.65;0.85)**	**0.00001**	**0.88 (0.77;0.99)**	**0.03995**
CV death	0.78 (0.64;0.96)	0.02053	0.96 (0.79;1.17)	0.69006
Mortality (all-cause)	**0.82 (0.71;0.96)**	**0.01062**	**0.97 (0.84;1.12)**	**0.66418**
Non-CV death	0.87 (0.70;1.08)	0.20357	0.98 (0.79;1.21)	0.83451

*Table displays **unrefuted** outcomes = outcome events meeting the definition in the event adjudication plan.*
Secondary efficacy outcomes are composed of the first occurrence of (i) MI, ischemic stroke, ALI, or CHD death, (ii), MI, ischemic stroke, ALI, or CV death and (iii) death. For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
n/100 p-yrs: incidence rate estimated as number of subjects with incident events divided by the cumulative at-risk time in the reference population, where a subject is no longer at risk once an incident event occurred.
HRs (95% CI) are based on the stratified Cox proportional hazards model.
Log-rank p-values (two-sided) are based on the stratified log-rank test.
CHD death includes death due to acute MI, sudden cardiac death, or death due to a CV procedure and is only identified via adjudication but not reported as such by the investigator.
ALI = acute limb ischemia; bid = twice daily; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; ITT = intention-to-treat; MI = myocardial infarction; od = once daily; riva = rivaroxaban.

The Kaplan-Meier estimates of the cumulative incidence risk for the composite secondary efficacy outcomes of MI, ischemic stroke, CHD death, or ALI and of of MI, ischemic stroke, CV death, or AL is shown in **Figures 5** and **6** respectively.

Figure 6. Kaplan-Meier estimates of cumulative incidence risk of the composite of MI, ischemic stroke, CHD death, or ALI- ITT, COMPASS study

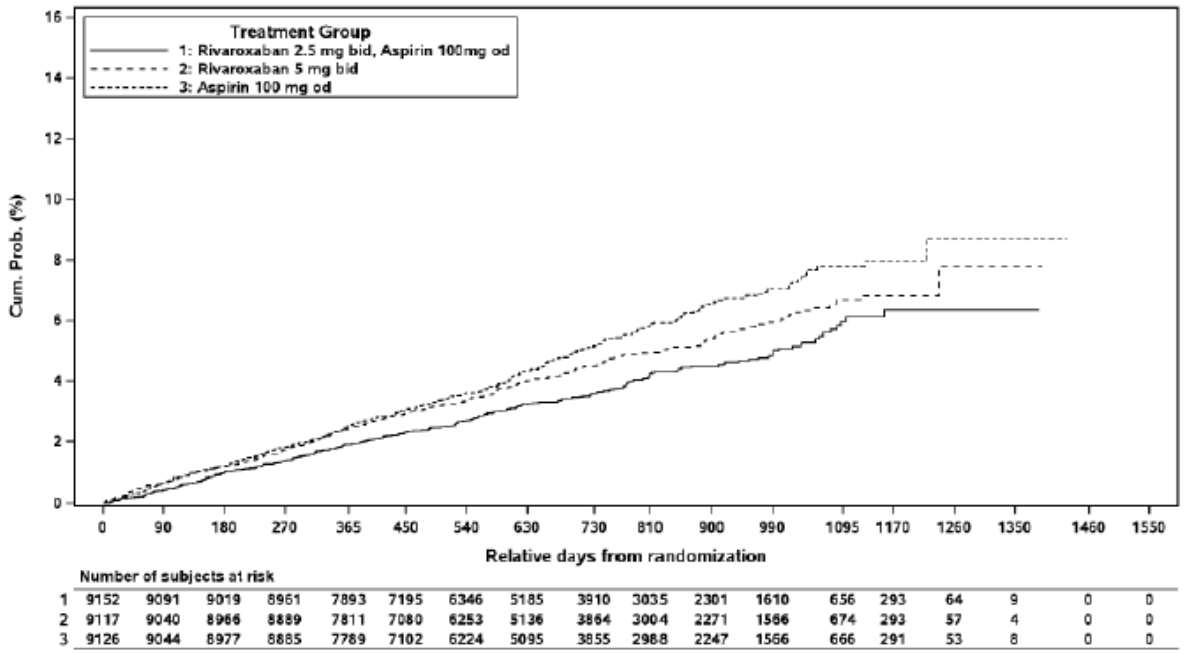


Figure 7. Kaplan-Meier estimates of cumulative incidence risk of the composite of MI, ischemic stroke, CV death, or ALI up until global rivaroxaban/aspirin outcomes cut-off date-ITT, COMPASS study

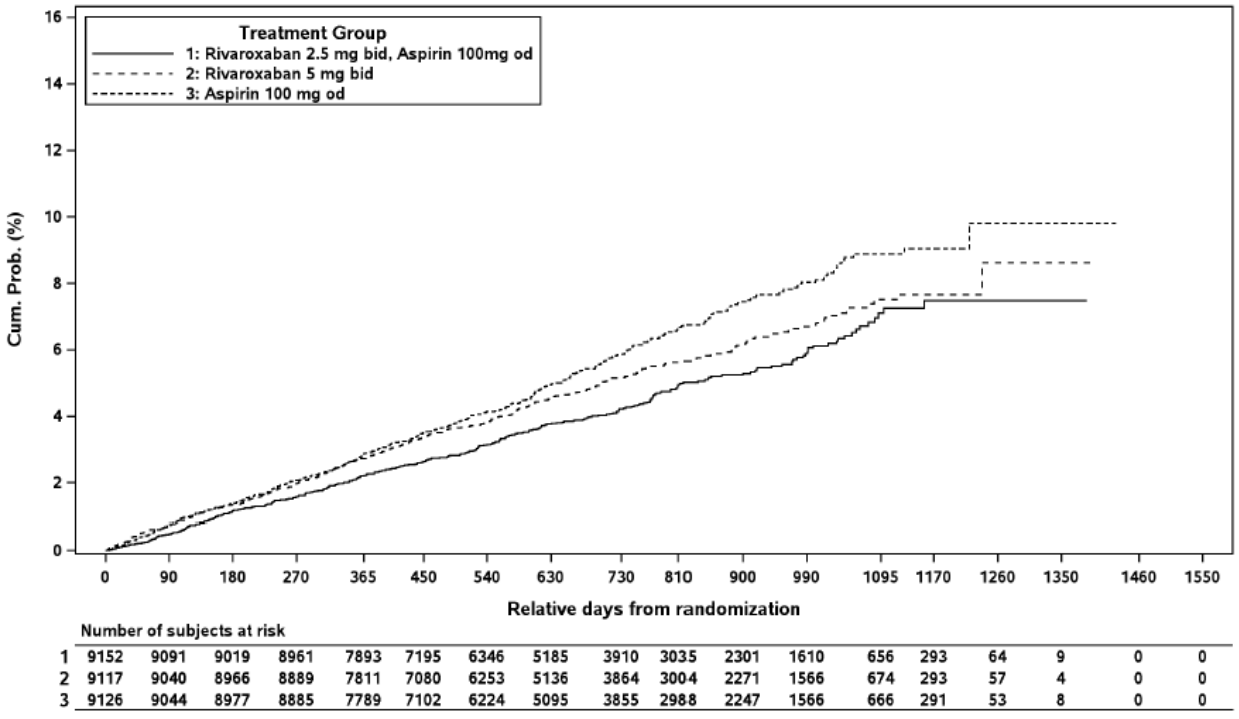


Figure displays **unrefuted** outcomes = outcome events meeting the definition in the event adjudication plan.
ALI = acute limb ischemia; bid = twice daily; Cum. = cumulative; CHD = coronary heart diseaseCV = cardiovascular; ITT = intention-to-treat; MI= myocardial infarction; od = once daily;

The numbers of subjects, crude incidences and incidence rates of the secondary efficacy outcome of all-cause mortality including death sub-categories and the statistical analyses are presented in **Table 9**.

Table 9. Number of subjects who died up until global rivaroxaban/aspirin outcomes cut-off date (ITT)

	Riva 2.5 mg bid/ Aspirin 100 mg od		Riva 5 mg bid		Aspirin 100 mg od	
	N=9152(100%)	n/100 p-yrs (95% CI)	N=9117(100%)	n/100 p-yrs (95% CI)	N=9126(100 %)	n/100 p-yrs (95% CI)
Death (all-cause mortality)	**313 (3.4%)**	**1.78 (1.58;1.98)**	**366 (4.0%)**	**2.09 (1.88;2.32)**	**378 (4.1%)**	**2.16 (1.95;2.39)**
Non-CV death	**153 (1.7%)**	**0.87 (0.74;1.02)**	**171 (1.9%)**	**0.98 (0.84;1.13)**	**175 (1.9%)**	**1.00 (0.86;1.16)**
Malignancy death	72 (0.8%)	0.41 (0.32;0.51)	88 (1.0%)	0.50 (0.40;0.62)	89 (1.0%)	0.51 (0.41;0.63)
Fatal bleeding other than due to hemorrhagic stroke	3 (<0.1%)	0.02 (0.00;0.05)	4 (<0.1%)	0.02 (0.01;0.06)	4 (<0.1%)	0.02 (0.01;0.06)
Other non-CV death not due to malignancy or bleeding	78 (0.9%)	0.44 (0.35;0.55)	79 (0.9%)	0.45 (0.36;0.56)	82 (0.9%)	0.47 (0.37;0.58)
CV death	**160 (1.7%)**	**0.91 (0.77;1.06)**	**195 (2.1%)**	**1.11 (0.96;1.28)**	**203 (2.2%)**	**1.16 (1.00;1.33)**
Within 30 days of acute MI	15 (0.2%)	0.09 (0.05;0.14)	13 (0.1%)	0.07 (0.04;0.13)	24 (0.3%)	0.14 (0.09;0.20)
Within 30 days of Stroke	11 (0.1%)	0.06 (0.03;0.11)	19 (0.2%)	0.11 (0.07;0.17)	13 (0.1%)	0.07 (0.04;0.13)
Within 14 days of heart Failure	17 (0.2%)	0.10 (0.06;0.15)	16 (0.2%)	0.09 (0.05;0.15)	15 (0.2%)	0.09 (0.05;0.14)
Within 3 days of a CV procedure	1 (<0.1%)	0.01 (0.00;0.03)	5 (<0.1%)	0.03 (0.01;0.07)	7 (<0.1%)	0.04 (0.02;0.08)
Sudden cardiac death	70 (0.8%)	0.40 (0.31;0.50)	110 (1.2%)	0.63 (0.52;0.76)	86 (0.9%)	0.49 (0.39;0.61)
Death due to other CV Cause	34 (0.4%)	0.19 (0.13;0.27)	29 (0.3%)	0.17 (0.11;0.24)	51 (0.6%)	0.29 (0.22;0.38)
Death due to unknown Causes	12 (0.1%)	0.07 (0.04;0.12)	3 (<0.1%)	0.02 (0.00;0.05)	7 (<0.1%)	0.04 (0.02;0.08)
CHD death	**86 (0.9%)**	**0.49 (0.39;0.60)**	**128 (1.4%)**	**0.73 (0.61;0.87)**	**117 (1.3%)**	**0.67 (0.55;0.80)**

Stroke includes hemorrhagic stroke.
CHD death is a sub-category of CV death and includes death due to acute MI, sudden cardiac death, or death due to a CV procedure and is only identified via adjudication.

Ancillary analyses

Potential testing strategies specified after the DSMB recommendation to terminate the antithrombotic study treatment arms

Since an early stop at approximately 50% of the target number of primary efficacy outcome events was not anticipated, the study protocol and SAP did not describe any plans for the testing of secondary efficacy outcomes in the unlikely case of a premature termination for efficacy. For the secondary efficacy hypotheses, nominal p-values are reported; the test decisions according to several testing strategies defined after the DSMB recommendation to terminate the antithrombotic study treatment arms, but before the release of the first clinical database are presented in **Table 10**.

Table 10. Test decisions for primary and secondary efficacy hypotheses according to potential testing strategies

Null hypothesis			Rejection of null hypotheses according to			
Outcome	Aspirin 100 mg compared with	Nominal p-value	(A) Hierarchical per comparison [a]	(B) Hochberg-based gatekeeping 1. Haybittle-Peto/ Haybittle-Peto at α = 0.0001267	(B) Hochberg-based gatekeeping 2. Haybittle-Peto/ Pocock at α = 0.0001267	(C) Hochberg-based gatekeeping at α = 0.05
MI, stroke, CV death	Riva 2.5 mg bid/Aspirin 100 mg od	0.0000369	yes	yes		yes
	Riva 5 mg bid	0.1148992	no	no		no
MI, ischemic stroke, ALI, CHD death	Riva 2.5 mg bid/Aspirin 100 mg od	0.0000068	yes	no	no	yes
	Riva 5 mg bid	0.0643731	no	no	no	no
MI, ischemic stroke, ALI, CV death	Riva 2.5 mg bid/Aspirin 100 mg od	0.0000107	yes	no	no	yes
	Riva 5 mg bid	0.0399506	no	no	no	no
Mortality (all-cause)	Riva 2.5 mg bid/Aspirin 100 mg od	0.0106195	no	no	no	no
	Riva 5 mg bid	0.6641774	no	no	no	no

a Hierarchical testing (per comparison) at α=0.0000633 (two-sided)
Note that p-values are only given with 5 digits in the source tables. Further digits are required to apply the testing algorithm as described above. These have been calculated from the log-rank test statistics given in the tables.
ALI = acute limb ischemia; bid = twice daily; CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction; od = once daily; Riva = rivaroxaban.

Analysis of the composite primary efficacy outcome for important subgroups: subjects with CAD and/or PAD

The CAD/PAD diagnoses used for all analyses of this trial took into account the diagnosis made by the investigator at screening. In addition to the investigator diagnosis supplemental information from baseline evaluation and medical history records was used for a diagnosis of CAD or PAD (according to protocol definition) and the main focus of all analyses is based on this diagnosis for the main subgroups CAD yes, PAD yes and CAD and PAD.

The distribution of subjects by CAD and PAD subgroups was comparable in the 3 treatment groups, both for investigator assessments and for the CAD and PAD diagnoses that took baseline evaluation and medical history records into account (**Table 11**).

Table 11. CAD and/or PAD diagnoses –ITT, COMPASS Study

		Riva 2.5 mg bid/ Aspirin 100 mg od	Riva 5 mg bid	Aspirin 100 mg od
		N = 9152 (100%)	N = 9117 (100%)	N = 9126 (100%)
		Assigned to CAD and PAD		
CAD	***Yes***	***8313 (90.8%)***	***8250 (90.5%)***	***8261 (90.5%)***
	No	839 (9.2%)	867 (9.5%)	865 (9.5%)
PAD	***Yes***	***2492 (27.2%)***	***2474 (27.1%)***	***2504 (27.4%)***
	No	6660 (72.8%)	6643 (72.9%)	6622 (72.6%)
CAD and PAD	***Yes***	***1656 (18.1%)***	***1609 (17.6%)***	***1641 (18.0%)***
CAD only [a]		6657 (72.7%)	6641 (72.8%)	6620 (72.5%)
PAD only [a]		836 (9.1%)	865 (9.5%)	863 (9.5%)

a Subjects for whom a CAD and/or PAD diagnosis was not confirmed or missing are not shown (n = 7)

For the 3 subgroups CAD yes, PAD yes, and CAD and PAD the numbers of subjects with a primary efficacy outcome, crude incidences and incidence rates of the composite, as well as the results from the statistical comparison are presented in **Table 12**.

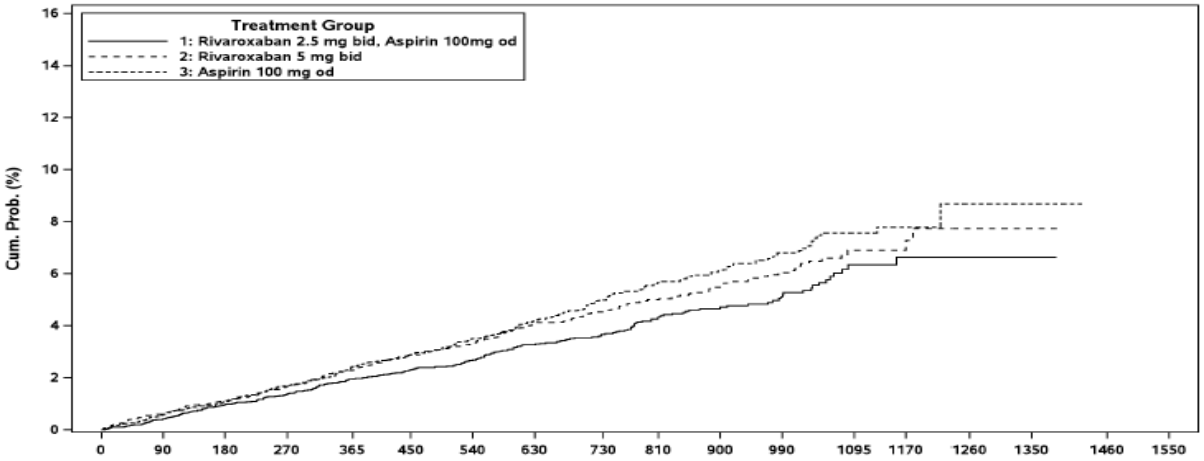
Table 12. Summary of the results for the primary efficacy outcome up until global rivaroxaban/aspirin outcomes cut-off date by CAD and/or PAD subgroups-ITT, COMPASS Study

Primary efficacy outcome: composite of MI, stroke, or CV death			
CAD yes (CAD only and CAD + PAD)		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=8313, 100%)	347 (4.2%)	2.17 (1.95;2.41)
Riva 5 mg bid	(N=8250, 100%)	411 (5.0%)	2.60 (2.36;2.87)
Aspirin 100 mg	(N=8261, 100%)	460 (5.6%)	2.91 (2.65;3.19)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.74 (0.65;0.86)
Log-rank p-value			0.00003
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.89 (0.78;1.02)
Log-rank p-value			0.09410
PAD yes (PAD only and PAD + CAD)		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=2492, 100%)	126 (5.1%)	2.82 (2.35;3.36)
Riva 5 mg bid	(N=2474, 100%)	149 (6.0%)	3.39 (2.87;3.98)
Aspirin 100 mg od	(N=2504, 100%)	174 (6.9%)	3.92 (3.36;4.54)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.72 (0.57;0.90)
Log-rank p-value			0.00466
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.86 (0.69;1.08)
Log-rank p-value			0.19223
CAD and PAD		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=1656, 100%)	94 (5.7%)	3.06 (2.47;3.75)
Riva 5 mg bid	(N=1609, 100%)	112 (7.0%)	3.76 (3.09;4.52)
Aspirin 100 mg od	(N=1641, 100%)	138 (8.4%)	4.55 (3.83;5.38)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.67 (0.52;0.87)
Log-rank p-value			0.00262
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.83 (0.64;1.06)
Log-rank p-value			0.13365
CAD only		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=6657, 100%)	253 (3.8%)	1.96 (1.72;2.22)
Riva 5 mg bid	(N=6641, 100%)	299 (4.5%)	2.33 (2.08;2.61)
Aspirin 100 mg od	(N=6620, 100%)	322 (4.9%)	2.53 (2.26;2.82)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.77 (0.66;0.91)
Log-rank p-value			0.00232
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.92 (0.79;1.08)
Log-rank p-value			0.32869
PAD only		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=836, 100%)	32 (3.8%)	2.29 (1.57;3.24)
Riva 5 mg bid	(N=865, 100%)	37 (4.3%)	2.62 (1.85;3.61)
Aspirin 100 mg od	(N=863, 100%)	36 (4.2%)	2.55 (1.79;3.53)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)			0.89 (0.55;1.44)
Log-rank p-value			0.63869
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)			1.02 (0.65;1.62)
Log-rank p-value			0.92659

*The diagnosis is based on the investigator assessment taking into account the individual medical history characteristics. Table displays **unrefuted** outcomes = outcome events meeting the definition in the event adjudication plan. The primary efficacy outcome is composed of the first occurrence of MI, stroke, or CV death (includes fatal MI and stroke). Stroke includes ischemic stroke, hemorrhagic stroke, and uncertain or unknown stroke.*

The Kaplan-Meier estimates of the cumulative incidence risk for the composite primary efficacy outcome in subjects with CAD and PAD are shown in **Figures 7** (CAD only), **8** (PAD only) and **9** (CAD and PAD).

Figure 8. Kaplan-Meier estimates of cumulative incidence risk of primary efficacy outcome, first occurrence of CV death, MI, and stroke up until global rivaroxaban/aspirin outcomes cut-off date by CAD/PAD subject (ITT analysis set). Subgroup CAD/PAD combined: CAD only

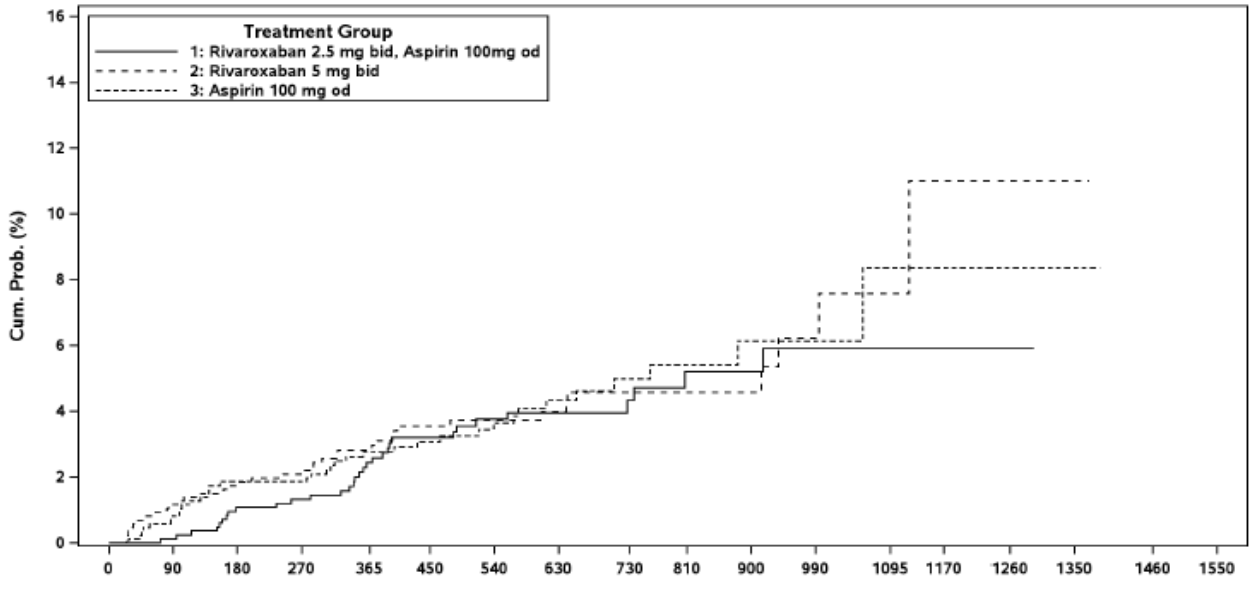


Number of subjects at risk

1	6657	6620	6577	6539	5811	5350	4767	3956	3004	2333	1764	1256	531	244	52	9	0	0
2	6641	6596	6550	6501	5774	5277	4708	3922	2992	2323	1744	1217	523	232	41	2	0	0
3	6620	6572	6533	6474	5738	5281	4668	3853	2930	2295	1734	1235	549	243	43	6	0	0

Figure displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
MI = myocardial infarction, CV = cardiovascular, bid = twice daily, od = once daily

Figure 9. Kaplan-Meier estimates of cumulative incidence risk of primary efficacy outcome, first occurrence of CV death, MI, and stroke up until global rivaroxaban/aspirin outcomes cut-off date by CAD/PAD subject (ITT analysis set). Subgroup CAD/PAD combined: PAD only



Number of subjects at risk

1	836	832	821	816	665	566	483	352	253	190	144	83	19	8	1	0	0	0
2	865	852	843	838	686	585	484	345	224	163	125	71	28	13	6	1	0	0
3	863	855	843	839	672	576	481	355	239	172	128	75	24	14	4	2	0	0

Figure displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
MI = myocardial infarction, CV = cardiovascular, bid = twice daily, od = once daily

Figure 10. Kaplan-Meier estimates of cumulative incidence risk of primary efficacy outcome, first occurrence of CV death, MI, and stroke up until global rivaroxaban/aspirin outcomes cut-off date by CAD/PAD subject (ITT analysis set). Subgroup CAD/PAD combined: CAD and PAD

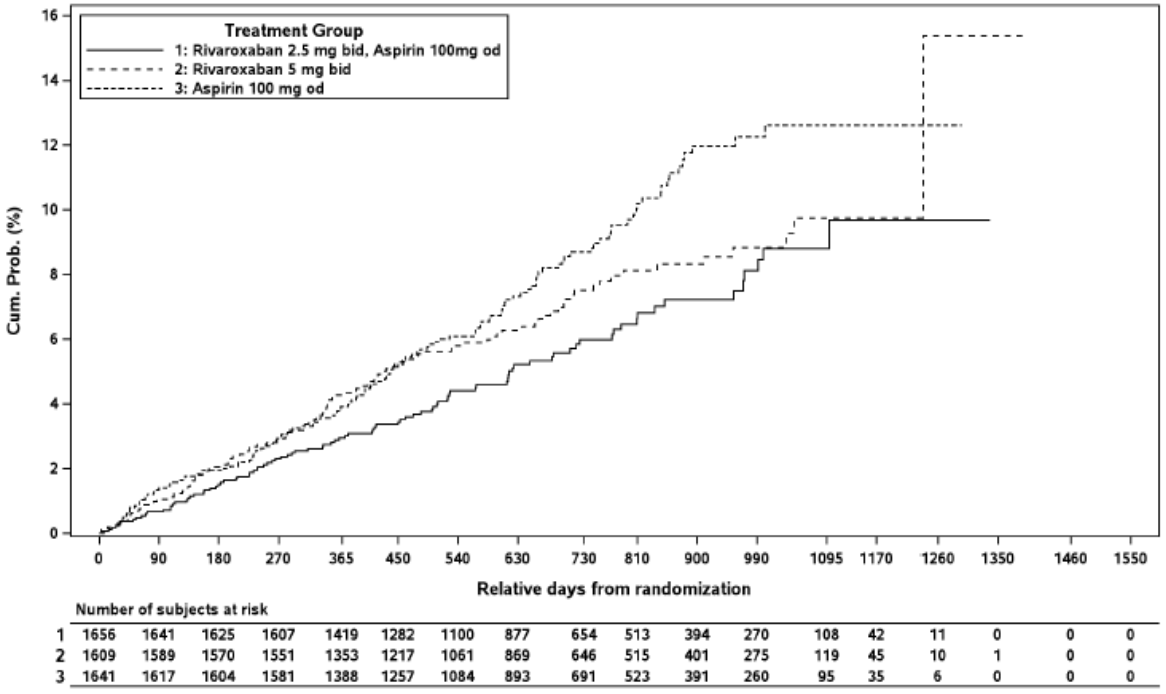
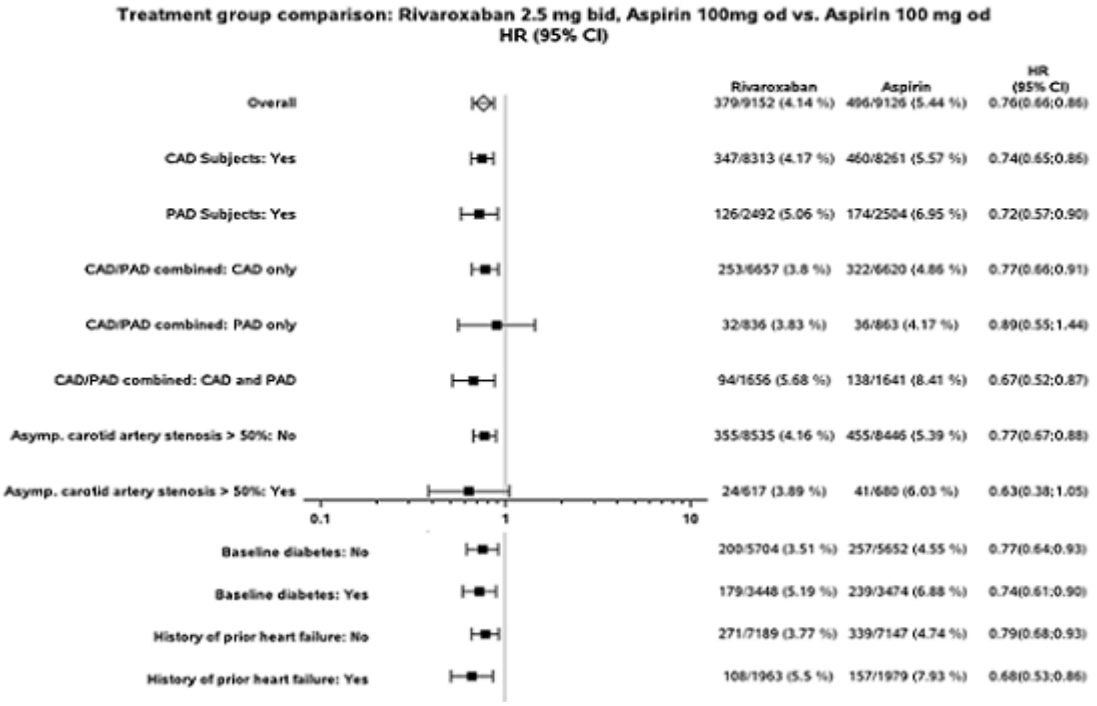
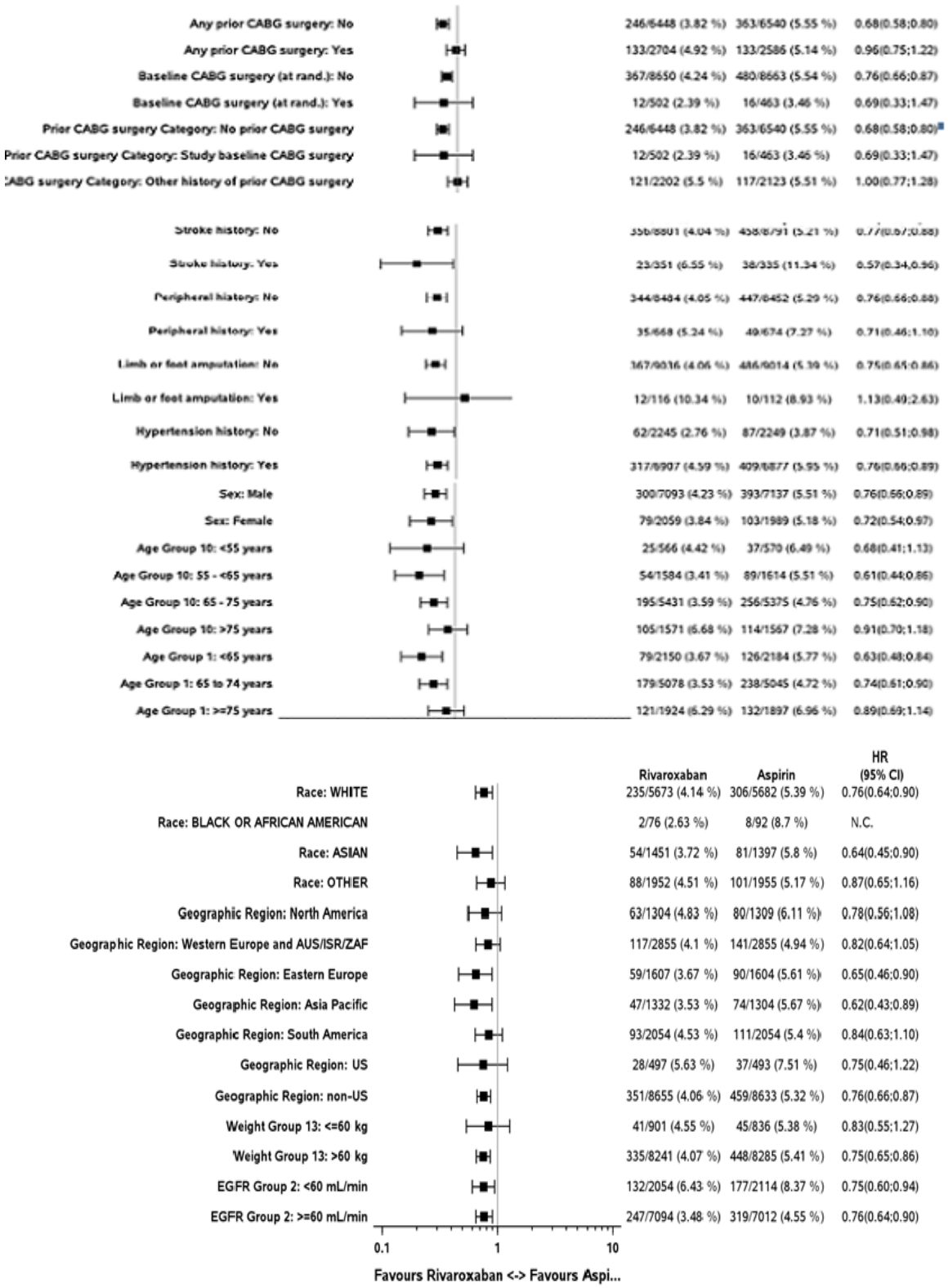


Figure displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
MI = myocardial infarction. CV = cardiovascular. bid = twice daily. od = once daily

Forest plots with crude incidences and results of the Cox proportional hazards model for different subgroup analyses of the primary efficacy outcome up until the global rivaroxaban/aspirin outcomes cut-off date for the comparison of rivaroxaban 2.5 mg bid/aspirin 100 mg od with aspirin 100 mg od are shown in **Figure 11**.

Figure 11. Forest plot for the first occurrence of MI, stroke or CV death in subgroups (ITT) (abridged)





	Rivaroxaban	Aspirin	HR (95% CI)
Any prior CABG surgery: No	246/6448 (3.82 %)	363/6540 (5.55 %)	0.68(0.58;0.80)
Any prior CABG surgery: Yes	133/2704 (4.92 %)	133/2586 (5.14 %)	0.96(0.75;1.22)
Baseline CABG surgery (at rand.): No	367/8650 (4.24 %)	480/8663 (5.54 %)	0.76(0.66;0.87)
Baseline CABG surgery (at rand.): Yes	12/502 (2.39 %)	16/463 (3.46 %)	0.69(0.33;1.47)
Prior CABG surgery Category: No prior CABG surgery	246/6448 (3.82 %)	363/6540 (5.55 %)	0.68(0.58;0.80)
Prior CABG surgery Category: Study baseline CABG surgery	12/502 (2.39 %)	16/463 (3.46 %)	0.69(0.33;1.47)
CABG surgery Category: Other history of prior CABG surgery	121/2202 (5.5 %)	117/2123 (5.51 %)	1.00(0.77;1.28)
Stroke history: No	356/8801 (4.04 %)	458/8791 (5.21 %)	0.77(0.67;0.88)
Stroke history: Yes	23/351 (6.55 %)	38/335 (11.34 %)	0.57(0.34;0.96)
Peripheral history: No	344/8484 (4.05 %)	447/8452 (5.29 %)	0.76(0.66;0.88)
Peripheral history: Yes	35/668 (5.24 %)	49/674 (7.27 %)	0.71(0.46;1.10)
Limb or foot amputation: No	367/9016 (4.07 %)	486/9014 (5.39 %)	0.75(0.65;0.86)
Limb or foot amputation: Yes	12/116 (10.34 %)	10/112 (8.93 %)	1.13(0.49;2.63)
Hypertension history: No	62/2245 (2.76 %)	87/2249 (3.87 %)	0.71(0.51;0.98)
Hypertension history: Yes	317/6907 (4.59 %)	409/6877 (5.95 %)	0.76(0.66;0.89)
Sex: Male	300/7093 (4.23 %)	393/7137 (5.51 %)	0.76(0.66;0.89)
Sex: Female	79/2059 (3.84 %)	103/1989 (5.18 %)	0.72(0.54;0.97)
Age Group 10: <55 years	25/566 (4.42 %)	37/570 (6.49 %)	0.68(0.41;1.13)
Age Group 10: 55 - <65 years	54/1584 (3.41 %)	89/1614 (5.51 %)	0.61(0.44;0.86)
Age Group 10: 65 - 75 years	195/5431 (3.59 %)	256/5375 (4.76 %)	0.75(0.62;0.90)
Age Group 10: >75 years	105/1571 (6.68 %)	114/1567 (7.28 %)	0.91(0.70;1.18)
Age Group 1: <65 years	79/2150 (3.67 %)	126/2184 (5.77 %)	0.63(0.48;0.84)
Age Group 1: 65 to 74 years	179/5078 (3.53 %)	238/5045 (4.72 %)	0.74(0.61;0.90)
Age Group 1: >=75 years	121/1924 (6.29 %)	132/1897 (6.96 %)	0.89(0.69;1.14)
Race: WHITE	235/5673 (4.14 %)	306/5682 (5.39 %)	0.76(0.64;0.90)
Race: BLACK OR AFRICAN AMERICAN	2/76 (2.63 %)	8/92 (8.7 %)	N.C.
Race: ASIAN	54/1451 (3.72 %)	81/1397 (5.8 %)	0.64(0.45;0.90)
Race: OTHER	88/1952 (4.51 %)	101/1955 (5.17 %)	0.87(0.65;1.16)
Geographic Region: North America	63/1304 (4.83 %)	80/1309 (6.11 %)	0.78(0.56;1.08)
Geographic Region: Western Europe and AUS/ISR/ZAF	117/2855 (4.1 %)	141/2855 (4.94 %)	0.82(0.64;1.05)
Geographic Region: Eastern Europe	59/1607 (3.67 %)	90/1604 (5.61 %)	0.65(0.46;0.90)
Geographic Region: Asia Pacific	47/1332 (3.53 %)	74/1304 (5.67 %)	0.62(0.43;0.89)
Geographic Region: South America	93/2054 (4.53 %)	111/2054 (5.4 %)	0.84(0.63;1.10)
Geographic Region: US	28/497 (5.63 %)	37/493 (7.51 %)	0.75(0.46;1.22)
Geographic Region: non-US	351/8655 (4.06 %)	459/8633 (5.32 %)	0.76(0.66;0.87)
Weight Group 13: <=60 kg	41/901 (4.55 %)	45/836 (5.38 %)	0.83(0.55;1.27)
Weight Group 13: >60 kg	335/8241 (4.07 %)	448/8285 (5.41 %)	0.75(0.65;0.86)
EGFR Group 2: <60 mL/min	132/2054 (6.43 %)	177/2114 (8.37 %)	0.75(0.60;0.94)
EGFR Group 2: >=60 mL/min	247/7094 (3.48 %)	319/7012 (4.55 %)	0.76(0.64;0.90)

Secondary efficacy outcomes

Results of the secondary efficacy outcomes by the main subgroups are presented in **Table 13**(CAD only), and **14** (PAD only).

Table 13. Rivaroxaban treatment effect for secondary efficacy outcomes, CAD only

	Riva 2.5 mg bid/ Aspirin 100 mg od vs Aspirin 100 mg od		Riva 5 mg bid versus Aspirin 100 mg od	
	HR (95% CI)	**Log-rank p-value**	**HR (95% CI)**	**Log-rank p-value**
MI, ischemic stroke, ALI, CHD death	**0.75 (0.63;0.90)**	**0.00151**	**0.88 (0.75;1.05)**	**0.15779**
MI	0.91 (0.72;1.16)	0.44773	0.91 (0.71;1.16)	0.44333
Ischemic stroke	0.49 (0.34;0.71)	0.00011	0.54 (0.38;0.77)	0.00059
ALI	Not calculated		0.83 (0.25;2.73)	0.76176
CHD death	0.73 (0.52;1.03)	0.06972	1.14 (0.84;1.55)	0.39874
MI, ischemic stroke, ALI, CV death	**0.77 (0.65;0.90)**	**0.00160**	**0.89 (0.76;1.05)**	**0.15747**
CV death	0.76 (0.58;0.99)	0.04227	1.03 (0.80;1.32)	0.81922
Mortality (all-cause)	**0.77 (0.64;0.94)**	**0.00840**	**0.98 (0.82;1.18)**	**0.83331**
Non-CV death	0.79 (0.59;1.04)	0.09133	0.93 (0.71;1.21)	0.57533

Table 14. Rivaroxaban treatment effect for secondary efficacy outcomes, PAD only

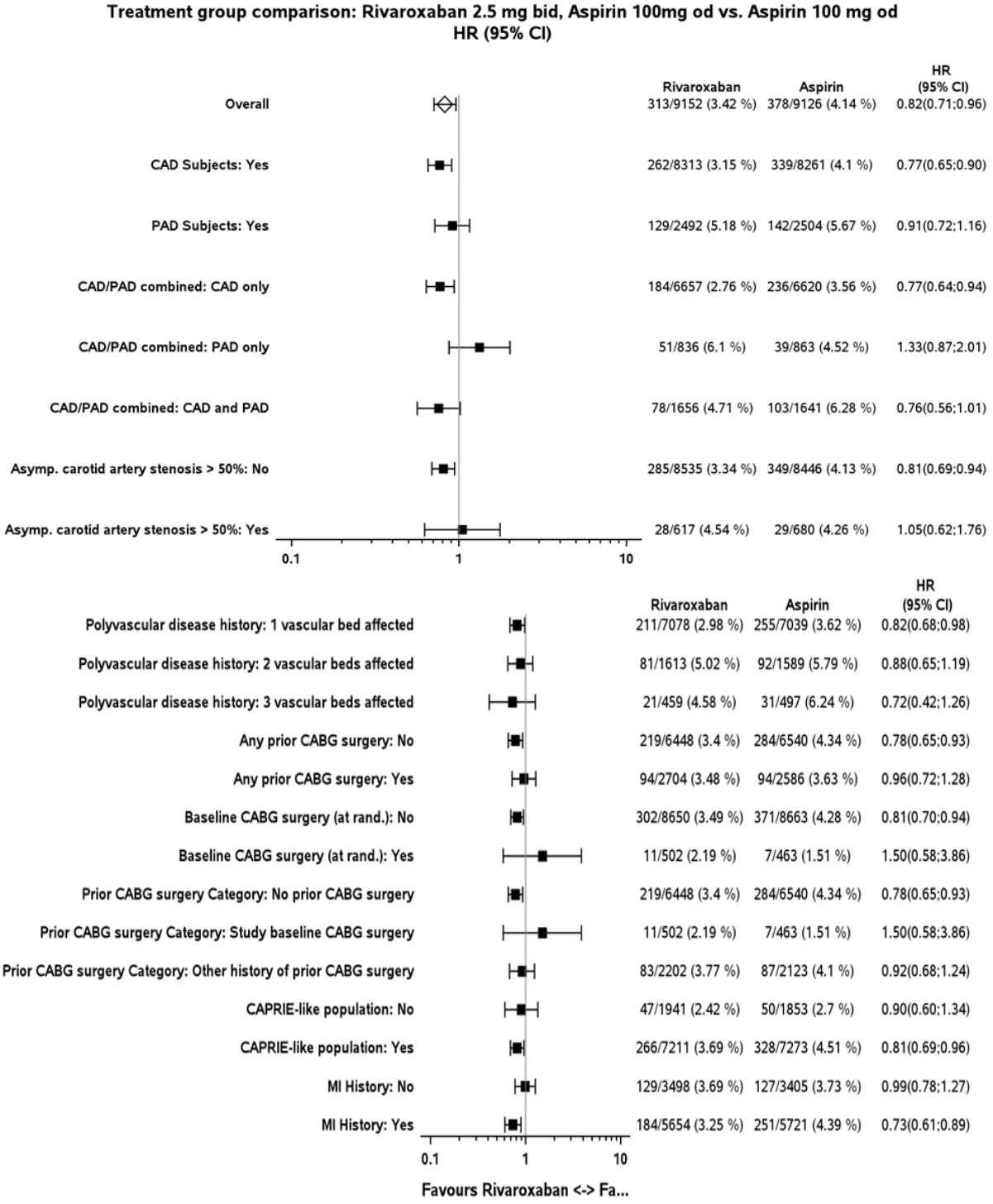
	Riva 2.5 mg bid/ Aspirin 100 mg od vs Aspirin 100 mg od		Riva 5 mg bid versus Aspirin 100 mg od	
	HR (95% CI)	**Log-rank p-value**	**HR (95% CI)**	**Log-rank p-value**
MI, ischemic stroke, ALI, CHD death	**0.78 (0.48;1.25)**	**0.29607**	**1.02 (0.65;1.58)**	**0.93632**
MI	0.92 (0.37;2.25)	0.84666	0.59 (0.21;1.62)	0.29680
Ischemic stroke	0.73 (0.29;1.81)	0.49509	1.09 (0.48;2.46)	0.84477
ALI	0.71 (0.30;1.66)	0.42396	0.77 (0.34;1.76)	0.53399
CHD death	0.61 (0.22;1.67)	0.32657	1.21 (0.52;2.80)	0.65566
MI, ischemic stroke, ALI, CV death	**0.88 (0.57;1.34)**	**0.53663**	**1.02 (0.68;1.53)**	**0.93924**
CV death	1.11 (0.59;2.06)	0.74909	1.05 (0.56;1.97)	0.87558
Mortality (all-cause)	**1.33 (0.87;2.01)**	**0.18283**	**1.29 (0.85;1.96)**	**0.23387**
Non-CV death	1.54 (0.87;2.71)	0.13325	1.52 (0.86;2.67)	0.14705

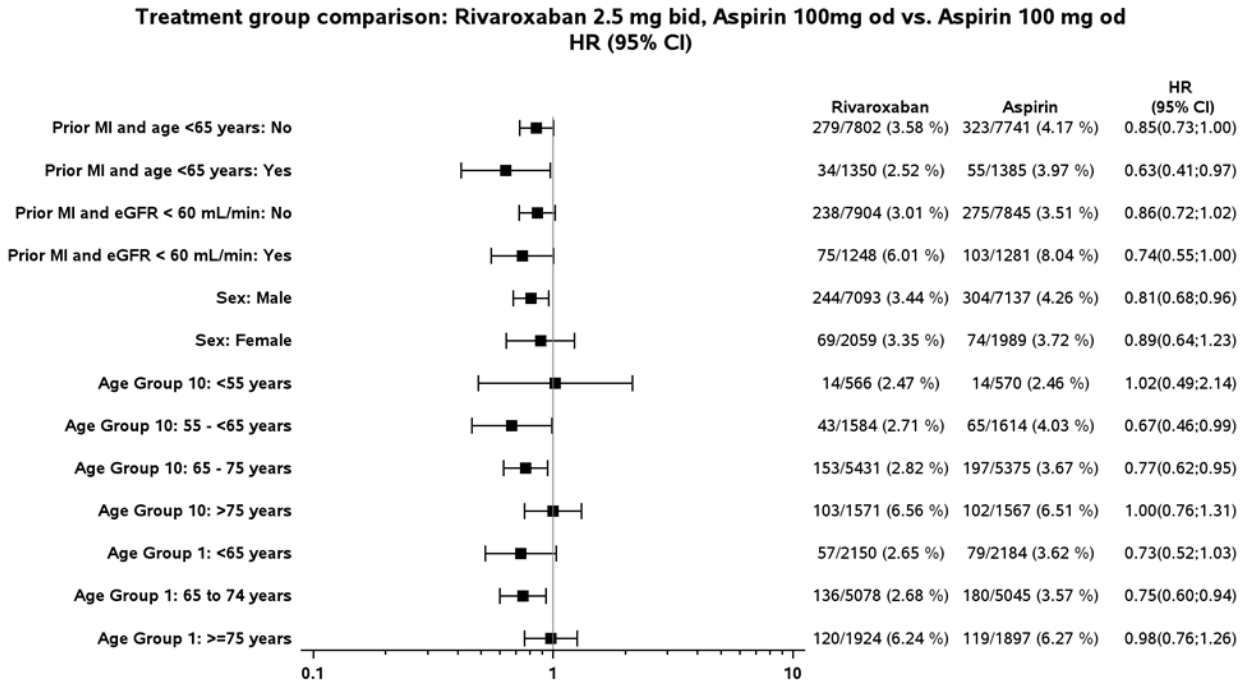
Tables displays unrefuted outcomes = outcome events meeting the definition in the event adjudication plan.
Secondary efficacy outcomes are composed of the first occurrence of (i) MI, ischemic stroke, ALI, and CHD death, (ii), MI, ischemic stroke, ALI, and CV death and (iii) death.
For composite outcomes and each component, the first event after randomization is considered. Subsequent events of the same type are not shown.
HR (95% CI): Hazard ratios (95% confidence interval) are based on the stratified Cox proportional hazards model.
Log-rank p-value: p-values (two-sided) are based on the stratified log rank test.
Log-rank test statistic: test statistic of the stratified log-rank test
MI = myocardial infarction, CV = cardiovascular, CHD = coronary heart disease, ALI = acute limb ischemia, p-yrs = patient years, bid = twice daily, od = once daily, CI = confidence interval.
CHD death includes death due to acute MI, sudden cardiac death, or death due to a CV procedure and is only identified via adjudication but not reported as such by the investigator.

All-cause mortality

Forest plots with crude incidences and the results of the Cox proportional hazards model for the subgroup analysis of all-cause mortality up until the global rivaroxaban/aspirin outcomes cut-off date are shown in **Figure 12** for the comparison of rivaroxaban 2.5 mg bid/aspirin 100 mg od with aspirin 100 mg od.

Figure 12. Forest plot for all-cause mortality up until global rivaroxaban/aspirin outcomes cut-off date (ITT) (abridged)





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 trial 15786

Title: A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease (COMPASS – Cardiovascular OutcoMes for People using Anticoagulation StrategieS)			
Study identifier	15786		
Design	Randomised, double-blind , controlled, event driven with a 3x2 partial factorial design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Up to 4 years 28 days for the majority of subjects not randomised after peri-operative CABG surgery not applicable (ongoing)
Hypothesis	Superiority		
Treatments groups	Rivaroxaban 2.5 mg bid/ASA 100 mg od		Duration (mean days± SD): 619.0 (297.9), number randomised: 9152
	Rivaroxaban 5 mg bid		Duration (mean days± SD): 616.4 (298.9), number randomised: 9117
	ASA 100 mg od (control)		Duration (mean days± SD): 623.8 (297.2), number randomised: 9126
Endpoints and definitions	Primary endpoint	Efficacy	Composite of MI, stroke or CV death

	Secondary	Efficacy	a) Composite of coronary heart disease death, MI, ischaemic stroke or acute limb ischaemia b) Composite of cardiovascular death, MI, , ischaemic stroke or acute limb ischaemia and c) mortality by any cause
Database lock	21 July 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability(n/100 p-yrs [95% CI])	Treatment group	Rivaroxaban 2.5 mg bid/ASA 100 mg od	ASA 100 mg od
	Number of subject	9152	9126
	Stroke, MI or CV death	2.18 (1.97;2.41)	2.88 (2.64;3.15)
	Stroke	0.47 (0.38;0.59)	0.82 (0.69;0.96)
	MI	1.02 (0.87;1.18)	1.18 (1.03;1.36)
	CV Death	0.91 (0.77;1.06)	1.16 (1.00;1.33)
	Primary endpoint	Comparison groups	Riva 2.5 mg bid/ASA 100 mg od versus ASA 100 mg od
Effect estimate per comparison	Stroke, MI or CV death	Hazard ratio (95% CI) Log-rank p-value	0.76 (0.66;0.86)* 0.00004
	Stroke	Hazard ratio (95% CI) Log-rank p-value	0.58 (0.44;0.76) 0.00006
	MI	Hazard ratio (95% CI) Log-rank p-value	0.86 (0.70;1.05) 0.14458
	CV Death	Hazard ratio (95% CI) Log-rank p-value	0.78 (0.64;0.96) 0.02053

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

COMPASS is a multicentre, randomized, double-blind, double-dummy, active comparator, event-driven study, in which 27 395 subjects with objectively confirmed CAD or PAD were randomised 1:1:1 to rivaroxaban 2.5 mg bid/ASA 100 mg od, rivaroxaban 5 mg bid, or ASA 100 mg od.

Additionally, subjects without a continuous need for treatment with a proton pump inhibitor (PPI) were randomised 1:1 to pantoprazole or pantoprazole placebo; this part of the study is ongoing.

The study population consists of patients with CAD, PAD or CAD and PAD. Most patients had either CAD only, or CAD and PAD. The majority of patients in the subgroup presented by the MAH as 'PAD yes' also had CAD.

Some information was lacking with regards to concomitant risk factors for CV disease, most importantly on glycaemic control in diabetic subjects. Despite excluding patients with dual antiplatelet therapy, the majority of patients had suffered a previous MI and a high proportion (about 30%) had a prior CABG surgery. However, the data were considered acceptable and to be representative of the intended target population and overall, subjects with high risk of incident cardiovascular disease were enrolled in the trial.

After a pre-planned interim analysis, the independent COMPASS DSMB recommended stopping the rivaroxaban/aspirin arms early. The DSMB also reviewed the efficacy and safety of the comparison of pantoprazole versus placebo but made no recommendation regarding early termination of this aspect of the overall study. Overall, the statistical methods used are appropriate as was planned analyses had the study been completed as planned. The key issue is multiplicity and interpretation of secondary ordered outcomes. When all antithrombotic treatment arms was stopped, the MAH concluded that the multiplicity strategy as planned was no longer valid since there was no pre-planned strategy on how to analyse key secondary endpoints. For the secondary efficacy endpoints therefore, nominal p-values have been reported. Hence, being strict, no formally valid claims can be made for secondary endpoints. Test decisions according to a number of post-hoc testing strategies (defined after the DSMB recommendation but before the release of the first clinical database) have, in addition, been presented.

The efficacy analysis population (ITT) included all randomised subjects and the majority of randomised subjects, 27332/27395 (99.8%), completed the follow-up period up until the global rivaroxaban/aspirin outcomes cut-off date. Reasons for non-completion were consent withdrawn and lost-to follow-up. At the cut-off date a total of 4587 (16.7%) of randomised subjects had discontinued both rivaroxaban/placebo and aspirin/placebo treatment permanently; 16.9%, 17.5%, and 15.9% in the rivaroxaban 2.5 mg bid/aspirin 100 mg od, rivaroxaban 5 mg bid group, and aspirin 100 mg od, arm respectively. In this population, these rates of discontinuation are considered acceptable.

Efficacy data and additional analyses

Rivaroxaban 2.5 mg bid in combination with aspirin 100 mg od significantly reduced the primary efficacy outcome, the time to first occurrence of stroke, MI, or CV death, compared with treatment with aspirin 100 mg od alone, in the ITT population. Since the study was terminated at the first interim report, not as many events for the primary efficacy outcome occurred as was originally planned. Treatment with rivaroxaban 5 mg bid did not show a statistically significant reduction in hazard ratio of the primary efficacy outcome compared to aspirin only.

The analysis of the primary composite endpoint (based on the global cut-off when the DSMB recommended that the antithrombotic treatment arms should be stopped) is also supported by the sensitivity analyses performed, the analysis of the composite primary efficacy outcome based on investigator-reported events and, the analysis of the primary endpoint based on data up until the final follow-up.

The reduction in occurrence of the primary efficacy outcome is considered clinically relevant in this heavily disease-burdened population. The effect is apparent early during treatment and remains consistent during the course of this study. The results with regards to both the primary and the secondary efficacy outcomes are consistent in the CAD only, CAD yes and CAD and PAD groups, but for the primary endpoint, the HR was less favourable and not statistically significant in the PAD only group However, the CHMP taking into account also the Additional expert consultation (see below), acknowledged that CAD are PAD are both characterised by atherosclerosis. Even though different arteries are affected, the

pathophysiology of the disease is similar across all vascular beds. Patients with clinical evidence of atherosclerosis in any territory should be expected to respond in a similar fashion to anti-thrombotic therapy. The lack of statistical significance in patients with PAD only was attributed to the smaller sample size of this sub-group, compared to the other sub-group of patients included in the COMPASS study. The CHMP concluded that patients with PAD should also be included in the target population for the proposed combination of rivaroxaban and acetylsalicylic acid.

However, the CHMP noted that CAD and PAD encompass a broad spectrum of patients, from patients with very mild or no symptoms, to patients with severe multi-vessel disease at high risk of infarction. Patients with severe coronary artery disease are also at risk of developing ischemic cardiomyopathy which is a common cause of heart failure in this population. Patients with mild CAD, patients with NYHA class III or IV symptoms or known ejection fraction <30% for example were not included in this study. Therefore the indication was revised to adult patients with coronary CAD or symptomatic PAD at high risk of ischaemic events. This reflects the studied population of the COMPASS study. CAD patients had multi-vessel CAD and/or prior MI. For patients < 65 years of age atherosclerosis involving at least two vascular beds or at least two additional cardiovascular risk factors were required. PAD patients had previous interventions such as bypass surgery or percutaneous transluminal angioplasty or limb or foot amputation for arterial vascular disease or intermittent claudication with ankle/arm blood pressure ratio < 0.90 and/ or significant peripheral artery stenosis or previous carotid revascularization or asymptomatic carotid artery stenosis ≥ 50%.

For the secondary efficacy outcome, the results are congruent with regards to the first two secondary endpoints (MI, ischemic stroke, ALI, CHD death and MI, ischemic stroke, ALI, CV death). For the third secondary endpoint, all-cause mortality, the picture is not as clear. All-cause mortality is lower in the riva 2.5/aspirin cohort, but the n/100 p-years (95% CI) are overlapping in all treatment groups. The number of malignancy deaths is lower in the riva 2.5/aspirin cohort, which accounts for the lower number of non-CV deaths in this cohort.

The pre-planned gatekeeping strategy and the failure of the 5 mg rivaroxaban arm implied (post-hoc proposed strategy that takes the stopping of treatments at the interim into account) that the testing of ordered secondary endpoints were to be made using the same conservative stopping boundary that was used at the interim analysis. As a consequence, no formally valid conclusion can be made for any of the secondary endpoints. The difference between rivaroxaban 2.5 mg treatment regimen and the aspirin control group in the ordered secondary composite endpoint 2 (MI, ischemic stroke, ALI, CHD death) and 3 (MI, ischemic stroke, ALI, CV death) finds, as concluded above, support in that they share components with the primary composite endpoint or relies on components that are subsets of primary components.

However, irrespective of testing strategy (to handle multiplicity) including the one that was pre-planned (hence ignoring the interim analysis and the early stopping of the antithrombotic treatment arms), no valid claim can be made regarding all-cause mortality. There is no effect on all-cause mortality in women, in the age group > 75 years and in patients that have not had a prior MI. All-cause mortality was higher in patients with CABG at baseline, PAD only, asymptomatic carotid stenosis > 50% and age groups <55 years. Therefore the CHMP concluded, that reduction of all-cause mortality should be removed from the proposed indication.

For ALI, there is a statistically significant reduction in the riva 2.5/aspirin group, but the numbers in all groups are very small (22 events in this group as compared to 40 in the aspirin only group). Apart from the analytical limitations of the secondary endpoints as described above, this small numerical decrease of events is not considered robust enough to allow for ‘reduction of ALI’ as a separate entity in the indication. Therefore the CHMP concluded, that reduction of all-cause mortality or ALI should be removed from the proposed indication which was revised to prevention of atherothrombotic events.

The CHMP also noted that for patients > 75 years the reduction in HR of the primary efficacy outcome was less pronounced and not statistically significant. This observation could partly be due to the smaller size of this group of patients (N=3821) compared to patients <75 years (14457). However, the effect with respect to reduction of stroke was of a relevant magnitude also in these elderly patients. The CHMP also noted that available data suggest that the risk of bleeding increases with age. Therefore it is recommended that rivaroxaban should be used with caution CAD/PAD patient and the benefit-risk of the treatment should be individually assessed on a regular basis.

Finally, as long term treatment is expected in these patients beyond the duration of the anti-thrombotic phase of the COMPASS study the CHMP advised that duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.

Additional expert consultation

The Scientific Advisory Group on Cardiovascular Issues (SAG-CVS) was asked to provide their view on the following issues:

1. The Marketing Authorisation Holder (MAH) is applying for an indication for Xarelto in combination with ASA for the prevention of major cardiovascular events in patients with coronary artery disease (CAD) at high risk of ischaemic events and/or documented peripheral artery disease (PAD) based on the results of the COMPASS study

a. **Please discuss the risk of cardiovascular events (CVE) in patients with PAD without coexisting diagnosed CAD and current standard of care with respect to prevention of CVE**
b. **What is your opinion concerning the strength and relevance of the results in the COMPASS study with respect to reduction of MACE as well as the risk of bleedings in the group of patients with PAD only. Do you think the results support a potential change of the standard of care of patients with PAD?**

The Group advised that there is a continuum between CAD and PAD (with many patients having both), as both conditions are linked with atherosclerosis which has developed in different territories. Therefore, there is no biological rationale to distinguish between the two. The Group also noted that there is a transition in the Standard of Care for patients with PAD, with treatment aiming at reducing the risk of cardiovascular events in such patients.

With regards to the results of the COMPASS study, the Group noted that the results in the pre-specified PAD only sub-group did not reach statistical significance for the reduction of CVE. This was however considered to be due to the smaller sample size of this group and chance fluctuation of treatment effect. The results in this sub-group of patients are consistent with those for the overall study population and the Group considered these as sufficient of demonstrating efficacy in the applied indication. The Group however noted that the evidence of an effect of rivaroxaban in acute limb ischaemia is much weaker - it was a tertiary endpoint without central adjudication than for the other investigated endpoints and recommended that this should reflected in the presentation of the results of the COMPASS study in the label.

The Group acknowledged that such results support a potential change in standard care of patients with PAD. Low dose rivaroxaban will then be added to aspirin.

2. Do the results of the COMPASS study and the known increased risk of bleeding associated with rivaroxaban, support use of rivaroxaban in CAD/PAD patients ≥ 75 years.

The Group advised that available data suggest that there is an increased risk of bleeding with increasing age. This is also known from previous experience with all factor Xa inhibitors. Despite this increased risk, the Group advised that this does not preclude use of rivaroxaban in in CAD/PAD patients ≥75 years. Instead it was considered that labelling with warnings about this risk would be appropriate to effectively manage this risk. Treatment with rivaroxaban in elderly patients should depend on careful assessment of the individual's personal circumstances and in particular the risk they may have for bleeding.

2.4.4. Conclusions on the clinical efficacy

The CHMP considers the following measures necessary to address issues related to efficacy:

2.5. Clinical safety

Introduction

In the approved indications, and congruent with the mode of action for rivaroxaban, bleeding is the most serious and most common adverse event of interest. For other components of the cardiovascular safety profile of rivaroxaban, treatment-emergent adverse reactions reported in patients in previous phase III studies include tachycardia (uncommon), hypotension (common), renal impairment (common) and peripheral oedema (common).

In the COMPASS study, the primary safety outcome was major bleeding according to modified ISTH criteria. The clinical hierarchy of modified ISTH major bleeding events was as follows

- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, respiratory, liver, pancreas, adrenal gland or kidney, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome (non-fatal)
- Bleeding into the surgical site requiring re-operation (non-fatal and non-critical organ)
- Bleeding leading to any hospitalization (*) (non-fatal, non-critical organ, not leading to re-operation)

(*) Major bleeding also includes hospitalization or presentation to an acute care facility with discharge on the same day, or associated with a > 1 day hospitalization.

Patient exposure

A total of 27351 subjects comprised the safety analysis set (rivaroxaban 2.5mg bid/aspirin: 9134 patients, exposed for a mean of 666 days; rivaroxaban 5 mg bid: 9110 patients, exposed for a mean of 662 days; aspirin only: 9107 patients exposed for a mean of 671 days).

Adverse events

Due to additional reporting of specified outcomes as (S)AE, reporting of non-serious AEs that did not lead to study drug discontinuation and more frequent visits in Japan, the crude incidences of AEs in Japan subjects are different compared with those in non-Japan subjects. Unless otherwise indicated, all tables displayed are with data excluding Japan subjects.

A summary of the (S)AEs/TE(S)AEs by treatment group in the Safety Analysis Set (SAF) is presented in **Table 16**.

Table 16. Overall summary of number of all subjects with AEs (SAF)

	Riva 2.5 mg bid/ Aspirin 100 mg od N=9134 (100%)	Riva 5 mg bid N=9110 (100%)	Aspirin 100 mg od N=9107 (100%)
Any AE	1344 (14.7%)	1329 (14.6%)	1254 (13.8%)
TEAE	1219 (13.3%)	1211 (13.3%)	1140 (12.5%)
Post-treatment AE	252 (2.8%)	242 (2.7%)	214 (2.3%)
Pre-discontinuation AE	410 (4.5%)	378 (4.1%)	331 (3.6%)
Serious AE	784 (8.6%)	772 (8.5%)	713 (7.8%)
Serious TEAE	641 (7.0%)	624 (6.8%)	582 (6.4%)
AE with outcome death	203 (2.2%)	210 (2.3%)	204 (2.2%)
Study drug-related TEAE – anti-thrombotic study medication	417 (4.6%)	369 (4.1%)	286 (3.1%)
Study drug-related TESAE – anti-thrombotic study medication	53 (0.6%)	41 (0.5%)	20 (0.2%)
Permanent discontinuation of anti-thrombotic study medication due to TEAE	312 (3.4%)	307 (3.4%)	238 (2.6%)
Permanent discontinuation of anti-thrombotic study medication due to TESAE	75 (0.8%)	74 (0.8%)	64 (0.7%)

Only AEs that occurred after randomization are taken into account.
"All subjects" includes both Japan and non-Japan subjects.
Pre-discontinuation AE: all events that started during the 30 days period before premature permanent discontinuation of any antithrombotic study treatment but not earlier than the day of randomization.
* Includes events of special interest (ESI).

The overall summary of AEs for non-Japan subjects by the subgroups CAD/PAD, sex, and age at baseline is shown in **Table 17**. For the purpose of safety reporting, the subgroups for CAD/PAD display subjects in a unique category based on their presentation of 'CAD only', 'PAD only' or both 'CAD/PAD combined' to avoid reporting a subject twice.

Table 17. Summary of AEs for non-Japan subjects by subgroups (SAF)*

Adverse event type (all events)		Riva 2.5 mg bid/ Aspirin 100 mg od	Riva 5 mg bid	Aspirin 100 mg od
CAD/PAD				
CAD only	*N*	6193	6197	6159
Any AE	n (%)	596 (9.6%)	588 (9.5%)	539 (8.8%)
Any TEAE	n (%)	520 (8.4%)	511 (8.2%)	471 (7.6%)
Any TESAE	n (%)	318 (5.1%)	312 (5.0%)	295 (4.8%)
PAD only	*N*	816	832	836
Any AE	n (%)	94 (11.5%)	91 (10.9%)	77 (9.2%)
Any TEAE	n (%)	80 (9.8%)	76 (9.1%)	60 (7.2%)
Any TESAE	n (%)	57 (7.0%)	51 (6.1%)	45 (5.4%)
CAD and PAD	*N*	1605	1562	1591
Any AE	n (%)	191 (11.9%)	203 (13.0%)	178 (11.2%)
Any TEAE	n (%)	164 (10.2%)	180 (11.5%)	158 (9.9%)
Any TESAE	n (%)	110 (6.9%)	113 (7.2%)	113 (7.1%)
Sex (males versus females)				
Males	*N*	6631	6701	6671
Any AE	n (%)	694 (10.5%)	678 (10.1%)	609 (9.1%)
Any TEAE	n (%)	596 (9.0%)	589 (8.8%)	530 (7.9%)
Any TESAE	n (%)	385 (5.8%)	362 (5.4%)	349 (5.2%)
Females	*N*	1986	1892	1917
Any AE	n (%)	187 (9.4%)	204 (10.8%)	185 (9.7%)
Any TEAE	n (%)	168 (8.5%)	178 (9.4%)	159 (8.3%)
Any TESAE	n (%)	100 (5.0%)	114 (6.0%)	104 (5.4%)
Age (years)				
< 65 years	*N*	2107	2133	2132
Any AE	n (%)	166 (7.9%)	146 (6.8%)	153 (7.2%)
Any TEAE	n (%)	143 (6.8%)	132 (6.2%)	135 (6.3%)
Any TESAE	n (%)	100 (4.7%)	83 (3.9%)	93 (4.4%)
≥ 65 to 74 years	*N*	4755	4733	4712
Any AE	n (%)	490 (10.3%)	509 (10.8%)	425 (9.0%)
Any TEAE	n (%)	434 (9.1%)	443 (9.4%)	368 (7.8%)
Any TESAE	n (%)	258 (5.4%)	269 (5.7%)	236 (5.0%)
≥ 75 years	*N*	1755	1727	1744
Any AE	n (%)	225 (12.8%)	227 (13.1%)	216 (12.4%)
Any TEAE	n (%)	187 (10.7%)	192 (11.1%)	186 (10.7%)
Any TESAE	n (%)	127 (7.2%)	124 (7.2%)	124 (7.1%)

TE(S)AEs are all events with onset at the date of or after randomization and up until 2 days following permanent discontinuation of any antithrombotic study treatment.
* Includes events of special interest (ESI).

A summary of the crude incidences of non-Japan subjects with TEAEs by MedDRA SOCs and treatment group is provided in **Table 18**.

Table 18. Number of non-Japan subjects with TEAEs by SOC (SAF)*

A summary of the most frequent (≥0.1% in any treatment group) TEAE PTs for non-Japan subjects by treatment group is provided in **Table 19**.

Primary system organ class	Riva 2.5 mg bid/ Aspirin 100 mg od N=8617 (100%)	Riva 5 mg bid N=8593 (100%)	Aspirin 100 mg od N=8588 (100%)
Number (%) of subjects with at least one such adverse event	765 (8.9%)	767 (8.9%)	689 (8.0%)
Blood and lymphatic system disorders	29 (0.3%)	24 (0.3%)	9 (0.1%)
Cardiac disorders	39 (0.5%)	40 (0.5%)	48 (0.6%)
Congenital, familial and genetic disorders	0	1 (<0.1%)	1 (<0.1%)
Ear and labyrinth disorders	7 (<0.1%)	12 (0.1%)	10 (0.1%)
Endocrine disorders	2 (<0.1%)	1 (<0.1%)	5 (<0.1%)
Eye disorders	11 (0.1%)	12 (0.1%)	8 (<0.1%)
Gastrointestinal disorders	171 (2.0%)	168 (2.0%)	150 (1.7%)
General disorders and administration site conditions	50 (0.6%)	54 (0.6%)	37 (0.4%)
Hepatobiliary disorders	25 (0.3%)	26 (0.3%)	28 (0.3%)
Immune system disorders	4 (<0.1%)	5 (<0.1%)	0
Infections and infestations	113 (1.3%)	120 (1.4%)	118 (1.4%)
Injury, poisoning and procedural complications	31 (0.4%)	13 (0.2%)	18 (0.2%)
Investigations	12 (0.1%)	7 (<0.1%)	8 (<0.1%)
Metabolism and nutrition disorders	14 (0.2%)	14 (0.2%)	9 (0.1%)
Musculoskeletal and connective tissue disorders	35 (0.4%)	34 (0.4%)	27 (0.3%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	67 (0.8%)	68 (0.8%)	71 (0.8%)
Nervous system disorders	60 (0.7%)	55 (0.6%)	54 (0.6%)
Psychiatric disorders	14 (0.2%)	13 (0.2%)	4 (<0.1%)
Renal and urinary disorders	49 (0.6%)	44 (0.5%)	30 (0.3%)
Reproductive system and breast disorders	5 (<0.1%)	1 (<0.1%)	4 (<0.1%)
Respiratory, thoracic and mediastinal disorders	36 (0.4%)	49 (0.6%)	47 (0.5%)
Skin and subcutaneous tissue disorders	48 (0.6%)	58 (0.7%)	32 (0.4%)
Surgical and medical procedures	11 (0.1%)	6 (<0.1%)	12 (0.1%)
Vascular disorders	11 (0.1%)	10 (0.1%)	15 (0.2%)
Uncoded**	1 (<0.1%)	5 (<0.1%)	6 (<0.1%)

All events with onset at the date of or after randomization and up until 2 days following permanent discontinuation of any antithrombotic study treatment
* Includes events of special interest (ESI).

Table 19. Number of non-Japan subjects with frequent (≥0.1%) TEAE PTs by PT (SAF) *

Primary system organ class Preferred term	Riva 2.5 mg bid/ Aspirin 100 mg od N=8617 (100%)	Riva 5 mg bid N=8593 (100%)	Aspirin 100 mg od N=8588 (100%)
Blood and lymphatic system disorders			
Anaemia	15 (0.2%)	11 (0.1%)	4 (<0.1%)
Cardiac disorders			
Atrial fibrillation	18 (0.2%)	16 (0.2%)	20 (0.2%)
Gastrointestinal disorder			
Diarrhoea	18 (0.2%)	34 (0.4%)	17 (0.2%)
Abdominal pain upper	24 (0.3%)	17 (0.2%)	16 (0.2%)
Gastritis	20 (0.2%)	7 (<0.1%)	14 (0.2%)
Dyspepsia	11 (0.1%)	10 (0.1%)	11 (0.1%)
Abdominal pain	8 (<0.1%)	14 (0.2%)	7 (<0.1%)
Nausea	11 (0.1%)	8 (<0.1%)	6 (<0.1%)
Pancreatitis	5 (<0.1%)	11 (0.1%)	8 (<0.1%)
Abdominal discomfort	10 (0.1%)	7 (<0.1%)	5 (<0.1%)
Constipation	6 (<0.1%)	2 (<0.1%)	9 (0.1%)
General disorders and administration site conditions			
Chest pain	8 (<0.1%)	12 (0.1%)	2 (<0.1%)
Non-cardiac chest pain	9 (0.1%)	4 (<0.1%)	7 (<0.1%)
Malaise	1 (<0.1%)	9 (0.1%)	2 (<0.1%)
Infections and infestations			
Sepsis	16 (0.2%)	16 (0.2%)	15 (0.2%)
Pneumonia	10 (0.1%)	12 (0.1%)	16 (0.2%)
Urinary tract infection	13 (0.2%)	12 (0.1%)	6 (<0.1%)
Cellulitis	8 (<0.1%)	9 (0.1%)	6 (<0.1%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Lung neoplasm malignant	14 (0.2%)	10 (0.1%)	10 (0.1%)
Neoplasm malignant	1 (<0.1%)	6 (<0.1%)	9 (0.1%)
Nervous system disorders			
Dizziness	16 (0.2%)	11 (0.1%)	11 (0.1%)
Headache	11 (0.1%)	14 (0.2%)	8 (<0.1%)
Renal and urinary disorders			
Acute kidney injury	23 (0.3%)	22 (0.3%)	17 (0.2%)
Renal failure	10 (0.1%)	6 (<0.1%)	5 (<0.1%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	4 (<0.1%)	9 (0.1%)	5 (<0.1%)
Skin and subcutaneous tissue disorders			
Rash	9 (0.1%)	11 (0.1%)	10 (0.1%)
Pruritus	9 (0.1%)	16 (0.2%)	3 (<0.1%)

All events with onset at the date of or after randomization and up until 2 days following permanent discontinuation of any antithrombotic study treatment

* Includes events of special interest (ESI).

Serious adverse event/deaths/other significant events

Efficacy and safety outcomes as well as expected events in this population were not reported as (S)AEs, but as outcomes (see Efficacy section above).

A summary of the crude incidences of non-Japan subjects with TESAEs by MedDRA SOCs and treatment group is provided in **Table 20**.

Table 20. Number of non-Japan subjects with TESAEs by SOC (SAF)*

Primary system organ class	Rivaroxaban 2.5 mg bid/ Aspirin 100mg od N=8617 (100%)	Rivaroxaban 5 mg bid N=8593 (100%)	Aspirin 100 mg od N=8588 (100%)
Number (%) of subjects with at least one such adverse event	485 (5.6%)	476 (5.5%)	453 (5.3%)
Blood and lymphatic system disorders	23 (0.3%)	15 (0.2%)	7 (<0.1%)
Cardiac disorders	14 (0.2%)	9 (0.1%)	21 (0.2%)
Congenital, familial and genetic disorders	0	0	1 (<0.1%)
Ear and labyrinth disorders	3 (<0.1%)	9 (0.1%)	6 (<0.1%)
Endocrine disorders	2 (<0.1%)	1 (<0.1%)	5 (<0.1%)
Eye disorders	9 (0.1%)	10 (0.1%)	8 (<0.1%)
Gastrointestinal disorders	48 (0.6%)	48 (0.6%)	52 (0.6%)
General disorders and administration site conditions	30 (0.3%)	30 (0.3%)	25 (0.3%)
Hepatobiliary disorders	23 (0.3%)	24 (0.3%)	27 (0.3%)
Immune system disorders	2 (<0.1%)	2 (<0.1%)	0
Infections and infestations	110 (1.3%)	118 (1.4%)	110 (1.3%)
Injury, poisoning and procedural complications	23 (0.3%)	10 (0.1%)	12 (0.1%)
Investigations	8 (<0.1%)	3 (<0.1%)	4 (<0.1%)
Metabolism and nutrition disorders	14 (0.2%)	13 (0.2%)	7 (<0.1%)
Musculoskeletal and connective tissue disorders	21 (0.2%)	15 (0.2%)	18 (0.2%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	65 (0.8%)	65 (0.8%)	66 (0.8%)
Nervous system disorders	29 (0.3%)	28 (0.3%)	19 (0.2%)
Psychiatric disorders	8 (<0.1%)	10 (0.1%)	2 (<0.1%)
Renal and urinary disorders	47 (0.5%)	40 (0.5%)	29 (0.3%)
Reproductive system and breast disorders	3 (<0.1%)	0	3 (<0.1%)
Respiratory, thoracic and mediastinal disorders	29 (0.3%)	41 (0.5%)	41 (0.5%)
Skin and subcutaneous tissue disorders	12 (0.1%)	15 (0.2%)	14 (0.2%)
Surgical and medical procedures	10 (0.1%)	4 (<0.1%)	8 (<0.1%)
Vascular disorders	10 (0.1%)	8 (<0.1%)	11 (0.1%)
Uncoded**	0	4 (<0.1%)	6 (<0.1%)

All events with onset at the date of or after randomization and up until 2 days following permanent discontinuation of any antithrombotic study treatment
* Includes events of special interest.
** A reason for the uncoded terms as well as a full list is provided in Section 16.1.9.2.
Coded by Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0
bid = twice daily; od= once daily; incl. = including; PT = preferred term; Riva = rivaroxaban; SAF = safety analysis set; SOC = system organ class; TESAE = treatment-emergent serious adverse event

A summary of the most frequent (≥0.1% in any treatment group) TESAE PTs for non-Japan subjects by treatment group is provided in **Table 21**.

Table 21. Number of non-Japan subjects with frequent (≥0.1%) TESAEs by SOC and PT (SAF)*

Primary system organ class Preferred term	Riva 2.5 mg bid/ Aspirin 100 mg od N=8617 (100%)	Riva 5 mg bid N=8593 (100%)	Aspirin 100 mg od N=8588(100%)
Blood and lymphatic system disorders			
Anaemia	11 (0.1%)	9 (0.1%)	2 (<0.1%)
Cardiac disorders			
Atrial fibrillation	4 (<0.1%)	4 (<0.1%)	10 (0.1%)
Gastrointestinal disorder			
Pancreatitis	5 (<0.1%)	10 (0.1%)	8 (<0.1%)
General disorders and administration site conditions			
Non-cardiac chest pain	9 (0.1%)	4 (<0.1%)	7 (<0.1%)
Chest pain	6 (<0.1%)	11 (0.1%)	2 (<0.1%)
Infections and infestations			
Sepsis	16 (0.2%)	16 (0.2%)	15 (0.2%)
Pneumonia	10 (0.1%)	11 (0.1%)	15 (0.2%)
Urinary tract infection	13 (0.2%)	12 (0.1%)	6 (<0.1%)
Cellulitis	8 (<0.1%)	9 (0.1%)	6 (<0.1%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Lung neoplasm malignant	14 (0.2%)	10 (0.1%)	9 (0.1%)
Renal and urinary disorders			
Acute kidney injury	23 (0.3%)	22 (0.3%)	16 (0.2%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	4 (<0.1%)	9 (0.1%)	5 (<0.1%)

All events with onset at the date of or after randomization and up until 2 days following permanent discontinuation of any antithrombotic study treatment.
* Includes events of special interest.
Coded by Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0
bid = twice daily; od= once daily; PT = preferred term; Riva = rivaroxaban; SAF = safety analysis set; SOC = system organ class; TESAE = treatment-emergent serious adverse event

Events of special interest were not reported separately but were included within and as part of the AE tables. For the ESIs 'hepatic failure', and 'pancytopenia', imbalances of potential clinical interest between treatment groups were noted.

Four cases of hepatic failure were reported, two each in the rivaroxaban 2.5 mg bid/ASA 100 mg od and rivaroxaban 5 mg bid cohorts respectively. One of the cases occurred four months after stop of study treatment; two of the cases were attributed to liver failure in conjunction with other organ failure (heart failure and multi-organ failure due to bleeding); and in one case, liver failure was considered as related to underlying malignant disease.

Six cases of pancytopenia were reported; four of those in the rivaroxaban 2.5 mg bid/ASA 100 mg od cohort, one in the rivaroxaban 5 mg cohort and one in the aspirin 100 mg od cohort. Of the rivaroxaban cases, one was considered attributed to alcohol/malnourishment; one was attributed to MDS diagnosed more than one year after discontinuation of study medication; one was attributed to paraneoplastic syndrome and viral infection; one occurred in a patient diagnosed with myelofibrosis and one occurred in conjunction with malignancy and chemotherapy.

Primary safety outcome: Treatment-emergent modified ISTH major bleeding events

The SAF analysis considered treatment-emergent ISTH major bleeding events which were in the database after closure on 22 JUL 2017.

The number of subjects with a primary safety outcome, crude incidences and incidence rates (n/100 patient-years) of treatment-emergent modified ISTH major bleeding event and the 4 clinical hierarchical categories as well as the results from the statistical comparison for thetreatment-emergent data scope in the SAF set are presented in **Table 22**.

Table 22. Summary of the results for treatment-emergent modified ISTH major bleeding events (SAF)

Modified ISTH major bleeding		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9134; 100%)	263 (2.9%)	1.58 (1.40;1.79)
Riva 5 mg bid	(N=9110; 100%)	225 (2.5%)	1.36 (1.19;1.55)
Aspirin 100 mg od	(N=9107; 100%)	144 (1.6%)	0.86 (0.72;1.01)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.84 (1.50;2.26)	
Log-rank p-value		<0.00001*	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.60 (1.30;1.97)	
Log-rank p-value		0.00001	
Fatal		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9134)	12 (0.1%)	0.07 (0.04;0.12)
Riva 5 mg bid	(N=9110)	13 (0.1%)	0.08 (0.04;0.13)
Aspirin 100 mg od	(N=9107)	8 (<0.1%)	0.05 (0.02;0.09)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.51 (0.62;3.69)	
Log-rank p-value		0.36360	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.64 (0.68;3.96)	
Log-rank p-value		0.26529	
Critical organ bleeding (non-fatal)		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9134)	58 (0.6%)	0.35 (0.26;0.45)
Riva 5 mg bid	(N=9110)	63 (0.7%)	0.38 (0.29;0.49)
Aspirin 100 mg od	(N=9107)	43 (0.5%)	0.26 (0.18;0.34)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.36 (0.91;2.01)	
Log-rank p-value		0.12821	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.50 (1.02;2.21)	
Log-rank p-value		0.03998	
Requiring re-operation (non-fatal and non-critical organ)		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9134)	7 (<0.1%)	0.04 (0.02;0.09)
Riva 5 mg bid	(N=9110)	14 (0.2%)	0.08 (0.05;0.14)
Aspirin 100 mg od	(N=9107)	6 (<0.1%)	0.04 (0.01;0.08)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.17 (0.39;3.48)	
Log-rank p-value		0.77596	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		2.36 (0.91;6.14)	
Log-rank p-value		0.06957	
Hospitalization (a) (non-fatal, non-critical organ, not leading to re-operation)		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9134)	188 (2.1%)	1.13 (0.97;1.30)
Riva 5 mg bid	(N=9110)	138 (1.5%)	0.83 (0.70;0.98)
Aspirin 100 mg od	(N=9107)	91 (1.0%)	0.54 (0.44;0.66)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		2.08 (1.62;2.67)	
Log-rank p-value		<0.00001*	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.54 (1.18;2.01)	
Log-rank p-value		0.00123	
Hospitalization where admission date < discharge date		**n (%)**	**n/100 p-yrs (95% CI)**

Riva 2.5 mg bid/aspirin 100 mg od	(N=9134)	155 (1.7%)	0.93 (0.79;1.09)
Riva 5 mg bid	(N=9110)	110 (1.2%)	0.66 (0.55;0.80)
Aspirin 100 mg od	(N=9107)	74 (0.8%)	0.44 (0.35;0.55)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		2.11 (1.60;2.78)	
Log-rank p-value		<0.00001*	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.51 (1.13;2.03)	
Log-rank p-value		0.00565	
Hospitalization where admission date = discharge date		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=9134)	33 (0.4%)	0.20 (0.14;0.28)
Riva 5 mg bid	(N=9110)	28 (0.3%)	0.17 (0.11;0.24)
Aspirin 100 mg od	(N=9107)	19 (0.2%)	0.11 (0.07;0.18)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.74 (0.99;3.07)	
Log-rank p-value		0.05060	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.50 (0.84;2.69)	
Log-rank p-value		0.17005	

Table includes events that are classified as major bleedings during the adjudication process

The Kaplan-Meier estimates of the cumulative incidence risk of treatment-emergent modified ISTH major bleeding events is shown in **Figure 13**.

Figure 13. Kaplan-Meier estimates of cumulative incidence risk of treatment-emergent modified ISTH major bleeding events (SAF)

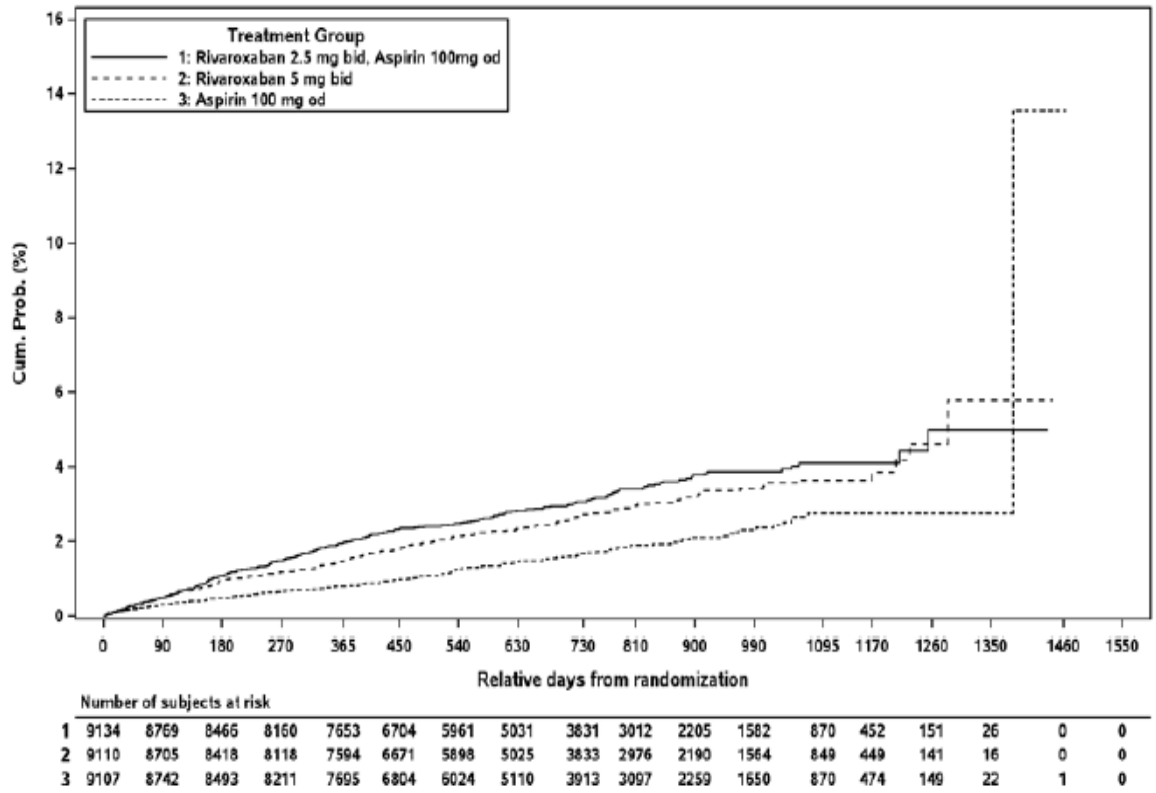


Figure includes events that are classified as major bleeding events during the adjudication process.
Treatment emergent outcomes data scope includes all events occurring after the date and time of randomization and up until 2 days following permanent discontinuation of antithrombotic study treatment.

The number and crude incidences of subjects with treatment-emergent modified ISTH major bleeding events by hierarchy and maximum intensity is displayed in **Table 23**.

Table 23. Number of subjects with treatment-emergent modified ISTH major bleeding events by hierarchy and maximum intensity (as reported by the investigator) (SAF)

	Riva 2.5 mg bid/ Aspirin 100 mg od	Riva 5 mg bid	Aspirin 100 mg od
	N= 9134 (100%)	N=9110 (100%)	N=9107 (100%)
Any modified ISTH major bleeding	263 (2.9%)	225 (2.5%)	144 (1.6%)
Fatal	12 (0.1%)	13 (0.1%)	8 (<0.1%)
Critical organ bleeding (non-fatal) *	58 (0.6%)	63 (0.7%)	43 (0.5%)
MILD	29 (0.3%)	27 (0.3%)	25 (0.3%)
MODERATE	15 (0.2%)	18 (0.2%)	12 (0.1%)
SEVERE	14 (0.2%)	18 (0.2%)	6 (<0.1%)
Bleeding into surgical site requiring re-operation (non-fatal, non-critical organ)	7 (<0.1%)	14 (0.2%)	6 (<0.1%)
MILD	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)
MODERATE	4 (<0.1%)	10 (0.1%)	3 (<0.1%)
SEVERE	2 (<0.1%)	3 (<0.1%)	1 (<0.1%)
Bleeding leading to any hospitalization (a) (non-fatal, non-critical organ, not leading to re-operation)	188 (2.1%)	138 (1.5%)	91 (1.0%)
Bleeding leading to hospitalization where admission date < discharge date	155 (1.7%)	110 (1.2%)	74 (0.8%)
Missing	1 (<0.1%)		
MILD	46 (0.5%)	28 (0.3%)	24 (0.3%)
MODERATE	76 (0.8%)	56 (0.6%)	37 (0.4%)
SEVERE	32 (0.4%)	26 (0.3%)	13 (0.1%)
Bleeding leading to hospitalization where admission date = discharge date	33 (0.4%)	28 (0.3%)	19 (0.2%)
MILD	15 (0.2%)	18 (0.2%)	13 (0.1%)
MODERATE	14 (0.2%)	9 (<0.1%)	6 (<0.1%)
SEVERE	4 (<0.1%)	1 (<0.1%)	0

The number of subjects with any treatment-emergent modified ISTH major bleeding event, crude incidences and incidence rates (n/100 patient-years), as well as the results from the statistical comparison by subgroups (subjects with CAD yes, PAD yes, and CAD and PAD based on the investigator diagnosis as well as the individual medical history records of the CRF) are presented in **Table 24**.

The first bleeding event experienced per subject was considered.

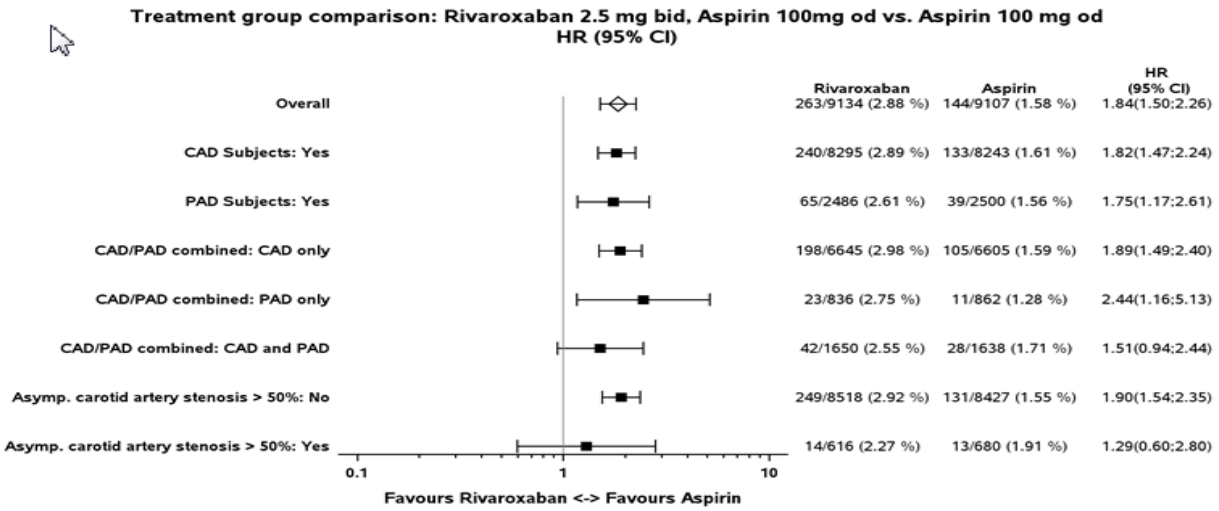
Table 24. Summary of the results for treatment–emergent modified ISTH major bleeding events by CAD and/or PAD subgroup (SAF)

Primary safety outcome: Any modified ISTH major bleeding			
CAD yes		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=8295; 100%)	240 (2.9%)	1.57 (1.38;1.78)
Riva 5 mg bid	(N=8243; 100%)	206 (2.5%	1.36 (1.18;1.56)
Aspirin 100 mg od	(N=8243; 100%)	133 (1.6%)	0.86 (0.72;1.02)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.82 (1.47;2.24)	
Log-rank p-value		<0.00001*	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.58 (1.27;1.97)	
Log-rank p-value		0.00003	
PAD yes		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=2486; 100%)	65 (2.6%)	1.55 (1.19;1.97)
Riva 5 mg bid	(N=2471; 100%)	61 (2.5%)	1.47 (1.12;1.88)
Aspirin 100 mg od	(N=2500; 100%)	39 (1.6%)	0.90 (0.64;1.23)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			

Hazard ratio (95% CI)		1.75 (1.17;2.61)	
Log-rank p-value		0.00561	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.63 (1.09;2.44)	
Log-rank p-value		0.01577	
CAD and PAD		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=1650; 100%)	42 (2.5%)	1.46 (1.05;1.97)
Riva 5 mg bid	(N=1606; 100%)	42 (2.6%)	1.51 (1.09;2.04)
Aspirin 100 mg od	(N=1638; 100%)	28 (1.7%)	0.95 (0.63;1.37)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.51 (0.94;2.44)	
Log-rank p-value		0.08772	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.60 (0.99;2.59)	
Log-rank p-value		0.05109	
CAD only		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=6645; 100%)	198 (3.0%)	1.59 (1.38;1.83)
Riva 5 mg bid	(N=6637; 100%)	164 (2.5%)	1.33 (1.13;1.55)
Aspirin 100 mg od	(N=6605; 100%)	105 (1.6%)	0.84 (0.69;1.02)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.89 (1.49;2.40)	
Log-rank p-value		0.00000	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.58 (1.24;2.02)	
Log-rank p-value		0.00022	
PAD only		**n (%)**	**n/100 p-yrs (95% CI)**
Riva 2.5 mg bid/aspirin 100 mg od	(N=836; 100%)	23 (2.8%)	1.74 (1.10;2.61)
Riva 5 mg bid	(N=865; 100%)	19 (2.2%)	1.38 (0.83;2.15)
Aspirin 100 mg od	(N=862; 100%)	11 (1.3%)	0.80 (0.40;1.43)
Comparison: Riva 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od			
Hazard ratio (95% CI)		2.44 (1.16;5.13)	
Log-rank p-value		0.01500	
Comparison: Riva 5 mg bid versus aspirin 100 mg od			
Hazard ratio (95% CI)		1.90 (0.88;4.09)	
Log-rank p-value		0.09472	

Forest plots with the number of subjects, crude incidences, and the results of the Cox proportional hazards model for the subgroup analyses of the treatment-emergent primary safety outcome are provided in Figure 10 for the comparison of rivaroxaban 2.5 mg bid/aspirin 100 mg od with aspirin 100 mg od.

Figure 14. Forest plot for treatment-emergent modified ISTH major bleeding events (SAF) - rivaroxaban 2.5 mg bid/aspirin 100 mg od versus aspirin 100 mg od



Treatment-emergent modified ISTH major bleeding events by hierarchy and bleeding site

Treatment-emergent fatal bleeding events

Treatment-emergent bleeding events in the SAF analysis set were fatal in 12 subjects (0.1%) in the rivaroxaban 2.5 mg bid/aspirin 100 mg od group, 13 subjects (0.1%) in the rivaroxaban 5 mg bid group, and 8 subjects (<0.1%) in the aspirin 100 mg od group. Fatal bleeding events were most frequently due to intracranial bleeding events, and of these mainly hemorrhagic stroke, with no notable differences between the 3 treatment groups (<0.1% in each group). Fatal, non-intracranial bleeding events were few and of diverse origin: gastrointestinal (5 cases), retroperitoneal (4 cases), respiratory tract (3 cases), skin or injection site (2 cases), other (2 cases) and unknown site (1 case).

Symptomatic critical organ bleeding events (non-fatal)

Symptomatic critical organ bleeding events (non-fatal) were reported by 0.6% of the subjects in the rivaroxaban 2.5 mg bid/aspirin 100 mg od group, 0.7% in the rivaroxaban 5 mg bid group, and 0.5% in the aspirin 100 mg od group. These bleeding events were most frequently due to intracranial (subarachnoid, intraventricular, intracerebral/intraparenchymal hemorrhage) and/or intraocular bleeding events with 0.2% each in the rivaroxaban 2.5 mg bid/aspirin 100 mg od group, 0.3% and <0.1%, respectively, in the rivaroxaban 5 mg bid group, and 0.2% and <0.1%, respectively, in the aspirin 100 mg od group. Symptomatic non-intracranial bleeding events were few and of diverse origin: intraocular (27 cases), respiratory tract (21 cases), retinal (17 cases), intraarticular (7 cases), other (7 cases), urinary tract (5 cases), intraabdominal (5 cases), unknown site (4 cases), intramuscular (3 cases), intraspinal (3 cases), retroperitoneal (3 cases), and pericardial (2 cases).

Bleeding events into a surgical site requiring re-operation (non- fatal and non-critical organ)

Bleeding events into a surgical site requiring re-operation were reported by <0.1% of the subjects in the rivaroxaban 2.5 mg bid/aspirin 100 mg od group, 0.2% in the rivaroxaban 5 mg bid group, and <0.1% in the aspirin 100 mg od group. These bleeding events were most frequently gastrointestinal, skin or injection site bleeding events with <0.1% each in all 3 treatment groups. The number of subjects with bleeding events on further sites was small and the sites were of diverse origin: urinary tract (4 cases), genital (1 case), and other (1 case).

Bleeding leading to any hospitalization (non-fatal, non-critical organ, not leading to re-operation)

Treatment-emergent modified ISTH major events leading to any hospitalization were reported by 2.1% of the subjects in the rivaroxaban 2.5 mg bid/aspirin 100 mg od group, 1.5% in the rivaroxaban 5 mg bid

group, and 1.0% in the aspirin 100 mg od group with significant differences between the individual rivaroxaban treatment arms versus the aspirin 100 mg od group.

Treatment-emergent modified ISTH major bleeding events were mainly driven by hospitalization with an overnight stay with twice as many subjects in the rivaroxaban 2.5 mg bid/aspirin 100 mg od group (1.7%) compared with the aspirin 100 mg od group (0.8%). These bleeding events were most frequently gastrointestinal (1.2% rivaroxaban 2.5 mg bid/aspirin 100 mg od, 0.7% rivaroxaban 5 mg bid, and 0.5% aspirin 100 mg od). The majority of the gastrointestinal bleeding events excluded the oral cavity and the esophagus. Of these mainly gastric and duodenal bleeding events were reported with a higher frequency (0.5%) in the rivaroxaban 2.5 mg bid/aspirin 100 mg od as compared with 0.3% in the rivaroxaban 5 mg bid group and 0.2% in the aspirin 100 mg od group followed by bleeding events of unknown gastrointestinal site (0.3% rivaroxaban 2.5 mg bid/aspirin 100 mg od, 0.1% each rivaroxaban 5 mg bid and aspirin 100 mg od). The number of subjects with other sites bleeding events was of diverse origin: urinary tract (overall 38 cases; 9 cases rivaroxaban 2.5 mg bid/aspirin 100 mg od), skin or injection site (overall 24 cases; 22 cases in both rivaroxaban groups), genital (16 cases), epistaxis (13 cases), unknown site (10 cases), respiratory tract (4 cases), for the remaining sites 3 cases or less per site were documented. The number of subjects with bleeding events leading to hospitalization without overnight stay was lower as compared with those with an overnight stay (0.4% rivaroxaban 2.5 mg bid/aspirin 100 mg od, 0.3% rivaroxaban 5 mg bid, and 0.2% aspirin 100 mg od) with no significant differences between the treatment arms. Gastrointestinal and skin or injection site bleeding events were most frequently reported (<0.1% and 0.1% rivaroxaban 2.5 mg bid/aspirin 100 mg od, 0.1% and <0.1% rivaroxaban 5 mg bid, and <0.1% each for aspirin 100 mg od, respectively). Further bleeding events were few and of diverse origin: epistaxis (15 cases), urinary tract (14 cases), intramuscular (1 case), respiratory tract (1 case), genital (1 case), unknown site (1 case), and other (1 case).

Other bleedings (not meeting the criteria of ISTH major bleeding events)

All treatment-emergent bleeding events that were not adjudicated as major and not refuted during stroke adjudication were counted as minor.

The number and crude incidences of subjects with treatment-emergent minor bleeding events by site is displayed in **Table 25**.

Table 25. Number of subjects with treatment-emergent minor bleeding events by bleeding site (SAF)

	Riva 2.5 mg bid/ Aspirin 100 mg od	Riva 5 mg bid	Aspirin 100 mg od
	N=9134 (100%)	N=9110 (100%)	N=9107 (100%)
Any bleeding	**1043 (11.4%)**	**910 (10.0%)**	**613 (6.7%)**
Minor bleeding	**821 (9.0%)**	**722 (7.9%)**	**485 (5.3%)**
Gastrointestinal	243 (2.7%)	246 (2.7%)	131 (1.4%)
Oral cavity and esophagus	50 (0.5%)	55 (0.6%)	28 (0.3%)
Gastrointestinal (excluding oral cavity and esophagus)	197 (2.2%)	195 (2.1%)	103 (1.1%)
Gastric and duodenal	28 (0.3%)	28 (0.3%)	21 (0.2%)
Small intestine	1 (<0.1%)	1 (<0.1%)	0
Large intestine/colon	23 (0.3%)	20 (0.2%)	8 (<0.1%)
Rectal	100 (1.1%)	99 (1.1%)	48 (0.5%)
Unknown	50 (0.5%)	54 (0.6%)	30 (0.3%)
Intracranial	2 (<0.1%)	0	4 (<0.1%)
Sub/epi/extradural	1 (<0.1%)	0	0
Hemorrhagic stroke *	2 (<0.1%)	0	4 (<0.1%)
Intracerebral/intraparenchymal	2 (<0.1%)	0	3 (<0.1%)
Subarachnoid	1 (<0.1%)	0	0
Intraventricular	0	0	1 (<0.1%)
Skin or injection site	251 (2.7%)	150 (1.6%)	161 (1.8%)
Intraarticular	3 (<0.1%)	0	0
Intramuscular	2 (<0.1%)	6 (<0.1%)	1 (<0.1%)
With compartment syndrome	0	1 (<0.1%)	0
Without compartment syndrome	2 (<0.1%)	5 (<0.1%)	1 (<0.1%)
Intraocular	1 (<0.1%)	3 (<0.1%)	1 (<0.1%)
Retinal	5 (<0.1%)	4 (<0.1%)	5 (<0.1%)
Eye, conjunctival/peri-orbital	37 (0.4%)	46 (0.5%)	22 (0.2%)
Epistaxis	205 (2.2%)	182 (2.0%)	109 (1.2%)
Respiratory tract	21 (0.2%)	21 (0.2%)	12 (0.1%)
Urinary tract	144 (1.6%)	115 (1.3%)	75 (0.8%)
Kidney	6 (<0.1%)	3 (<0.1%)	1 (<0.1%)
Urinary tract, other	140 (1.5%)	112 (1.2%)	74 (0.8%)
Genital	23 (0.3%)	21 (0.2%)	10 (0.1%)
Unknown site	13 (0.1%)	11 (0.1%)	8 (<0.1%)
Other	5 (<0.1%)	1 (<0.1%)	4 (<0.1%)

Table includes events that are classified as minor bleedings during the adjudication process.

The number of subjects with adjudicated gastrointestinal events (bleeding and non-bleeding events) up until the global rivaroxaban/aspirin outcomes cut-off date (06 FEB 2017) is displayed in **Table 26**.

Table 26. Number of subjects with adjudicated gastrointestinal events (ITT; no SAF analysis available)

	Riva 2.5 mg bid/ Aspirin 100 mg od	Riva 5 mg bid	Aspirin 100 mg od
	N=9152 (100%)	N=9117 (100%)	N=9126 (100%)
Gastrointestinal events	**138 (100.0%)**	**110 (100.0%)**	**90 (100.0%)**
Gastrointestinal bleeding events			
Overt bleeding of gastroduodenal origin confirmed by endoscopy or radiography	27 (19.6%)	16 (14.5%)	12 (13.3%)
Overt upper gastrointestinal bleeding of unknown origin	51 (37.0%)	42 (38.2%)	36 (40.0%)
Bleeding of presumed occult upper gastrointestinal tract origin with documented decreased in Hb of 2 g/dL	17 (12.3%)	13 (11.8%)	8 (8.9%)
Gastrointestinal non-bleeding events			
Symptomatic gastroduodenal ulcer	7 (5.1%)	10 (9.1%)	8 (8.9%)
Gastrointestinal pain with underlying multiple gastroduodenal erosions	3 (2.2%)	4 (3.6%)	5 (5.6%)
Obstruction or perforation	33 (23.9%)	25 (22.7%)	21 (23.3%)

Laboratory findings

There was no mandatory laboratory testing during the study in the global study protocol. Investigator-reported cardiac markers in events of myocardial infarction were largely similar across the antithrombotic treatment arms (data not shown).

For Swedish subjects, additional laboratory monitoring throughout the study was performed for haemoglobin and haematocrit, and also creatinine clearance in subjects with e GFR below 60 ml/min, at screening and at 6 months intervals thereafter. There were no relevant changes from baseline or any difference between rivaroxaban-treated subjects (N = 246 for rivaroxaban 2.5 bid/aspirin and N = 244 for rivaroxaban 5 mg) and aspirin-treated subjects, with regards to either haemoglobin/haematocrit or eGFR.

Safety related to drug-drug interactions and other interactions

Separate Cox proportional hazards models have been fitted to assess if the effect of the randomised antithrombotic treatment on the primary safety outcome is different for subjects randomised to pantoprazole compared with those randomised to pantoprazole placebo (subjects not randomised to pantoprazole/placebo were not considered).

No interaction of the antithrombotic treatment and the pantoprazole/placebo treatment on the primary safety outcome was found (interaction p-value for rivaroxaban 2.5 mg bid/aspirin 100 mg od p=0.7342 and for rivaroxaban 5 mg bid p=0.5685.

Discontinuation due to adverse events

Overall, 3.1% of all non-Japan subjects had permanent premature discontinuation of study drug intake due to (TE)(S)AE. Percentages were 3.4% in the rivaroxaban 2.5 mg bid/aspirin 100 mg od group, 3.4% in the rivaroxaban 5 mg bid group, and 2.7% in the aspirin 100 mg od group (**Table 27**).

Table 27. Number of non-Japan subjects with premature permanent discontinuation of any antithrombotic study drug intake due to TEAEs by SOC (SAF) *

Primary system organ class	Rivaroxaban 2.5 mg bid/ Aspirin 100mg od N=8617 (100%)	Rivaroxaban 5 mg bid N=8593 (100%)	Aspirin 100 mg od N=8588 (100%)
Number (%) of subjects with at least one such adverse event	291 (3.4%)	289 (3.4%)	228 (2.7%)
Blood and lymphatic system disorders	16 (0.2%)	13 (0.2%)	4 (<0.1%)
Cardiac disorders	26 (0.3%)	33 (0.4%)	32 (0.4%)
Ear and labyrinth disorders	4 (<0.1%)	3 (<0.1%)	3 (<0.1%)
Eye disorders	5 (<0.1%)	5 (<0.1%)	2 (<0.1%)
Gastrointestinal disorders	76 (0.9%)	70 (0.8%)	54 (0.6%)
General disorders and administration site conditions	23 (0.3%)	20 (0.2%)	13 (0.2%)
Hepatobiliary disorders	2 (<0.1%)	4 (<0.1%)	1 (<0.1%)
Immune system disorders	2 (<0.1%)	2 (<0.1%)	0
Infections and infestations	5 (<0.1%)	15 (0.2%)	11 (0.1%)
Injury, poisoning and procedural complications	10 (0.1%)	4 (<0.1%)	6 (<0.1%)
Investigations	4 (<0.1%)	3 (<0.1%)	3 (<0.1%)
Metabolism and nutrition disorders	0	2 (<0.1%)	1 (<0.1%)
Musculoskeletal and connective tissue disorders	10 (0.1%)	12 (0.1%)	10 (0.1%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	15 (0.2%)	11 (0.1%)	20 (0.2%)
Nervous system disorders	32 (0.4%)	23 (0.3%)	27 (0.3%)
Psychiatric disorders	6 (<0.1%)	3 (<0.1%)	2 (<0.1%)
Renal and urinary disorders	8 (<0.1%)	10 (0.1%)	6 (<0.1%)
Reproductive system and breast disorders	2 (<0.1%)	1 (<0.1%)	0
Respiratory, thoracic and mediastinal disorders	6 (<0.1%)	10 (0.1%)	8 (<0.1%)
Skin and subcutaneous tissue disorders	34 (0.4%)	41 (0.5%)	18 (0.2%)
Surgical and medical procedures	1 (<0.1%)	1 (<0.1%)	4 (<0.1%)
Vascular disorders	3 (<0.1%)	2 (<0.1%)	3 (<0.1%)
Uncoded**	1 (<0.1%)	1 (<0.1%)	0

Permanent discontinuation of antithrombotic medication refers to the last report of premature permanent discontinuation of rivaroxaban and/or aspirin due to AE before global rivaroxaban/aspirin outcomes cut-off date (06 FEB 2017).
All events with onset at the date of or after randomization and up until 2 days following permanent discontinuation of antithrombotic study treatment. Events with missing start date and end date of or after randomization are also considered.
* Includes events of special interest.

Most frequently reported PTs were 'atrial fibrillation' (total: 0.2%; rivaroxaban 2.5 mg bid/aspirin 100 mg od: 0.2%, rivaroxaban 5 mg bid: 0.2%, and aspirin 100 mg od: 0.1%) and 'abdominal pain upper' (total: <0.1%; rivaroxaban 2.5 mg bid/aspirin 100 mg od: 0.2%, rivaroxaban 5 mg bid: <0.1%, and aspirin 100 mg od: <0.1%). All other PTs related to premature permanent discontinuations of any antithrombotic study drug due to TEAEs were ≤0.1%.

2.5.1. Discussion on clinical safety

No new safety concerns were identified in the COMPASS study for rivaroxaban. As expected, the main safety concern with rivaroxaban use is bleeding.

There were significantly more modified ISTH major bleedings in the rivaroxaban treated participants as compared to the aspirin only treatment arm, with the highest HR in the rivaroxaban 2.5 mg bid/aspirin

100 mg od group (absolute risk difference 1.3%). The difference was statistically significant for bleedings that required hospitalization; more fatal and critical organ bleedings also occurred in the rivaroxaban treated arms, but the numbers were small.

The combination of rivaroxaban 2.5 mg bid and aspirin 100 mg od also increased minor bleedings with roughly the same magnitude (HR 1.73) as major bleedings.

Overall, there were slightly more AEs and TEAEs in the rivaroxaban cohorts vs the aspirin only cohort, mainly due to more reported gastrointestinal events and blood/lymphatic system disorders. The described AEs and TEAEs are in line with the known safety profile of rivaroxaban and there are no imbalances that give rise to any particular concern; however, bleedings were not reported as AEs but as outcomes, see above. As expected, the numbers of both bleeding and other AEs increase with increasing age. Therefore a waring has been included in the product information, that, the combination of rivaroxaban 2.5 mg twice daily and ASA 100 mg once daily should be used with caution in elderly patients with CAD and/or PAD; the potential benefit must be weighed against the risk.

There was number of a gastrointestinal obstruction or perforation which is not a known adverse event for rivaroxaban. The overall number of these events was nevertheless low and distributed across the three treatment arms with crude incidences of 0.36%, 0.27% and 0.23% in the rivaroxaban 2.5 mg bid/ASA 100 mg od arm, rivaroxaban 5 mg bid arm, and ASA 100 mg od arm, respectively. Analysis of the individual cases did not reveal any new safety concerns, and having considered the low incidence rates od events which are not uncommon especially in the intended target population for rivaroxaban the CHMP considered that no action is required at this stage.

As the COMPASS study excluded patients with any history of haemorrhagic or lacunar stroke (as well as any type o stroke within 1 month) treatment of CAD or PAD with rivaroxaban 2.5 mg twice daily in combination with ASA is contraindicated in these patients.

Additional expert consultations

See discussion on clinical efficacy.

2.5.2. Conclusions on clinical safety

Bleeding remains the main safety concern associated with rivaroxaban. The CHMP concluded that the available clinical safety data were adequate to support use of rivaroxaban in combination with aspirin for the treatment of patients with CAD or PAD.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version **11.4** is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be

submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version **11.4** with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) • Patients < 18 years

Pharmacovigilance pla

There are no proposed additional pharmacovigilance activities based on the applied extension of indication to CAD/PAD patients.

The additional pharmacovigilance activities are based on an integrated PASS programme for use of rivaroxaban in the long-term indications (DVT, PE, SPAF and ACS).

Table 28. On-going and planned studies in the post-authorisation pharmacovigilance development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
SN 16647 pharmacoepidemiological study of	To evaluate specific safety outcomes (intracranial,	**Important identified risk:** • Haemorrhage	Started	Start Q4 2011

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
rivaroxaban use and potential adverse outcomes in routine clinical practice in the UK **Category 1**	gastrointestinal and genitourinary bleedings; other bleeding leading to hospitalisation; and non-infective liver disease) and effectiveness outcomes (DVT and PE, ischaemic stroke, myocardial infarction and death)	**Important potential risk:** • Embryo-fetal toxicity **Missing information:** • Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic CYP3A4 and/or P-gp inhibitors other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Pregnant or breast-feeding women • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting • Patients with significant liver diseases (severe hepatic impairment/ Child Pugh C) Patients < 18 years		Interim report 1 21 Dec 2015 Interim report 2 Q4 2017 End of data collection Q4 2018 Final data available Q4 2019 Final report of study results Q4 2020
SN 16159 pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in DE **Category 1**	Same as SN 16647	Same as SN 16647	Started	Start Q1 2012 Interim report 1 submitted 21 Dec 2015 Interim report 2 Q4 2017 End of data collection Q4 2018

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
				Final data /report Q4 2020
SN 16646 pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in NL **Category 1**	Same as SN 16647	Same as SN 16647	Started	Same as SN 16159
SN 17543 pharmacoepidemiological study of rivaroxaban use and potential adverse outcomes in routine clinical practice in SE **Category 1**	Same as SN 16647	Same as SN 16647	Started	Same as 16647
SN 16164 observational post-authorisation MPEM safety study to monitor the safety and utilisation of rivaroxaban for the prevention of stroke in patients with AF, treatment of DVT and PE, and prevention of recurrent DVT and PE following an acute DVT in the primary care setting in England, extended to include ACS patients **Category 1**	To proactively capture safety and drug utilisation data for rivaroxaban as prescribed to patients by general practitioners in primary care	Same as SN 16647	Started	Start Q4 2011 Start of extended data collection Q4 2014 (continued from original M-PEM study) End of data collection Q4 2016 Interim report 1 Q1 2014 (presented in the

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
				PSUR/PBRER No 11) Interim report 2 submitted 21 Dec 2015 Final report of study results Q4 2017 (estimated)
SN 17542 observational post-authorisation safety SCEM study to monitor the safety and utilisation of rivaroxaban initiated in secondary care for prevention of atherothrombotic events in patients who have had ACS in England and Wales. **Category 1**	To proactively monitor the short-term safety and drug utilisation of rivaroxaban for the secondary prevention of major cardiovascular events in patients with ACS with elevated biomarkers as prescribed to patients by specialists	Same as SN 16647	Started	Start Q3 2015 Interim report 1 Q4 2017 (estimated) End of data collection Q1 2019 (estimated) Final report of study results Q4 2019 (estimated)
SN 16167 Rivaroxaban RMP evaluation: patient and physician knowledge of key safety messages **Category 3**	To measure physician and patient awareness and understanding of the key messages in the prescriber guide and patient alert card	**Important identified risk:** • Haemorrhage	Started	Start Q3 2014 … Final report of study results (Wave 3) Q1/Q2 2020 (estimated)
Paediatric Investigational Programme	To assess rivaroxaban exposure and safety in patients < 18 years	**Missing information:** • Patients < 18 years	Started	PIP Programme completion

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PIP for 'Treatment of thromboembolic events' **Category 3**				Q1 2019 (estimated)

**Category 1 studies are imposed activities considered key to the benefit risk of the product.*
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

There are no proposed additional pharmacovigilance activities based on the applied extension of indication to CAD/PAD patients.

Risk minimisation measures

Summary of risk minimisation measures from the RMP

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: haemorrhage	SmPC: Section 4.3 (Contraindications): Section 4.4 (Special warnings and precautions for use): Section 4.8 (Undesirable effects) Prescription-only medicine Limited pack sizes	Educational material for prescribers Patient alert cards <u>Additional PhV activities:</u> Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Important potential risk: embryo-fetal toxicity	SmPC: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data) Prescription-only medicine Limited pack sizes	<u>Additional PhV activities:</u> Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information: Patients with severe renal impairment (CrCl < 30 mL/min)	SmPC: Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Prescription-only medicine Limited pack sizes	Additional PhV activities: Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	SmPC: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Prescription-only medicine Limited pack sizes	Additional PhV activities: Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: Remedial pro-coagulant therapy for excessive haemorrhage	SmPC: Section 4.9 (Overdose) Prescription-only medicine Limited pack sizes Exclusion from clinical development program	None
Missing information: Pregnant or breast-feeding women	SmPC: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data) Prescription-only medicine Limited pack sizes	Additional PhV activities: Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: Patients with atrial fibrillation (AF) and a prosthetic heart valve	SmPC: Section 4.4 (Special warnings and precautions for use) Prescription-only medicine Limited pack sizes	None
Missing information: Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF, ACS and CAD/PAD in real-life setting	None	Additional PhV activities: Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: Patients	SmPC:	Additional PhV activities:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
with significant liver diseases (severe hepatic impairment/Child Pugh C)	Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Section 5.2 (Pharmacokinetic properties) Prescription-only medicine Limited pack sizes Exclusion from clinical development program	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)
Missing information: Patients < 18 years	SmPC: Section 4.2 (Posology and method of administration) Prescription-only medicine Limited pack sizes	Paediatric Investigation Plan (PIP) Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, a new contraindication of rivaroxaban with a history of haemorrhagic or lacunar stroke has been added to the product information. The Package Leaflet has been updated accordingly.

In addition, section 4.8 of the SmPC has been updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data. Furthermore, the PI for all dose strengths is brought in line with the latest QRD template version 10.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xarelto 2.5 mg film-coated tablets and Xarelto 15 mg/20 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Stable CAD (coronary artery disease) is predominantly an atherosclerotic disease with narrowings of coronary arteries that give rise to episodes of myocardial ischaemia causing angina pectoris. CAD can also be caused by microvascular dysfunction and coronary vasospasm, and other conditions than CAD can cause similar symptoms such as valvular disease, tachyarrhythmia and severe anaemia. PAD (peripheral

arterial disease) is also typically caused by atherosclerosis. CAD and PAD share similar risk factors; both increase with increasing age and could present in different severities entailing different risks of future major cardiovascular events (MACE). Risk of future MACE varies considerably between patients with stable disease as compared to those with unstable disease, and also based on evidence of more generalized atherosclerotic disease and previous atherothrombotic events.

3.1.2. Available therapies and unmet medical need

Treatment of CAD or PAD aims at reducing symptoms and preventing future cardiovascular events. For prevention, antithrombotic therapy, lipid-lowering therapy and antihypertensive therapy are used. At present, single antiplatelet therapy is the most common antithrombotic therapy in both CAD and PAD, with modifications in e.g. acute illness such as myocardial infarction and revascularization procedures. There are approved combination therapies with two antiplatelets that significantly reduce the risk of cardiovascular events but at the cost of an increased risk of bleeding. Despite existing available therapies, the disease burden carried by the more severely affected individuals with CAD or PAD is quite high, with an increased risk of cardiovascular events including mortality.

3.1.3. Main clinical studies

One multi-centre, randomised, double-blind, double-dummy, active comparator, event-driven phase III study, snr 15786 (COMPASS). 27,395 subjects with objectively confirmed CAD or PAD were randomized 1:1:1 to rivaroxaban 2.5 mg bid/ASA 100 mg od, or rivaroxaban 5 mg bid, or ASA 100 mg od. Additionally, subjects without a continuous need for treatment with a proton pump inhibitor (PPI) were randomized 1:1 to pantoprazole or pantoprazole placebo.

Subjects included were required to be >/=65 years, or <65 years with at least 2 additional risk factors or documented atherosclerosis in at least 2 vascular beds. CAD subjects should have objectively verified multi-vessel disease or previous MI. PAD subjects included had verified lower extremity arterial disease or carotid artery disease. Patients excluded were, importantly, those with high risk of bleeding, history of lacunar or haemorrhagic stroke, any stroke within one month, and patients with heart failure with known LV-EF <30% or NYHA III or IV symptoms.

3.2. Favourable effects

The primary efficacy outcome was a composite of stroke, myocardial infarction or cardiovascular death. In the rivaroxaban 2.5 mg bid/aspirin 100 mg od arm, there was a clinically relevant and statistically significant reduction with HR 0.76 (95% CI 0.66; 0.86) when compared to the aspirin 100 od only cohort; primary efficacy outcome events were reduced by 1.3% and occurred in 4.1% of the subjects in the 2.5 mg bid/aspirin 100 mg od arm as compared to 5.4% in the aspirin only arm. When divided into the separate components of the composite, the effect was most pronounced for stroke (absolute risk reduction 0.7%; HR 0.58 (0.44; 0.76). CV death was reduced by 0.5% [HR 0.78 (0.64; 0.96)] and MI was reduced by 0.3% [HR 0.86 (0.70; 1.05)].

The secondary outcomes were all-cause mortality and two composites (death in coronary heart disease, myocardial infarction, ischaemic stroke or acute limb ischaemia, and death in cardiovascular disease, myocardial infarction, ischaemic stroke or acute limb ischaemia). For all-cause mortality, absolute reduction was 0.7% [HR 0.82 (0.71;0.96)] in the rivaroxaban 2.5 mg bid/aspirin 100 mg od arm when compared to aspirin 100 od only. For the two composites, absolute risk reduction in the composite including coronary heart disease was 1.3% [HR 0.72 (0.63; 0.83)] and for the composite including cardiovascular disease 1.4% [HR 0.74 (0.65; 0.85)].

3.3. Uncertainties and limitations about favourable effects

The participants in the COMPASS trial could have CAD, PAD or both CAD and PAD. 91% of the participants had CAD; 73% had CAD only and 18% had both CAD and PAD. 9% had PAD only. The primary efficacy outcome of rivaroxaban 2.5 mg bid/aspirin 100 mg od was not statistically significantly reduced in the PAD only cohort, with an absolute risk reduction of 0.4% [HR 0.89 (0.55;1.44)] compared to aspirin 100 od only.

There are analytical shortcomings with regards to the secondary endpoints, as this testing was not predefined in the way that was later carried out due to the premature stopping at the first interim analysis. ALI was numerically reduced, but the numbers were small (18 patients in the rivaroxaban 2.5 mg bid/aspirin 100 mg od vs 40 in the ASA only cohort).

For amputations, this was a non-adjudicated tertiary outcome. Although there was a numerical reduction in favour of rivaroxaban 2.5 bid/aspirin 100 od treatment, these data or not robust enough to allow for an inclusion in the product information.

The participants in the COMPASS trial with CAD had CAD with either previous MI or objectively verified multi-vessel disease. Thus, there are no efficacy data on patients with less severe CAD. Patients with heart failure of NYHA class III and IV were excluded from the study. For this reason, the indication was revised to include only patients at high risk of ischaemic events.

The numerical reduction in all-cause mortality is of interest in interpreting the reduction of CV death and is appropriate to include in the product information.

The effect for the primary endpoint seemed to be somewhat lower for patients aged 75 years and above (HR 0.89, CI 0.69-1.14). However, there was a relevant effect for reduction of the risk of stroke.

3.4. Unfavourable effects

In general, the safety profile of rivaroxaban in the current study in CAD/PAD subjects did not markedly differ from that in previous studies conducted with rivaroxaban.

Both major and minor bleedings were increased in participants treated with rivaroxaban 2.5 bid/aspirin 100 mg od compared to aspirin only. In total, 11.4% of the safety population in the rivaroxaban 2.5 bid/aspirin 100 mg cohort experienced any bleeding vs 6.7% in the aspirin only cohort. Major bleeding was defined by modified ISTH criteria including hospitalization; this endpoint is considered clinically relevant. 2.9% of the safety population experienced a major bleeding event in the rivaroxaban 2.5 bid/aspirin 100 mg od cohort, as compared to 1.6% in the aspirin only cohort; the HR of major bleeding was 1.84 (95% CI 1.50-2.26) in the rivaroxaban 2.5 bid/aspirin 100 mg od compared to aspirin only.

Bleeding that required hospitalization contributed predominantly to the relative increase in the primary safety outcome, but there were numerically more fatal and critical organ bleeding in the rivaroxaban 2.5 bid/aspirin 100 mg od cohort. Fatal and critical organ bleeding events were most frequently intracranial, whereas the bleeding events that required hospitalization were most frequently gastrointestinal. The absolute risk increase in subjects ≥ 75 years of age was 2.2% in the riva2.5bid/ASA group vs ASA only; for patients with PAD only, the absolute risk increase in modified major bleeding was 1.5%.

For minor bleeding, absolute risk increased by 3.7% in the rivaroxaban 2.5 bid/aspirin 100 mg od compared to aspirin only [HR 1.73 (95% CI 1.55; 1.94)] in the rivaroxaban 2.5 bid/aspirin 100 mg od compared to aspirin only. Gastrointestinal bleeding, skin or injection site bleeding, epistaxis and urinary tract bleeding were the most common sites of minor bleeding.

3.5. Uncertainties and limitations about unfavourable effects

Patients with high risk of bleeding were excluded from the COMPASS trial.

The numbers of gastrointestinal events were lower than expected. It is not clear if the randomization to PPI/placebo in previously non-PPI-treated patients could have affected the risk of minor bleeding.

There are no safety data on patients with previous haemorrhagic or lacunar stroke, or patients with any stroke within one month from randomization. These patients were excluded from the pivotal trial for safety reasons, due to a higher incipient risk of intracranial bleeding. Use of rivaroxaban in such patients is therefore contraindicated.

More subjects in the rivaroxaban 2.5 mg bid/aspirin cohort permanently discontinued with study drug as compared to aspirin only. The were numerously more patients who discontinued due to 'adverse event', 'bleeding' or 'SAE/ESI' in the rivaroxaban 2.5 mg bid/aspirin cohort.

3.6. Effects Table

Table 29. Effects Table for Xarelto in in CAD/PAD (data cut-off: 22 July 2017)

Effect	Unit	Rivaroxaban 2.5 bid + ASA 100 mg od	ASA 100 mg od	Strength of evidence	References
Favourable effects					
Composite of CV death, MI and stroke	n/100 p-yrs. (95% CI)	2.18 (1.97;2.41)	2.88 (2.64;3.15)	Superiority study Riva2.5+ASA vs ASA: HR 0.76 (0.66;0.86) P=0.00004	COMPASS study CSR
Unfavourable effects					
Major bleedings [a]	n/100 p-yrs. (95% CI)	1.58 (1.40;1.79)	0.86 (0.72;1.01)	Riva2.5+ASA vs ASA: HR 1.84 (1.50;2.26) P<0.00001	
Minor bleedings	%	9.0	5.3		

Abbreviations: CI: Confidence interval, CV: cardiovascular, MI: myocardial infarction, HR: Hazard Ration, ASA: Acetylsalicylic acid

Notes: [a]Major bleedings: Major bleeding according to Modified ISTH criteria, including fatal bleeding, symptomatic bleeding in a critical area/organ, bleeding into the surgical site requiring reoperation, or bleeding leading to hospitalization

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with CAD and PAD are at high risk of cardiovascular events despite current standard of care. Adding rivaroxaban 2.5 mg bid to ASA 100 mg od is shown to reduce the composite primary efficacy outcome (composed of a reduction in stroke, MI and CV death) in a proportion that is considered to be of

clinical value for the studied population, which are judged to be at high risk of ischaemic events. The absolute reduction of the primary efficacy endpoint was numerically equal to the absolute increase in the primary safety outcome (1.3% each).

For patients with PAD without concomitant CAD, even if the results did not reach statistical significance, as the pathophysiology is the same between the two conditions, the overall result of the study should apply equally to this subgroup of patients.

In the COMPASS study, the effect on the primary efficacy outcome was not statistically significant among subjects ≥ 75 years of age; however, there was a clinically relevant reduction of the incidence of stroke. On the other hand, the risk of bleeding increased with increasing age. Therefore, the benefit risk balance in this population should be individually assessed on a regular basis.

3.7.2. Balance of benefits and risks

The benefit of more intense antithrombotic therapy with the combination of Xarelto and ASA as documented is consider to counterbalance the risk of bleeding in the studied population.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Xarelto is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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, II, IIIA and IIIB

Extension of Indication to include prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events for Xarelto 2.5 mg co-administered with acetylsalicylic acid; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.

In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data. Furthermore, the PI for all dose strengths is brought in line with the latest QRD template version 10.
The RMP has been updated to version 11.4.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events for Xarelto 2.5 mg co-administered with acetylsalicylic acid; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance.

In addition, section 4.8 of the SmPC is updated for all other dose strengths (10/15/20 mg) of Xarelto with relevant exposure information based on the provided clinical data. Furthermore, the PI for all dose strengths is brought in line with the latest QRD template version 10.
The RMP has been updated to version 11.4.

Summary

Please refer to the published assessment report Xarelto H-944-II-058: EPAR - Assessment Report – Variation