Statement of Acceptance

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Report Title: An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales

Test Compound Number(s): BAY59-7939, Rivaroxaban ACS - OS

INN/Generic Name: XARELTO®

Cooperation organization:

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Department	*Name (print)*	*Signature, date*
Epidemiology	PPD	PPD

This external report is acceptable as to content and presentation but does not comply with the Bayer report format.

Drug Safety Research Unit (DSRU)

Rivaroxaban in Acute Coronary Syndrome

Final report

October 2019

PPD

PPD

PPD

PASS information

Title	An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales
Version identifier of the final study report	Version 1
Date of last version of the final study report	N/A
EU PAS register number	EUPAS 9977
Active substance	Xarelto pharmacotherapeutic group: Direct factor Xa inhibitors ATC code: B01AF01 Active substance: Rivaroxaban
Medicinal product	Xarelto 2.5mg Tablets
Product reference	2.5mg Tablet: EU/1/08/472/025-035, EU/1/08/472/041
Procedure number	EMEA/H/C/00944
Marketing authorisation holder(s)	Bayer AG 51368 Leverkusen Germany
Joint PASS	No
Research question and objectives	Aim: To monitor the short-term (up to 12-weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as prescribed for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) by specialist HCPs in the secondary care hospital setting in England and Wales. Primary objective: • To quantify the cumulative incidence of major bleeding according to the TIMI classification of non-CABG Related bleeding occurring in the 12-week observation period. Secondary objectives: • Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS including drug utilisation characteristics. • Describing changes of health profile of patients, assessment of adherence, number of indication related episodes

	plus any alterations of the treatment programme. • Quantifying the risk of other major (in any other site not specified in the primary objective) or minor bleeding outcomes (in any site) reported in the 12-week observation period. Both the primary and secondary objectives relate to the rivaroxaban cohort and the contextual cohort. Exploratory objectives (for rivaroxaban cohort): • Quantify the incidence of other important identified, potential and special risks and any other events reported during treatment. • Describe clinical features and management of cases of overdose and major bleeding.
Country(-ies) of study	England and Wales
Author	PPD PPD PPD

Marketing authorisation holder(s)

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1 Abstract

Title

An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome (ACS) in England and Wales (The ROSE-ACS study).

Keywords

Rivaroxaban – Post-marketing – Safety – SCEM – ROSE-ACS

Rationale and background

Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers in the EU.

Research question and objectives

The primary objective was to quantify the cumulative incidence of major bleeding according to the TIMI classification occurring during the study period, overall and stratified by intracranial, gastrointestinal and urogenital sites. In addition there were several secondary and exploratory objectives aimed at understanding the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS including drug utilisation characteristics as well as describing changes in the health profile of patients over the course of the study and the risk of other major and minor bleeds and other events of interest.

Study design

An observational, population-based cohort design of two cohorts (rivaroxaban and a contextual cohort of patients receiving the current standard treatment of care; dual antiplatelet therapy) with data collection at start of treatment with rivaroxaban or contextual medication (index date) and 12-weeks post-index date.

Setting

Secondary care hospital setting in England and Wales.

Subjects and study size, including dropouts

Six hundred and ninety-nine patients have provided consent to participate in the study within the period from September 2015 to October 2018. Forty-seven patients were

subsequently found to be ineligible for participation; 33 incorrectly identified, 10 had insufficient clinical information, and four patients were withdrawn. Baseline and Outcome Data case report forms (CRFs) were provided for 652 (93.3%) patients of which 528 (81.0%) were prescribed standard oral antiplatelet combination therapy alone i.e. the contextual cohort, and 124 (19.0%) were prescribed rivaroxaban in combination with standard oral antiplatelet therapy.

Variables and data sources

Patient data were derived by healthcare professionals from medical charts at index date and 12-weeks post-index date.

Results

Participants

A total of 47 HCPs from 26 sites recruited 652 evaluable patients (124 rivaroxaban and 528 contextual) to the study.

Descriptive data

The majority of both rivaroxaban and contextual cohorts were male (83.1% and 75.2% respectively) and overall, the rivaroxaban cohort tended to be slightly younger than the contextual cohort (mean age 60.2 vs. 64.3 years). In both treatment cohorts females were older than males (mean age: rivaroxaban 61.1 vs. 60.0 years; contextual 68.2 vs. 63.0 years). The majority of patients were treated for STEMI in the rivaroxaban cohort (51.6%) and NSTEMI (56.6%) in the contextual cohort.

Patient general health characteristics were broadly similar between the rivaroxaban and contextual cohorts. The majority of patients had their treatment initiation in the inpatient setting however in the rivaroxaban cohort, patients were most frequently initiated on rivaroxaban within three days of being admitted (82.3%) whereas in the contextual cohort 69.7% were initiated treatment the same day of admission.

Outcomes

The cumulative incidence of major bleeding according to the TIMI classification of non-CABG Related Bleeding was 0.8% (n=1) in the rivaroxaban cohort and 0.9% (n=5) in the contextual cohort. In the rivaroxaban cohort, the major bleed occurred within the gastrointestinal site. In the contextual cohort, four of the major bleeds occurred within the gastrointestinal site (cumulative incidence 0.8%) and one occurred in another site (0.2%). No bleeding events were reported within urogenital or intracranial sites in either of the cohorts.

Deaths

Three (2.4%) deaths occurred on treatment in the rivaroxaban cohort and eight (1.5%) occurred in the contextual cohort. For both cohorts, all causes of death (where specified) were cardiac related.

Discussion

The ROSE-ACS study shows that rivaroxaban is largely being prescribed to populations in accordance with prescribing recommendations and national clinical guidelines. In terms of the primary outcome risk of major bleeding, the numbers of bleeds in the rivaroxaban cohort which fulfilled the TIMI definition of non-CABG related major bleeding were low (<1%). However, interpretation of the results needs to consider the small sample size of patients treated with rivaroxaban due to low usage in ACS. The SCEM design provides a framework suitable to evaluate the safety of newly marketed medicines in secondary care setting.

Marketing Authorisation Holder(s)

Bayer AG, 51368, Leverkusen, Germany

Names and affiliations of principal investigators

PPD

PPD

2 List of Abbreviations

Abbreviation	Term
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AHA	American Heart Association
ASA	Acetylsalicylic Acid
ATLAS ACS 2 TIMI 51	Anti Xa Therapy to Lower cardiovascular events in addition to standard therapy in subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 51
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CKD	Chronic Kidney Disease
CLRN	Local Clinical Research Network
CRF	Case Report Form
CYP3A4	Cytochrome P450 3A4

Abbreviation	Term
DSRU	Drug Safety Research Unit
DVT	Deep Vein Thrombosis
ESC	European Society of Cardiology
GP	General Practitioner
GTN	Glyceryl Trinitrate
EU	European Union
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
LBBB	Left bundle branch block
MAOI	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MINAP	Myocardial Ischaemia National Audit Project
M-PEM	Modified Prescription-Event Monitoring
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
NSAID	Non-Steroidal Anti-inflammatory Drugs
NSTE-ACS	non-ST-elevation Acute Coronary Syndromes
NSTEMI	non-ST-segment elevation myocardial infarction
NVAF	Non Valvular Atrial Fibrillation
PASS	Post-authorisation Safety Study
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PEA	Pulseless Electrical Activity
P-gp	Permeability glycoprotein 1
PTs	Preferred Terms
RAIDAR	Rare and Iatrogenic Adverse Reactions
RETs	Reported Event Terms
RMP	Risk Management Plan
SCEM	Specialist Cohort Event Monitoring
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitor
STE-ACS	ST-elevation acute coronary syndrome
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction
VTE	Venous Thromboembolism
WHF	World Heart Federation

3 Investigators

Investigator	Appointed person(s)
Principal investigator	PPD
Principal investigator	PPD

Co-investigator	PPD

4 Other Responsible Parties

Responsible party	Appointed person(s)
Marketing Authorisation holder contact	PPD PPD Bayer AG 13342 Berlin Germany

Clinical Research Network:

The ROSE-ACS study was adopted by the National Institute for Health Research Clinical Research Network (NIHR CRN). The CRN offers research support to researchers conducting studies within the National Health Service (NHS). The CRN comprises of 15 Local Clinical Research Networks (CLRN) covering England. Each CLRN delivers research across 30 clinical specialties. The ROSE-ACS study has been adopted by the Cardiovascular speciality group. These speciality groups bring together communities of clinical practice to provide national networks of research expertise. They are made up of research-interested clinicians and practitioners at both national and local levels whose role is to ensure that the studies included in their national portfolio of research receive the right support to ensure they are delivered successfully in the NHS.

5 Milestones

Milestone	Planned Date	Actual Date	Comments
Study Approval by Research Ethics Committee	May 2014	June 2015	Delay in submission to ethics to allow for PRAC review
Start of data collection	September 2015	September 2015	
End of data collection	December 2018	April 2019	Dates moved to allow for the receipt of all outstanding CRFs and complete follow up of events of interest
Registration in the EU PAS register	July 2014	July 2015	Delayed due to delays in ethics approval (see above)
Interim I report	September 2017	November 2017	
Final report of study results	August 2019	August 2019	

6 Rationale and Background

6.1 Rivaroxaban

Rivaroxaban, a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacements (1). On 19 December 2011, the European Commission granted authorization of extension of the license of rivaroxaban to include prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Approval for the indication treatment of PE, and prevention of recurrent DVT and PE following an acute DVT in adults was granted in the European Union (EU) on 15 December 2012.

Rivaroxaban, co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine, was approved in May 2013 for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers in the EU. The marketing application for secondary prevention in ACS patients was based on data from the pivotal ATLAS ACS 2 TIMI 51 study (2) which showed that 2.5 mg of the drug twice daily in combination with standard oral antiplatelet therapy significantly reduced the primary composite end point of cardiovascular death, myocardial infarction (MI), or stroke after ACS compared with standard oral antiplatelet therapy alone. These findings have been supported by the recent COMPASS trial investigating whether rivaroxaban alone or in combination with aspirin is more effective than aspirin alone for secondary cardiovascular prevention. This study showed that among patients with stable atherosclerotic vascular disease (coronary artery disease (CAD), peripheral artery disease (PAD) or both), the rate of the primary outcome (a composite of cardiovascular death, stroke, or myocardial infarction) was lower by 24% with rivaroxaban (2.5 mg twice daily) plus aspirin than with aspirin alone. However this group was also shown to have more major bleeding events. No further benefit on cardiovascular outcomes was observed for patients taking rivaroxaban 5mg twice daily alone, as compared to aspirin (3). Based on the data from the COMPASS trial, rivaroxaban, co-administered with ASA, was approved in August 2018 for the prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischaemic events.

A Risk Management Plan (RMP) has been developed for rivaroxaban by the manufacturer. This plan includes tools designed to monitor the important risks (including class effects and off-label use) (4). This post marketing safety study of rivaroxaban (XARELTO®) was carried out by the Drug Safety Research Unit (DSRU) as part of a broader Post-Authorisation Commitment requested by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of rivaroxaban in clinical practice, with a focus on ACS.

This Specialist Cohort Event Monitoring (SCEM) study, is designed to monitor the safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as initiated by specialist healthcare professionals (hereafter Specialist HCPs) within the secondary care hospital setting in England and Wales as part of a treatment strategy to reduce overall and cardiovascular mortality in patients with recent ACS. The study is one of three complementary studies conducted by the DSRU. Another SCEM study is designed to monitor the safety and drug utilisation of rivaroxaban, as initiated by specialist HCPs for prevention of stroke and systemic embolism in adult patients with non-valvular AF, treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. The third study, based in primary care, is a Modified Prescription-Event Monitoring (M-PEM) Study, the aim of which is to proactively capture safety and drug utilisation data in the post-marketing phase of license approval of rivaroxaban as prescribed to patients by general practitioners in England for all relevant indications.

6.2 Acute Coronary Syndrome

The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) convened a consensus conference in 1999 in order to re-examine jointly the definition of myocardial infarction (published in the year 2000 in the European Heart Journal and Journal of the American College of Cardiology) (5). Given the considerable advances in the diagnosis and management of myocardial infarction since the original document was published, the leadership of the ESC, the ACC and the American Heart Association (AHA) convened, together with the World Heart Federation (WHF), a Global Task Force to update the 2000 consensus document (6).

The acute coronary syndrome model espoused by the American College of Cardiology places unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) at increasingly severe points along a disease continuum (5-7). At presentation, the working diagnosis of non-STE-

ACS (NSTE-ACS), based on the measurement of troponins, is further classified into non-ST elevation MI, (NSTEMI) or unstable angina. The therapeutic management is guided by the final diagnosis (8).

Registry data consistently show that NSTE-ACS is more frequent than STE-ACS (9). The annual incidence is ~ 3 per 1000 inhabitants, but varies between countries (10). Hospital mortality is higher in patients with STEMI than among those with NSTE-ACS (7% vs. 3-5% respectively), but at six months the mortality rates are very similar in both conditions (12 and 13%, respectively) (9, 11, 12).

Rivaroxaban is the only novel oral anticoagulant to have received a licence for this indication in the EU.

6.3 ATLAS ACS 2 TIMI 51

ATLAS ACS 2 TIMI 51 (Anti Xa Therapy to Lower cardiovascular events in addition to standard therapy in subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 51) study was published in the NEJM, in January 2012 (2).

The study recruited over 15000 patients diagnosed with a recent acute coronary syndrome. Patients were randomised to three different treatment groups receiving either placebo, 2.5mg Rivaroxaban or 5mg Rivaroxaban (both given twice daily). The mean duration of study treatment was 13 months, however patients were treated with rivaroxaban for up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke. The patients' medical condition was stabilized before enrolment into the trial, with the initial management strategies (e.g. revascularization) completed before entry. All patients received standard pharmacotherapy - including low dose aspirin; they received a thienopyridine (either clopidogrel or ticlopidine) according to the national or local guidelines. Randomization was stratified on the basis of planned use of a thienopyridine. Patients were seen at four weeks, at 12-weeks, and thereafter every 12-weeks, with a maximum follow up of 31 months. The primary safety end point was TIMI (Thrombolysis in Myocardial Infarction) major bleeding not related to coronary artery bypass grafting (CABG).

In the analysis of the two doses of rivaroxaban, each of the doses reduced the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke, as compared with placebo, with rates in patients receiving the 2.5-mg dose of 9.1% and 10.7%, respectively (hazard ratio, 0.84; 95% CI, 0.72 to 0.97; P = 0.02)

and rates in patients receiving the 5mg dose of 8.8% and 10.7%, respectively (hazard ratio, 0.85; 95% CI, 0.73 to 0.98; P = 0.03) (4). Rivaroxaban significantly increased the rate of TIMI major bleeding that was not related to CABG, as compared with placebo, and these events were lower in patients receiving the 2.5 mg dose than in those receiving the 5 mg dose (2).

7 Research Question and Objectives

7.1 Overall Aim

The aim of this SCEM study is to proactively monitor the short-term (up to 12-weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as prescribed to patients for the prevention of atherothrombotic events in adult patients after an ACS as initiated by specialist HCPs in the secondary care hospital setting in England and Wales.

7.2 Objectives

Primary objective:

To quantify the cumulative incidence (risk and rate) of major bleeding according to the TIMI classification of non-CABG Related Bleeding (Table 1) occurring in the 12-week observation period, overall and stratified by the following bleeding sites:

- Intracranial
- Gastrointestinal
- Urogenital

Secondary objectives:

1. Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics.
2. Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12-week study observation period.
3. Quantifying the risk of other major (in any other site not specified in the primary objective) or minor bleeding outcomes (in any site) reported in the 12-week observation period overall (as defined by TIMI and BARC guidelines; Tables 1 and 2) and, if number of reports are sufficient, in patient subgroups of special

interest in first 12-weeks of treatment under conditions of the routine secondary care hospital setting in England and Wales.

Both the primary and secondary objectives relate to the rivaroxaban cohort and the contextual cohort.

Exploratory objectives:

The study will also include (for rivaroxaban cohort only) several exploratory analyses to 1) where possible, to quantify the incidence of other important identified, potential and special risks not mentioned in the primary objective and any other events reported during treatment with rivaroxaban; and 2) describe clinical features and management of cases of overdose, major bleeding (including bleeding sites specified in the primary objective, in addition to other major bleeds identified) (as defined by TIMI and BARC guidelines; Tables 1 and 2) during observation of the cohort exposed to rivaroxaban.

Table 1. Haemorrhage outcomes (TIMI definitions for use for the primary secondary and exploratory objectives)

A non CABG related major[†] bleeding event will be defined using TIMI criteria as:
• Any symptomatic intracranial haemorrhage • Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL • Fatal bleeding (bleeding that directly results in death within 7 days)
A non CABG related minor bleeding event will be defined using TIMI criteria as:
• Any clinically overt sign of haemorrhage that was associated with a fall in haemoglobin concentration of 3 to <5 g/dL
A non CABG related bleeding event requiring medical attention will be defined using TIMI criteria as:
Any overt sign of haemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above • Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) • Leading to or prolonging hospitalization • Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
A non CABG related minimal bleeding event will be defined using TIMI criteria as:
• Any overt bleeding event that does not meet the criteria above
A CABG related major bleeding event will be defined using TIMI criteria as any of the following bleeding events that were CABG related:
• Fatal bleeding (bleeding that directly results in death) • Perioperative intracranial bleeding • Reoperation following closure of the sternotomy incision to control bleeding • Transfusion of greater than or equal to 5 units of whole blood or PRBCs within a 48 hour period • chest tube output > 2 L within a 24 hour period

[†] The three organ sites included in the primary objective are gastrointestinal and urogenital, in addition to intracranial

Table 2. Haemorrhage outcomes (Bleeding Academic Research Consortium [BARC] definitions for use for the secondary and exploratory objectives only)

Type 0
• No bleeding
Type 1
• Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2
• Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3
Type 3a
• Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed)
• Any transfusion with overt bleeding
Type 3b
• Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed)
• Cardiac tamponade
• Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
• Bleeding requiring intravenous vasoactive agents
Type 3c
• Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal)
• Subcategories confirmed by autopsy or imaging or lumbar puncture
• Intraocular bleed compromising vision
Type 4: CABG-related bleeding
• Perioperative intracranial bleeding within 48 h
• Reoperation after closure of sternotomy for the purpose of controlling bleeding
• Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
• Chest tube output ≥2L within a 24-h period
Type 5: fatal bleeding
Type 5a
• Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
• Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1g/dL hemoglobin).†Cell saver products are not counted

8 Amendments and Updates

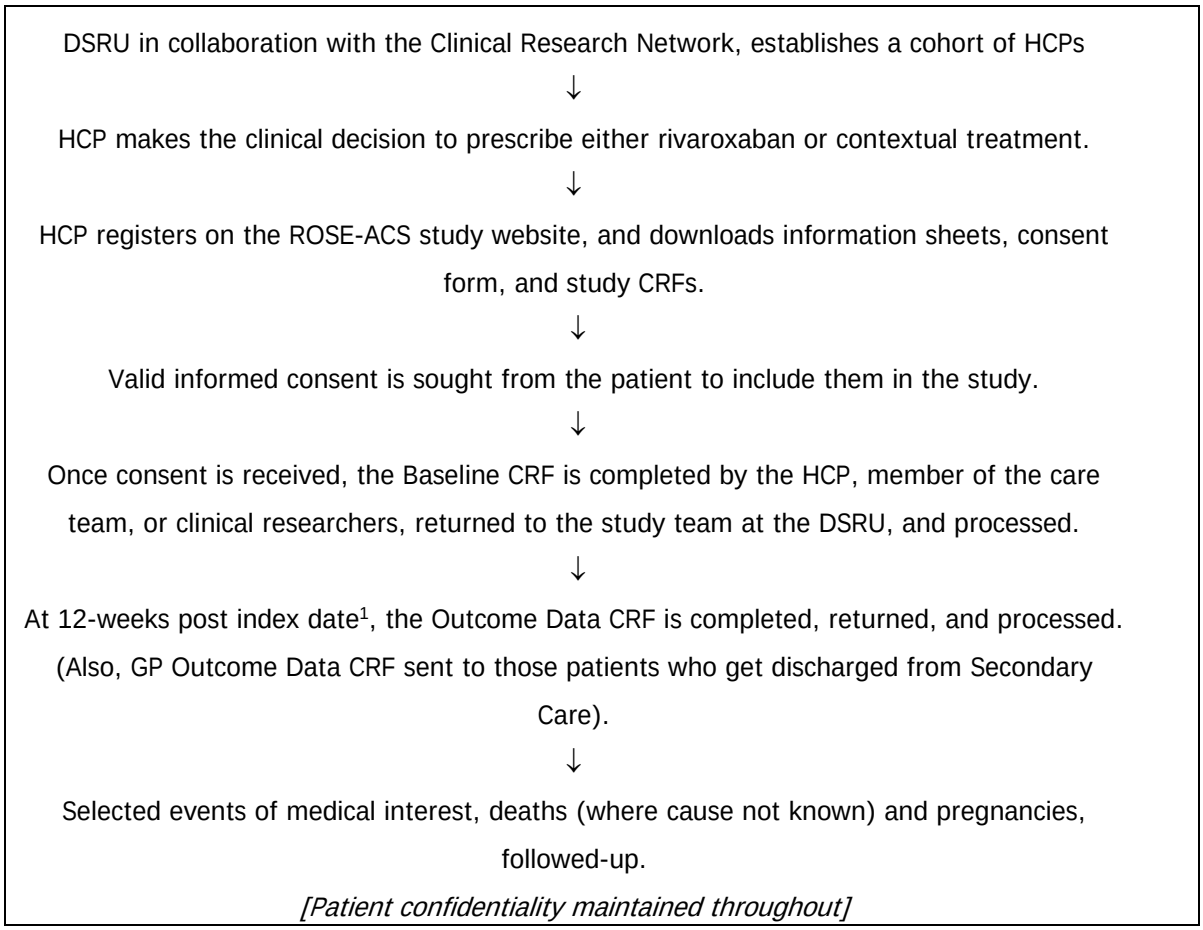
Number	Date	Section of study protocol	Amendment or update	Reason
1	12/12/2017	4 Abstract 9.1 Study Design 9.2 Setting	Amendment	To broaden the inclusion criteria and minimize exclusions for patients prescribed rivaroxaban for ACS and in response to questions from PRAC

9 Research Methods

9.1 Study Design

This observational cohort study with a contextual cohort was conducted in England and Wales using the technique of SCEM. Figure 1 outlines the methodology used in this study.

Figure 1. SCEM Study of rivaroxaban (Xarelto®)



Further information on study design and strengths of SCEM can be found in Section 9.1 of the study protocol (Appendix 1).

9.2 Setting

The study was conducted in the secondary care hospital setting in England and Wales in the immediate post-marketing period of rivaroxaban for the ACS indication. Cohort accrual started in September 2015 and ended in October 2018. Recruited patients had 12-weeks of follow up.

9.3 Subjects

9.3.1 Specialist prescribers

Specialists and members of their clinical team from within the secondary care hospital setting were systematically identified across the country, facilitated where possible by existing clinical research networks, and were invited to participate in the study prior to study start. These specialist HCPs were informed that they were participating in a

[1] Date of their first rivaroxaban or contextual medication (i.e. dual antiplatelet therapy) dispensation

cohort study to monitor the use of rivaroxaban in any combination with standard oral antiplatelet therapy, in accordance with requirements within the RMP. In addition they were informed that a contextual cohort of patients taking standard oral antiplatelet combination therapy for secondary prevention following ACS was also being monitored.

9.3.2 Eligible patients

Eligible patients were those within the accessible treated target study population to which participating HCPs had access, presenting for standard course of care as in- or out-patients for treatment of relevant indications during the study period. The identification of the study population occurred after the pharmacotherapeutic treatment decision had been made. Participation within the study was not required as a condition of receiving treatment. This approach was intended to reduce conscious or unconscious selection bias on the part of the prescriber as to whom to enrol in the study, especially with regard to factors that may be related to prognosis. The patient was not asked to attend the specialist more than usual or undergo any additional treatment. Patient consent was requested after the decision to start treatment had been made.

Since this was an observational cohort study conducted in a naturalistic setting, open patient entry criteria were applied to maximise external validity. However, due to the paucity of rivaroxaban patients that were being recruited, an amendment was made to the eligibility criteria in order to further broaden the inclusion criteria and minimize exclusions included below. Details of this amendment can be found in Appendix 2

9.3.2.1 Eligible patient inclusion criteria

The inclusion criteria were:

- Age 18 years or above
- Patients newly prescribed rivaroxaban in any combination with standard oral antiplatelet therapy for the indication of secondary prevention in patients after ACS
- Patients prescribed dual antiplatelet therapy (contextual cohort) for the indication of secondary prevention after ACS
- Patients had provided signed, informed consent

9.3.2.2 Eligible patient exclusion criteria

Patients who did not provide consent were excluded from the study. Patients were automatically withdrawn if the patient or specialist provided informed written or verbal notification that they no longer wished to participate at any stage of the study.

Patient exclusion criteria were:

- Patients prescribed with oral anticoagulants including rivaroxaban within six months prior to the index date for any indication
- Patients commenced rivaroxaban between date of market launch (28th October 2014) for the indication of secondary prevention after ACS and study start (18th September 2015)

9.3.3 Cohort definitions

9.3.3.1 Cohort allocation

Patients were allocated to one of two mutually exclusive treatment groups based on rivaroxaban prescribing or dual antiplatelet prescribing for secondary prevention of atherothrombotic events post ACS.

- The rivaroxaban cohort consists of those patients newly prescribed rivaroxaban in any combination with standard oral antiplatelet therapy
- The contextual cohort consists of those patients prescribed dual antiplatelet therapy

9.3.3.2 Cohort entry and exit

9.3.3.2.1 Cohort entry

Cohort entry for each patient was defined according to the date of their first rivaroxaban or contextual medication dispensation (i.e. dual antiplatelet treatment), known as 'index date', if all inclusion and exclusion criteria were fulfilled.

9.3.3.2.2 Cohort exit

Cohort exit for each patient was defined according to the end of study period, or at point of censoring whichever was the earliest.

9.3.3.3 Censoring

Exposure to treatment was defined between cohort entry and cohort exit. A continuous variable representing total period of treatment with either rivaroxaban or dual antiplatelet therapy for each patient was derived from primary data on cohort entry and exit dates. Each patient was regarded as being treated between index date

and last known date of treatment. The number of days will vary between patients. For event analysis purposes, this period was restricted to where cohort exit was defined according to the first of the following dates:

- End of 12-week study treatment period
- Censoring from loss to follow-up
- Death
- Censoring at first report of stopping treatment. For the rivaroxaban cohort, censoring at stop date occurred on the date rivaroxaban treatment was stopped (regardless of whether antiplatelet therapy was stopped). For the contextual cohort, censoring at stop date occurred on the date the first antiplatelet was stopped from the antiplatelet therapy regimen (regardless of whether any other antiplatelets were stopped)
- First report of outcome of interest

The assumption was made that person-time exposure is continuous up to event or censor date. Denominator data is presented according to person-time treated per 100 years. To account for drug elimination, sensitivity analyses were performed to examine event incidence including five drug half-lives.

9.4 Variables

For eligible patients the following information was obtained from the consent form, the CRF relating to start of treatment (index date) and the CRF at the end of the 12-weeks observation period.

Consent CRF (Appendix 3) included:

- Socioeconomic/lifestyle factors (marital status, employment status, ethnicity, smoking and alcohol use)

Baseline CRF (Appendix 3) included:

- Demographic characteristics (age, gender)
- Setting of first prescription (e.g. inpatient hospital ward, outpatient clinic)
- Reasons for prescribing (e.g. clinical judgement, recommendation from NICE, expert committee guidelines, trust formulary committee guidelines)
- Which anticoagulant/antiplatelet regimen was prescribed and start date
- Clinical condition requiring anticoagulant/antiplatelet therapy (indication) and details of the clinical condition (e.g. STEMI, NSTEMI)
- Any prior anticoagulant/antiplatelet treatment

- Risk factors for bleeding at baseline (e.g. creatinine, white cell count, anaemia, presentation, antithrombotic medications)

12-week end of observation CRF (Appendix 3) included:

- Additional information on anticoagulation treatment regimen:
  - Details of prior use of oral and parenteral anticoagulant and antiplatelet therapy (e.g. thienopyridines, aspirin, glycoprotein IIb/IIa inhibitors, heparins) in the past 12 months if known
  - Treatment regimen during the 12-weeks observation period
  - If study treatment regimen had changed: date and reason for change, details of transition plan to alternative; if required, details of reversal of anticoagulation therapy and management of bleeding complication
- Recent (< 4 weeks prior to index date) and concomitant medications (at index or during treatment):
  - Medications not recommended for concomitant use (including azole antimycotics [e.g. ketoconazole] and HIV protease inhibitors)
  - Medications to be used with caution (including fluconazole, strong CYP3A4 inducers, strong P-gp inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, oral steroids, hormone and oral contraceptive therapy, platelet aggregation inhibitors or other antithrombotic agents)
- Medical history relevant for important potential, identified and special risks of interest (plus dates of first diagnosis/report), see Outcome CRF Appendix 3
- Specific information on renal function status and creatinine clearance at index date and any changes during 12-week observation period
- Specific information on hepatic disorders present at index date and any recent abnormal liver function tests
- Event reports including selected risks of interest (Protocol - Table 3)
- Cause and date of death (if died) in the first 12-weeks after starting treatment;
- Behaviours prior to and/or starting treatment (e.g. smoking, alcohol/substance misuse)

Abridged 12-week end of observation CRF for GP (Appendix 3) included:

- Anticoagulant/antiplatelet treatment regimen which the patient had received
- Event reports of selected risks of interest (Protocol -Table 3)
- Cause and date of death (if died)
- Date and reasons for treatment regimen change (if changed) including switching
- Any newly prescribed concomitant treatments

9.5 Data Sources and Measurement

SCEM data was derived through secondary use of medical charts as abstracted onto study specific CRFs by HCPs and GPs in England and Wales.

9.5.1 Recruitment

The first phase of data collection had two parts; Part 1: Recruitment of eligible HCPs; prescriber type and setting of specialist HCPs is collected upon registration with the DSRU. Part 2: Recruitment of consenting patients initiated with the study drug under clinical care of participating specialist HCPs; date of recruitment into the study was recorded. The DSRU allocated a unique study reference number for study audit and data management processes.

9.5.2 Exposure/outcome data collection

The second phase of data collection had multiple parts; Part 1: For all eligible patients invited to participate a consent form was completed. This also included optional questions to be completed by the eligible patient on selected demographic data. Part 2: For each individual consenting patient the specialist HCP was asked to collect "baseline" information (Baseline CRF) recorded within medical charts including date of start of treatment (either rivaroxaban in any combination with standard oral antiplatelet therapy or dual antiplatelet therapy (index date)). These CRFs were then submitted to the DSRU and the data entered into the study database. Part 3: Thereafter, 13 weeks post dual antiplatelet therapy start date, the specialist HCP was prompted to complete an end of observation CRF derived from data within existing medical charts. Part 4: The patient's GP was contacted to complete an abridged end of survey 12-week CRF using data recorded within primary care medical charts. Part 5: Reported data were examined for clinical events of medical interest and serious adverse event reports [classified using the International Conference on Harmonisation definitions] (13). Events of interest were followed-up using event-specific CRFs which captured additional information required to characterise the event and patient. This included all Rare and Iatrogenic Adverse reactions (RAIDAR) events compiled by the DSRU (listed in the protocol, Appendix 1). The CRFs were sent to the specialist HCP and/or GP depending on the reporter and all returned initial CRFs were reviewed by a DSRU Research Fellow.

9.5.3 Data coding

Following review by a Research Fellow, all information on the CRFs (including follow up CRFs) was entered into the DSRU database including events collected as free-text

which were coded onto the database using the MedDRA dictionary, as detailed in the protocol (Appendix 1).

9.6 Bias

Bias in epidemiological studies occurs when there is a systematic difference in the likelihood of or accuracy of response based on specific participant characteristics.

In a SCEM study prescribers (specialists and members of their clinical team) from within the secondary care hospital setting are systematically identified across the country, facilitated where possible by existing clinical research networks, and are invited to participate in the study prior to study start. For this rivaroxaban SCEM study in ACS patients, the specialists recruited patients into the study at the start of the ACS treatment episode with the completion of a baseline CRF based on information in medical records and patient consent (Figure 1, Section 9.1). These specialist HCPs were informed that they were participating in a cohort study to monitor the use of rivaroxaban in any combination with standard oral antiplatelet therapy, in accordance with requirements within the RMP. In addition they were informed that a contextual cohort of patients taking standard oral antiplatelet combination therapy for secondary prevention following ACS was also being monitored.

A SCEM study is a cohort study by design, as patients are recruited on the basis of exposure or non-exposure to a drug and their subsequent event course examines temporal relationships (14). However in any cohort study there is a potential for bias and in a SCEM study, bias may arise at a number of data collection points.

The first consideration is the impact of specialist non-response to requests for participation and non-responses to CRFs as non-responding specialists may be different to responding specialists. This may be introduced as a result of external influences such as local formulary decisions and local research governance frameworks which are beyond the ability of the study investigators to control. However, since this study was national in scale, it aimed to include a broad range of specialists HCP across many regions. Information on prescriber characteristics is provided in Section 10.1.1.

A second consideration is that if patients included by specialists are systematically different to patients not included, selection bias will occur. However, in this study patients are recruited at "baseline" which should limit the impact of selection bias due to later events. The specialist HCPs were asked to make the decisions whether to use rivaroxaban in combination with standard oral antiplatelet therapy or standard oral

antiplatelet combination therapy alone based on their clinical judgement prior to the decision to include the patient in the study. Confounding is still possible and there may be differences in the distribution of confounders between the two cohorts. Since this is a non-comparative study design, confounding should not introduce systematic error because comparative measures of effect were not calculated.

In this study, there were two CRFs, the first covering baseline information at treatment initiation and the second covering the three month period post treatment initiation. An important point to consider in studies designed to follow patients over time is information bias whereby under- and mis-reporting of outcomes can be possible; specialist HCPs' notes may be incomplete with regard to medical history and non-cardiovascular related outcomes associated with current treatment. Outcome misclassification is possible as a result but differential misclassification is unlikely considering that outcomes were collected through the same process for both cohorts. In addition, since this is a non-comparative study design, no estimates of effect from comparing the two cohorts, which could potentially be biased by such misclassification, were produced. Further, the two-phase data capture approach was intended to facilitate compliance with data recording and reporting as well as spreading workload for specialist HCPs.

The standard oral antiplatelet combination treatment is not a comparative, but a contextual cohort. Any difference in the distribution of covariates will impact the incidence of outcomes in the contextual and rivaroxaban cohorts. Since data are abstracted from patient medical charts held by specialist HCPs, they are likely to be biased towards events recorded within secondary care and may not contain data on variables that are relevant to the study that have been reported elsewhere. However, the study asked specialist HCPs to provide data where available and report events affecting all body symptoms. Since patient consent was also obtained to access primary medical records, the researchers were also able to contact the GP of each individual patient if necessary to obtain data on outcomes relevant to the study during the observation period.

Possible impact of bias is discussed further in Section 11.2 of this report and Section 9.9 of the study protocol.

9.7 Study Size

For this SCEM study, a minimum sample size of 1193 evaluable[2] patients for rivaroxaban was considered desirable in order to estimate the expected (true) cumulative incidence of specified primary outcomes of interest with desired precision. A similar number of evaluable patients receiving current standard care treatments was to be collected for the internal contextual cohort. Due to low usage of rivaroxaban for the ACS indication in England and Wales, the number of patients in our study is significantly lower than the planned sample size, despite a number of strategies undertaken to improve recruitment which are detailed in Appendix 2.

Further information on study sample size can be found in the study protocol Section 9.5 (Appendix 1).

9.8 Data Transformation

There were very few data transformations performed. Some quantitative variables such as age were grouped, but in those cases means (standard deviations (SD)) and medians (Interquartile range (IQR)) are also provided. Age groupings were introduced using ten-year age bands as this gave sufficient numbers in each band but also allowed for good discrimination between different age groups. Other quantitative variables that were grouped were BMI, weight, lab test values following admission and number of days on treatment.

Patients were allocated to one of two mutually exclusive treatment groups based on rivaroxaban prescribing or dual antiplatelet prescribing for secondary prevention of atherothrombotic events post ACS. Throughout the report analyses has been stratified by the 'rivaroxaban cohort' and the 'contextual cohort' (i.e. dual antiplatelet treatment). Further information on these treatment exposure groups can be found in Section 9.3.3.1.

9.9 Statistical Methods

9.9.1 Main Summary Measures

Demographic information and baseline health characteristics are tabulated and provided as counts and percentages for categorical variables. In some instances, where this is meaningful, medians and IQR are also provided for categorical variables. Continuous variables are provided as means with standard deviations, and as medians

[2] For this report, evaluable patients were those patients who provided consent and for whom analysable clinical data was provided in the data collection CRF at baseline and at 12-weeks (from either the specialist HCP and/or GP).

with IQR. The primary and secondary bleeding outcome measures are presented as unadjusted cumulative incidence estimates, and unadjusted cumulative incidence rates.

9.9.2 Main Statistical Methods

Descriptive statistics were applied to the demographic data and baseline health characteristics, no formal statistical testing was conducted. Analyses of bleeding events identified within the primary and secondary objectives were explored using unadjusted cumulative incidence (risk and rate) with 95% Binomial exact CI. For these event analyses, right censoring at the end of the 12-weeks observation was undertaken. Where events were reported but with no supporting event date, and/or treatment exit date, these patients were excluded from numerator and denominator of this primary analysis.

9.9.3 Missing Values

All evaluable patients with data for a specific variable were included in the tabulations for demographic and baseline health characteristics. Patients with missing data were excluded from the analysis for that specific variable. Cumulative incidence estimates and incidence rate estimates included all patients with an event date and a treatment exit date. No imputation for missing data on event variables was conducted.

9.9.4 Sensitivity Analyses

A sensitivity analysis was performed to examine the impact on event incidence estimates of a treatment washout period for both cohorts. The main analysis includes all events reported to occur on treatment (i.e. as defined in Section 9.3.3.3). The sensitivity analysis includes all events reported to occur on treatment (as defined above) but extends the observation time after stopping to include five drug half-lives for each treatment cohort[3].

9.9.5 Amendments to the Statistical Analysis Plan

None

9.10 Quality Control

The DSRU have Quality Assurance procedures for data entry and coding which are fully documented.

[3] Washout period: rivaroxaban cohort 3 days, contextual cohort 2 days

For the ROSE-ACS data entry system, a software testing phase was undertaken to ensure the system could accurately capture data to the quality standards required. Data entry interfaces have appropriate 'on screen' validation to ensure data is within specified parameters. Validation messages generated are either 'Error' or 'Warning' type messages. Errors are always corrected or the coder cannot exit the system. Warnings are provided if data conflicted or were out of range, allowing the coder to check relevant values and correct if necessary. If the value conflicted or was out of range it would be entered as such and handled accordingly in the analysis stage. For the final study report, double entry was conducted on 100% of CRFs for each CRF type.

10 Results

10.1 Participants

10.1.1 Site engagement/ HCP recruitment

For this study, the desire was to obtain a representative sample of patients for rivaroxaban and the contextual cohort across England and Wales.

Specialist healthcare professionals responsible for prescribing rivaroxaban or contextual cohort treatment for the licensed indications as outlined in the protocol were systematically identified by the DSRU and invited to participate in the study prior to the study start. Continued invitations were made and participants welcomed throughout the study. Routes of identifying relevant specialist HCPs within these settings included the use of existing clinical research networks and support networks provided by allied healthcare professionals, such as hospital pharmacists.

Table 3 and Figures 2 and 3 show the geographical distribution of hospitals and specialist HCPs[4] engaged in the study across England and Wales for the evaluable cohort. The largest proportion of hospitals and HCPs were located in the Southwest and South Wales region (n=10, 38.5% and n=19, 40.4% respectively) and the North of England (n=9, 34.6% and n=11, 23.4% respectively). While hospitals and HCPs from the Midlands and North Wales were not engaged in the study, patients who resided in this region were recruited (Section 10.1.2).

[4] The recruiter may or may not be the prescribing HCP. However it is assumed that they have permission from the responsible HCP to engage with the eligible patient.

Table 3. Geographical distribution of hospitals and healthcare professionals, for the evaluable cohort

Region	Hospital		Healthcare Professionals	
	n	%	n	%
London and South East	6	23.1	13	27.7
North of England	9	34.6	11	23.4
Midlands and North Wales	0	0.0	0	0.0
South West and South Wales	10	38.5	19	40.4
Postcode not specified	1	3.8	4	8.5
Total (N)	26	100.0	47	100.0

Figure 2. Distribution of participating sites, for the evaluable cohort

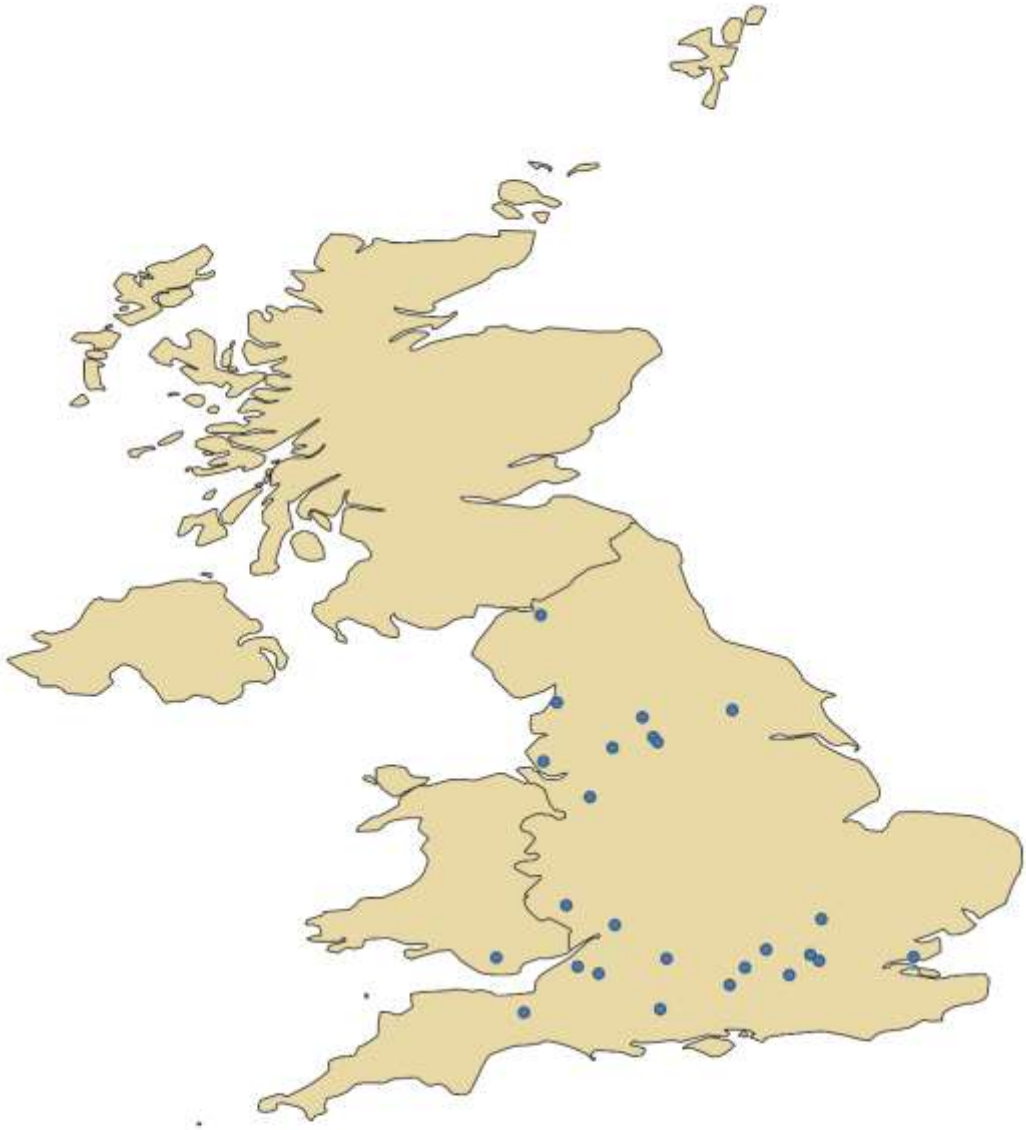
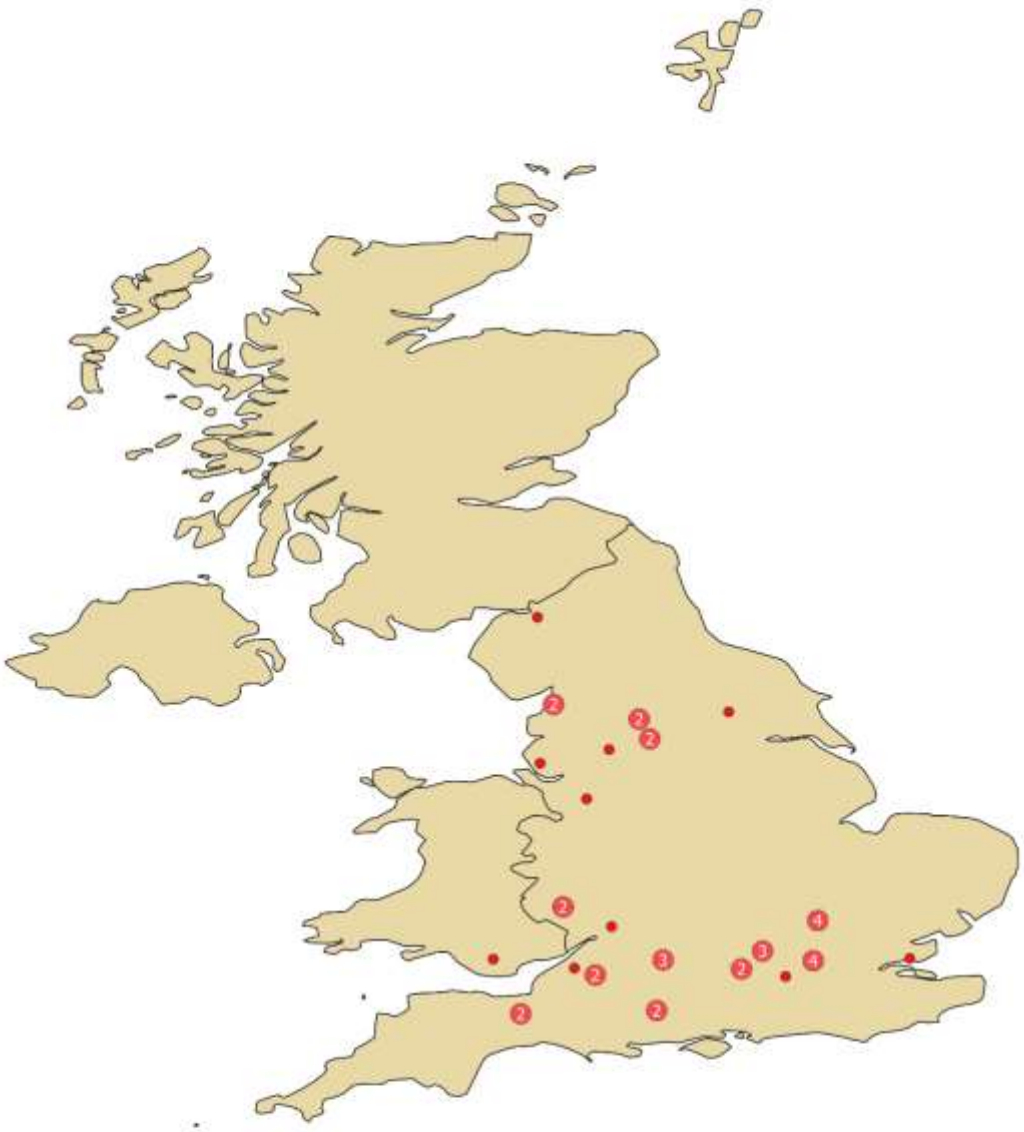


Figure 3. Distribution of HCP cohort, for the evaluable cohort*



*Number of HCPs at each site indicated where n>1

10.1.2 Patient recruitment

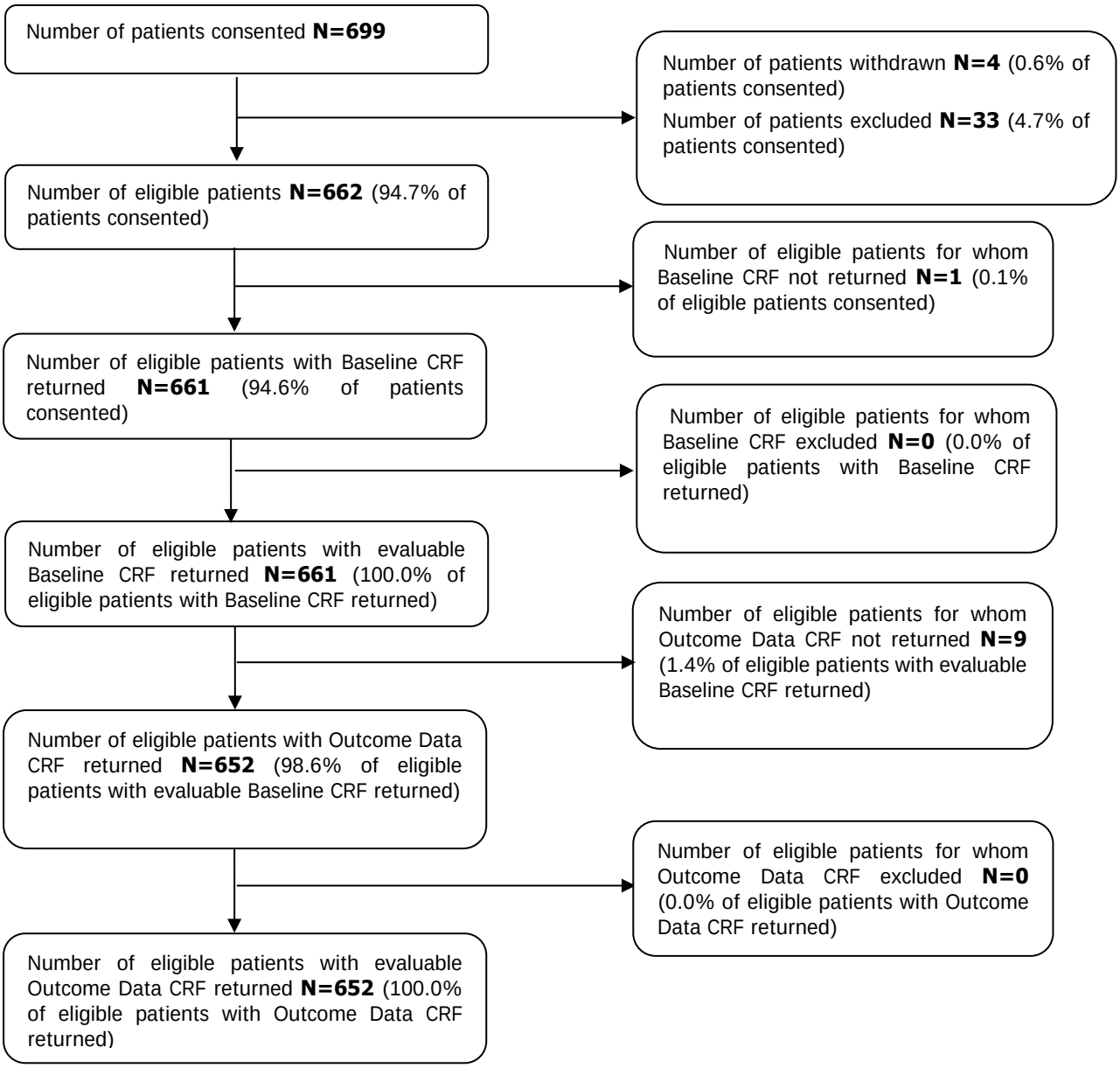
Figure 4 below presents data regarding the patient cohort, by treatment at date of last patient consented (4th October 2018). Number of patients consented is the total number of patients who gave consent to participate in the study, regardless of eligibility for inclusion. Following consent, it was found that some patients were not eligible to be included (Table 4 shows the reasons for ineligibility) and so these patients were excluded from further analyses. The number of patients with Baseline CRFs returned is also shown in Figure 4, and following receipt of the Baseline CRF, data were reviewed to determine how many patients had analysable data and thus considered evaluable. This information is also shown for all Outcome Data CRFs returned.

For this report, evaluable patients were those patients who provided consent and for whom analysable clinical data was provided in the data collection CRF at baseline and at 12-weeks (from either the specialist HCP and/or GP).

From the accessible target population treated by specialists in England and Wales, a total of 699 patients, irrespective of treatment (rivaroxaban or standard oral antiplatelet combination therapy), provided consent to participate in the study (Figure 4). Four (0.6%) of these patients had initially provided consent but later were withdrawn by the trust. A further 33 of the consented patients (4.7%) were ineligible following consent. For the remaining 662 patients who had consented and were considered eligible (94.7%), 661 (94.6%) Baseline CRFs were returned, all of which were evaluable. Of these 661 patients with eligible Baseline CRFs, Outcome Data CRFs were returned for 652 (98.6%) patients, all of which were evaluable. Thus 652 patients were evaluable.

Using information collected on medications prescribed for secondary prevention of ACS on the Baseline CRF, evaluable patients were allocated to either the rivaroxaban or contextual cohort. Of the 652 evaluable patients, 528 (81.0%) were prescribed standard oral antiplatelet combination therapy alone (i.e. the contextual cohort), and 124 (19.0%) were prescribed rivaroxaban in combination with standard oral antiplatelet therapy (i.e. the rivaroxaban cohort). Stratification of the total cohort between rivaroxaban and the contextual cohort has been performed for all subsequent analyses throughout the report.

Figure 4. STROBE flowchart of the number of patients recruited over the course of the study



Of the 47 patients out of 699 who provided consent to participate in the study but were subsequently found to be ineligible for participation, 33 (70.2%) were ineligible according to the inclusion/exclusion criteria and 10 (21.3%) had insufficient clinical information provided (one patient did not have a Baseline CRF returned and nine patients did not have an Outcome CRF returned). A further four patients (8.5%) were withdrawn by the trust (Table 4).

Table 4. Reasons for ineligibility post consent, by treatment choice

Cohort data – reasons for ineligibility	Rivaroxaban N=3		Contextual N=31		Unknown N=13		Total N=47	
	n	%	n	%	n	%	n	%
Patient incorrectly identified [a]	3	100.0	21	67.7	9	69.2	33	70.2
Insufficient clinical information [b]	0	0.0	7	22.6	3	23.1	10	21.3
Consent withdrawn	0	0.0	3	9.7	1	7.7	4	8.5
Total (N)	**3**	**100.0**	**31**	**100.0**	**13**	**100.0**	**47**	**100.0**

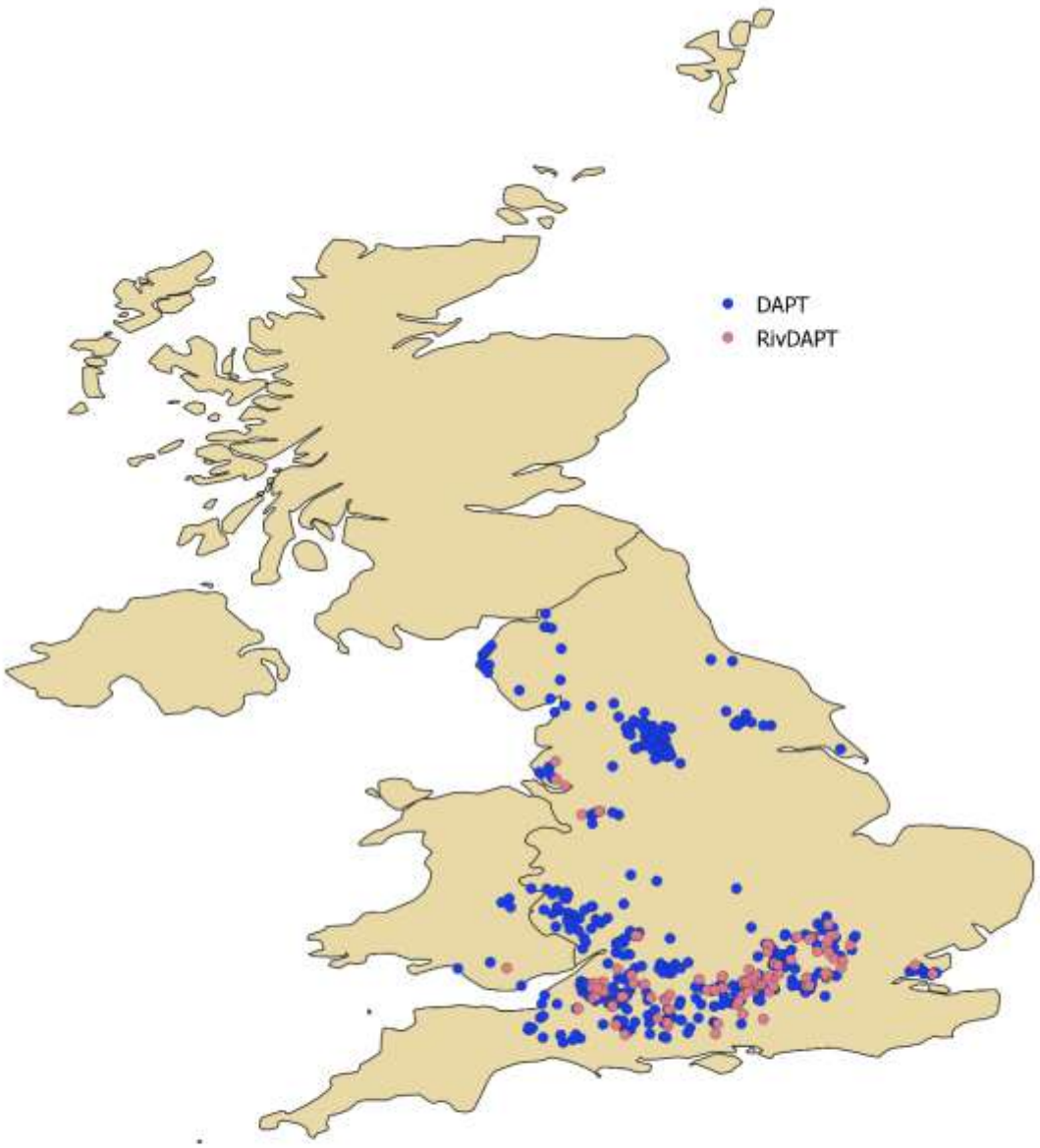
[a] Relates to exclusion criteria
[b] Complete set of CRFs not returned or CRF incomplete

The accessible study population is the proportion of the target population of interest to whom participating specialist HCPs have access. The identification of the actual study population (which was a subset of the accessible study population) was through (non-probability) systematic sampling. All consecutively identified eligible new user patients treated by a participating specialist HCP who provide consent have been enrolled. Patients were enrolled in the study after the pharmacotherapeutic treatment decision had been made that either rivaroxaban or contextual treatment was the most appropriate treatment based on clinical need. All patients were recruited in secondary care and in line with the location of sites and HCPs (described in Section 10.1.1 above), overall, the largest proportion of patients were recruited from the Southwest and South Wales region (n=329, 50.5%) (Table 5; Figure 5).

Table 5. Geographical distribution of recruited patients

Region	Rivaroxaban N=124		Contextual N=528		Total N=652	
	n	%	n	%	n	%
London and South East	37	29.8	94	17.8	131	20.1
North of England	5	4.0	143	27.1	148	22.7
Midlands and North Wales	0	0.0	13	2.5	13	2.0
South West and South Wales	77	62.1	252	47.7	329	50.5
Postcode not specified	5	4.0	26	4.9	31	4.8
Total (N)	**124**	**100.0**	**528**	**100.0**	**652**	**100.0**

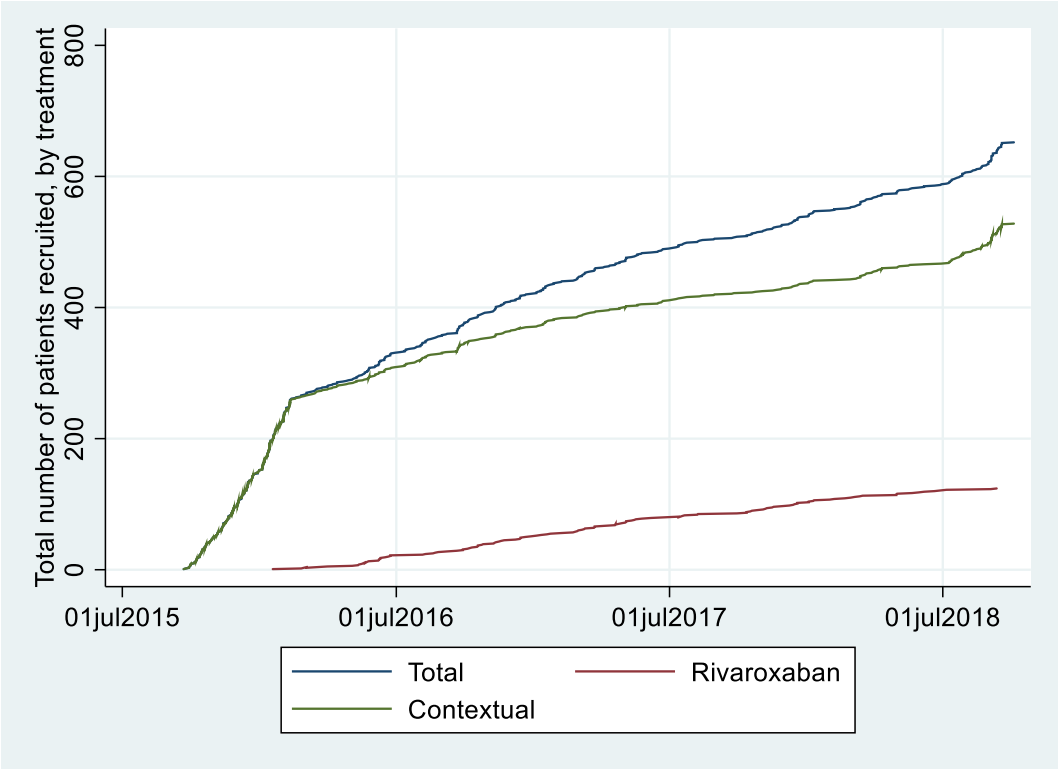
Figure 5. Distribution of patients in the evaluable cohort



It is of interest to analyse any trend over time of patients identified. Figure 6 shows the number of consented evaluable patients recruited over the course of the study

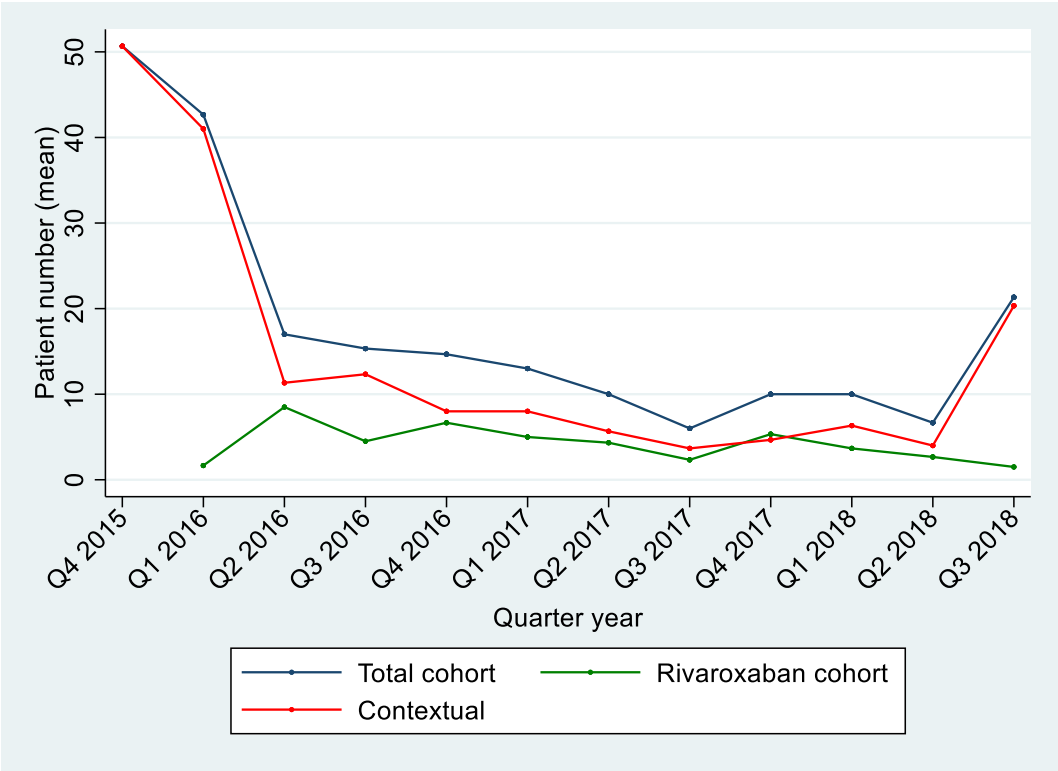
period, overall and by treatment group. Initially patients were only recruited to the contextual cohort and recruitment tapered off as restrictions to recruit in a 1:1 ratio to both cohorts were imposed on the trusts. Recruitment to the rivaroxaban cohort experienced a delayed start and reflects the low usage of rivaroxaban for the ACS indication, however after recruitment started, it retained a relatively steady, patient accrual over time.

Figure 6. Number of evaluable patients consented over the course of the study, overall, and by treatment group



This pattern is also reflected in Figure 7 which shows a plot of the three month moving average of consented evaluable patients for the whole cohort and by treatment group. Of note is the drop in the first quarter year of 2016 directly reflecting the drop in the monthly recruitment following the imposed restrictions as described above.

Figure 7. Mean number of evaluable patients consented by quarter year overall, and by treatment group



10.2 Descriptive Data

10.2.1 Patient characteristics at baseline

10.2.1.1 Patient demographics

Demographic data was collected for patients recruited to the study and is presented by cohort in the tables below. These demographics provide information on any baseline differences between the rivaroxaban and contextual cohorts and also help to identify potential channelling/selective prescribing.

Table 6 provides the age and gender composition by treatment group and in both groups it can be seen that the majority of the cohort was male (83.1% of the rivaroxaban cohort and 75.2% of the contextual cohort). Overall, the rivaroxaban cohort tended to be slightly younger than the contextual cohort (mean (SD) age 60.2 (12.2) years vs. 64.3 (12.4) years, respectively). In addition, in both treatment cohorts females were older than males: mean age (SD) for the rivaroxaban group was 61.1 (13.2) years for females and 60.0 (12.0) years for males; for the contextual cohort the mean age (SD) was 68.2 (12.3) years for females and 63.0 (12.2) years for males. The median (IQR) age for the rivaroxaban group was 60 (50, 71) years for females

and 59 (51, 68) years for males. For the contextual cohort it was 69 (59, 77) years for females and 62 (54, 73) years for males.

Table 6. Age and sex stratified by treatment choice

	Rivaroxaban N=124						Contextual treatment N=528					
	Male		Female		Total		Male		Female		Total	
Age range (years)	n	%	n	%	n	%	n	%	n	%	n	%
<18	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
18-29	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
30-39	3	2.4	0	0.0	3	2.4	3	0.6	0	0.0	3	0.6
40-49	18	14.5	5	4.0	23	18.5	60	11.4	10	1.9	70	13.3
50-59	31	25.0	5	4.0	36	29.0	104	19.7	26	4.9	130	24.6
60-69	31	25.0	5	4.0	36	29.0	107	20.3	31	5.9	138	26.1
70-79	15	12.1	3	2.4	18	14.5	83	15.7	36	6.8	119	22.5
80-89	5	4.0	3	2.4	8	6.5	36	6.8	25	4.7	61	11.6
90+	0	0.0	0	0.0	0	0.0	4	0.8	3	0.6	7	1.3
Total	103	83.1	21	16.9	124	100.0	397	75.2	131	24.8	528	100.0
Median (IQR)	59 (51, 68)	n/a	60 (50, 71)	n/a	59.5 (51, 68)	n/a	62 (54, 73)	n/a	69 (59, 77)	n/a	64 (55, 73.5)	n/a
Mean (SD)	60.0 (12.0)	n/a	61.1 (13.2)	n/a	60.2 (12.2)	n/a	63.0 (12.2)	n/a	68.2 (12.3)	n/a	64.3 (12.4)	n/a
Minimum	32	n/a	44	n/a	32	n/a	35	n/a	40	n/a	35	n/a
Maximum	87	n/a	84	n/a	87	n/a	93	n/a	93	n/a	93	n/a

10.2.1.2 Primary clinical condition for treatment

Table 7 shows the primary clinical condition for which rivaroxaban or standard oral antiplatelet combination therapy was indicated. All patients in both cohorts were reported to have been prescribed treatment for prevention of atherothrombotic events post ACS[5]. Healthcare professionals were further requested to provide information on the type of ACS via pre-specified "ACS type" tick boxes or free text under "Other". Information reported as free text has been provided as a footnote to Table 7. More than one tick box could have been selected by the HCP so counts are not mutually exclusive.

After further stratification by type of ACS, the most common indication in the rivaroxaban cohort was STEMI (n=64, 51.6%), followed by NSTEMI (n=53, 42.7%). In the contextual cohort the majority of patients were treated for NSTEMI (n=299, 56.6%) and approximately one-third were treated for STEMI (n=170, 32.2%). A small number of patients had free text entries for the type of ACS; these have been reported as specified by the HCP in a footnote to Table 7.

Table 7. Primary clinical condition for which rivaroxaban or contextual cohort treatment was indicated

Indication	Rivaroxaban N=124		Contextual cohort N=528	
	n	%	n	%
Prevention of atherothrombotic events in adults after an Acute Coronary Syndrome[a]	124	100.0	528	100.0
Type of ACS[b]				
ST-segment elevation myocardial infarction (STEMI)	64	51.6	170	32.2
Non ST-segment elevation myocardial infarction (NSTEMI) with raised biomarkers	53	42.7	299	56.6
Unstable angina	6	4.8	54	10.2
Other ACS[c]	2[d]	1.6	14[e]	2.7

[a] according to tick box on CRF

[b] More than one indication may have been reported per patient e.g. HCP may have ticked STEMI and Other and provided free text information in "if Other specify"

[c] Other ACS refers to free text information provided. This may or may not be additional to one of the pre-specified ACS tick box. Four patients for whom other ACS was specified also had STEMI/NSTEMI ticked (all in contextual cohort). For the remaining 12 patients only other ACS was specified as free text.

[d] "ECG- LBBB and troponin 106 at peak, admitted with pulmonary oedema" (n=1), "Fast AF, LBBB on ECG with chest pain and troponin rise" (n=1)

[e] "ACS normal ECG sinus rhythm no changes" (n=1), "Coronary artery disease with angina" (n=1), "LAD syndrome" (n=1), "PEA" (n=1), "Patient has stable Angina already" (n=1), "T-wave inversion (lateral)" (n=1), "TNT positive and chest pain" (n=1), "Biomarkers not raised, suspected missed NSTEMI" (n=1),

[5] According to Baseline CRF Q2 "Specify the indication requiring oral antiplatelet/anticoagulant treatment"

"Cardiac arrest" (n=1), "Critical coronary artery stenosis" (n=1), "Deep anterior T wave inversion 11/11/16 on ECG which was not present on 8/11/16 ECG" (n=1), "Drug induced ACS – sumatriptan" (n=1), "Intermittent LBBB with Trop +ve" (n=1), "New LBBB +AF. Primary PCI x 1 stent circumflex" (n=1)

10.2.1.3 Patient general health characteristics

Information on anthropometric and important general health risk factors were collected at baseline and are summarised below.

These data includes patient self-reported smoking and alcohol consumption patterns (Table 8 and Table 9) plus any prior history of smoking, alcohol or substance misuse as recorded in the medical notes and reported by the specialist HCP (Table 10). In the rivaroxaban cohort, where specified, the most frequent patient self-reported smoking status was ex-regular smoker (n=39, 31.5% (37.9% where specified); Table 8) and approximately one fifth (n=25, 20.2% (25% where specified) reported consuming alcohol once a month or less (Table 9). In the contextual cohort, where specified, the most frequent patient self-reported smoking status was also ex-regular smoker (n=193, 36.6% (43.6% where specified); Table 8) however the largest proportion of patients reported consuming alcohol 2-3 times a week (n=115, 21.8% (26.0% where specified) (Table 9). According to the specialist recorded history of smoking, 50.0% (n=62) of the rivaroxaban treated cohort and 38.8% (n=205) of the contextual cohort were reported to be smokers prior to index date (Table 10).

Table 10 also examines the "risk seeking" behaviours that may be associated with different prescribing behaviours. In this study the risk seeking behaviours were defined as those that may indicate a history of prior substance or alcohol misuse, as these may introduce prescribing variation if there are specific reasons why one of the treatments would be used preferentially in an at risk group. Prescriber reported information on alcohol and substance misuse for the evaluable patients shows that 3.2% of the rivaroxaban cohort were reported by the specialist to have history of alcohol misuse and none were reported to have a history of substance misuse. In the contextual cohort, 4.5% were reported by the specialist to have history of alcohol misuse and 0.6% were reported to have a history of substance misuse.

Table 8. Patient self-reported smoking status at Index

Smoking status	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
Current smoker[a]	27	21.8	73	13.8
Ex-regular smoker[b]	39	31.5	193	36.6
Ex-occasional smoker[c]	2	1.6	23	4.4
Second-hand smoking[d]	0	0.0	7	1.3
Never smoked	35	28.2	147	27.8
Not specified	21	16.9	85	16.1
Total (N)	**124**	**100.0**	**528**	**100.0**

[a] within the past year
[b] more than 1 year ago
[c] more than 1 year ago
[d] Exposed regularly to second hand-smoke at own/others home, work, public place

Table 9. Patient self-reported alcohol consumption status at Index

Alcohol Consumption	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
Never	20	16.1	76	14.4
Once a month or less	25	20.2	103	19.5
2-4 times a month	21	16.9	73	13.8
2-3 times a week	19	15.3	115	21.8
4 or more times a week	15	12.1	75	14.2
Not specified	24	19.4	86	16.3
Total (N)	**124**	**100.0**	**528**	**100.0**

Table 10. Specialist recorded history of patient aberrant general health behaviours prior to index date

Risk seeking behaviour	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
Smoking	62	50.0	205	38.8
Alcohol misuse	4	3.2	24	4.5
Substance misuse	0	0.0	3[a]	0.6

[a] 'Previously smoking 20 a day, cut down to 5. Previous regular cocaine use, now stopped' (n=1); 'patient has chronic pain syndrome- smokes cannabis for pain/stress. Although has stopped smoking regular cigarettes, does mix tobacco with cannabis. Is attending smoking cessation' (n=1); 'professional body builder- uses anabolic steroids' (n=1)

For this report, the baseline Body Mass Index (BMI) and weight has been presented as reported by the patient (Table 11). Information on BMI (kg/m2) was provided for 88 rivaroxaban patients (71.0% of the rivaroxaban cohort) and 376 contextual cohort patients (71.2% of the contextual cohort). Of these, the highest proportion of patients were classified as overweight in both the rivaroxaban cohort (n=39, 31.5% of the total cohort, 44.3% where BMI specified) and contextual cohort (n=166, 31.4% of the total cohort, 44.1% where BMI specified). Data are also presented on patient weight at the time of starting either rivaroxaban or contextual medication. Overall, median/mean BMI and weight was similar between the two cohorts.

Table 11. Patient self-reported BMI and weight at baseline

	Rivaroxaban N=124		Contextual N=528	
BMI (kg/m²)	**n**	**% cohort**	**n**	**% cohort**
<18.5 (Below Normal)	0	0.0	4	0.8
18.5-24.9 (Normal)	19	15.3	93	17.6
25.0-29.9 (Overweight)	39	31.5	166	31.4
30.0-39.9 (Obese)	30	24.2	98	18.6
40.0+ (Morbidly Obese)	0	0.0	15	2.8
Unknown /Not completed	36	29.0	152	28.8
Total	124	100.0	528	100.0
Median (IQR)	28.4 (25.6, 31.5)		27.6 (24.9, 31.3)	
Mean (SD)	28.5 (4.2)		28.6 (6.6)	
Weight (kg)	**n**	**% cohort**	**n**	**% cohort**
<50	1	0.8	5	0.9
50-69.9	12	9.7	67	12.7
70-89.9	40	32.3	184	34.8
90-109.9	31	25.0	93	17.6
110+	5	4.0	32	6.1
Unknown /Not completed	35	28.2	147	27.8
Total	124	100.0	528	100.0
Median (IQR)	87.5 (73.9, 96.0)		83.9 (73.0, 94.3)	
Mean (SD)	86.2 (14.3)		84.7 (18.3)	

10.2.1.4 Prior medical conditions

Investigators were asked to indicate if the patient had any of the pre-specified target (tick box) events or conditions (as described below) prior to admission with ACS within two time periods: within three months prior (recent) to admission with ACS to capture information on any recent acute events or newly diagnosed conditions that may impact on individual patient baseline risk; and if the event/condition had been recorded at any time prior (past) to the three month period immediately in advance of admission with ACS to capture information on chronic conditions. This includes prior bleeding events. cardiovascular disorders and other prior medical history, including liver and renal conditions. Table 12 presents these prior medication conditions reported by HCPs as per the tick-box responses on the outcome CRF. More than one event or condition could be reported for each patient and so counts are not mutually exclusive.

Reports of prior bleeding events in both cohorts were low, the most frequently reported being vitreous haemorrhage in the rivaroxaban cohort (n=2, 1.6%) and gastrointestinal related bleeds in the contextual cohort (gastrointestinal bleed (n=3, 0.6%); rectal haemorrhage (n=3, 0.6%)) (Table 12).

Investigators were also asked to indicate whether the patient had any history of the pre-specified cardiovascular disorders and other conditions listed in Table 12 below. The most frequently reported pre-specified cardiovascular disorder was NSTEMI in the rivaroxaban cohort (n=11, 8.9%). In the contextual cohort, the most frequently reported pre-specified cardiovascular disorder was angina (n=35, 6.6%). The most frequently reported pre-specified other condition reported in both cohorts was renal impairment (stage 3-4 CKD) (rivaroxaban n=8, 6.5%; contextual n=22, 4.2%).

Investigators were also asked to report any other events/conditions occurring prior to admission with ACS which were captured via free text and are reported in Appendix 4 using PTs according to the MedDRA dictionary[6]. The most common other event in both cohorts was hypertension reported > 3 months prior (rivaroxaban n=16, 12.9%; contextual n=81, 15.3%)

[6] Free text events have not been reclassified to the pre-specified tick box events.

Table 12. History of events/conditions prior to admission with ACS

	Rivaroxaban N=124						Contextual N=528					
	Past (>3 months)		Recent (<3 months)		Total		Past (>3 months)		Recent (<3 months)		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Bleeding events												
Intracranial	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Gastrointestinal	1	0.8	0	0.0	1	0.8	1	0.2	2	0.4	3	0.6
Urogenital	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2	2	0.4
Stopping of anticoagulation therapy for bleeding	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4	2	0.4
Reversal of anticoagulation therapy for bleeding	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2
Other Bleeds[a]: (at least one other bleed)	2[b]	1.6	1[c]	0.8	3	2.4	6[d]	1.1	0	0.0	6	1.1
Cardiovascular Disorders												
STEMI	4	3.2	6	4.8	10	8.1	11	2.1	2	0.4	13	2.5
NSTEMI	7	5.6	4	3.2	11	8.9	26	4.9	4	0.8	30	5.7
Angina	4	3.2	1	0.8	5	4.0	24	4.5	11	2.1	35	6.6
Congestive heart failure	1	0.8	0	0.0	1	0.8	4	0.8	1	0.2	5	0.9
Peripheral arterial disease	2	1.6	0	0.0	2	1.6	0	0.0	0	0.0	0	0.0
Cardiac arrhythmias	1	0.8	2	1.6	3	2.4	9	1.7	1	0.2	10	1.9
Other Conditions												
Liver Disorder	0	0.0	0	0.0	0	0.0	2	0.4	1	0.2	3	0.6
Abnormal liver function tests	1	0.8	0	0.0	1	0.8	2	0.4	2	0.4	4	0.8
Renal Failure (Stage 5 CKD)	1	0.8	0	0.0	1	0.8	1	0.2	1	0.2	2	0.4
Renal Impairment (Stage 3-4 CKD)	5	4.0	3	2.4	8	6.5	20	3.8	2	0.4	22	4.2
Renal Impairment (Stage 1-2 CKD)	2	1.6	1	0.8	3	2.4	4	0.8	3	0.6	7	1.3
Pregnancies (within the last 12 months)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

	Rivaroxaban N=124						Contextual N=528					
	Past (>3 months)		Recent (<3 months)		Total		Past (>3 months)		Recent (<3 months)		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Breastfeeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Injury/Trauma	0	0.0	0	0.0	0	0.0	11	2.1	3	0.6	14	2.7
Overdose	0	0.0	0	0.0	0	0.0	2	0.4	0	0.0	2	0.4
Other events[ae] (at least one other event)	44	35.5	6	4.8	51[f]	41.1	267	50.6	38	7.2	316[g]	59.8

[a] Presented as reported by the HCP in relation to "Other Bleed" tick box, free text events not been reclassified to the pre-specified tick box events.
[b] Epistaxis n=1, vitreous haemorrhage n=2
[c] Rectal haemorrhage n=1
[d] Crush injury n=1, duodenal ulcer haemorrhage n=1, epistaxis n=1, haemorrhoidal haemorrhage n=1, haemorrhoids n=1, pelvic haematoma n=1, rectal haemorrhage n=3
[e] Listed in Appendix 4
[f] One patient has an event where it was unknown whether prior event was past or recent
[g] 11 patients had an event where it unknown whether prior event was past or recent

10.2.1.5 Risk of bleeding on admission with ACS

It is known that patients with ACS have marked variation in their risk of major bleeding. A scoring system has been proposed to provide reliable estimates of the risk of non-CABG related major bleeding in patients with ACS and their subsequent one-year mortality. The following six clinical and laboratory variables plus the anticoagulation regimen contribute to the scoring system; female sex, advanced age, elevated serum creatinine, white blood cell count, anaemia, presentation (NSTEMI or STEMI), antithrombotic medications (heparin + glycoprotein IIb/III inhibitor rather than bivalirudin alone) (15). In order to provide information on the laboratory variables which contribute to this risk score, measures of serum creatinine, white blood cells and haemoglobin taken on admission were collected on the baseline CRF. Results of these are presented in Table 13, Table 14 and Table 15 below.

Information on serum creatinine, white blood cell count and haemoglobin at baseline was provided for 100% of the rivaroxaban cohort and 99.6% (n=526) of the contextual cohort (Table 13). The majority of patients in both cohorts had a serum creatinine of <88 µmol/L (rivaroxaban n= 75, 60.5% of the total rivaroxaban cohort; contextual n=323, 61.2% of the total contextual cohort, 61.4% where specified) which falls within the typical reference range (60 to 110 µmol/L for men and 45 to 90 µmol/L for women) and yields a score of zero for the creatinine variable of the risk score (15) (Table 13).

Table 13. Serum creatinine categories on admission with ACS, by cohort

Serum creatinine (µmol/L)*	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
<88	75	60.5	323	61.2
88-106	28	22.6	124	23.5
107-124	10	8.1	30	5.7
125-141	5	4.0	21	4.0
142-159	2	1.6	9	1.7
160-177	1	0.8	5	0.9
>177	3	2.4	14	2.7
Unknown /Not completed	0	0.0	2	0.4
Total	**124**	**100.0**	**528**	**100.0**

* Typical reference range for serum creatinine is 60 to 110 µmol/L for men and 45 to 90 µmol/L for women.

With regards to white blood cell count, the highest proportion of patients in both cohorts had a white blood cell count of <10.0 x 10^9/L (rivaroxaban n= 62, 50.0% of the total rivaroxaban cohort; contextual n=295, 55.9% of the total contextual cohort,

56.1% where specified) which falls within the typical reference range (4-11 x 10^9/L) and yields a score of zero for the white blood cell variable of the risk score. (Table 14).

Table 14. White blood cell categories on admission with ACS, by cohort

White blood cell (10^9/L)*	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
<10.0	62	50.0	295	55.9
10.0-11.9	23	18.5	92	17.4
12.0-13.9	17	13.7	59	11.2
14.0-15.9	9	7.3	41	7.8
16.0-19.7	9	7.3	20	3.8
18.0-19.9	1	0.8	8	1.5
≥20	3	2.4	11	2.1
Unknown /Not completed	0	0.0	2	0.4
Total	**124**	**100.0**	**528**	**100.0**

* Normal white blood cell count is 4-11 x 10^9/L.

The majority of patients in both cohorts had a haemoglobin level of >130 g/L (rivaroxaban n= 92, 74.2% of the total cohort; contextual n=407, 77.1% of the total cohort, 77.4% where specified) which falls within the typical reference range (adult female 115-165 g/L; adult male 130-180 g/L) (Table 15). These results suggest that most patients did not meet the risk score criteria for anaemia.

Table 15. Haemoglobin categories on admission with ACS, by cohort

Haemoglobin (g/L)*	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
<80	0	0.0	0	0.0
80-89	0	0.0	1	0.2
90-99	0	0.0	7	1.3
100-109	4	3.2	14	2.7
110-119	11	8.9	33	6.3
120-129	17	13.7	64	12.1
>130	92	74.2	407	77.1
Unknown /Not completed	0	0.0	2	0.4
Total	**124**	**100.0**	**528**	**100.0**

***** Normal Hb adult F 115-165 g/L adult M 130-180 g/L; Anaemia: Men: haemoglobin <130 g/l; women: haemoglobin <120 g/l.

10.2.2 Drug utilisation

10.2.2.1 Prior medication use

Investigators were asked to indicate if the patient had been prescribed any anticoagulant, antiplatelet, antithrombin and fibrinolytic medications within four weeks prior to admission with ACS and within 12 months prior to admission to capture information on any recent use or newly prescribed medications that may impact on individual patient baseline risk. More than one medication could be reported for each patient and so counts are not mutually exclusive. The prevalence of use of each therapeutic class of medicines is presented in Table 16.

In both the rivaroxaban and contextual cohorts patients had most frequently used oral antiplatelets. No patients were reported to have previously used Glycoprotein IIb/IIIa inhibitors or fibrinolytic medication prior to admission with ACS.

Table 16. Anticoagulant, antiplatelet, antithrombin and fibrinolytic medication history prior to admission with ACS*

Prior Medication	Rivaroxaban N=124				Contextual N=528			
	Started in 12 months prior to admission		Taken in 4 weeks prior to admission		Started in 12 months prior to admission		Taken in 4 weeks prior to admission	
	n	%	n	%	n	%	n	%
Oral Anticoagulants								
Rivaroxaban	1	0.8	0	0.0	0	0.0	0	0.0
Warfarin	0	0.0	0	0.0	1	0.2	0	0.0
Phenindione	0	0.0	0	0.0	0	0.0	0	0.0
Nicoumalone	0	0.0	0	0.0	0	0.0	0	0.0
Dabigatran Etexilate	0	0.0	0	0.0	0	0.0	0	0.0
Apixaban	0	0.0	0	0.0	0	0.0	0	0.0
Any (At Least One) Oral Anticoagulant	1	0.8	0	0.0	1	0.2	0	0.0
Oral Antiplatelets								
Aspirin (≤300mg/day)	11	8.9	30	24.2	47	8.9	133	25.2
Clopidogrel	7	5.6	9	7.3	9	1.7	21	4.0
Dipyridamole	0	0.0	0	0.0	0	0.0	1	0.2
Prasugrel	2	1.6	2	1.6	0	0.0	0	0.0
Ticagrelor	0	0.0	2	1.6	0	0.0	2	0.4
Any (At Least One) Oral Antiplatelet	16	12.9	37	29.8	56	10.6	151	28.6

Prior Medication	Rivaroxaban N=124				Contextual N=528			
	Started in 12 months prior to admission		Taken in 4 weeks prior to admission		Started in 12 months prior to admission		Taken in 4 weeks prior to admission	
	n	%	n	%	n	%	n	%
Glycoprotein IIb/IIIa inhibitors								
Abciximab	0	0.0	0	0.0	0	0.0	0	0.0
Eptifibatide	0	0.0	0	0.0	0	0.0	0	0.0
Tirofiban	0	0.0	0	0.0	0	0.0	0	0.0
Any (at least one) Glycoprotein IIb/IIIa inhibitor	0	0.0	0	0.0	0	0.0	0	0.0
Antithrombins								
Bivalirudin	0	0.0	0	0.0	0	0.0	0	0.0
Unfractionated Heparin[a]	1	0.8	0	0.0	0	0.0	0	0.0
Low Molecular Weight Heparin[b]	0	0.0	0	0.0	2	0.4	4	0.8
Fondaparinux Sodium	0	0.0	0	0.0	0	0.0	2	0.4
Any (At Least One) Antithrombin	1	0.8	0	0.0	2	0.4	6	1.1
Fibrinolytics								
Streptokinase	0	0.0	0	0.0	0	0.0	0	0.0
Alteplase	0	0.0	0	0.0	0	0.0	0	0.0
Reteplase	0	0.0	0	0.0	0	0.0	0	0.0
Tenecteplase	0	0.0	0	0.0	0	0.0	0	0.0
Any (At Least One) Fibrinolytic	0	0.0	0	0.0	0	0.0	0	0.0

* some medications were reported by the HCP but it was not indicated whether they were prior or during/after admission, these are listed in Appendix 5

[a] including Monoparin, Monoparin Calcium and Multiparin

[b] including Bemiparin, Enoxaparin, Tinzaparin and Dalteparin

Investigators were also asked to indicate whether the patient had used any of the other selected therapeutic classes of medications in the month prior to the day of admission with ACS (Table 17).

The most frequently reported medication used in both the rivaroxaban and contextual cohorts was paracetamol (4.0% and 9.8% respectively).

Investigators were also asked to indicate whether the patient had used any other medications which did not fall in to the selected therapeutic classes in the month prior to the day of admission with ACS (Appendix 6). The most frequently reported medications used in both the rivaroxaban and contextual cohorts were lipid modifying agents (16.9% and 27.7% respectively).

Table 17. Other medication history within 4 weeks prior to admission with ACS

ATC code	Drug class/name	Rivaroxaban N=124		Contextual N=528	
		n	%	n	%
Analgesics/Anti-inflammatories					
N02	Paracetamol	5	4.0	52	9.8
N02	Aspirin (>300mg)	2	1.6	13	2.5
	NSAIDs				
A01	Other local NSAIDs	1	0.8	0	0.0
M01	Oral NSAIDs	1	0.8	37	7.0
M02	Topical NSAIDs	0	0.0	3	0.6
S01	Ocular NSAIDs	0	0.0	1	0.2
	Other analgesics				
N02	Antimigraine Preparations	0	0.0	4	0.8
N02	Opioids	3	2.4	43	8.1
Anticonvulsants					
N03	Phenytoin	0	0.0	1	0.2
N03	Phenobarbital	0	0.0	0	0.0
N03	Carbamazepine	0	0.0	2	0.4
N03	Primidone	0	0.0	0	0.0
N03	Clonazepam	0	0.0	1	0.2
N03	Gabapentin	2	1.6	13	2.5
N03	Pregabalin	1	0.8	4	0.8
Anti-infectives					
J02	Ketoconazole	0	0.0	1	0.2
J02	Itraconazole	0	0.0	0	0.0
J02	Posaconazole	0	0.0	0	0.0
J05	Ritonavir	0	0.0	1	0.2
J01	Clarithromycin	0	0.0	4	0.8
J01	Erythromycin	0	0.0	2	0.4
J04	Rifampicin	0	0.0	0	0.0
J01	Sulfamethoxazole	0	0.0	0	0.0
J01	Metronidazole	0	0.0	2	0.4
D01	Griseofulvin	0	0.0	0	0.0
	Other anti-infectives				
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	0	0.0	2	0.4
D01	Antifungals For Dermatological Use	0	0.0	4	0.8
J01	Antibacterials For Systemic Use	0	0.0	22	4.2
J02	Antimycotics For Systemic Use	0	0.0	1	0.2
J05	Antivirals For Systemic Use	0	0.0	2	0.4
Antidepressants					
N06	Tricyclic	4	3.2	12	2.3
N06	MAOIs	0	0.0	0	0.0
N06	SSRI	4	3.2	36	6.8

ATC code	Drug class/name	Rivaroxaban N=124		Contextual N=528	
		n	%	n	%
N06	St John's Wort	0	0.0	1	0.2
N06	Duloxetine	1	0.8	1	0.2
N06	Mirtazapine	0	0.0	4	0.8
N06	Venlafaxine	0	0.0	1	0.2
Female hormones					
G03	Oestrogens	1	0.8	1	0.2
G03	Hormone Replacement Therapies	0	0.0	2	0.4
Systemic steroids					
H02	Prednisolone	2	1.6	16	3.0
H02	Triamcinolone	0	0.0	1	0.2
H02	Cortisone	0	0.0	1	0.2
H02	Dexamethasone	0	0.0	1	0.2
Herbal					
V03	Garlic	0	0.0	1	0.2
Juices					
V07	Grapefruit	0	0.0	1	0.2
Other medication*					
Over-the-counter medication*					

* listed in Appendix 6

10.2.2.2 Acute management of ACS

Details of acute treatment of ACS, including medications prescribed, percutaneous coronary interventions (PCI) and coronary artery bypass grafts (CABG) during admission are presented.

Investigators were asked to indicate which medications were prescribed for the acute treatment of ACS and the date they were prescribed. More than one medication could be reported for each patient and so counts are not mutually exclusive.

The most frequently prescribed medication for the acute treatment of ACS in the rivaroxaban cohort was aspirin (n= 115, 92.7%) and this was most frequently prescribed before rivaroxaban Index date (n=97, 78.2%) as per recommendations (1). Low molecular weight heparin (n=46, 37.1%) and unfractionated heparin (n=42, 33.9%) were also prescribed for the acute treatment and were most frequently initiated before the rivaroxaban Index date (n=40 (32.3%) and n=31 (25.0%) respectively), again in line with the recommendations (1) (Table 18).

The most frequently prescribed medication for the acute treatment of ACS in the contextual cohort was aspirin (n=488, 92.4%) and this was most frequently prescribed on contextual therapy Index date (n=343 (65.0%). Low molecular weight heparin

(n=161, 30.5%) and fondaparinux sodium (n=124, 23.5%) were also prescribed for the acute treatment and most frequently initiated on Index date (n=99 (18.8%) and n=71 (13.4%) respectively) (Table 18).

Table 18. Medications prescribed for acute treatment of ACS

Medication	Rivaroxaban N=124										Contextual N=528									
	Before Index Date		On Index Date		After Index Date		Date unknown		Total		Before Index Date		On Index Date		After Index Date		Date unknown		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Oral Antiplatelets																				
Aspirin	97	78.2	14	11.3	4	3.2	0	0.0	115	92.7	95	18.0	343	65.0	39	7.4	11	2.1	488	92.4
Clopidogrel	48	38.7	13	10.5	5	4.0	1	0.8	67	54.0	64	12.1	204	38.6	22	4.2	1	0.2	291	55.1
Prasugrel	2	1.6	0	0.0	0	0.0	0	0.0	2	1.6	0	0.0	2	0.4	0	0.0	1	0.2	3	0.6
Ticagrelor	58	46.8	12	9.7	1	0.8	0	0.0	71	57.3	43	8.1	193	36.6	47	8.9	1	0.2	284	53.8
Antithrombin Therapy																				
Unfractionated Heparin[a]	31	25.0	11	8.9	0	0.0	0	0.0	42	33.9	17	3.2	48	9.1	32	6.1	0	0.0	97	18.4
Low Molecular Weight Heparin[b]	40	32.3	4	3.2	2	1.6	0	0.0	46	37.1	25	4.7	99	18.8	36	6.8	1	0.2	161	30.5
Fondaparinux Sodium	21	16.9	3	2.4	0	0.0	0	0.0	24	19.4	42	8.0	71	13.4	11	2.1	0	0.0	124	23.5
Bivalirudin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2
Glycoprotein IIb/IIIa inhibitors																				
Eptifibatide	3	2.4	0	0.0	0	0.0	0	0.0	3	2.4	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2
Tirofiban	9	7.3	2	1.6	0	0.0	0	0.0	11	8.9	7	1.3	15	2.8	4	0.8	0	0.0	26	4.9
Abciximab	5	4.0	0	0.0	0	0.0	0	0.0	5	4.0	1	0.2	11	2.1	3	0.6	0	0.0	15	2.8
Fibrinolytics																				
Streptokinase	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Alteplase	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2

Medication	Rivaroxaban N=124										Contextual N=528									
	Before Index Date		On Index Date		After Index Date		Date unknown		Total		Before Index Date		On Index Date		After Index Date		Date unknown		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Reteplase	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Tenecteplase	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	1	0.2

[a] including Monoparin, Monoparin Calcium and Multiparin; [b] including Bemiparin, Enoxaparin, Tinzaparin and Dalteparin.

Investigators were asked to indicate whether patients had undergone a primary coronary intervention during their admission and to specify the type of procedure (Table 19a). More than one procedure could be reported for each patient and so counts are not mutually exclusive. Note, a number of PTs were provided by the HCP which were not deemed to be "procedures" and as such only included as a footnote to Table 20a. In the rivaroxaban treated cohort, 116 patients (93.5%) had undergone a primary coronary intervention according to the tick box; for 88.8% of these patients the HCP had specified 'percutaneous coronary intervention' and for 50.9% the HCP reported 'coronary arterial stent insertion'. In the contextual cohort, 84.8% (n=448) had undergone a primary coronary intervention according to the tick box; for 64.5% of these patients the HCP had specified percutaneous coronary intervention and for 50.2% coronary arterial stent insertion was reported.

Investigators were also asked to indicate whether patients had undergone a CABG during their admission; no patients in the rivaroxaban treated cohort were reported to have undergone a CABG during their admission whereas 5.5% of the contextual cohort were reported to have undergone a CABG (Table 19b).

Table 19. Invasive procedures during admission

a) Primary coronary intervention

	Rivaroxaban N=124				**Contextual N=528**			
	Yes		**No**		**Yes**		**No**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Primary coronary intervention	116	93.5	8	6.5	448	84.8	80	15.2
	N=116				**N=448**			
Procedure*	**n**	**%**			**n**	**%**		
Percutaneous coronary intervention	103	88.8			289	64.5		
Coronary arterial stent insertion	59	50.9			225	50.2		
Coronary angioplasty	6	5.2			56	12.5		
Stent placement	0	0.0			1	0.2		
Thrombectomy	0	0.0			2	0.4		

*More than one procedure could be reported for each patient and so counts are not mutually exclusive; The following PTs were provided by the HCP but were not deemed to be "procedures" which alone met the criteria for PCI and as such not included in the table: Acute myocardial infarction (rivaroxaban n=2, contextual n=4), Angiocardiogram (rivaroxaban n=11, contextual n=120), Angiogram (contextual n=15), Aortic valve replacement (contextual n=1), Aortogram (rivaroxaban n=1), Catheterisation cardiac (rivaroxaban n=3, contextual n=8), Coronary artery bypass (rivaroxaban n=1 (note, reported by HCP as "vein graft" and HCP specified that the patient had not undergone a CABG), contextual n=1 (HCP also specified that the patient had undergone a CABG so patient included in Table 19b), Fractional flow reserve

(contextual n-3), Hospitalisation (contextual n=1), Implantable defibrillator insertion (contextual n=2), Nuclear magnetic resonance imaging (contextual n=1), Thrombolysis (contextual; n=1), Vascular graft (contextual n=1)

b) Coronary artery bypass graft (CABG)

	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
Coronary artery bypass graft (CABG)	0	0.0	29	5.5

10.2.2.3 Medications prescribed for the secondary prevention and setting

Investigators were requested to specify which medications were prescribed for the secondary prevention of atherothrombotic events after an ACS. Note, some of the medications reported may be part of the treatment of ACS and not for secondary prevention. Medications reported as being prescribed for secondary prevention post ACS were used to derive the two treatment cohorts (rivaroxaban cohort and contextual cohort) as reported in Section 10.1.2. Table 20 below provides information on the individual medications reported for secondary prevention post ACS for the two treatment cohorts and also describes the setting in which the medications were initiated.

In the rivaroxaban cohort, the majority of patients were prescribed rivaroxaban in combination with aspirin (n=117, 94.4%). Of the remaining seven patients, three were already taking aspirin on admission. Therefore four patients were not co-administered aspirin with rivaroxaban as per the recommendations (1). The second most frequently reported antiplatelet was clopidogrel (n=74, 59.7%) followed by ticagrelor (n=64, 51.6%). Prasugrel was only prescribed for one patient (0.8%). For the contextual cohort, nearly all patients were taking aspirin (n=527, 99.8%), and approximately equal proportions were taking clopidogrel (n=276, 52.3%) and ticagrelor (n=291, 55.1%). Similar to the rivaroxaban cohort, only one patient was initiated on prasugrel (0.2%). For both cohorts, the HCP also provided other medications which may be part of the treatment of ACS and not for secondary prevention; these have been listed as a footnote to Table 20.

In terms of setting in which the medications were initiated, inpatient setting was the most frequently reported treatment setting for both the rivaroxaban and contextual cohorts (Table 20). In the rivaroxaban cohort, 123 patients (99.2%) had their rivaroxaban treatment initiated in the inpatient setting; the remaining patient was

initiated rivaroxaban by the GP. Aspirin, clopidogrel and ticagrelor were also predominately started in rivaroxaban patients as an inpatient (n=104, 88.9% of rivaroxaban patients taking aspirin, n=70, 94.6% of rivaroxaban patients taking clopidogrel and n=63, 98.4% of rivaroxaban patients taking ticagrelor, respectively). Similarly in the contextual cohort group, aspirin, clopidogrel and ticagrelor were also predominately started in the inpatient setting (n=425, 80.6% of contextual patients taking aspirin; n=263, 95.3% of contextual patients taking clopidogrel and n=290, 99.7% of contextual patients taking ticagrelor, respectively).

Table 20. Treatments prescribed for secondary prevention of atherothrombotic events after an ACS by treatment setting

	Rivaroxaban N=124										Contextual N=528									
	Hospital Inpatient		Hospital Outpatient		GP		Not specified		Total		Hospital Inpatient		Hospital Outpatient		GP		Not specified		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Aspirin	104	83.9	0	0.0	4	3.2	9	7.3	117	94.4	425	80.5	5	0.9	18	3.4	79	15.0	527	99.8
Clopidogrel	70	56.5	0	0.0	1	0.8	3	2.4	74	59.7	263	49.8	5	0.9	2	0.4	6	1.1	276	52.3
Prasugrel	1	0.8	0	0.0	0	0.0	0	0.0	1	0.8	1	0.2	0	0.0	0	0.0	0	0.0	1	0.2
Ticagrelor	63	50.8	0	0.0	0	0.0	1	0.8	64	51.6	290	54.9	0	0.0	0	0.0	1	0.2	291	55.1
Rivaroxaban	123	99.2	0	0.0	1	0.8	0	0.0	124	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other	2	1.6	0	0.0	0	0.0	1	0.8	3[a]	2.4	13	2.5	0	0.0	0	0.0	0	0.0	13[b]	2.5

[a] Four other medications reported in three patients; bisoprolol (n=1), enoxaparin (n=1), ramipril (n=1), ranolazine (n=1)

[b] 20 counts of six other medications reported in 13 patients; atorvastatin (n=3), bisoprolol (n=3), dalteparin sodium (n=1), enoxaparin (n=3), fondaparinux sodium (n=7), ramipril (n=3)

10.2.2.4 Reasons for prescribing

Investigators were asked to provide the supporting reasons for prescribing either rivaroxaban in combination with standard oral antiplatelet therapy or standard oral antiplatelet combination therapy alone for the clinical diagnosis indicated. Table 21 provides the reasons for prescribing including those associated with external considerations and/or non-medical patient factors. Investigators could have reported more than one reason for prescribing and so counts are not mutually exclusive.

In both cohorts clinical judgement was the most frequently reported reason for treatment choice (96.0% and 89.4% respectively), followed by NICE recommendation (83.9% and 58.9% respectively). The impact of NICE guidelines seemed to be particularly relevant in the rivaroxaban cohort, being cited as a supporting reason for 104 patients (83.9%). Trust formulary committee guidelines was cited as a supporting reason for more patients in the contextual cohort compared to the rivaroxaban cohort (30.3% vs 8.1%) (Table 21).

Table 21. Supporting Reasons for prescribing

Supporting reason	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
Clinical judgement	119	96.0	472	89.4
NICE recommendation	104	83.9	311	58.9
Expert committee guidelines	6	4.8	39	7.4
Trust formulary committee guidelines	10	8.1	160	30.3
Patient choice	0	0.0	3	0.6
Other[a]	7[b]	5.6	1[c]	0.2

[a] Other reasons reported in the footnotes as specified by the HCP
[b] 'NSTEMI reoccurred on DAPT already. Therefore further secondary prevention required' (n=1), 'PI's decision (n=2),'Thrombus RCA whilst on aspirin & statin therapy already' (n=1), 'aspirin allergy' (n=1), 'occluded main cx-proximal stent but distal clot remained in situ' (n=1), 'patient had further ACS event whilst on DAPT therefore rivaroxaban 2.5mg BD added' (n=1)
[c] 'clopidogrel due to history of stroke' (n=1)

10.2.2.5 Duration between admission and treatment initiation

The interval duration between hospital admission and initiation of either rivaroxaban or dual antiplatelet therapy for the rivaroxaban and contextual cohorts respectively, is presented in Table 22. In the rivaroxaban cohort, patients were most frequently initiated on rivaroxaban two days after being admitted to hospital (n=39, 31.5%) and the majority were initiated within three days of being admitted (n=102, 82.3%). In the contextual cohort, the majority of patients were initiated treatment the same day of admission (n=368, 69.7%).

Table 22. Interval duration (days) between hospital admission and treatment initiation

Days prior to index	Rivaroxaban N=124			Contextual N=528		
	n	%	Cumulative %	n	%	Cumulative %
-1	0	0.0	0.0	2[a]	0.4	0.4
0	14	11.3	11.3	368	69.7	70.1
1	32	25.8	37.1	141	26.7	96.8
2	39	31.5	68.5	9	1.7	98.5
3	17	13.7	82.3	3	0.6	99.1
4	5	4.0	86.3	0	0.0	99.1
5	3	2.4	88.7	2	0.4	99.4
6	3	2.4	91.1	2	0.4	99.8
7	4	3.2	94.4	1	0.2	100.0
8	1	0.8	95.2	0	0.0	100.0
9	1	0.8	96.0	0	0.0	100.0
10	2	1.6	97.6	0	0.0	100.0
11	1	0.8	98.4	0	0.0	100.0
12	1	0.8	99.2	0	0.0	100.0
13	1	0.8	100.0	0	0.0	100.0
Missing	0	0.0		0	0.0	
Median (IOR)	2 (1, 3)			0 (0, 1)		

[a] Two patients were repatriated from another hospital, in which their treatment was started, to the recruiting hospital

10.2.2.6 Therapy plan and treatment initiation

Details of the therapy plan given to the patients at index date for the secondary prevention of atherothrombotic events and any medication prescribed during or following admission in both the rivaroxaban and contextual cohorts are presented below.

In the rivaroxaban cohort (N=124), patients most frequently initiated rivaroxaban treatment with a total daily dose of 5mg (n=116, 93.5%) (Table 23). Two patients were initiated rivaroxaban treatment with a total daily dose of 15mg, in one of these patients the HCP indicated that rivaroxaban was being prescribed to cover both indications of ACS and AF. In addition, four patients were initiated rivaroxaban treatment with a total daily dose of 20mg; in one of these patients the HCP reported the clinical condition for which treatment with rivaroxaban was indicated to be 'Fast AF' in addition to ACS. Although the HCP did not indicate any reason for this choice of dose in the remaining three patients, it is also possible that rivaroxaban was being

prescribed to cover both indications of ACS and AF. Two patients were initiated rivaroxaban treatment with a total daily dose of 2.5mg which is lower than the recommended total daily dose of 5mg (1) however it is possible that the HCP didn't record the "total" daily dose. Treatment initiation dose has also been provided for the oral antiplatelet treatment in the rivaroxaban group. The majority of rivaroxaban patients were initiated on aspirin at a total daily dose of 75mg (92.7%), clopidogrel at a total daily dose of 75mg (58.9%) or ticagrelor at a total daily dose of 180mg (51.6%) for secondary prevention.

In the contextual cohort (N=528), aspirin was most frequently initiated at a daily dose of 75mg (98.5%), clopidogrel treatment at a total daily dose of 75mg (51.3%) or ticagrelor at a total daily dose of 180mg (51.1%) for secondary prevention (Table 23).

Table 23. Posology of treatment: total daily dose given at index date

Rivaroxaban N=124 **Total daily dose (mg) at index**	**n**	**%**	**Contextual N=528** **Total daily dose (mg) at index**	**n**	**%**
Rivaroxaban					
2.5	2	1.6			
5	116	93.5			
15	2	1.6			
20	4	3.2			
Aspirin			**Aspirin**		
75	115	92.7	75	520	98.5
300	2	1.6	150	1	0.2
			300	2	0.4
			375	3	0.6
			Unspecified	1	0.2
Clopidogrel			**Clopidogrel**		
75	73	58.9	75	271	51.3
300	1	0.8	300	4	0.8
			675	1	0.2
Prasugrel			**Prasugrel**		
10	1	0.8	Unspecified	1	0.2
Ticagrelor			**Ticagrelor**		
180	64	51.6	180	270	51.1
			90	20	3.8
			Unspecified	1	0.2

Investigators were asked to indicate whether the patient had been prescribed any of the selected therapeutic classes of medications during or following admission with ACS,

including those with potential drug interactions to rivaroxaban. More than one medication could be reported for each patient and so counts are not mutually exclusive. Aggregate counts are provided according to tick box responses in Table 24.

In both the rivaroxaban and contextual cohorts, the most frequently reported therapeutic class of medications prescribed during or following admission with ACS were analgesics, predominantly paracetamol (28.2% and 31.1% respectively) and opioids (21.8% and 20.8% respectively) (Table 24).

Investigators were also asked to indicate whether the patient had been prescribed any other medications during or following admission with ACS. The most frequently reported medications prescribed in both the rivaroxaban and contextual cohort were agents acting on the renin-angiotensin system (68.5% and 64.6% respectively), lipid modifying agents (67.7% and 69.9% respectively) and beta blocking agents (66.9% and 68.6% respectively) (Appendix 7).

Table 24. Medications prescribed during or following admission with ACS*

ATC code	Drug class/name	Rivaroxaban N=124		Contextual N=528	
		n	%	n	%
Analgesics/Anti-inflammatories					
N02	Paracetamol	35	28.2	164	31.1
N02	Aspirin (>300mg)[a]	8	6.5	30	5.7
	NSAIDs				
M01	Oral NSAIDs	3	2.4	17	3.2
M02	Topical NSAIDs	0	0.0	3	0.6
S01	Ocular NSAIDs	1	0.8	0	0.0
	Other analgesics				
M02	Topical Products For Joint And Muscular Pain	0	0.0	1	0.2
N02	Opioids	27	21.8	110	20.8
Anticonvulsants					
N03	Phenytoin	0	0.0	0	0.0
N03	Phenobarbital	0	0.0	0	0.0
N03	Carbamazepine	0	0.0	2	0.4
N03	Primidone	0	0.0	0	0.0
N03	Gabapentin	3	2.4	9	1.7
N03	Pregabalin	2	1.6	3	0.6
Anti-infectives					
D01	Topical Ketoconazole	0	0.0	1	0.2
J02	Ketoconazole	0	0.0	2	0.4
J02	Itraconazole	0	0.0	0	0.0

ATC code	Drug class/name	Rivaroxaban N=124		Contextual N=528	
		n	%	n	%
J02	Posaconazole	0	0.0	0	0.0
J05	Ritonavir	0	0.0	0	0.0
J01	Clarithromycin	0	0.0	15	2.8
J01	Erythromycin	0	0.0	1	0.2
J04	Rifampicin	0	0.0	0	0.0
J01	Sulfamethoxazole	1	0.8	5	0.9
J01	Metronidazole	1	0.8	5	0.9
D01	Griseofulvin	0	0.0	0	0.0
	Other anti-infectives				
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	0	0.0	3	0.6
D01	Antifungals For Dermatological Use	1	0.8	4	0.8
D06	Antibiotics And Chemotherapeutics For Dermatological Use	0	0.0	5	0.9
J01	Antibacterials For Systemic Use	11	8.9	72	13.6
J02	Antimycotics For Systemic Use	0	0.0	2	0.4
J05	Antivirals For Systemic Use	0	0.0	5	0.9
J07	Vaccines	0	0.0	4	0.8
Antidepressants					
N06	Tricyclic	4	3.2	11	2.1
N06	MAOIs	0	0.0	0	0.0
N06	SSRI	7	5.6	16	3.0
N06	St John's Wort	0	0.0	0	0.0
N06	Duloxetine	1	0.8	2	0.4
N06	Mirtazapine	0	0.0	6	1.1
N06	Venlafaxine	1	0.8	2	0.4
Female hormones					
G03	Oestrogens	1	0.8	1	0.2
G03	Hormone Replacement Therapies	0	0.0	0	0.0
Systemic steroids					
H02	Prednisolone	1	0.8	18	3.4
H02	Dexamethasone	0	0.0	1	0.2
H02	Hydrocortisone	0	0.0	2	0.4
H02	Triamcinolone	0	0.0	1	0.2
Other medication[b]					
Over-the-counter medication[b]					

* some medications were reported by the HCP but it was not indicated whether they were prior or during/after admission, these are listed in Appendix 5

[a] HCPs may have included aspirin prescribed for the acute treatment

[b] listed in Appendix 7

10.2.3 Cohort exposure, dose patterns over time and treatment cessation

The posology at the end of the 12-week observation period for the medications prescribed for the secondary prevention were captured for both the rivaroxaban and contextual cohorts. In the rivaroxaban evaluable cohort (n=124), total daily dose of rivaroxaban at the end of the 12-week observation period was most frequently 5mg (n=111, 89.5%) (Table 25). This is slightly lower than the number of patients who were initiated on a total daily dose of 5mg at Index (n=116, 93.5%) (see Section 10.2.2.6, Table 23). In addition, one patient was on a dose of 10mg, two patients on a dose of 15mg and seven patients on a dose of 20mg at the end of the 12-week period. Treatment status at the end of the 12-week observational period has also been provided for the oral antiplatelet treatment in the rivaroxaban group. The dose at the end of the 12-weeks remained the same as the initiation dose (see Section 10.2.2.6, Table 23).

In the contextual cohort (n=528), the treatment status at the end of the 12-week observational period was predominately unchanged from the initiation treatment except for one patient whose treatment changed from a start dose of aspirin 75mg to a dose of 300mg at the end of the 12-week period. (Table 25 and Section 10.2.2.6, Table 23).

Table 25. Treatment status end of 12-week observation period, for rivaroxaban and contextual cohorts*

Rivaroxaban N=124 **End of observation total daily dose (mg)**	**n**	**%**	**Contextual N=528** **End of observation total daily dose (mg)**	**n**	**%**
Rivaroxaban					
2.5	3	2.4			
5	111	89.5			
10	1	0.8			
15	2	1.6			
20mg	7	5.6			
Aspirin			**Aspirin**		
75	115	92.7	75	519	98.3
300	2	1.6	150	1	0.2
			300	3	0.6
			375	3	0.6
			Unspecified	1	0.2
Clopidogrel			**Clopidogrel**		
75	73	58.9	75	271	51.3
300	1	0.8	300	4	0.8

Rivaroxaban N=124 End of observation total daily dose (mg)	n	%	Contextual N=528 End of observation total daily dose (mg)	n	%
			675	1	0.2
Prasugrel			**Prasugrel**		
10	1	0.8	Unspecified	1	0.2
Ticagrelor			**Ticagrelor**		
180	64	51.6	180	270	51.1
			90	20	3.8
			Unspecified	1	0.2

* Information on dose was as reported by the HCP on the main study Outcome form

Posology on stopping treatments prescribed for secondary prevention within the 12-week observational period were also captured, where specified, for both the rivaroxaban and contextual cohorts. Total daily dose on stopping has been provided for all drugs stopped during the 12-week observation period. For example, if both rivaroxaban and aspirin were stopped in the rivaroxaban cohort, total daily dose on stopping has been provided for both medications, where specified. In the rivaroxaban cohort (N=124), total daily dose on stopping rivaroxaban was most frequently 5mg (13.7%) (Table 26). In the contextual cohort (N=528), total daily dose on stopping was most frequently: aspirin 75mg, clopidogrel 75mg and ticagrelor 180mg (Table 26)

Table 26. Posology on stopping treatment in rivaroxaban and contextual cohorts*

Rivaroxaban N=124 Total daily dose on stopping (mg)	n	%	Contextual N=528 Total daily dose on stopping (mg)	n	%
Rivaroxaban					
2.5	1	0.8			
5	17	13.7			
10	1	0.8			
15	3	2.4			
20	1	0.8			
Aspirin			**Aspirin**		
75	3	2.4	75	25	4.7
Clopidogrel			**Clopidogrel**		
75	3	2.4	75	35	6.6
			300	2	0.4
Ticagrelor			**Ticagrelor**		
180	4	3.2	180	26	4.9
			90	4	0.8

* Information on dose was as reported by the HCP on the main study Outcome form

As specified in Section 9.3.3.3, censoring at stop date occurred for the date rivaroxaban was stopped in the rivaroxaban cohort and the date the first antiplatelet medication was stopped in the contextual cohort. In total, 24 patients (19.4%) stopped rivaroxaban treatment within the 12-week study period[7]. In the contextual cohort, 76 patients (14.4%) stopped at least one of their antiplatelet medications from their antiplatelet treatment regimen within the 12-week study period[8].

The reported reasons for stopping treatment within the 12-week observation period were also collected. Table 27 and Table 28 present the top five most frequently reported reasons for stopping (grouped by frequency) for both cohorts, all reasons are provided in Appendix 8. More than one reason for stopping could be provided for each patient, so counts are not mutually exclusive. The most frequently reported reason for stopping rivaroxaban in the rivaroxaban cohort was 'Therapy change' (12.5%). In the contextual cohort 'coronary artery bypass' (10.2%) and 'therapy change' (10.2%) were most frequently reported as reasons for stopping first antiplatelet treatment.

Table 27. Top 5 most frequently reported reasons for stopping rivaroxaban in the rivaroxaban cohort

	N=24	
Reason for stopping	**n**	**% reasons**
Therapy change	3	12.5
Drug course complete	2	8.3
Haemorrhage	2	8.3
Hospitalisation	2	8.3
Percutaneous coronary intervention	2	8.3
Secondary care advice, formulary or guidelines	2	8.3
Acute coronary syndrome	1	4.2
Acute kidney injury	1	4.2
Angiocardiogram	1	4.2
Atrial fibrillation	1	4.2
Cardiovascular evaluation	1	4.2
Chest pain	1	4.2
Contusion	1	4.2
Coronary artery bypass	1	4.2
Death	1	4.2
Diarrhoea	1	4.2
Epistaxis	1	4.2

[7] For two patients in the rivaroxaban cohort, a stop date was provided on the same day as death date
[8] For two patients in the contextual cohort, a stop date was provided on the same day as death date

	N=24	
Reason for stopping	**n**	**% reasons**
Faeces discoloured	1	4.2
Haematuria	1	4.2
Haemoglobin decreased	1	4.2
Increased tendency to bruise	1	4.2
Local Health Authority advice, formulary or guidelines	1	4.2
Melaena	1	4.2
Menorrhagia	1	4.2
Patient concerns with drug	1	4.2
Preoperative care	1	4.2
Product dose omission	1	4.2
Refusal of treatment by patient	1	4.2
Sinus rhythm	1	4.2
Stent placement	1	4.2
Vascular graft	1	4.2
Vascular stent thrombosis	1	4.2

Table 28. Top 5 most frequently reported reasons for stopping antiplatelet treatment in the contextual cohort

	N=528	
Reason for stopping	**n**	**% reasons**
Coronary artery bypass	13	10.2
Therapy change	13	10.2
Pre-existing condition improved	7	5.5
Angiogram normal	5	3.9
Preoperative care	5	3.9
Rectal haemorrhage	5	3.9
Secondary care advice, formulary or guidelines	5	3.9
Atrial fibrillation	4	3.1
Cardiovascular evaluation	4	3.1
Review of diagnosis	4	3.1
Drug course complete	3	2.3
Dyspnoea	3	2.3
Supraventricular tachycardia	3	2.3
Surgery	3	2.3

Data on cohort exposure has been presented in Table 29 below, censored as per rules provided in Section 9.3.3.3. The majority of patients in both cohorts had 84 or more days on treatment; 81.5% of the rivaroxaban cohort and 84.5% of the contextual cohort. Less than 5% of patients in both cohorts stopped treatment within the first week.

Table 29. Count and percent of number of days on treatment (by week) for rivaroxaban and contextual cohorts

Days on Treatment	Rivaroxaban N=124		Contextual N=528	
	n	%	n	%
0-7	5	4.0	26	4.9
8-14	2	1.6	14	2.7
15-21	3	2.4	13	2.5
22-28	3	2.4	3	0.6
29-35	3	2.4	10	1.9
36-42	0	0.0	4	0.8
43-49	1	0.8	2	0.4
50-56	1	0.8	1	0.2
57-63	1	0.8	1	0.2
64-70	1	0.8	2	0.4
71-77	1	0.8	5	0.9
78-83	2	1.6	1	0.2
84+	101[1]	81.5	446[2]	84.5
Total	124	100.0	528	100.0

[1]Two rivaroxaban cohort patients stopped treatment on day 84
[2]One contextual cohort patient stopped treatment on day 84

10.3 Outcome Data

10.3.1 Classification of haemorrhagic events

The reports of haemorrhagic events were categorised using information from the Outcome CRF and haemorrhage supplementary CRFs, where available. Both targeted 'tick box' elicited answers and reported 'free text' format, where specified, were used to classify haemorrhagic events according to the TIMI and BARC definitions listed below.

TIMI classification:

a) Non-CABG related major bleeding

b) Non-CABG related minor bleeding

c) Non-CABG related bleeding requiring medical attention

d) Non-CABG related minimal bleeding

e) CABG related major bleeding

f) Unclassifiable - bleeds which cannot be classified into one of the above TIMI categories

BARC classification:

g) Type 0

h) Type 1

i) Type 2

j) Type 3

Type 3a

Type 3b

Type 3c

k) Type 4

l) Type 5

Type 5a

Type 5b

m) Unclassifiable - bleeds which cannot be classified into one of the above BARC categories

Bleeds were presented overall and stratified by the following sites for each treatment cohort:

- Intracranial
- Gastrointestinal
- Urogenital
- Other

For some patients, the investigator may have reported multiple TIMI/BARC classification criterion and/or multiple bleeding episodes within the same site (e.g. gastrointestinal). These were followed up to identify all dates and the bleeding event of interest was that indicative of the most serious episode of bleeding within a given site. It is this bleeding event, its associated event date and classification which is evaluated in the subsequent analyses. However, bleeds within the same overall organ site (e.g. gastrointestinal) but different anatomical sites (e.g. upper GI or lower GI) have been classified separately.

Overall three bleeding events (two rivaroxaban and one contextual cohort) were unclassifiable even after follow-up information was requested.

10.4 Main Results

10.4.1 Haemorrhagic events

As described above, each bleed was classified according to TIMI and BARC criteria. The criteria for classifying bleeds according to TIMI and BARC are overlapping and therefore bleeds may be included within both TIMI and BARC categories i.e. bleeds

reported in Table 30, Table 32 and Table 34 (rivaroxaban) and Table 31, Table 33 and Table 35 (contextual) are not mutually exclusive.

The following section relates to the primary objective of quantifying the risk and rate of major bleeding according to the TIMI classification of non-CABG related bleeding occurring in the 12-week observation period, overall and within gastrointestinal, urogenital and intracranial sites (Table 30 to Table 33). In addition the results for the secondary objective of quantifying the risk of other major (in any other site not specified in the primary objective) or minor bleeding outcomes (in any site) reported in the 12-week observation period has also been presented below (Table 30 to Table 33) Patients may have experienced more than one type of bleeding event (e.g. TIMI non-CABG major and TIMI non-CABG minor) within different sites, so these counts are not mutually exclusive. The tables below provide estimates based on the number of patients experiencing bleeding events by bleeding classification and site. If a patient had more than one bleed of the same classification and at the same overall site (e.g. Other) but different anatomical sites (e.g. skin or respiratory), the first event only was used to calculate incidence. Hence the numerator is the number of patients with at least one bleeding event of the same classification at the same overall site.

10.4.1.1 Risk and rate according to TIMI classification

Table 30 provides counts and cumulative incidence (with 95% CI) of incident reports of bleeding episodes reported on treatment with rivaroxaban during the 12-week observation period. Only one major bleed was reported and this occurred within the gastrointestinal site (cumulative incidence 0.8%; 95% CI [0.0, 4.4]). There were no reports of minor bleeding events. The most frequently reported TIMI bleeding classification in the rivaroxaban cohort was non-CABG related bleeding requiring medical attention (n= 13, 10.5%; 95% CI [5.7, 17.3] in all sites); of these bleeds, equal numbers (n=4, 3.2%; 95% CI [0.9, 8.1]) were reported within gastrointestinal and urogenital sites. Only two patients experienced non-CABG minimal bleeds (1.6%; 95% CI [0.2, 5.7]) and no patients experienced CABG related major bleeding. For two rivaroxaban patients, classification into one of TIMI bleed criteria could not be made and thus these bleeding events were labelled unclassifiable. No bleeds occurred within intracranial sites.

Corresponding incidence rates were also calculated for the rivaroxaban cohort and these are presented in Table 33. As a result of low bleeding event counts large incidence rates with wide 95% CIs are observed, thus results should be interpreted

with caution. A sensitivity analysis was performed which included a treatment wash-out period, no additional bleeds were observed (Appendix 9).

Table 31 provides counts and cumulative incidence (with 95% CI) of incident reports of bleeding episodes reported on treatment in the contextual cohort during the 12-week observation period. Five patients experienced a non-CABG related major bleed (0.9%; 95% CI [0.3, 2.2]) with four of these bleeds occurring within the gastrointestinal site (cumulative incidence 0.8%; 95% CI [0.2, 1.9]). The remaining one non-CABG related major bleed occurred in another site (0.2%; 95% CI [0.0, 1.1]). No bleeding events were reported within urogenital or intracranial sites. The cumulative incidence of minor bleeding in all sites within the contextual cohort was 0.6% (95% CI [0.1, 1.7]; n=3); two minor bleeding events occurred within the gastrointestinal site and one in another site. The most frequently reported TIMI bleeding classification in the contextual cohort was non-CABG related bleeding requiring medical attention (n=20, 3.8%; 95% CI [2.3, 5.8] in all sites); of these bleeds, nine occurred within the gastrointestinal site (1.7%; 95% CI [0.8, 3.2]) and one occurred within the urogenital site (0.2%; 95% CI [0.0, 1.1]). No non-CABG minimal or CABG major bleeds were reported in the contextual cohort, however, there was an additional bleed for which classification into one of TIMI bleed criteria could not be made and thus was labelled unclassifiable. Corresponding incidence rates were also calculated for the contextual cohort and these are presented in Table 33. A sensitivity analysis was performed which included a treatment wash-out period, no additional bleeds were observed (Appendix 9).

Reports of bleeding events on treatment but outside of the 12-weeks observation period are presented for both cohorts in Appendix 10, according to TIMI classification. Only two additional bleeds were reported for rivaroxaban patients and three for the contextual cohort; none were classified as TIMI non-CABG major.

Table 30. Cumulative incidence of bleeding events in the rivaroxaban cohort reported during 12-week observation period, by TIMI category

Bleeding event	Rivaroxaban cohort N=124														
	All[a]			Intracranial			Gastrointestinal			Urogenital			Other[b]		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Non-CABG major	1	0.8	0.0, 4.4	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	0	0.0	n/a
Non-CABG minor	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Non-CABG requiring medical attention	13	10.5	5.7, 17.3	0	0.0	n/a	4	3.2	0.9, 8.1	4	3.2	0.9, 8.1	7[c]	5.6	2.3, 11.3
Non-CABG minimal	2	1.6	0.2, 5.7	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	1[d]	0.8	0.0, 4.4
CABG related major	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	2	1.6	0.2, 5.7	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	1[e]	0.8	0.0, 4.4

[a] Number of patients with at least one bleeding event (NB. This may not equal the row total if patients experienced more than one bleed of the same classification at different sites)
[b] includes all sites other than intracranial, gastrointestinal and urogenital
[c] Respiratory (n=4), skin (n=4); one patient had bleeding within respiratory site and skin
[d] Respiratory (n=1)
[e] Skin (n=1)

Table 31. Cumulative incidence of bleeding events in the contextual cohort reported during 12-week observation period, by TIMI category

Bleeding event	Contextual cohort N=528														
	All[a]			Intracranial			Gastrointestinal			Urogenital			Other[b]		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Non-CABG major	5	0.9	0.3, 2.2	0	0	n/a	4	0.8	0.2, 1.9	0	0.0	n/a	1[d]	0.2	0.0, 1.1
Non-CABG minor	3	0.6	0.1, 1.7	0	0	n/a	2	0.4	0.0, 1.4	0	0.0	n/a	1[e]	0.2	0.0, 1.1
Non-CABG requiring medical attention	20	3.8	2.3, 5.8	0	0	n/a	9[c]	1.7	0.8, 3.2	1	0.2	0.0, 1.1	11[f]	2.1	1.0, 3.7
Non-CABG minimal	0	0.0	n/a	0	0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
CABG major	0	0.0	n/a	0	0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	1	0.2	0.0, 1.1	0	0	n/a	0	0.0	n/a	0	0.0	n/a	1[g]	0.2	0.0, 1.1

[a] Number of patients with at least one bleeding event (NB. This may not equal the row total if patients experienced more than one bleed of the same classification at different sites)
[b] includes all sites other than intracranial, gastrointestinal and urogenital
[c] One patient had two gastrointestinal bleeding events within different anatomical sites
[d] Post procedural (n=1)
[e] Post procedural (n=1)
[f] Post procedural (n=1), Respiratory (n=4), Retroperitoneal (n=1), skin (n=6); one patient had bleeding within respiratory site and skin
[g] Respiratory (n=1)

Table 32. Incidence rate of bleeding events in the rivaroxaban cohort reported during 12-week observation period, by TIMI category

Bleeding event	Rivaroxaban cohort N=124																			
	All					Intracranial				Gastrointestinal				Urogenital				Other			
	n	Total person-time (years)	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI
Non-CABG related major	1	24.0	4.2	0.6	29.6	0	n/a	n/a	n/a	1	4.2	0.6	29.6	0	n/a	n/a	n/a	0	n/a	n/a	n/a
Non-CABG related minor bleeding	0	24.0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a
Non-CABG related bleeding requiring medical attention	13	24.0	54.3	31.5	93.5	0	n/a	n/a	n/a	4	16.7	6.3	44.5	4	16.7	6.3	44.5	7	29.2	13.9	61.2
Non-CABG related minimal bleeding	2	24.0	8.3	2.1	33.4	0	n/a	n/a	n/a	1	4.2	0.6	29.6	0	n/a	n/a	n/a	1	4.2	0.6	29.6
CABG related major bleeding	0	24.0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a
Unclassifiable	2	24.0	8.3	2.1	33.4	0	n/a	n/a	n/a	1	4.2	0.6	29.6	0	n/a	n/a	n/a	1	4.2	0.6	29.6

IR (incidence rate) = (Number of events / Total person-time) where person-time is derived from index date until the earliest of time until event of interest, date at which patient is censored or end of 12-week observation period; per 100 person years

Table 33. Incidence rate of bleeding events in the contextual cohort reported during 12-week observation period, by TIMI Category

Bleeding event	Contextual cohort N=528																			
	All					Intracranial				Gastrointestinal				Urogenital				Other			
	n	Total person-time (years)	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI	n	IR	Lower 95% CI	Upper 95% CI
Non-CABG major	5	104.1	4.8	2.0	11.5	0	n/a	n/a	n/a	4	3.8	1.4	10.2	0	n/a	n/a	n/a	1	1.0	0.1	6.8
Non-CABG minor	3	104.1	2.9	0.9	8.9	0	n/a	n/a	n/a	2	1.9	0.5	7.7	0	n/a	n/a	n/a	1	1.0	0.1	6.8
Non-CABG requiring medical attention	20	104.1	19.2	12.4	29.8	0	n/a	n/a	n/a	9	8.6	4.5	16.6	1	1.0	0.1	6.8	11	10.6	5.8	19.1
Non-CABG minimal	0	104.1	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a
CABG major	0	104.1	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a
Unclassifiable	1	104.1	1.0	0.1	6.8	0	n/a	n/a	n/a	0	n/a	n/a	n/a	0	n/a	n/a	n/a	1		0.1	6.8

IR (incidence rate) = (Number of events / Total person-time) where person-time is derived from index date until the earliest of time until event of interest, date at which patient is censored or end of 12-week observation period; per 100 person years

10.4.1.2 Risk according to BARC classification

As part of the secondary objective of the study, the same bleeding events described above were also classified according to the BARC definition and these are presented in Table 34 and Table 35. In both cohorts, the most frequently reported BARC bleeding classification overall was BARC Type 2 (rivaroxaban: n=12; 9.7%; 95% CI [5.1, 16.3]; contextual: n=19; 3.6%; 95% CI [2.2, 5.6]). In the rivaroxaban cohort, two bleeding events were classified as BARC Type 3b (cumulative incidence 1.6%; 95% CI [0.2, 5.7] and two as BARC Type 1 (1.6%; 95% CI [0.2, 5.7]). In the contextual cohort, two bleeds were classified as BARC Type 3a and seven as BARC Type 3b (0.4%; 95% CI [0.0, 1.4] and 1.3%; 95% CI [0.5, 2.7] respectively). The same bleeds which were unclassifiable according to TIMI were also unclassifiable according to BARC.

For bleeding events occurring on treatment within the 12-weeks observation period as described in the sections above, information on their TIMI bleed classification along with their corresponding BARC classification have been summarized in Appendix 11. There was some overlapping of the BARC type 3b classification which corresponded to TIMI major (n=6), TIMI minor (n=1) and TIMI requiring medical attention (n= 2) whereas all bleeds classified as BARC Type 3a corresponded to TIMI minor, all BARC Type 2 bleeds corresponded to TIMI requiring medical attention and all BARC Type 1 bleeds corresponded to TIMI minimal.

Table 34. Cumulative incidence of bleeding events in the rivaroxaban cohort reported during 12-week observation period, by BARC category

Bleeding event	Rivaroxaban cohort N=124														
	All[a]			Intracranial			Gastrointestinal			Urogenital			Other[b]		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Type 0	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 1	2	1.6	0.2, 5.7	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	1[c]	0.8	0.0, 4.4
Type 2	12	9.7	5.1, 16.3	0	0.0	n/a	3	2.4	0.5, 6.9	4	3.2	0.9, 8.1	7[d]	5.6	2.3, 11.3
Type 3															
Type 3a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 3b	2	1.6	0.2, 5.7	0	0.0	n/a	2	1.6	0.2, 5.7	0	0.0	n/a	0	0.0	n/a
Type 3c	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 4	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 5															
Type 5a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 5b	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	2	1.6	0.2, 5.7	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	1[e]	0.8	0.0, 4.4

[a] At least one bleeding event (NB. This may not equal the row total if patients experienced more than one bleed of the same classification at different sites)
[b] includes all sites other than intracranial, gastrointestinal and urogenital
[c] Respiratory (n=1)
[d] Respiratory (n=4), skin (n=4); one patient had bleeding within respiratory site and skin
[e] Skin (n=1)

Table 35. Cumulative incidence of bleeding events in the contextual cohort reported during 12-week observation period, by BARC category

Bleeding event	Contextual cohort N=528														
	All[a]			Intracranial			Gastrointestinal			Urogenital			Other[a]		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Type 0	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 1	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 2	19	3.6	2.2, 5.6	0	0.0	n/a	9[c]	1.7	0.8, 3.2	1	0.2	0.0, 1.1	10[d]	1.9	0.9, 3.5
Type 3															
Type 3a	2	0.4	0.0, 1.4	0	0.0	n/a	1	0.2	0.0, 1.1	0	0.0	n/a	1[e]	0.2	0.0, 1.1
Type 3b	7	1.3	0.5, 2.7	0	0.0	n/a	5	0.9	0.3, 2.2	0	0.0	n/a	2[f]	0.4	0.0, 1.4
Type 3c	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 4	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 5															
Type 5a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Type 5b	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	1	0.2	0.0, 1.1	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	1[g]	0.2	0.0, 1.1

[a] At least one bleeding event (NB. This may not equal the row total if patients experienced more than one bleed of the same classification at different sites)
[b] includes all sites other than intracranial, gastrointestinal and urogenital
[c] One patient had two gastrointestinal bleeding events within different anatomical sites
[d] Respiratory (n=4), retroperitoneal (n=1), skin (n=6), one patient had bleeding within respiratory site and skin
[e] Post procedural (n=1)
[f] Post procedural (n=2)
[g] Respiratory (n=1)

10.4.2 Quantitative case series summary for selected events

10.4.2.1 To describe clinical features and management of cases of overdose, major bleeding (including bleeding sites specified in the primary objective, in addition to other major bleeds identified) during observation of the cohort exposed to rivaroxaban

This section relates to the second exploratory objective for the rivaroxaban cohort only. There were no patients in the rivaroxaban cohort for whom overdose was reported. There was one case of TIMI non-CABG major bleeding in the rivaroxaban cohort, which occurred within the gastrointestinal site and resulted in a drop in haemoglobin of ≥5 g/dL. This event was reported in a male patient in his fifties who was taking rivaroxaban for an NSTEMI with raised biomarkers. The patient had not been previously exposed to alternative anticoagulant or antiplatelet therapies and there were no reports of a prior history of bleeding. The patient was exposed to rivaroxaban for 28 days prior to the bleed and was on a total daily dose of 5mg at the time of the event. The bleed was not fatal but resulted in treatment with rivaroxaban being stopped.

10.4.3 Other targeted event counts (excluding haemorrhage related events)

Specialist HCPs were asked to report if the patient had any of the per protocol targeted events of interest during or following admission with ACS. More than one event or condition could be reported for each patient and so counts are not mutually exclusive. Reports of events from GPs are summarised separately as a footnote to the table.

Table 36 provides counts of cardiovascular disorders and other conditions reported by HCPs as per the tick-box responses on the outcome, on treatment with rivaroxaban or contextual treatment CRF during the 12-week observation period. It is important to note that some events may have occurred on index date and may have been the indication for treatment. ACS events reported on index have been highlighted as a footnote to Table 36. The most frequently reported cardiovascular disorder in the rivaroxaban and contextual cohorts was NSTEMI (6.5% and 16.3% respectively). The incidence of STEMI reported on treatment in the rivaroxaban and contextual cohorts was 4.8% and 15.3% respectively. The incidence of cardiac arrhythmias and congestive heart failure was 5.6% and 3.2% respectively in the rivaroxaban cohort, and 3.6% and 1.9% respectively in the contextual cohort. The incidence of angina was 2.4% in the rivaroxaban cohort and 4.9% in the contextual cohort. There were no reports of peripheral arterial disease in either cohorts.

In terms of the other conditions listed in Table 36, the most frequently reported pre-specified other condition was abnormal liver function test in both the rivaroxaban and contextual cohort (3.2% and 2.5% respectively). This was followed by renal impairment (stage 3-4 CKD) for

the rivaroxaban cohort (2.4%) and stage 1-2 CKD for the contextual cohort (1.9%). Only one patient was reported to have stage 5 CKD and this patient was in the contextual cohort.

A sensitivity analysis was performed which included a treatment wash-out period (Appendix 9). There was one additional report of NSTEMI and one additional report of renal impairment (Stage 3-4 CKD) in the rivaroxaban cohort; no additional events were reported in the contextual treatment group.

Reports of target events on treatment but outside of the 12-weeks observation period are presented for both cohorts in Appendix 10. Counts of events beyond 12-weeks observation for both cohorts were low.

Table 36. Count of number of targeted events within 12-week observation period*

Event[a]	Rivaroxaban (N=124)		Contextual (N=528)	
	n	%	n	%
Cardiovascular Disorders				
STEMI	6[1]	4.8	81[2]	15.3
NSTEMI	8[3]	6.5	86[4]	16.3
Angina	3[5]	2.4	26[6]	4.9
Congestive heart failure	4	3.2	10	1.9
Peripheral arterial disease	0	0.0	0	0.0
Cardiac Arrhythmias	7	5.6	19	3.6
Other Conditions				
Liver Disorder	0	0.0	0	0.0
Abnormal liver function test[b]	4	3.2	13	2.5
Renal Failure (Stage 5 CKD)	0	0.0	1	0.2
Renal Impairment (Stage 3-4 CKD)	3	2.4	4	0.8
Renal Impairment (Stage 1-2 CKD)	2	1.6	10	1.9
Pregnancies	0	0.0	0	0.0
Breastfeeding	0	0.0	0	0.0
Injury/Trauma	0	0.0	1	0.2
Overdose	0	0.0	0	0.0

* Responses provided as "tick all that apply". Where no response was provided for each medical condition listed, the patient was assumed not to have had the condition. This approach was justified in that physicians are more likely to record presence of a condition rather than confirm absence.

[a] Events reported by GP: rivaroxaban cohort: Injury/Trauma (n=1), abnormal liver function test (n=3); contextual cohort: Injury/Trauma (n=5), abnormal liver function test (n=9).

[b] irrespective of lab parameters

[1] 5 STEMI reported on index date

[2] 75 STEMI reported on index date

[3] 6 NSTEMI reported on index date

[4] 64 NSTEMI reported on index date

[5] 1 angina reported on index date

[6] 9 angina reported on index date

As detailed in the protocol, selected events of interest included abnormal liver function tests where laboratory results indicated 3 X ULN of the relevant parameters. To identify these cases, any reports of abnormal liver function tests reported either via 'tick box' elicited answers (as specified in Table 36 above) and/or 'free text' format' which occurred on treatment within the 12-week observation period were further evaluated to assess if the criteria for 3 X ULN were met. There were three reports of abnormal LFTs which met the criteria for greater than 3 X ULN within the rivaroxaban cohort and four reports within the contextual cohort. A sensitivity analysis was performed which included a treatment wash-out period, no additional reports of abnormal LFTs (greater than 3 X ULN) were observed in either cohort (Appendix 9). However two additional reports of abnormal LFTs (greater than 3 X ULN) occurred on treatment outside of the 12-weeks in the contextual cohort group (Appendix 10).

10.4.4 Event surveillance

In addition to the selected events of interest which have been described above, HCPs were also requested to specify any other events recorded in the patient's medical charts on treatment within the first 12-weeks of observation. These events captured via free text were coded to the MedDRA dictionary and have been reported as Preferred Term level in Appendix 12. Events have been presented as reported by the HCP on the outcome CRF and more than one event could be specified per individual patient, so counts are not mutually exclusive. Note, the general event analysis excludes events which have been reported in other sections of the report (e.g. reasons for stopping, targeted event, deaths) and events reported here have not been used to derive the pre-specified tick box events described in Section 10.4.3 above. In addition, any bleeds reported as free text have been used in the bleed analysis described in Section 10.4.1. Reports of other events from GPs are also presented (Appendix 12).

Reports of events were low with the most frequent event reported as hospitalisation in both the rivaroxaban and contextual cohorts (4.8% and 3.0% respectively).

A sensitivity analysis was performed which included a treatment wash-out period (Appendix 12). There was one additional report of acute myocardial infarction and one additional report of stent placement in the rivaroxaban cohort; no additional events were reported in the contextual treatment group.

Reports of target events on treatment but outside of the 12-weeks observation period are presented for both cohorts in Appendix 12. Reports outside of the 12-weeks period for both cohorts were low.

10.4.5 Aggregate Assessment of Drug-Relatedness of Selected Events

Table 37 to Table 39 below provide an assessment of drug relatedness for selected events of interest (RAIDAR events) listed in the protocol (Appendix 1[9]). Events included are those which occurred within the 12-week observation period and during rivaroxaban treatment[10]. Only RAIDAR cases of 'potential drug-induced liver injury', 'cardiac arrhythmias' and 'acute kidney injury' were reported for the rivaroxaban cohort. Corresponding drug relatedness assessments were performed by a medically qualified research fellow for these cases which utilised all the relevant information on the outcome CRF and supplementary CRFs, where available.

Potential Drug Induced Liver Injury

All reports of abnormal liver function tests[11] occurring on rivaroxaban treatment during the 12-week observation period were assessed for potential cases of drug-induced liver injury (DILI)[12]. The following thresholds were used for potential DILI cases: (a) Alanine aminotransferase (ALT) value ≥5× upper limit of normal (ULN), or (b) Alkaline phosphatase (ALP) value ≥2× ULN, or (c) ALT value ≥3× ULN[13] and Total Bilirubin (TB) ≥2× ULN (16). In this study, where measurements were reported for the above liver function tests within 12-weeks after index, the above criteria for potential DILI was met for three patients. These cases have been summarised in Table 37 below.

Potential drug induced liver injury was reported in two male patients and one female patient with a median (IQR) age of 66 (63, 85) years. All patients were taking a rivaroxaban total daily dose of 5mg at index and median (IQR) time to onset was 23 (2, 49) days. All three patients did not have a prior history of the event reported but were considered to have other possible risk factors for the potential drug induced liver injury. Rivaroxaban was not stopped due to the event for all three patients. One patient had a fatal outcome (according to the supplementary CRF), although the event was not reported as a cause of death on the outcome CRF. Two cases were assessed as possibly related to rivaroxaban and one was considered unlikely related[14].

[9] In addition, a few events included in the EMA designated medical events (DME) list but not included in the DRSU RAIDAR list but considered relevant were evaluated (e.g. drug-induced liver injury).
[10] Drug relatedness assessments were not performed for the contextual cohort
[11] Described in Section 10.4.3 above
[12] Liver function lab test values reported without a physician diagnosis of 'abnormal liver function tests' were not examined further
[13] Also included AST value ≥3 x ULN
[14] HCP reported 'symptom profile suggestive of sepsis'

Table 37. Case series table for relatedness assessments of potential drug induced liver injury

Event - Potential drug induced liver injury			
		n	**%**
Event details			
Number of events (N)		3[a]	n/a
Events had fatal outcome		1[b]	33.3
Index dose of rivaroxaban (total daily dose)			
	5mg	3	100.0
Rivaroxaban stopped		0	0.0
Patient demographics			
Sex			
	Male	2	66.7
	Female	1	33.3
Age (years)			
	Median (IQR)	66 (63, 85)	
Relatedness assessment criteria[b]			
Recognised association		3	100.0
Pharmacological plausibility		3	100.0
Temporality		3	100.0
	Time to onset (days): Median (IQR)[c]	23 (2, 49)	
Prior history of same event		0	0.0
Risk factors[d]		3	100.0
Dose relationship		0	0.0
Positive de-challenge[e]		0	0.0
Positive re-challenge[f]		0	0.0
Drug relatedness assessment decision [g]			
Probable		0	0.0
Possible		2	66.7
Unlikely		1	33.3
Unassessable		0	0.0

[a] an additional case of abnormal liver function tests meeting the laboratory criteria for DILI was identified. This case was only reported on a supplementary form for a different event for the same patient and was not reported on the outcome CRF; therefore this case has not been included in the main analysis. The event occurred in a male patient in his fifties who was taking rivaroxaban 5mg daily. Laboratory values meeting the criteria for potential DILI were first reported two days after index. This patient also experienced AKI on the same date (reported in Table 39 below). Rivaroxaban was stopped due to the AKI event; TB and ALT had improved evident by blood test results approximately one week later, however ALP remained high. All values were reported as normal approximately three weeks later.

[b] The HCP had ticked fatal on the supplementary CRF for this event. Event occurred on the same date as the date of death, however, liver related conditions/events not provided as cause of death on outcome CRF.

[b] Austin-Bradford Hill criteria;

c derived from time to onset analysis;

d co-morbidities and/or concomitant medication associated with event of interest;

e derived from information on outcome relating to treatment cessation; positive de-challenge was 'not known' for all three patients n=3

f positive re-challenge was 'not known' for all three patients n=3

g (17)

Cardiac Arrhythmias

Cardiac arrhythmias of specific interest[15] (i.e. ventricular arrhythmias) occurring within the 12-week observation period on rivaroxaban were evaluated further and corresponding drug relatedness assessments were performed (Table 38). Cardiac (ventricular) arrhythmias were reported in three patients in total; two male and one female. The median (IQR) age of the three patients was 55 (50, 72) years. Two patients were taking a rivaroxaban total daily dose of 5mg and one patient was taking a total daily dose of 15mg at index. Median (IQR) time to onset was 15 (10, 55) days. None of the patients were reported to have a prior history of the same event but all three were considered to have other possible risk factors for the cardiac arrhythmia specified. There was no evidence to suggest that rivaroxaban was stopped due to the event for all three cases. All cases were assessed as unlikely related to rivaroxaban.

Table 38. Case series table for relatedness assessments of cardiac arrhythmias

Event – Cardiac arrhythmias			
		n	**%**
Event details			
Number of events (N)		3	n/a
Events had fatal outcome		0	0.0
Index dose of rivaroxaban (total daily dose)			
	5mg	2	66.7
	15mg	1	33.3
Rivaroxaban stopped		0	0.0
Patient demographics			
Sex			
	Male	2	66.7
	Female	1	33.3
Age (years)			
	Median (IQR)	55	50, 72
Relatedness assessment criteria[a]			
Recognised association		0	0.0
Pharmacological plausibility		0	0.0
Temporality		3	100.0
	Time to onset (days): Median (IQR)[b]	15 (10, 55)	
Prior history of same event[c]		0	0.0
Risk factors[d]		3	100.0
Dose relationship		0	0.0
Positive de-challenge[e]		0	0.0
Positive re-challenge[f]		0	0.0
Drug relatedness assessment decision [g]			
Probable		0	0.0

[15] Includes Torsade de pointes, Ventricular fibrillation, Ventricular flutter, Ventricular arrhythmia, Ventricular tachyarrhythmia, and Ventricular tachycardia, QT prolongation only

Event – Cardiac arrhythmias	n	%
Possible	0	0.0
Unlikely	3	100.0
Unassessable	0	0.0

*information available from baseline CRF, outcome CRF, and supplementary CRFs, where available;
[a] Austin-Bradford Hill criteria;
b derived from time to onset analysis;
c prior history was 'not known' n=1, prior history 'no' n=1
d co-morbidities and/or concomitant medication associated with event of interest;
e derived from information on outcome relating to treatment cessation; positive de-challenge was 'not known' for all three patients n=3
f positive re-challenge was 'not known' for all three patients n=3
g (17)

Acute Kidney Injury

Cases of acute kidney injury occurring within the 12-week observation period on rivaroxaban were evaluated further and corresponding drug relatedness assessments were performed (Table 39). Acute kidney injury were reported in two patients in total; one male and one female. The median (IQR) age was 70.5 (59, 82) years. One patient was taking rivaroxaban at a total daily dose of 5mg and the other patient was taking a total daily dose of 20mg at index. Median (IQR) time to onset was 3.5 (2, 5) days. None of the patients were reported to have a prior history of the same event but both were considered to have other possible risk factors for acute kidney injury. Rivaroxaban was stopped due to the acute kidney injury event in one patient; there was some evidence of improvement in renal function but renal function continued to fluctuate thereafter, despite stopping rivaroxaban. The other patient was reported to have a fatal outcome on the supplementary CRF but this was not reported as the cause of death (on the outcome CRF)[16]. Both cases were assessed as unlikely related to rivaroxaban.

Table 39. Case series table for relatedness assessments of acute kidney injury

Event- Acute kidney injury		n	%
Event details			
Number of events (N)		2	n/a
Events had fatal outcome		1[a]	50.0
Index dose of rivaroxaban (total daily dose)			
	5mg	1	50.0
	20mg	1	50.0
Rivaroxaban stopped		1	50.0
Patient demographics			
Sex			

[16] This patient refers to the patient described in footnote to Table 43 in Section 10.4.7 for whom renal failure was reported in a question in relation to death, however, it was not possible to confirm it was the cause of death on the outcome CRF.

Event- Acute kidney injury			
		n	**%**
	Male	1	50.0
	Female	1	50.0
Age (years)			
	Median (IQR)	70.5 (59, 82)	
Relatedness assessment criteria[b]			
Recognised association		2[c]	100.0
Pharmacological plausibility		0[d]	0.0
Temporality		2	100.0
Time to onset (days): Median (IQR)[e]		3.5 (2, 5)	
Prior history of same event		0	0.0
Risk factors[f]		2	100.0
Dose relationship		0	0.0
Positive de-challenge [g]		0	0.0
Positive re-challenge [h]		0	0.0
Drug relatedness assessment decision[i]			
Probable		0	0.0
Possible		0	0.0
Unlikely		2	100.0
Unassessable		0	0.0

*information available from baseline CRF, outcome CRF, and supplementary CRFs, where available;
[a] The HCP had ticked fatal on the supplementary CRF for this event but did not provide this as a cause of death on the outcome CRF.
[b] Austin-Bradford Hill criteria;
[c] for events of acute kidney injury associated with hypoperfusion related to bleeding events
[d] no clinically overt bleeding reported for the two patients
[e] derived from time to onset analysis;
[f] co-morbidities and/or concomitant medication associated with event of interest;
[g] derived from information on outcome relating to treatment cessation; positive de-challenge: 'not known' n=1, 'no' n=1
[h] positive re-challenge: 'not known' n=1, 'no' n=1
[i] (17)

10.4.6 Pregnancies

There were no pregnancies reported in either the rivaroxaban or contextual cohorts within the 12-week observation period or beyond 12-weeks of observation.

10.4.7 Deaths

The total number of deaths reported during the 12-week observation period have been presented in Table 40. Reports of death were captured using Outcome and event follow-up information (using both targeted 'tick box' elicited answers and 'free text' format). In total, four (3.2%) patients in the rivaroxaban cohort and 11 (2.1%) patients in the contextual cohort died within the 12-week observation period. Of these reported deaths in the rivaroxaban cohort, three (2.4% of cohort, 75.0% of all deaths during the 12-week period) occurred on treatment. In the contextual cohort, eight of the 11 reported deaths occurred on treatment (1.5% of cohort, 72.7% of all deaths during the 12-week period). A sensitivity analysis was

performed which included a treatment wash-out period (Appendix 13). There were no additional deaths reported in the washout period for the rivaroxaban cohort but for the contextual cohort one death occurred during the period of washout. In addition, there were no additional deaths reported to occur outside the 12-week observation period on treatment in both the rivaroxaban and contextual cohorts (Appendix 13).

Table 40. Number of deaths reported during the 12-week observation period in the rivaroxaban and contextual cohorts

	Rivaroxaban N=124		Contextual N=528	
Treatment status	**n**	**%**	**n**	**%**
Deaths on treatment	3	2.4	8	1.5
Deaths off treatment	1	0.8	3	0.6
Total	**4**	**3.2**	**11**	**2.1**

For deaths occurring on treatment with rivaroxaban or contextual treatment during the 12-week observation period, the immediate causes of death have been presented in Table 41 according to MedDRA Preferred Terms. The immediate cause of death has also been grouped according to MedDRA System Organ Class (SOC) and Higher Level Term (HLT) as presented in Table 42. Where death cause was specified, all deaths were cardiac related. In the rivaroxaban cohort, the immediate cause of death in all three patients who died was 'myocardial infarction'. In the contextual cohort, the most frequently reported cause of death was 'acute myocardial infarction' and 'cardiogenic shock', each with two counts.

Table 41. Immediate cause of death reported on treatment during the 12-week observation period*

Rivaroxaban N=124			Contextual N=528		
Immediate cause of death	**n**	**%**	**Immediate cause of death**	**n**	**%**
Myocardial infarction	3	2.4	Acute myocardial infarction	2	0.4
			Cardiogenic shock	2	0.4
			Cardiac arrest[a]	1	0.2
			Cardiac failure congestive	1	0.2
			Death cause unspecified	1	0.2
			Myocardial infarction	1	0.2

* cause of death events may not be included in the events on treatment tables

[a] Underlying cause/condition reported for this patient: 'left ventricular impairment' and 'acute kidney injury'. In addition, 'VT/VF – not resuscitated' was reported by the HCP in the event section of the form.

Table 42. Immediate cause of death reported on treatment during the 12-week observation period, grouped by SOC and HLT

	Rivaroxaban N=124		
Immediate cause of death			
SOC	**HLT**	**n**	**%**
Cardiac disorders	Ischaemic coronary artery disorders	3	2.4
	Contextual N=528		
Immediate cause of death			
SOC	**HLT**	**n**	**%**
Cardiac disorders	Heart failures NEC	3	0.6
	Ischaemic coronary artery disorders	3	0.6
	Ventricular arrhythmias and cardiac Arrest	1	0.2
General disorders and administration site conditions	Death and sudden death	1	0.2

All immediate causes of death (at PT level) reported on treatment including the wash-out period and off treatment within the 12-week observation period have been provided in Appendix 13.

In addition to the immediate cause of death, HCPs were also requested to report underlying cause/condition(s) leading or contributing to death. Multiple cause/conditions could be reported per patient, so counts are not mutually exclusive. Table 43 provides reported underlying cause/condition(s) in those patients who died during the 12-week observation period according to MedDRA PTs. In the rivaroxaban cohort, four different underlying cause/conditions were reported in the three patients who had died on treatment within the first 12-weeks after index; all were reported in single counts. In the contextual cohort, 20 counts of 18 different underlying cause/conditions were reported for the eight patients who had died on treatment within the first 12-weeks after index. The most commonly reported underlying cause/condition in the contextual cohort was acute kidney injury (n=2) and hypertension (n=2); all other underlying cause/conditions were reported once.

Table 43. Underlying cause/conditions of death reported on treatment during the 12-week observation period*

Rivaroxaban N=124			Contextual N=528		
Underlying cause/condition[a]	**n**	**%**	**Underlying cause/condition**	**n**	**%**
Cardiac failure	1	0.8	Acute kidney injury	2	0.4
Diabetes mellitus	1	0.8	Hypertension	2	0.4
Hypertension	1	0.8	Acute myocardial infarction	1	0.2
Myocardial ischaemia	1	0.8	Arteriosclerosis coronary artery	1	0.2
			Cardiac failure congestive	1	0.2
			Carotid artery stenosis	1	0.2
			Chronic kidney disease	1	0.2
			Coronary artery disease	1	0.2
			Coronary artery occlusion	1	0.2
			Ischaemic cardiomyopathy	1	0.2
			Left ventricular dysfunction	1	0.2
			Myocardial infarction	1	0.2
			Myocardial ischaemia	1	0.2
			Pleural effusion	1	0.2
			Pneumonia	1	0.2
			Pulmonary oedema	1	0.2
			Type 2 diabetes mellitus	1	0.2
			Ventricular fibrillation	1	0.2

* Underlying cause/conditions of death events may not be included in the events on treatment tables

[a] Two additional events of renal failure and left ventricular failure were reported in relation to the cause of death for a patient who died on treatment with rivaroxaban in the 12-week observational period. However these events were not specifically reported as the underlying cause/conditions to death and therefore have not been presented in the table above but the case of renal failure has been analysed further in Section 10.4.5, Table 40.

All underlying cause/conditions of death reported on treatment including the wash-out period and off treatment within the 12-week observation period have been provided in Appendix 13.

10.5 Other Analyses

10.5.1 Other outcomes

10.5.1.1 Change in general health parameters

Information on anthropometric measures (BMI and weight) were collected at baseline (as reported by the patient) and during the 12-week observational period (reported by the prescriber) to determine whether any change had been reported, since these factors were considered to have a time-dependent effect on any subsequent estimates of risk. For each characteristic both baseline and 12-week data are presented and summarised for completeness, with BMI and weight categories for both rivaroxaban and contextual cohorts

presented in Table 44 and Table 45. Any change in the values of BMI and weight are also presented.

Information on BMI was provided for 71.0% (n=88) of the rivaroxaban cohort at baseline and 28.2% (n=35) of the rivaroxaban cohort in the 12-week follow up period. In the contextual cohort, information on BMI was provided for 71.2% (n=376) at baseline and 60.4% (n=319) in the 12-week follow up. In the rivaroxaban cohort the mean (SD) BMI at baseline was 28.5 (4.2) and 28.6 (4.6) at 12-weeks. In the contextual cohort the mean (SD) BMI at baseline was 28.6 (6.6) and 27.9 (5.2) at 12-weeks. Overall, in both cohorts there was little change in mean BMI between baseline and 12-weeks.

Table 44. BMI categories at baseline and 12-week follow up

BMI (kg/m²)	Rivaroxaban N=124		Contextual N=528	
	Baseline	12-Week	Baseline	12-Week
	n (% where specified)	n (% where specified)	n (% where specified)	n (% where specified)
<18.5 (Below Normal)	0 (0.0)	1 (2.9)	4 (1.1)	2 (0.6)
18.5-24.9 (Normal)	19 (21.6)	8 (22.9)	93 (24.7)	81 (25.4)
25.0-29.9 (Overweight)	39 (44.3)	11 (31.4)	166 (44.1)	154 (48.3)
30.0-39.9 (Obese)	30 (34.1)	15 (42.9)	98 (26.1)	74 (23.2)
40.0+ (Morbidly Obese)	0 (0.0)	0 (0.0)	15 (4.0)	8 (2.5)
Unknown/Not completed*	36 (29.0*)	89 (71.8*)	152 (28.8*)	209 (39.6*)
Median (IQR)	28.4 (25.6, 31.5)	29.0 (24.2, 31.7)	27.6 (24.9, 31.3)	27.0 (24.7, 30.0)
Mean (SD)	28.5 (4.2)	28.6 (4.6)	28.6 (6.6)	27.9 (5.2)
Median change (IQR)	-0.3 (-1.0, 0.3)		-0.0 (-0.5, 0.4)	
Mean change (SD)	0.1 (1.7)		-0.4 (5.8)	

*% cohort

Information on weight was provided for 71.8% (n=89) of the rivaroxaban cohort at baseline and 38.7% (n=48) of the rivaroxaban cohort in the 12-week follow up period. In the contextual cohort, information on weight was provided for 72.2% (n=381) at baseline and 75.8% (n=400) in the 12-week follow up. In the rivaroxaban cohort the mean (SD) weight at baseline was 86.2kg (14.3) and 88.1kg (15.4) at 12-weeks. In the contextual cohort the mean (SD) weight at baseline and 12-weeks was 84.7kg (18.3 and 17.8 respectively). Overall, in both cohorts there was little change in mean weight between baseline and 12-weeks.

Table 45. Weight categories at baseline and 12-week follow up

Weight (kg)	Rivaroxaban N=124		Contextual N=528	
	Baseline	12-Week	Baseline	12-Week
	n (% where specified)	n (% where specified)	n (% where specified)	n (% where specified)
<50	1 (1.1)	1 (2.1)	5 (1.3)	3 (0.8)
50-69.9	12 (13.5)	5 (10.4)	67 (17.6)	72 (18.0)
70-89.9	40 (44.9)	19 (39.6)	184 (48.3)	190 (47.5)
90-109.9	31 (34.8)	20 (41.7)	93 (24.4)	105 (26.3)
110+	5 (5.6)	3 (6.3)	32 (8.4)	30 (7.5)
Unknown /Not completed*	35 (28.2*)	76 (61.3*)	147 (27.8*)	128 (24.2*)
Median (IQR)	87.5 (73.9, 96.0)	88.5 (78.0, 97.9)	83.9 (73.0, 94.3)	83.6 (73.0, 94.0)
Mean (SD)	86.2 (14.3)	88.1 (15.4)	84.7 (18.3)	84.7 (17.8)
Median change (IQR)	0.0 (-1.0, 1.6)		0.0 (-0.4, 0.9)	
Mean change (SD)	1.1 (5.2)		0.5 (5.8)	

*% cohort

10.5.1.2 Changes in laboratory test results

Investigators were asked to provide results of haemoglobin and serum creatinine levels at baseline and in the 12-week follow up period. (Table 46 and Table 47).

Information on haemoglobin was provided for 100% of the rivaroxaban cohort at baseline and 62.1% (n=77) of the rivaroxaban cohort in the 12-week follow up period. In the contextual cohort, information on haemoglobin was provided for 99.6% (n=526) at baseline and 90.3% (n=477) in the 12-week follow up period.

In both cohorts the largest proportion of patients had a haemoglobin level of >130 g/L at baseline and 12-weeks; in the rivaroxaban cohort 74.2% of the total cohort at baseline and 74.0% of the total cohort at 12-weeks, where specified; in the contextual 77.4% of the total cohort at baseline (where specified) and 73.8% at 12-weeks (where specified) (Table 46). In terms of a change in the baseline haemoglobin result, for those patients where information was provided, in the rivaroxaban cohort 79.2% (n=61) had the same category value at baseline and 12-weeks, 10.4% (n=8) had an increase from baseline and 10.4% (n=8) had a decrease from baseline. In the contextual cohort 76.7% (n=366) had the same category value at baseline and 12-weeks, 8.0% (n=38) had an increase from baseline and 15.3% (n=73) had a decrease from baseline.

Table 46. Haemoglobin categories at baseline and 12-week follow up

Haemoglobin (g/L)	Rivaroxaban N=124		Contextual treatment N=528	
	On admission	Following admission	On admission	Following admission
	n (% where specified)	n (% where specified)	n (% where specified)	n (% where specified)
<80	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)
80-89	0 (0.0)	0 (0.0)	1 (0.2)	5 (1.0)
90-99	0 (0.0)	2 (2.6)	7 (1.3)	6 (1.3)
100-109	4 (3.2)	3 (3.9)	14 (2.7)	15 (3.1)
110-119	11 (8.9)	7 (9.1)	33 (6.3)	34 (7.1)
120-129	17 (13.7)	8 (10.4)	64 (12.2)	61 (12.8)
>130	92 (74.2)	57 (74.0)	407 (77.4)	352 (73.8)
Unknown/Not completed[a]	0 (0.0[a])	47 (37.9[a])	2 (0.4[a])	51 (9.7[a])
Median (IQR)	n/a[b]	139 (125, 148)	n/a[b]	139 (128, 150)
Mean (SD)	n/a[b]	137.9 (16.1)	n/a[b]	137.6 (20.2)
Same category value at baseline and following admission[a]	61 (49.2[a])		366 (69.3[a])	
Increase from baseline[a]	8 (6.5[a])		38 (7.2[a])	
Decrease from baseline[a]	8 (6.5[a])		73 (13.8[a])	
Unknown /Not completed change from baseline[a]	47 (37.9[a])		51 (9.7[a])	

[a] % cohort
[b] Median and mean values not available as collected as categorical values

Information on serum creatinine was provided for 100% of the rivaroxaban cohort at baseline and 66.1% (n=82) of the rivaroxaban cohort in the 12-week follow up period. In the contextual cohort, information on serum creatinine was provided for 99.6% (n=526) at baseline and 90.3% (n=477) in the 12-week follow up period.

In both cohorts the largest proportion of patients had a serum creatinine of <88 µmol/L at baseline and 12-weeks; in the rivaroxaban cohort 60.5% of the total cohort at baseline and 46.3% of the total cohort at 12-weeks, where specified; in the contextual 61.4% of the total cohort at baseline (where specified) and 59.7% at 12-weeks (where specified) (Table 47). In terms of a change in the baseline serum creatinine result, for those patients where information was provided, in the rivaroxaban cohort 64.6% (n=53) had the same category value at baseline and 12-weeks, 23.2% (n=19) had an increase from baseline and 12.2% (n=10) had a decrease from baseline. In the contextual cohort 71.3% (n=340) had the same

category value at baseline and 12-weeks, 14.3% (n=68) had an increase from baseline and 14.5% (n=69) had a decrease from baseline.

Table 47. Serum creatinine categories at baseline and 12-week follow up

Serum creatinine (µmol/L)	Rivaroxaban N=124		Contextual N=528	
	On admission n (% where specified)	Following admission n (% where specified)	On admission n (% where specified)	Following admission n (% where specified)
<88	75 (60.5)	38 (46.3)	323 (61.4)	285 (59.7)
88-106	28 (22.6)	21 (25.6)	124 (23.6)	123 (25.8)
107-124	10 (8.1)	12 (14.6)	30 (5.7)	33 (6.9)
125-141	5 (4.0)	5 (6.1)	21 (4.0)	14 (2.9)
142-159	2 (1.6)	2 (2.4)	9 (1.7)	6 (1.3)
160-177	1 (0.8)	1 (1.2)	5 (1.0)	4 (0.8)
>177	3 (2.4)	3 (3.7)	14 (2.7)	12 (2.5)
Unknown /Not completed[a]	0 (0.0[a])	42 (33.9[a])	2 (0.4[a])	51 (9.7[a])
Median (IQR)	n/a[b]	90 (78, 109)	n/a[b]	83 (73, 98)
Mean (SD)	n/a[b]	100.4 (50.9)	n/a[b]	104.0 (277.7)
Same category value at baseline and following admission[a]	53 (42.7[a])		340 (64.4[a])	
Increase from baseline[a]	19 (15.3[a])		68 (12.9[a])	
Decrease from baseline[a]	10 (8.1[a])		69 (13.1[a])	
Unknown /Not completed change from baseline[a]	42 (33.9[a])		51 (9.7[a])	

[a] % cohort

[b] Median and mean values not available as collected as categorical values

10.5.1.3 Indicators of treatment adherence

The outcome CRF asked HCPs if they were aware of any behaviours regarding patient adherence to treatment. Prevalence of criteria identifying poor anticoagulant medication compliance was low in both cohorts; the most frequently reported in the rivaroxaban group was 'overall general poor medication-taking behaviour' (n=4, 3.2%) and in the contextual group was 'overall general poor medication-taking behaviour' (n=3, 0.6%) and 'missed clinical review appointments' (n=3, 0.6%) (Table 48). No patients were reported to have taken extra anticoagulant doses, however, there were reports of missed anticoagulant doses (n=2, 1.6%) in the rivaroxaban group. This coincides with 'demonstrates poor understanding of need for regular use' also being reported for a patient taking rivaroxaban.

Table 48. Counts and percent of behaviour indicators, by cohort

Indicators of treatment adherence	Rivaroxaban N=124		Contextual N=528	
	n	% of cohort	n	% of cohort
Overall general poor medication-taking behaviour	4	3.2	3	0.6
Missed clinical review appointments	2	1.6	3	0.6
Missed anticoagulant doses	2	1.6	0	0.0
Extra anticoagulant doses	0	0.0	0	0.0
Demonstrated poor understanding of need for regular use	1	0.8	0	0.0

10.6 Adverse Events/Adverse Reactions

Not applicable.

11 Discussion

This final report summarises data on patients prescribed rivaroxaban in the secondary care setting in England and Wales in the ROSE-ACS SCEM Study conducted as a Post-authorisation Safety Study (PASS) in the EU. Within the study the rivaroxaban cohort consists of new users of rivaroxaban (no anticoagulant prescription within six months prior to index date) with any combination of oral antiplatelet therapy. The contextual cohort consists of patients receiving the current standard treatment of care (at least dual antiplatelet therapy, but not monotherapy). Data analyses were performed on all patients for whom both baseline and 12-week data from specialists were available (n=652; [n=124 (19.0%) rivaroxaban cohort and n=528 (81.0%) contextual cohort]) identified in the study period from September 2015 to October 2018.

11.1 Key Results

The primary objective of the study was to quantify the cumulative incidence of major bleeding according to the TIMI classification occurring during the study period, overall and stratified by intracranial, gastrointestinal and urogenital sites. In addition there were several secondary and exploratory objectives aimed at understanding the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS including drug utilisation characteristics as well as describing changes in the health profile of patients over the course of the study and the risk of other major and minor bleeds and other events of interest.

Major bleeds

In the ROSE-ACS study, there were six major bleeds which fulfilled the TIMI definition of non-CABG related major bleeding; one of which occurred in the rivaroxaban cohort and was within the gastrointestinal site (cumulative incidence 0.8%; 95% CI [0.0, 4.4]; incidence rate 4.2 per 100 person years; 95% CI [0.6, 29.6]). There were no reports of TIMI minor bleeding events within the rivaroxaban cohort. The majority of bleeding events reported within the rivaroxaban cohort were classified as TIMI non-CABG related bleeding requiring medical attention (cumulative incidence 10.5%; 95% CI [5.7, 17.3]; incidence rate 54.3 per 100 person years; 95% CI [31.5, 93.5]).

Within the contextual cohort, the cumulative incidence of TIMI major bleeding overall was 0.9%; 95% CI [0.3, 2.2]; incidence rate 4.8 per 100 person years; 95% CI [2.0, 11.5]. The cumulative incidence of major gastrointestinal bleeding was 0.8%; 95% CI [0.2, 1.9]. There were no reports of major bleeding within intracranial and urogenital sites. The cumulative incidence of major bleeding within other sites was 0.2%; 95% CI [0.0, 1.1]). Within the contextual cohort the cumulative incidence of minor bleeding in all sites was 0.6%; 95% CI [0.1, 1.7]; incidence rate 2.9 per 100 person years; 95% CI [0.9, 8.9]). The majority of bleeding events reported in the contextual cohort were classified as non-CABG related bleeding requiring medical attention, (3.8%; 95% CI [2.3, 5.8]; incidence rate 19.2; 95% CI 12.4, 29.8]).

Risk according to BARC classification

As part of the secondary objective of the study, bleeding events were also classified according to the BARC definition. In the rivaroxaban cohort, the highest BARC category was BARC 3b which included two patients (cumulative incidence 1.6%). In the contextual cohort, the highest BARC category was BARC 3b which included seven patients (cumulative incidence 1.3%). Two patients (0.4%) had a BARC Type 3a classification (BARC 3a and higher 1.7%).

There are relatively few studies looking at the risk of bleeding with rivaroxaban in ACS. Since the ROSE-ACS study has a very different design, in particular the observation period, and different objectives to the trials, no direct comparisons have been undertaken. In the pivotal ATLAS ACS 2 TIMI 51 study, rivaroxaban 2.5 mg orally twice daily (BD) (N=5174), rivaroxaban 5 mg orally BD (N=5176) or placebo BD (N=5176) was co-administered with aspirin alone or with aspirin plus a thienopyridine (clopidogrel or ticlopidine) (2). The mean duration of treatment with study drug was 13.1 months. Index events were as follows: rivaroxaban 2.5 mg BD group, STEMI (50.3%), NSTEMI (25.5%) UA (24.2%); rivaroxaban 5.0 mg BD group, STEMI (49.9%), NSTEMI (25.8%) UA (24.3%); placebo group, STEMI (50.9%), NSTEMI (25.6%) UA (23.6%). As compared with placebo, rivaroxaban significantly increased the

rates of TIMI major bleeding not related to CABG (combined 2.5 mg/5.0 mg doses: 2.1% vs. 0.6%, P<0.001; 2.5 mg BD: 1.8% vs. 0.6%, P<0.001; 5mg BD: 2.5% vs. 0.6%, P<0.001) (2). In the ATLAS trial, 65 (1.3%) of the 5114 patients in the rivaroxaban 2.5 mg BD modified intention-to-treat group, experienced a TIMI non-CABG related major bleed. This compared to 19 (0.4%) of the 5113 patients in the placebo group. In addition, 14 of the 5114 rivaroxaban patients (0.3%) had an intracranial haemorrhage and six (0.1%) had fatal bleeding. In the placebo group, five (0.1%) had an intracranial haemorrhage and nine (0.2%) had fatal bleeding. Thirty-two (0.6%) of the 5114 patients in the rivaroxaban 2.5 mg BD group experienced a TIMI minor bleed compared with 20 (0.4%) patients in the placebo group. The majority of bleeding events reported in the ATLAS trial were classified as TIMI bleeding requiring medical attention; 492 (9.6%) of the 5114 patients in the 2.5 mg BD rivaroxaban group compared to 282 (5.5%) in the placebo group.

In the GEMINI-ACS-1 trial (18), patients with recent ACS were randomised to receive either rivaroxaban 2.5 mg twice daily (N=1519) or aspirin 100 mg (N=1518) once daily on top of standard therapy with either clopidogrel or ticagrelor. The median duration of treatment with blinded study drug was 291 days (IQR 239–354) and median duration of follow-up was 326 days (284–383). In both the rivaroxaban and aspirin groups, 49% presented with STEMI, 40% with NSTEMI and 11% with UA. TIMI non-CABG major bleeding was noted in 1% of patients in both the rivaroxaban and aspirin group. The frequency of fatal or intracranial bleeding was <1% in the rivaroxaban group, there were no reports of fatal or intracranial bleeding in the aspirin group. TIMI minor bleeding occurred in 1% of rivaroxaban patients and <1% of patients in the aspirin group. The most common type of bleeding in the GEMINI-ACS-1 trial was TIMI bleeding requiring medical attention (4% in both the rivaroxaban and aspirin groups). The GEMINI-ACS-1 trial also used other bleeding classifications including BARC categories; 1% of rivaroxaban patients had a bleeding category of BARC 3a and higher, 1% a bleeding category of BARC 3b and higher and <1% were categorised as BARC fatal bleeding. In the aspirin group, 1% also had a bleeding category of BARC 3a and higher but 0.5% had a bleeding category of BARC 3b and higher and no patients were categorised as BARC fatal bleeding.

Other targeted /RAIDAR events

An additional targeted outcome within this study was abnormal liver function tests where laboratory results indicated 3 X ULN. There were three reports of incident abnormal LFTs (greater than 3 X upper limit of normal) within the rivaroxaban cohort and four reports within the contextual cohort reported on treatment within the 12-week observation period. In addition, the three reports occurring on rivaroxaban treatment during the 12-week observation period were assessed for potential cases of drug-induced liver injury (DILI); two

cases were assessed as possibly related to rivaroxaban and one was considered unlikely related.

Data was also collected on possible complications associated with the ACS event, including information on angina, congestive heart failure, peripheral arterial disease and cardiac arrhythmias, which occurred on treatment with rivaroxaban or contextual treatment. Of these, the most frequently reported was cardiac arrhythmias (5.6% of rivaroxaban cohort, 3.6% of contextual cohort). A subset of cardiac arrhythmias in the rivaroxaban cohort which met the RAIDAR criteria were assessed for drug relatedness; the three reported cases of cardiac (ventricular) arrhythmias were assessed as unlikely related to rivaroxaban. The only arrhythmia included in the SPC is tachycardia, which is noted to occur at a frequency of ≥0.1 to <1.0% (1).

An assessment of drug relatedness was also conducted on two reported cases of acute kidney injury, occurring within the 12-week observation period on rivaroxaban. Both cases were assessed as unlikely related to rivaroxaban. The incidence of renal failure secondary to a bleeding event sufficient to cause hypoperfusion is not known (1).

Deaths

Three (2.4%) deaths occurred on treatment in the rivaroxaban cohort and eight (1.5%) occurred in the contextual cohort. For both cohorts, all causes of death (where specified) were cardiac related; in the rivaroxaban cohort, the immediate cause of death in all three patients who died was 'myocardial infarction' and in the contextual cohort, the most frequently reported cause of death was 'acute myocardial infarction' and 'cardiogenic shock', each with two counts. In the ATLAS study, 205 (4.0%) of the 5114 patients in the 2.5 mg BD rivaroxaban group were reported to have died from myocardial infarction (2). The incidence of myocardial infarction in the GEMINI-ACS-1 trial was also 4.0% (18).

Patient determinants of prescribing

The secondary focus of this study was to advance the understanding of the patient population prescribed rivaroxaban in the secondary care hospital setting by exploring differences between rivaroxaban and the contextual cohort with regard to the prevalence of non-clinical reasons for prescribing, demography and indication.

In terms of prescribing decisions, in both cohorts clinical judgement was the most frequently reported reason for treatment choice, followed by NICE recommendation. The impact of NICE guidelines seemed to be particularly relevant in the rivaroxaban cohort (NICE guidelines cited as a supporting reason for 83.9% of rivaroxaban patients compared to 58.9% of patients in

the contextual cohort). In terms of demographics and indication for treatment, these were similar between the two cohorts; the majority of the cohort was male (83.1% of the rivaroxaban cohort and 75.2% of the contextual cohort) which is in line with the prevalence of MI being higher in men than woman (19). Irrespective of gender, the mean age for the rivaroxaban group was 60.2 years and for the contextual cohort was 64.3 years; this is lower than data collected from the Myocardial Ischaemia National Audit Project (MINAP) where overall almost half of all MIs recorded in MINAP were in people over 70 years of age (19). In both treatment cohorts females were older than males: mean age for the rivaroxaban group was 61.1 years for females and 60.0 years for males; for the contextual cohort the mean age was 68.2 for females and 63.0 for males which is also in line with the MINAP study that women tend to be older than men (average age of male STEMI patients was 63 years compared with 71 years for females; the average age for male NSTEMI patients was 69 years compared with 75 years for females) (19).

In the rivaroxaban cohort the majority of patients were initiated treatment for STEMI (n=64, 51.6% of total cohort) with 42.7% treated for NSTEMI and in the contextual cohort the majority of patients were treated for an NSTEMI (n=299, 56.6% of total cohort) with 32.2% treated for STEMI. Although numbers are small, this may indicate that patients with more severe ACS were prescribed rivaroxaban. In terms of invasive procedures during admission, 93.5% of the rivaroxaban cohort and 84.8% of the contextual cohort had undergone a PCI during admission. Coronary artery bypass grafting was only reported in the contextual cohort (5.5%). The interval duration between hospital admission and initiation of either rivaroxaban or dual antiplatelet therapy for the rivaroxaban and contextual cohorts respectively was also collected. In the rivaroxaban cohort, patients were most frequently initiated on rivaroxaban two days after being admitted to hospital (n=39, 31.5%) and the majority were initiated within three days of being admitted (n=102, 82.3%). This is in line with prescribing guidance for rivaroxaban (1). In the contextual cohort, the majority of patients were initiated treatment the same day as being admitted to hospital (n=368, 69.7%). The majority of patients (n=116, 93.5%) in the rivaroxaban cohort were initiated on a total daily dose of 5mg rivaroxaban as per the recommendations (1). Two patients (1.6%) were initiated rivaroxaban treatment with a total daily dose of 15mg, in one of these patients the HCP indicated that rivaroxaban was being prescribed to cover both indications of ACS and AF. In addition, four patients (3.2%) were initiated rivaroxaban treatment with a total daily dose of 20mg. In one of these patients the HCP reported 'Fast AF' as the clinical condition for which treatment with rivaroxaban was indicated, in addition to ACS. Although the HCP did not indicate any reason for this choice of dose in the remaining three patients, it is also possible that rivaroxaban was being prescribed to cover both indications of ACS and AF.

The characteristics of the patients (general health, selected prior and concurrent medical conditions and events) in both cohorts were also collected, since these data may identify vulnerable patients at risk and/or patients who have important risk factors for outcomes of interest. Where specified, the prevalence of prescriber-reported risk seeking behaviours (substance misuse and alcohol abuse) was low in both rivaroxaban and contextual cohorts (0.0% and 3.2% and 0.6% and 4.5% respectively). Reports of prior bleeding events and other prior disorders/conditions in both cohorts were also low. The presence of hypertension was 12.9% and 17.4% in patients treated with rivaroxaban and contextual therapy respectively and the presence of Type 2 diabetes was 7.3% and 8.0% respectively. In the rivaroxaban cohort, 21% of patients had a previous ACS event (8.1% STEMI, 8.9% NSTEMI and 4.0% angina) and in the contextual cohort 14.8% of patients had a previous ACS event (2.5% STEMI, 5.7% NSTEMI and 6.6% angina). According to the specialist recorded history of smoking, 50.0% of the rivaroxaban treated cohort and 38.8% of the contextual cohort were reported to be smokers prior to index date. Where BMI was specified, 34.1% of rivaroxaban patients and 26.1% of contextual therapy patients were classified as obese. In addition, 4.0% of the contextual cohort were classified as morbidly obese. Minimal changes in health profile were seen between baseline and the end of the 12-weeks observation period in both cohorts, while the overall incidence of poor treatment adherence indicators was low. There were few alterations in the treatment programme in either cohort over the 12-week observation period.

Additional risk factors based on an ACUITY/HORIZONS-AMI scoring system (15) for non-CABG-related major bleeding present on admission for ACS were also collected; the majority of patients in both cohorts had a serum creatinine of <88 µmol/L which falls within the typical reference range (60 to 110 µmol/L for men and 45 to 90 µmol/L for women) and yields a score of zero for the creatinine variable of the risk score. With regards to white blood cell count, the highest proportion of patients in both cohorts had a white blood cell count of <10 x 10^9/L, which again falls within the typical reference range (4-11 x 10^9/L) and yields a score of zero for the white blood cell variable of the risk score. In addition the majority of patients in both cohorts had a haemoglobin level of >130 g/L (reference range, adult female 115-165 g/L; adult male 130-180 g/L) suggesting that most patients did not meet the risk score criteria for anaemia.

Information on the use of specific therapeutic drug classes (including analgesics/anti-inflammatory agents, anti-convulsants, anti-infectives, antidepressants, female hormone products), both prior to and during or following admission with ACS was also obtained in addition to information on the use of OTC medication, herbal agents and juices, in order to identify patients at possible risk of drug interactions. The pattern of medication use was broadly similar in both the rivaroxaban and contextual cohorts; the most frequently reported

medications prior to admission were oral antiplatelets and lipid modifying agents and the most frequently reported medications prescribed (not necessarily for secondary prevention) during or following admission with ACS were analgesic and anti-inflammatory agents, agents acting on the renin-angiotensin system, lipid modifying agents and beta blocking agents. The use of NSAIDs, which may predispose the patient to bleeding, during or following admission was low in both the rivaroxaban and contextual cohorts (3.2% and 3.8% respectively).

11.2 Limitations

A major limitation for this final report is the small number of patients treated with rivaroxaban despite a number of strategies undertaken to ensure maximal recruitment to the study (Appendix 2). This has been due to the low uptake of rivaroxaban for ACS in the secondary care setting which has been verified by usage data obtained from primary care (i.e. The Health Improvement Network (THIN) database study[17] and the Modified Prescription Event Monitoring (MPEM) study (20)) as well as from rivaroxaban sales data. (Appendix 2)

In addition as this is an observational epidemiological study, we recognise several potential sources of bias in our study (14).

A potential source of bias in this study relating to the specialist HCP is non-response bias. It is unknown whether the prescribing patterns and/or patients of specialist HCP who returned the CRF are different to those of the specialist HCPs who did not return the CRF. Despite efforts to recruit HCPs across the country, no HCPs participated from the Midlands and North Wales. An assessment of these sites suggests that approximately 60.0% have rivaroxaban 2.5mg on their local formulary, however this may have not been the case at study initiation. In contrast, nearly a quarter of HCPs who participated in the study were from the North of England however 2.5mg rivaroxaban is on the formulary in less than 40.0% of sites based in this region. This suggests additional external influences, such as local formulary decisions on restricted use and local research governance frameworks. There is also the potential selection bias in terms of representativeness of patients included in this cohort. However, in this study patients are recruited at "baseline", consequently we do not believe that selection bias affects the types or number of events experienced by a patient after treatment was initiated. As events are then reported by the HCP on standardised forms, there should be minimal bias associated with reporting of these events.

However, it is possible that specialist HCPs may under-report or selectively report particular events in particular patients. The direction of any bias within this study is unknown.

[17] Results from THIN database study (IMPACT number 16647) included in PBRER/PSUR update submitted November 2019.

Misclassification bias is addressed by use of follow up CRFs which aim to gather additional information on reported events to allow consistent recording. The study also requested such data from the GPs of patients who were discharged from the care of the specialist HCP prior to the end of the 12-week observation period. In common with other studies using data collected for other purposes (secondary use of data) source data cannot always be verified. Additionally, different HCPs may interpret the questions differently leading to some "noise" in the analyses. The impact of misclassification due to inaccurate reporting of data is not known.

In SCEM, exposure is based on prescription data as recorded in medical charts. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be fully ascertained and therefore patient exposure may be overestimated, or the time frame may be slightly inaccurate.

As this study utilised medical chart review using standardised CRFs, it is acknowledged that some conditions may have been present prior to commencing treatment with either rivaroxaban in combination with standard oral antiplatelet therapy or standard oral antiplatelet combination therapy alone, as specific information was not collected regarding baseline screening for events prior to starting therapy. Furthermore, for events reported on index date, in particular cardiovascular disorders, it is not possible to differentiate whether these are new events since starting treatment or whether they are the conditions that had led to hospitalisation.

Information on relevant confounders in the estimates of risk and rate may be missing or incomplete since data abstracted from patient medical records held by specialist HCPs are likely to be biased towards recording cardiovascular-related medical events for the acute period of care and may not contain data on all variables for the full 12-week observation period that are relevant to the study. However, the study asked HCPs to provide data where available and report events affecting all body symptoms, without making any prior assessment on relatedness. In addition estimates of risk and rate were unadjusted and no formal comparative analyses were conducted between the cohorts.

As this is an observational study, information on patient characteristics i.e. reported medication use is only available as reported by patients. However, there no reason to suspect this would differ between rivaroxaban and contextual cohorts.

11.3 Interpretation

Overall rivaroxaban is largely being prescribed to populations in accordance with prescribing recommendations and national clinical guidelines and the numbers of bleeding events were

low. However, interpretation of the results needs to consider the sample size of patients treated with rivaroxaban due to low usage in ACS.

11.4 Generalisability

The study aimed to recruit Specialist HCPs and patients from across England and Wales from both urban and rural areas. The NHS use of rivaroxaban for the ACS indication has been low, as measured by the use of the 2.5mg dose and this is reflected in the results of this final report. The geographical distribution of all prescribers and evaluable patients participating in the ROSE-ACS SCEM study corresponds generally to those urbanised areas where health service utilisation is likely to be higher, nevertheless there appear to be external influences additional to whether 2.5mg rivaroxaban is on the Trust formulary which are beyond the ability of the study to control. From this study, it is not possible to determine if the evaluable cohort is likely to be systematically different to the population in England and Wales treated with rivaroxaban for similar indications within secondary care, but there is no reason to believe this is the case. However, this study is part of a broader literature in the safety of rivaroxaban and any conclusions on safety should be put into context with results from other post-marketing studies for the product.

12 Other Information

None.

13 Conclusion

The SCEM design provides a framework suitable to evaluate the safety of newly marketed medicines in secondary care setting. The analysis of The ROSE-ACS Study data shows that rivaroxaban use in ACS in the UK is low but overall rivaroxaban is largely being prescribed to populations in accordance with prescribing recommendations and national clinical guidelines and the numbers of bleeding events were low.

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Appendices

Annex 1. List of stand-alone documents

None

Annex 2. Additional information

Drug Safety Research Unit (DSRU)

Rivaroxaban in Acute Coronary Syndrome

Protocol Amendment
August 2017

PPD

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Version 7 Date: 30/08/2017

PASS information

Title	An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales
Protocol version identifier	7.0
Date of last version of protocol	30/08/2017
EU PAS register number	EUPAS9977
Active substance	Rivaroxaban
Product reference	EU/1/08/472/001-010 EU/1/08/472/022
Marketing authorisation holder(s)	Bayer AG, D-13353 Berlin, Germany
Research question and objectives	Aim: To monitor the short-term (up to 12 weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as prescribed for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) by specialist HCPs in the secondary care hospital setting in England and Wales. Objectives: 1. To quantify the cumulative incidence (risk and rate) of haemorrhage (major bleeding within intracranial, gastrointestinal and urogenital organ sites) occurring in the 12 week observation period 2. Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics 3. Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period 4. Quantifying the risk of other major or minor bleeding outcomes not specified in the primary objectives reported in the 12 week observation period overall and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting

	in England and Wales.
Country(-ies) of study	England and Wales
Author	PPD PPD PPD PPD Email: PPD Tel: PPD

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Bayer AG, D-13353 Berlin, Germany
MAH contact person	PPD PPD Bayer AG Tel: PPD Email:PPD

1 Table of Contents

2 List of Abbreviations

Abbreviation	Term
AC	Advisory committee
ACS	Acute coronary syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
BP	Blood Pressure
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CYP P450	Cytochrome P-450
DSRU	Drug Safety Research Unit
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drugs Administration
GGT	Gamma-Glutamyl Transferase
GP	General Practitioner
HCP	Healthcare Professional
HLT	Higher Level Term
ID	Incidence Density
IQR	Interquartile Range
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
M-PEM	Modified Prescription-Event Monitoring
NDA	New Drug Application
NHS	National Health Service
NHSBSA	National Health Service Business Services Authority
OTC	Over-The-Counter
PCI	Percutaneous coronary intervention
PEM	Prescription Event Monitoring
PIP	Paediatric Investigation Plan
RCT	Randomised Controlled Trial
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCEM	Specialist Cohort Event Monitoring
SOC	System Organ Class
SPC	Summary of Product Characteristics
TIMI	Thrombolysis In Myocardial Infarction
UK	United Kingdom
US	United States

3 Responsible Parties

Responsible party	Appointed person(s)
Principal investigator	PPD
Principal investigator	PPD
Co-investigator	PPD
Co-investigator	PPD
Marketing Authorisation holder contact	PPD

4 Abstract

Title

An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales.

Rationale and background

Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers in the EU.

Research question and objectives

Aim: To monitor the short-term (up to 12 weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as initiated to patients for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) by specialist HCPs in the secondary care hospital setting in England and Wales.

Objectives:

1. To quantify the cumulative incidence (risk and rate) of haemorrhage (major bleeding within intracranial, gastrointestinal and urogenital organ sites) occurring in the 12 week observation period
2. Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics
3. Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period
4. Quantifying the risk of other major or minor bleeding outcomes not specified in the primary objectives reported in the 12 week observation period overall and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in England and Wales.

Study design

This study will be a prospective observational, population-based cohort study of rivaroxaban with a contextual comparator (reference cohort). The rivaroxaban cohort consists of new rivaroxaban users (no anticoagulant prescription within 6 months prior to index date) with any combination of oral antiplatelet therapy for the prevention of atherothrombotic events following ACS. The contextual cohort consists of patients receiving the current standard treatment of care for the prevention of atherothrombotic events following an ACS (at least dual antiplatelet therapy, but not monotherapy) utilising the technique of specialist cohort event monitoring (SCEM), based on review of patient medical charts. The contextual comparator will be recruited concurrently to the rivaroxaban cohort in order to characterise the adoption of rivaroxaban into clinical practice and the prevalence of reasons for prescribing and those clinical characteristics which are known risk factors for the primary outcomes of interest.

Population

Patients in the secondary care hospital setting in England and Wales.

Variables

Demographic data on prescribers, a summary of non-clinical reasons for prescribing, demography (age and sex), indication, selected treatment details, medical history and medication use prior to or present on index date; changes on general health and medications during treatment, clinical events of medical interest.

Data sources

Medical chart based data collection from review of patient medical charts (secondary use of medical records information) in England and Wales.

Study size

A sample size of 1193 patients in each cohort (total 2386) is desirable for this study.

Data analysis

Summary descriptive statistics, event incidence risk and rate calculation and time to onset regression modelling will be used.

Milestones

One interim report 18 months after study start and one final report at 36 months.

5 Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	05/03/2013	All	Creation	-
2	31/03/2014	All	Amendment	Amended to incorporate comments from Bayer and additional updates
3	14/11/2014	12 Management and reporting of adverse events/ adverse reactions	Amendment	DSRU statement on reporting in light of GVP module VI
4	16/01/2015	10.7 Data analysis	Amendment	Addition of section to handle missing data Addition to limitation section
5	16/4/2015	PASS Information Section 5- abstract Various sections renumbering Addition of Annex 1 and 2	Amendment	Request from PRAC following review
6	24/03/2017	9.1 Study Design 9.2 Setting	Amendment	To broaden the inclusion criteria and minimize exclusions for patients prescribed rivaroxaban for ACS.
7	25/08/2017	4 Abstract 9.1 Study Design 9.2 Setting	Amendment	In response to the questions from PRAC

6 Milestones

Milestone	Planned date
Start of data collection	18th September 2015

End of data collection	18th September 2018
Interim report 1	1st November 2017
Final report of study results	August 2019

7 Rationale and Background

7.1 Rivaroxaban

Rivaroxaban, a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacements.(1) On 19 December 2011, the European Commission granted authorization of extension of the license of rivaroxaban to include prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of deep vein thrombosis (DVT) and Pulmonary Embolism (PE) and prevention of recurrent DVT and PE following an acute DVT in adults.(2) Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is also indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers in the EU, where approval was obtained in May 2013.(3) The marketing application for secondary prevention in ACS patients was based on data from the pivotal ATLAS ACS 2 TIMI 51 study (4) which showed that 2.5 mg of the drug twice daily significantly reduced the primary composite end point of cardiovascular death, MI, or stroke after ACS compared with standard oral antiplatelet therapy.

A Risk Management Plan (RMP) has been developed for rivaroxaban by the manufacturer. This plan includes tools designed to monitor the important risks (including class effects and off-label use).(5) A postmarketing safety study of rivaroxaban (XARELTO®) is to be carried out by the Drug Safety Research Unit (DSRU) as part of a broader Post-Authorisation Commitment requested by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of rivaroxaban in clinical practice, with a focus on ACS.

This Specialist Cohort Event Monitoring (SCEM) study, which is designed to monitor the safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as initiated by specialist healthcare professionals (hereafter Specialist HCPs)

within the secondary care hospital setting in England and Wales as part of a treatment strategy to reduce overall and cardiovascular mortality in patients with recent ACS, is one of three complementary studies conducted by the DSRU. One is another SCEM study, designed to monitor the safety and drug utilisation of rivaroxaban, as initiated by specialist HCPs for prevention of stroke and systemic embolism in adult patients with non-valvular AF, for the treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults. The third, based in primary care, is a Modified Prescription-Event Monitoring (M-PEM) Study, the aim of which is to proactively capture safety and drug utilisation data in the post-marketing phase of license approval of rivaroxaban as prescribed to patients by general practitioners in England for all relevant indications.

7.2 Acute Coronary Syndrome

The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) convened a consensus conference in 1999 in order to re-examine jointly the definition of myocardial infarction (published in the year 2000 in the European Heart Journal and Journal of the American College of Cardiology).(6) Given the considerable advances in the diagnosis and management of myocardial infarction since the original document was published, the leadership of the ESC, the ACC and the American Heart Association (AHA) convened, together with the World Heart Federation (WHF), a Global Task Force to update the 2000 consensus document.(7)

The acute coronary syndrome model espoused by the American College of Cardiology places unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) at increasingly severe points along a disease continuum.(6;8) At presentation, the working diagnosis of non-STE-ACS (NSTE-ACS), based on the measurement of troponins, is further classified into non-ST elevation MI, (NSTEMI) or unstable angina. The therapeutic management is guided by the final diagnosis.(9)

Registry data consistently show that NSTE-ACS is more frequent than STE-ACS.(10) The annual incidence is ~ 3 per 1000 inhabitants, but varies between countries.(11) Hospital mortality is higher in patients with STEMI than among those with NSTE-ACS (7% vs. 3-5% respectively), but at six months the mortality rates are very similar in both conditions (12 and 13%, respectively).(10;12;13)

Rivaroxaban is the only novel oral anticoagulant to have received a licence for this indication in the EU.

7.3 ATLAS ACS 2 TIMI 51

ATLAS ACS 2 TIMI 51 (Anti Xa Therapy to Lower cardiovascular events in addition to standard therapy in subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 51) study was published in the NEJM, in January 2012.(4)

The study recruited over 15000 patients diagnosed with a recent acute coronary syndrome. Patients were randomised to three different treatment groups receiving either placebo, 2.5mg Rivaroxaban or 5mg Rivaroxaban (both given twice daily). The mean duration of study treatment was 13 months, however patients were treated with rivaroxaban for up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke. The patients' medical condition was stabilized before enrollment into the trial, with the initial management strategies (e.g. revascularization) completed before entry. All patients received standard pharmacotherapy - including low dose aspirin; they received a thienopyridine (either clopidogrel or ticlopidine) according to the national or local guidelines. Randomization was stratified on the basis of planned use of a thienopyridine. Patients were seen at four weeks, at 12 weeks, and thereafter every 12 weeks. The primary safety end point was TIMI (Thrombolysis in Myocardial Infarction) major bleeding not related to coronary artery bypass grafting (CABG).

In the analysis of the two doses of rivaroxaban, each of the doses reduced the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke, as compared with placebo, with rates in patients receiving the 2.5-mg dose of 9.1% and 10.7%, respectively (hazard ratio, 0.84; 95% CI, 0.72 to 0.97; P = 0.02) and rates in patients receiving the 5-mg dose of 8.8% and 10.7%, respectively (hazard ratio, 0.85; 95% CI, 0.73 to 0.98; P = 0.03).(4) Rivaroxaban significantly increased the rate of TIMI major bleeding that was not related to CABG, as compared with placebo, and these events were lower in patients receiving the 2.5 mg dose than in those receiving the 5 mg dose.(4)

8 Research Question and Objectives

8.1 Overall aim:

The aim of this SCEM study is to proactively monitor the short-term (up to 12 weeks) safety and drug utilisation of rivaroxaban in combination with standard oral antiplatelet therapy as prescribed to patients for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) as initiated by specialist HCPs in the secondary care hospital setting in England and Wales.

8.2 Objectives:

Primary objective

- to quantify the cumulative incidence (risk and rate) of major bleeding according to the TIMI classification of non-CABG Related Bleeding (Table 1) occurring in the 12 week observation period, overall and stratified by the following bleeding sites:
  - Intracranial,
  - Gastrointestinal
  - Urogenital

Secondary objectives

1. Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics
2. Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period
3. Quantifying the risk of other major (in any other site not specified in the primary objective) or minor bleeding outcomes (in any site) reported in the 12 week observation period overall (Tables 1 and 2) and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in England and Wales.

Both the primary and secondary objectives relate to the rivaroxaban cohort and the contextual comparator (reference) cohort.

Exploratory objectives

The study will also include (for rivaroxaban cohort only) several exploratory analyses to

1) where possible, to quantify the incidence of other important identified, potential and special risks not mentioned in the primary objective and any other events reported during treatment with rivaroxaban; and

2) describe clinical features and management of cases of overdose, major bleeding (including bleeding sites specified in the primary objective, in addition to other major bleeds identified) (Tables 1 and 2) during observation of the cohort exposed to rivaroxaban.

Table 1. Haemorrhage outcomes (TIMI definitions for use in the primary secondary and exploratory objectives)

A non CABG related major[†] bleeding event will be defined using TIMI criteria as:
• Any symptomatic intracranial haemorrhage • Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL • Fatal bleeding (bleeding that directly results in death within 7 days)
A non CABG related minor bleeding event will be defined using TIMI criteria as:
• any clinically overt sign of haemorrhage that was associated with a fall in haemoglobin concentration of 3 to <5 g/dL
A CABG related major bleeding event will be defined using TIMI criteria as any of the following bleeding events that were CABG related:
• Fatal bleeding (bleeding that directly results in death • Perioperative intracranial bleeding • Reoperation following closure of the sternotomy incision to control bleeding • Transfusion of greater than or equal to 5 units of whole blood or PRBCs within a 48 hour period • chest tube output > 2 L within a 24 hour period

[†] The three organ sites included in the primary objective are gastrointestinal and urogenital, in addition to intracranial.

Table 2. Haemorrhage outcomes (Bleeding Academic Research Consortium [BARC] definitions for use in the secondary and exploratory objectives only)

Type 0
• No bleeding
Type 1
• Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2
• Any overt, actionable sign of haemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Table 2. Haemorrhage outcomes (Bleeding Academic Research Consortium [BARC] definitions for use in the secondary and exploratory objectives only) (continued)

Type 3
Type 3a
• Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed) • Any transfusion with overt bleeding
Type 3b
• Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid) • Bleeding requiring intravenous vasoactive agents
Type 3c
• Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal) • Subcategories confirmed by autopsy or imaging or lumbar puncture • Intraocular bleed compromising vision
Type 4: CABG-related bleeding
• Perioperative intracranial bleeding within 48 h • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period† • Chest tube output ≥2L within a 24-h period
Type 5: fatal bleeding
Type 5a
• Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
• Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
**Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).*
†Cell saver products are not counted.

9 Research Methods

9.1 Study Design

This study will be a observational, population-based cohort study with a contextual comparator (reference cohort) utilising the technique of cohort event monitoring (with retrospective patient chart review) to study the short-term (up to 12 weeks) safety and use of rivaroxaban in combination with standard oral antiplatelet therapy in patients following an ACS event, as initiated by specialist HCPs in the secondary care hospital setting. Secondary use of medical records information will be used in this study as specialist HCPs will be asked to abstract information from patient medical charts onto a questionnaire.

Twelve weeks observation is regarded as a period of time sufficient for data from all relevant patient populations (which informs on any post initiation health events related to short-term exposure that they might have experienced) to be recorded in medical charts.

In addition to the desire to study the use of rivaroxaban in combination with standard oral antiplatelet therapy in a population that is more heterogeneous than those observed in clinical trials, it is also desirable to put these observations into context. This will be achieved through comparison with current standard care treatments for the prevention of atherothrombotic events following an ACS in order to examine treatment decisions and differences. Therefore, a contextual cohort of evaluable patients treated with current standard treatment of care (dependent on clinical manifestation, early management and subsequent surgical intervention) will be recruited concurrently in order to characterise the adoption of rivaroxaban into clinical practice and the prevalence of (non-clinical)[1] reasons for prescribing and those clinical characteristics which are known risk factors for the primary outcomes of interest.(14) To avoid confusion, for the contextual cohort, patients who receive other factor Xa inhibitors or direct thrombin inhibitors will be excluded from the study.

According to the forthcoming NICE appraisal scope document for the use of rivaroxaban in the treatment of ACS[2] (15) the following possible contextual comparators have been

[1] Non-clinical reasons for prescribing include: factors associated with accumulation of authoritative evidence (formulary committee approval; recommendation from NICE; expert committee guidelines); and behavioural factors (personal expertise in treating condition; history of clinical success with similar treatments).

[2] http://www.nice.org.uk/media/6F2/BD/AcuteCoronarySyndromeRivaroxabanDraftScope.pdf

identified based on different clinical needs of subgroups (the contextual comparator will be a single group consisting of all possible standard of care combinations combined) :

- Clopidogrel in combination with aspirin
- Ticagrelor in combination with aspirin
- Prasugrel in combination with aspirin
- Additional dual antiplatelet therapies (not specified above)

After the pharmacotherapeutic treatment decision has been made by the clinician, such that the most appropriate treatment based on clinical need is prescribed, a patient will be invited to participate in the study and consent obtained for access to information from secondary care medical charts and general practice primary care medical charts via the GP. Participants will be invited to take part in the study by a member of the research or clinical team. This will usually be a research nurse, or practitioner, or clinical researcher or treating clinician (junior doctor or consultant).

To allow inclusion of patients with a previous history of ACS or other co-morbidities requiring antiplatelet treatment, a modified version of the new user design will be used in this study. The new user design will be used for the anticoagulant treatment and is defined as no use of oral anticoagulants including rivaroxaban within the 6 months prior to index date in both cohorts. In the rivaroxaban cohort, naïve users are defined as those who never used any oral anticoagulants in the past and they will be distinguished from non-naïve users in the analysis. The new user design will not be applied to antiplatelet treatments; ongoing antiplatelet treatment will be allowed in both cohorts and presented by naivety status.

Study start is defined as the date that the first patient is recruited into the study (18th September 2015), and continue for a maximum of 36 months, or until the target sample size (1193 tbc) for both cohorts has been achieved (whichever is the soonest). The final cohort sizes, period of observation and the duration of the SCEM study will be dependent on the level of prescribing of rivaroxaban in combination with standard oral antiplatelet therapy by specialist HCPs in England and Wales. Data collected during later calendar time periods can be compared with earlier periods to identify any trends that may emerge. Slow uptake may impact on the ability to meet the study objectives; in this instance, further discussions with the regulatory authorities regarding study feasibility will be needed.

Patients will be observed from the date antiplatelet therapy was prescribed as part of the acute management of the ACS in both the rivaroxaban group and the contextual

cohort for 13 weeks in order to allow for detection of outcomes associated with treatment initiation (this will allow for a delay between antiplatelet therapy administration as part of the acute treatment for the ACS, and the subsequent start of rivaroxaban to ensure 12 complete weeks of observation time for analysis). The index date for analysis for both groups will be defined dependent on the prescribing patterns observed in real life use. Since patient care is likely to be shared between secondary and primary care for most patients during the observation period, the patient's GP will be contacted[1] at least 13 weeks after antiplatelet therapy start date to complete an abridged questionnaire to collect any information on outcomes of interest that they are aware of during the observation period to minimise under-reporting on selected outcomes. For the main statistical analysis, events will be censored at 12 weeks post index date, should they be reported after this time period. However, events of interest will be included and detailed in study reports even if they occurred after the 12 week time period. Where additional outcomes are identified that have not be reported by the initiating prescriber, these will be followed-up with the GP to ascertain further information.

9.1.1 Strengths

- The observational and inclusive design allows for the surveillance of a diverse patient population under the care of specialist HCPs, particularly those with different characteristics in terms of underlying disease, co-morbidities and concomitant medications that would not have been included in clinical trials. Thus bias introduced through selection based on disease severity or type will be minimised. The approach also allows for surveillance of rivaroxaban when used off-label within the context of ACS.
- The prescribing of relevant pharmacological therapy should not be affected because of participation in this study, as the decision to prescribe has already been made prior to patient inclusion therefore the observational non-interventional nature of the study design is maintained.
- Data is collected on large numbers of cohorts given the relevant treatment combinations under study in conditions of routine clinical practice.
- Special populations can be characterised.

[1] Overlap of data collection between SCEM and M-PEM should minimise any under-reporting of events of interest associated with the primary objective. However due consideration should be given to a) possible non-response of GPs for the long-term M-PEM study that might arise from the GP's knowledge that the patient is participating in the SCEM and b) that some patients are managed by specialist GPs purely on an outpatient basis and thus may never be officially admitted to hospital. The emphasis must be made that the two studies are complementary and participation in both is highly desirable.

- Time-dependent effects can be examined. This method is longitudinal and thus will enable more reliable examination of exposures in relation to outcomes over time.
- By obtaining patient consent, additional information from medical charts from other clinical specialities may be examined for selected outcomes.
- Extension to monitor long-term safety is possible.
- The DSRU uses established networks of specialists in the UK to conduct such studies.

9.2 Setting

9.2.1 Selection of specialists

Specialists and members of their clinical team from within the secondary care hospital setting will be systematically identified across the country, facilitated where possible by existing clinical research networks, and will be invited to participate in the study prior to study start (exact date to be determined). These specialist HCPs will be informed that they will be participating in a cohort study which will monitor the use of rivaroxaban in any combination with standard oral antiplatelet therapy, in accordance with requirements within the Risk Management Plan. In addition they will be informed that a contextual cohort of patients taking standard antiplatelet combination therapy for secondary prevention following ACS will also be monitored.

9.2.2 Selection of patients

The accessible study population will be that portion of the target population of interest to whom participating HCPs have access. The identification of the study population, will be through (non-probability) systematic sampling whereby all consecutively identified[1] eligible new rivaroxaban user patients (within the context of ACS) treated by any specialist HCP (after the pharmacotherapeutic treatment decision has been made) and who provide consent (see section 10.3) will be enrolled until the desired sample size is reached. A corresponding procedure will be used for the contextual cohort. This method will be used because a probability sampling framework is not feasible and because participation within the study is not required as a condition of receiving treatment. This approach is intended to reduce conscious or unconscious selection bias on the part of the prescriber as to whom to enrol in the study, especially with regard to prognostic factors that may be related to prognosis.

New users of rivaroxaban will be comprised of rivaroxaban patients, who may or may not be naïve to anticoagulant treatment, with no use of oral anticoagulants including rivaroxaban prior to 6 months of index date and who are newly initiated by specialist HCPs after the ACS event. In the UK, when stabilised many patients may then have medicines management transferred to the GP in primary care. Thus, the GP may take on the primary role of monitoring treatment, providing prescriptions and altering the dose when necessary, with the option of referral to secondary care if and when required. Alternatively, the patient may be primarily managed within the secondary care hospital setting alone.

[1] As relevant to the date that the specialist HCP registers to participate in the study

By enrolling new rivaroxaban users (an inception or incidence cohort), this study avoids the introduction of a number of biases associated with existing users (including incidence/prevalence bias, survivorship bias, and follow-up bias). Furthermore, data will be available for the contextual comparator group which will have been collected prospectively during the same calendar period, for similar indications using the same data collection methods, and all subject to the same protocol.

A cross sectional random sample of investigative sites will be surveyed to explore the representativeness of the study population. Using medicines management audit information the demographic characteristics of patients treated for ACS will be examined and compared to those enrolled within this study.

Cohort recruitment will be examined regularly to monitor the number of evaluable patients included, so as to ensure that the desired ratio of 1:1 for the two exposure groups is achieved in the final overall study cohort for analysis.

9.2.3 Patient Inclusion Criteria

Since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria apply to maximise external validity. The inclusion criteria are:

- Age 18 years or above
- Patients newly prescribed rivaroxaban in any combination with standard oral antiplatelet therapy for the indication of secondary prevention in patients after ACS
- Patients prescribed dual antiplatelet therapy (contextual cohort) for the indication of secondary prevention after ACS
- Patients have provided signed, informed consent

9.2.4 Patient Exclusion Criteria

Patient exclusion criteria are:

- Patients prescribed with oral anticoagulants including rivaroxaban within 6 months prior to the index date for any indication
- Patients commenced rivaroxaban between date of market launch (28th October 2014) for the indication of secondary prevention after ACS and study start (18th September 2015)

9.2.5 Evaluable cohort

Evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaires. Evaluable patients for whom the 12 week survey questionnaire (from both specialist HCP and GP) is returned blank (contain no clinical information) or has not been returned will

only be included for analysis of secondary and exploratory objectives, where appropriate.

Consented patients will not be considered evaluable if the specialist HCP reports that the patient did not take either combination therapies. If there is evidence to suggest duplication of patients, either through inadvertent duplication between different prescribers within the same clinical setting, or if a patient was switched from one combination therapy to the other, then the records identified will be considered for inclusion on a case by case basis by the advisory committee.

Patients will be automatically withdrawn if the patient or specialist HCP provides informed written or verbal notification that they no longer wish to participate at any stage of the study.

9.3 Variables

9.3.1 Eligible patient baseline information

For all eligible patients invited to participate, the following anonymised information will be collected on a baseline questionnaire from the specialist HCP using information contained within medical charts:

- Demographic characteristics (age, gender)
- Setting of first prescription- (e.g. inpatient hospital ward, outpatient clinic)
- Reasons for prescribing (clinical judgement, recommendation from NICE, expert committee guidelines, trust formulary committee guidelines)
- Which anticoagulant/antiplatelet regimen was prescribed and start date
- Clinical condition requiring anticoagulant/antiplatelet therapy (indication) and details of the clinical condition (e.g. STEMI, NSTEMI)
- Any prior anticoagulant/antiplatelet treatment
- Risk factors for bleeding at baseline (e.g. creatinine, white cell count, anaemia, presentation, antithrombotic medications)

9.3.2 Patient 12 week end of observation questionnaire

For evaluable patients providing consent and for whom a completed baseline questionnaire has been received by the DSRU, at least 13 weeks after starting antiplatelet therapy, a second questionnaire will be systematically generated to collect clinical information from the specialist HCP relevant to start of observation and any clinical events of medical interest as recorded in the medical charts during the first 13 weeks (to ensure a full 12 week observation period post index date for each patient).

Data obtained from the 12-week end of observation questionnaire will include:

- Additional information on anticoagulation treatment regimen:
  - Details of prior use of oral and parenteral anticoagulant and antiplatelet therapy (e.g. thienopyridines, aspirin, glycoprotein IIb/IIa inhibitors, heparins) in the past 12 months if known
  - Treatment regimen during the 12 weeks observation period
  - If study treatment regimen has changed: date and reason for change, details of transition plan to alternative; if required, details of reversal of anticoagulation therapy and management of bleeding complication
- Recent (< 4 weeks prior to index date) and concomitant medications (at index or during treatment):
  - not recommended for concomitant use (including azole antimycotics [e.g. ketoconazole] and HIV protease inhibitors)
  - to be used with caution (including fluconazole, strong CYP3A4 inducers, strong P-gp inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, oral steroids, hormone and oral contraceptive therapy, platelet aggregation inhibitors or other antithrombotic agents)
- Medical history relevant for important potential, identified and special risks of interest (plus dates of first diagnosis/report)
- Specific information on renal function status and creatinine clearance at index date and any changes during 12 week observation period
- Specific information on hepatic disorders present at index date and any recent abnormal liver function tests
- Event reports including selected risks of interest (Table 3)
- Cause and date of death (if died) in the first 12 weeks after starting treatment;
- Behaviours prior to and/or starting treatment (e.g. smoking, alcohol/substance misuse)
- Demographic characteristics of specialist HCP; (age, sex, ethnicity, medical profession, year of first registration as HCP and awarding institution, specialism and year of first registration as specialist and awarding institution, year of start of employment at current institution)
- Institution type (teaching, general, private) and region of location
- Participation response/non-response rates (of eligible specialist HCPs within relevant existing research networks where available)

Table 3. Selected events of interest requiring further evaluation

Risk/Missing Information	Proposed data capture	Comment
IDENTIFIED, POTENTIAL AND SPECIAL RISKS AND OUTCOMES for targeted data collection on SCEM questionnaires		
Non CABG major bleeding episode	Targeted outcome questions on major bleeds	Selected risk factors collected on SCEM questionnaire. Further data on severity, management and risk

		factors to be collected via follow-up.
Non CABG minor bleeding episodes	Targeted outcome question on minor bleeds	Selected risk factors collected on SCEM questionnaire. Not for follow-up
Overdose, accidental trauma and Reversal of anticoagulation therapy	Targeted outcome question	Events of overdose (dose > 50mg/day) and accidental trauma are those of clinical medical importance which require acute medical/surgical treatment (with or without) hospitalisation Further data may be collected via follow-up
Management of homeostasis	Targeted outcome question	Data on management of homeostasis in patients reported with events of surgery (elective or urgent) during the observation period will be collected via follow-up
Increased liver transaminases and Gamma-Glutamyl Transferase (GGT)	Targeted outcome question	Data on diagnosis of hepatic failure and where abnormal laboratory results indicate 3 X ULN relevant parameters will be collected via follow-up.
Concomitant use of contraindicated medications and medications to be used with caution	Targeted outcome question on other medications to gather duration and changes	Further data may be collected via follow-up
IMPORTANT MISSING INFORMATION for general surveillance		
Use during pregnancy and lactation	General event report	Further data to be collected via follow-up

9.3.3 Abridged 12 week end of observation questionnaire for GP

For evaluable patients providing consent and for whom a completed baseline questionnaire has been received by the DSRU, at least 13 weeks after starting antiplatelet therapy, their GP will be contacted and invited to complete an abridged "end of observation" SCEM questionnaire. This will gather information on clinical events of medical interest reported since the date of discharge from secondary care up to the end of the 12 week observation period, and recorded within patients medical charts. This may not be required for all patients and will be dependent on the care pathway, as some patients may not be seen again by the specialist. The purpose of sending an abridged questionnaire to the GP is to ensure complete information on the primary outcomes of interest is obtained where possible. Data obtained from this abridged 12 week SCEM questionnaire will include:

- Anticoagulant/antiplatelet treatment regimen which the patient had received
- Event reports of selected risks of interest (Table 3)
- Cause and date of death (if died)
- Date and reasons for treatment regimen change (if changed) including switching
- Any newly prescribed concomitant treatments

9.3.4 Follow-up Questionnaires

During the course of the study, selected outcomes of interest (arising from Table 3) may undergo further evaluation for aggregate assessment of drug- relatedness to inform on any unusual features/manifestations, relevant risk factors, clinical course and behaviours. Where necessary, a supplementary follow-up questionnaire which is bespoke to the outcome of interest may gather additional relevant information where recorded within medical charts.(16)

With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection will occur post survey period. In accordance with Good Pharmacovigilance Practice (GVP) sections VI.C.1.2.1 and VI.C.2.2.2,(17) data will be analysed at aggregate level partially at the time of compiling the interim report (because all information may be available then) and at study completion. Such aggregate analyses can help formulate possible hypotheses which then require further analytical study. Because of the epidemiological nature of the design of this cohort study, any conclusions on drug-relatedness will be made on aggregate basis at study milestones, i.e. when the interim and final reports are written (see Section 12.1.1 on Communications).

If any other safety issues become apparent during the conduct of this study, additional events and/or event categories may be added to the list of events for follow up and this will be documented accordingly.

Specific events of interest for further evaluation:

1. Deaths: All reported deaths will be followed-up to try to establish the cause of death.

2. Events: Selected events of interest as defined in Table 3 may be followed-up for additional information on relevant risk factors, where insufficient information is provided on the questionnaire. The event of switching given as a reason for changing treatment regimen (although not defined in Table 3) will undergo further evaluation, though may not be followed up.

3. Adverse events: Other adverse events deemed of medical importance by the DSRU which are considered to be possible safety signals (either arising from literature reports post marketing, or subsequent to interim data analysis) may also be followed-up for additional information on relevant risk factors for signal strengthening purposes.

4. Adverse events: Events within the list of Rare and Iatrogenic Adverse Reactions (RAIDAR) compiled by the DSRU (Annex 1) will be automatically followed up if a more likely alternative explanation for their occurrence is not given.

9.3.5 Methods to Maximise Questionnaire Response Rate

Patient 12 week end of observation questionnaire

A proportion of Specialist HCPs or GPs are likely to fail to submit these questionnaires. Methods to maximise response rates will include prompts from study facilitators by phone, email and personal contact and reminder questionnaires targeted at those who have not responded within one month of the date the initial questionnaire was sent.

Specific event follow-up questionnaires

A duplicate event follow-up questionnaire will be sent to specialist HCPs or GPs for the specific patient(s) for whom they have not responded to the initial follow-up questionnaire; within six weeks of the date the initial event follow-up questionnaire was sent. Specialist HCPs and GPs will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

9.4 Data Sources

Medical chart based data collection in this study will be conducted in various phases; relevant documentation (such as information leaflets, questionnaire, consent forms, etc) will be available both as hard copies and electronically for download by the participating specialist HCPs.

9.4.1 Recruitment

This first phase will have two parts.

<u>Part 1: Recruitment of eligible specialist HCPs.</u>

The DSRU will allocate a unique study reference number to each participating specialist HCP for study audit and data management processes.

<u>Part 2: Recruitment of eligible patients initiated with the study drug combination under clinical care of participating specialist HCPs.</u>

For all eligible consented patients invited to participate, the specialist HCP or a member of their clinical team, will be asked to record anonymously (using the study reference number provided on patient study documentation) a summary of non-clinical reasons for prescribing, demography (age and sex), indication and selected treatment details onto a simple questionnaire and submit these data to the DSRU coordinating centre either through a secure online website, or via surface mail. Date of recruitment into the study

will also be recorded by the specialist HCP, if known, or, retrospectively once the consent form is obtained, by the DSRU research staff. The unique study reference number allocated to each patient will be used for study audit and data management processes.

9.4.2 Exposure and outcome data

This second phase will also have two parts.

Part 1: Covariate data

Thirteen weeks post antiplatelet therapy start date, the specialist HCP will be prompted to complete a second questionnaire which will gather information on medical history and medication use prior to or present on start date; changes on general health and medications during treatment and clinical events of medical interest. For some patients, the patient's GP will also be contacted to complete an abridged end of survey questionnaire. This will depend on the care pathway and whether the specialist HCP will have any further contact with the patient after discharge to primary care.

Part 2. Follow-up.

Events of interest will be collectively evaluated to inform on clinical features that may be important when considering drug-relatedness; this requires follow-up using event-specific questionnaires sent to the specialist HCP (see 9.3.4) or GP depending on reporter. With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection will occur post the survey period.

9.5 Study Size

The ability to detect an adverse event is dependent on the expected incidence rate of the adverse event in those exposed to the drug, the background rate in those not exposed to the drug, and the total number of patients.

Where studies, such as clinical trials, have already estimated the impact of the exposure on the outcome of interest, the objective should be to estimate the magnitude of the effect as precisely as possible (21). As such, in this study it is more appropriate to choose a sample size that will yield a confidence interval of a predefined width for those identified risks defined within the primary outcome which are of greatest clinical and medical importance i.e. major bleeding outcomes. Table 4 displays the samples sizes (95% confidence intervals) across a range of expected incidences and levels of precision.

From rivaroxaban clinical trial data, the cumulative incidence risk of first occurrence of adjudicated major bleeding events (intracranial, GI and urogenital) in patients taking rivaroxaban for secondary prevention after ACS over the first 12 weeks of treatment was approximately 0.5% (0.1%, 0.3% and 0.1%). Thus in this population of patients with ACS treated with rivaroxaban, in order to estimate the expected (true) cumulative incidence of primary outcomes of major bleeding events of 0.5% within +/- 0.4%, we would ideally need a sample size of 1193 patients (Table 4). An equivalent number of patients within the contextual comparator cohort is desirable.

Table 4. Sample sizes of evaluable patients required to estimate the expected (true) cumulative incidence of a specified adverse event with 95% confidence intervals of different precisions (0.2% to 5%).

Incidence from RCT (%)	Precision 0.2%	Precision 0.3%	Precision 0.4%	Precision 0.5%	Precision 0.6%	Precision 1%	Precision 2%	Precision 3%	Precision 5%
0.10	958	426	240	153	107	38	10	4	2
0.20	1913	851	479	307	213	77	19	9	3
0.30	2864	1275	718	459	319	115	29	13	5
0.40	3812	1698	956	612	425	153	38	17	6
0.50	4755	2119	1193	764	531	191	48	21	8
0.70	6631	2958	1666	1067	741	267	67	30	11
0.80	7564	3376	1902	1218	846	305	76	34	12
1.00	9418	4208	2371	1519	1055	380	95	42	15
1.25	11716	5241	2955	1893	1315	474	119	53	19
1.50	13991	6267	3535	2265	1574	567	142	63	23
2.00	18475	8296	4684	3003	2087	752	188	84	30
3.00	27187	12268	6938	4452	3096	1117	279	124	45
4.00	35566	16126	9135	5866	4081	1473	369	164	59
5.00	43627	19871	11276	7246	5043	1821	456	203	73

9.6 Data Management

9.6.1 Data Processing

Specialist HCP/ GP/ patient identifiable information will be stored within a unique database. All original documents and individual correspondence from HCPs will be stored for 15 years at the DSRU, with considerable care taken to preserve patient confidentiality (see below).

9.6.1.1 Review of data

All returned questionnaires with clinical data will be coded onto the study database. Medically important adverse events selected for follow-up will be coded as a priority. There will be a regular monthly review of both the number of patients identified and study questionnaires returned, processed, and classified as void. This will assist in determining the point at which the final cohort size will be achieved. Aggregate data will be reviewed at interim and end of study milestones.

9.6.1.2 Coding of data

Data on indications, exposure, relevant medical history and medication use plus events of interest will be coded directly from targeted closed format questions on the questionnaire (which reference Medical Dictionary for Regulatory Activities (MedDRA) terminology) and coded onto the bespoke study database. Other events reported on the questionnaires as free text will be coded onto this database using the DSRU Event Dictionary Doctor Summary Term synonym list that is mapped to MedDRA, in order to enable consistent reporting to be provided using MedDRA terminology.

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific SCEM database and will be maintained within the DSRU. Regular meetings of DSRU staff will be held to discuss study questionnaires that are difficult to code. A consensus opinion will be reached by medically qualified staff.

9.6.1.3 Confidentiality procedures

All DSRU staff sign confidentiality agreements and the DSRU is registered with the office of the Data Protection Registrar (Registration No. Z5438861).

DSRU information security policies are in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring the premises provides suitable physical and environmental security, all DSRU equipment is secure and protected against malicious software, the network can only be accessed by authorised DSRU staff, telecommunication lines to the DSRU premises are protected from interception by being routed overhead or underground and personal receive training regarding security awareness.

All original documents, individual correspondence from specialist HCPs, will be stored for 15 years at the DSRU, with considerable care taken to preserve the confidentiality of data. The DSRU databases are well protected. To ensure patient anonymity, the names and addresses of patients will be deleted from the DSRU database at an appropriate time point (provisionally this is at datalock or earlier if patients have provided informed

notification that they wish to withdraw from the study, but the DSRU will request an extension to this to comply with CHMP requirements). Until this time, only appointed staff would have access to such data.

9.6.2 Project Advisory Committee

A Project Advisory Committee (AC) will be set up to be comprised of the study investigators and other experts. The role of the AC will be to oversee the smooth running of the project and provide scientific, statistical and technical advice when needed and will meet at regular intervals (3 to 12 monthly depending on the stage of the study, either in person or by teleconference).

The AC is broadly analogous to a Safety Monitoring Committee or Review Board, but the purpose may be slightly different in that the AC advises on the effective progress of the study. The first AC meeting will orientate the project team members and establish the logistics for specialist and patient recruitment and confirm patient inclusion criteria. Subsequent AC meetings will clarify the understanding of the ongoing project requirements, monitor progress through assessment of data within the interim reports [specialist/cohort accrual rates, preliminary analyses of individual variable responses on questionnaires], consider any additional proposed inclusion criteria, and act as a forum to review and discuss any queries.

9.7 Data Analysis

The data analysis plan and study objectives will be constructively aligned to meet study aim.

9.7.1 To quantify the cumulative incidence (risk and rate) of major bleeding according to the TIMI classification of non-CABG Related Bleeding (Table 1) occurring in the 12 week observation period, overall and stratified by intracranial, gastrointestinal and urogenital bleeding sites.

The following relates to Section 8.2 primary objective and relates to haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a TIMI major non CABG related bleed) and all intracranial sites (as defined in Table 1). This time to event analysis will be performed separately for the rivaroxaban exposed cohort and the contextual cohort, as defined according to exposure at index (date antiplatelet therapy was prescribed as part of the acute management of the ACS).[1]

[1] In the event of a change in treatment resulting in a switch in treatment group, person-time contributed will be censored at the time of switching, thus analysis will not be 'intention to treat' as this is an observational study.

For each cohort, for whom acute management of ACS applies[1], the numerator for this analysis will comprise of adjudicated incident major bleeding events (overall and stratified by intracranial, gastrointestinal and urogenital bleeding sites) defined according to primary objective that were reported during the 12 week observation period post index date. These adjudicated events will have been reviewed by an expert panel using all available information from SCEM questionnaires, follow-up and any additional documentation. Patients for whom events were misreported will be excluded from the analysis (events will be excluded, but denominator data will still be included); patients for whom events were misclassified will be reclassified as appropriate. In addition, for each cohort, for the three organ sites specified in the primary outcome, counts of each of the individual components of the TIMI major non CABG related bleeding criteria will be summarised. Where an individual has one or more criterion for an individual organ site of interest, counts will also be summarised – in such individuals the first report will be regarded as the incident event. Since SCEM data are right censored, the cumulative incidence (risk and rate) of the primary outcomes reported during treatment within the 12 week observation period will be calculated using survival analysis methodology.

For each individual case, relevant person-time will be estimated according to duration of observation up to event date. For each individual non-case, relevant person-time will estimated by either exit date – index date; or censor[2] date – index date; or stop date (+ 2 days [3]) – index date. For each cohort separately, a semi-parametric time-dependent Cox Proportional Hazards regression model will be used to estimate the crude cumulative incidence over the 12 week observation period.

Non-parametric Kaplan-Meier plots will be presented to describe time-to event as well as smoothed estimates of the empirical hazard function to describe how the crude baseline risk of the event changes over time.

Estimates of the hazard function will also be modelled to determine whether the baseline hazard (risk) of the event increases or decreases with time. A constant hazard over time may be consistent with a background (not caused by the drug) event rate, whereas a non-constant hazard over time may be an indicator of a drug-event relationship. The null hypothesis that the hazard rate of the selected event in patients will be constant during the 12 week period following the start of treatment will be tested

[1] This excludes patients prescribed rivaroxaban 2.5mg for non-ACS related indications

[2] Censor date = date of loss to follow-up

[3] 2 days allocated to person-time to account for half-life of drug

by fitting a parametric time to event model (e.g. Weibull). Such models have a shape parameter that indicates whether the hazard is significantly increasing or decreasing over time. At least five reports of an event are deemed necessary for modelling purposes.[1]

Several sensitivity analyses will be performed to assess the robustness of findings. In one, the possible impact of misclassification of exposure because of possible immortal time on hazard estimates will be explored. In the primary analysis, patients within either cohort may have the same entry event prior to chosen exposure to treatment regimen, however the proportion of unexposed survival time is unknown, particularly for the rivaroxaban cohort where rivaroxaban is regarded as an add-on therapy. The inclusion of a time-varying covariate to define exposure status (0 before time of first rivaroxaban or standard care prescription and 1 after until end of observation) will enable examination of the impact of the transition from existing treatment regimen given as part of initial standard care to additional anticoagulation therapy on the results. In addition, since the primary analysis will be run only to include all reported cases of incident major bleeding irrespective of adjudication to explore the impact of exclusion of incomplete cases on the estimated hazard.

Where possible, data may be stratified according to relevant strong risk factors (e.g. gender, age ($\leq$60, 60-74, $\geq$75 years), indication and past history of haemorrhage) considered significant from a univariate analysis performed to explore associations of potential risk factors on case status, with calculation of stratum-specific incidence rates.

Graphs of cumulative counts of events of interest, by month over the study period, will be examined for possible change in reporting over calendar time.

9.7.2 Advancing the understanding of the patient population prescribed rivaroxaban in combination with standard oral antiplatelet therapy for ACS in the secondary care hospital setting including drug utilisation characteristics

The following relates to Section 8.2 secondary objective 1.

[1] e.g. when the shape parameter (p) for the Weibull model is equal to one, the hazard is estimated to be constant over time, if p is greater than one the hazard is increasing, if p is less than one the hazard is decreasing. The hazard function will be determined as non-constant if the 95% CI excludes the value one

9.7.2.1 Descriptive exploratory analysis

Valid cohort demography (patient self-reported: age, gender, ethnicity, socioeconomic index) will be presented separately for both rivaroxaban and the contextual cohort, as reported at index date using all available information from questionnaires (completed by patient and specialist HCP). Other patient self-reported general health factors [BMI, weight, height, smoking and alcohol use] and indication-related characteristics [primary (and secondary if provided) diagnosis/decision, date and duration since first ever recorded; reported bleeding risk factors]; antiplatelet treatment initiation programme by specialist HCP (index date, dose and frequency) and prescribing reasons. A synopsis of pre-index and concurrent relevant morbidities and medication use will also be provided.

For rivaroxaban cohort only, patient subgroups of special interest (Table 5 – 'off-label' use defined as arising from contraindications and those for which: a) precautions for use are recommended; b) appropriate clinical monitoring is recommended; c) limited information is available; and d) selected concomitant drug use) will be summarised in order to inform on real-life use of rivaroxaban. The proportion of patients within each special population sub-group prescribed rivaroxaban who had *one or more* relevant characteristics/conditions/co-prescribed medications at index date will also be summarised within each indicator group by simple aggregation of counts (Table 5).

Further stratification within-cohort by calendar period *may* also be undertaken to identify any cohort effects or trends that may be emerging.

Table 5. Special Population Indicators of Use for Rivaroxaban

5a) Indicators of Contraindicated Use *(Patients can have up to 5 indicators)*
Treatment for medical indications other than licensed indications
Clinically significant active bleeding
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk

Use in pregnancy and lactation
Hypersensitivity to the active substance or to any of the excipients
5b) Indicators of Use with Special Warnings or Precautions *(Patients can have up to 11 indicators)*
Patients with liver cirrhosis with moderate hepatic impairment (classified as Child Pugh B), not associated with coagulopathy
Severe renal impairment (patients with creatinine clearance < 30 ml/min)
Moderate renal impairment (patients with creatinine clearance 30-49 ml/min)
Congenital or acquired bleeding disorders
Uncontrolled severe arterial hypertension
Active ulcerative gastrointestinal disease
Recent gastrointestinal ulcerations
Vascular retinopathy
Recent intracranial or intracerebral haemorrhage
Intraspinal or intracerebral vascular abnormalities
Recent brain, spinal or ophthalmological surgery.
5c). Indicators of Use in Patients with Limited Information *(Patients can have up to 1 indicator)*
Children aged $\leq$ 15 years
5d) Indicators of Use with Potential Drug-Drug Interactions *(Patients can have up to 4 indicators)*
Concomitant systemic treatment with azole-antimycotics, e.g ketoconazole or HIV protease inhibitors
Concomitant treatment with CYP3A4 inhibitors/inducers or P-gp inhibitors
Concomitant treatment with other anticoagulants
Concomitant use with NSAIDs and platelet aggregation inhibitors

9.7.2.2 Understanding treatment decisions between trusts

A multilevel framework approach with its simultaneous examination of characteristics of individuals at one level and the setting in which they are located at another level offers a contextual framework for understanding the way in which setting can affect patient health. Clustering can also arise from sampling strategy; this SCEM study involves HCPs within hospital settings as well as individual patients which generates a hierarchical clustered structure. Individual patients treated by the same HCP within a hospital can be expected to be more similar than if sampling were truly random. Because of hierarchical structure of the data, with patients (first level) nested within HCP specialist clinics (second level) which are in turn nested within trusts (third level) the probability of prescribing rivaroxaban will be analysed using multilevel logistic regression analysis of pooled study data. This type of analysis reveals the role of different levels for understanding drug prescription and utilisation. Thus it will enable the study of a) the influence of the patient, HCP and trust characteristics on anticoagulation use simultaneously and b) the variance in prescribing.

The multivariate analysis will inform on the influence of those characteristics identified for each level as significant from a univariate analysis of association between those characteristics and treatment (rivaroxaban or not). A base model will describe the crude association between treatment decision, HCP and trust. This will give the variance estimate for levels 2 and 3 without correcting for differences that might exists in patients within each cluster. In the first model, the variance estimates for levels 2 and 3 will be obtained, accounting for significant predictors (identified from univariate analysis). This will inform on which patient characteristics are associated with treatment with rivaroxaban. The association between selected fixed level 1 patient characteristics and prescribing anticoagulation medication will be expressed using odds ratios and 95% confidence intervals from the regression coefficients and their standard error (SE) in the fixed-effect part of the multi-level analysis. In the random-effects part of the multi-level analysis, the variance (SE) at HCP and trust level will be obtained as will the variance that is unexplained by these patient characteristics. A second model will allow level 2 HCP factors to be explored, whilst a third model will allow level 3 (trust) factors to be explored. Thus this analysis will identify source of variation in prescribing and identify whether there are significant differences in treatment decisions between trusts after taking into account individual differences.

9.7.3 Describing changes of health profile of patients, assessment of adherence, number of indication related episodes (ACS related events), plus any alterations of the treatment programme in respect of antiplatelet and anticoagulant therapy during the 12 week study observation period

The following relates to Section 8.2 secondary objective 2. Status of indication-related characteristics (alteration of diagnosis and bleeding risk score if available) will be summarised, plus pattern of antiplatelet treatment adherence at the end of the 12 week observation period (as estimated from Medication Possession Ratio[1]) will be summarised. The frequency and reasons for attendance to clinics for review and management of ACS and/or acute hospitalisations (including hospital referrals) will also be summarised, where reported. Alterations in treatment programme (change in dose, other drugs) will be described, as will any reason(s) for changing treatment regimen (including switching) and transition plans to other antiplatelets.

Changes in these indication-related characteristics and treatment details will be examined by comparing values at index and at 12 weeks post index date. Exploratory analysis may include data mining and descriptive measures for describing alterations in treatment programme.

The number of pregnancies, trimester of first exposure and details of births, terminations and miscarriages will be presented. The number of deaths (as recorded in medical charts) in the total cohort for each month of exposure will be calculated. Causes of death will also be described by system-organ class.

Sensitivity analyses will examine any under-reporting using data provided from the patients GP.

[1] For this study, MPR will be defined as: $\frac{\text{No. days supply held during treatment}}{\text{No. days supply expected during treatment}} \times 100$

Where no. days held will be calculated from information derived from 12 week questionnaire on number of prescriptions and average treatment length of prescriptions (usually given in 7, 14,28,56 day repeats); no. days supply expected will assume chronic use from start to end of study observation or treatment stop date (if stopped)

9.7.4 Quantifying the risk of other major (in any other site not specified in the primary objective) or minor bleeding outcomes (in any site) reported in the 12 week observation period overall (Tables 1 and 2) and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in England and Wales. Also, where possible, to quantify the incidence of other important identified, potential and special risks not mentioned in the primary objective and any other events reported during treatment with rivaroxaban (rivaroxaban cohort only)

The following relates to Section 8.2 secondary objective 3 and exploratory objective 1) and 2) regarding a) other major and minor bleeding outcomes not specified in the primary objectives in both cohorts and b) any other events reported in the 12 week observation period for rivaroxaban cohort only.

For major bleeding events not specified in the primary outcome, each of the individual components of the major bleeding will be summarised. Where an individual has one or more criterion for an individual organ site of interest, this will also be summarised – in such individuals the first report will be regarded as the incident event.

For minor bleeding events, each of the individual associated components (as per Table 1) will be summarised. Where an individual has one or more criterion for a minor bleeding event, this will also be summarised – in such individuals the first event report will be regarded as the incident event.

Analysis of event data for purposes of signal detection includes exploring overall risk and rate for the observation period and time to onset profiles. The methodology provides a numerator (the number of reports of an event) and a denominator (person-time at risk), both collected within a known time frame. This allows for the calculation of crude risks (percent of total valid cohort exposed) and rates (Incidence Densities-ID; person-time incidence rates) for each event separately. Each event may be reported in response to a closed question (for example information on each individual major and/or clinically relevant non-major bleeding risk component), or as free text in response to open questions on the data collection forms. Such analyses will be performed using 'Higher-level' event terms from the MedDRA dictionary where possible. The risk profile of the overall cohorts and sub-group of interest (based on index date characteristics, including whether anticoagulant naïve, rivaroxaban naive or past (other anticoagulant user) will be described by presenting summary tabulations (by rank) of counts and incidence risk of reported events, and crude event rates (IDs).

Calculating and ranking crude ID rates is one of a number of standard quantitative evaluations used in event monitoring methodology for signal generation purposes as part of initial inspection of all event data for general safety surveillance. It is used as a means of alerting early potential signals as priorities for further evaluation. Medical judgment however is also part of this evaluation and prioritization process. Crude Incidence Densities (ID)[1] can be calculated by week in order to quantify rates of events. IDs will be calculated, for each given time period (t), for all events reported in patients who continue to take rivaroxaban for a given time period, or for whom the date of stopping is known. Only the first report of an event in an individual patient is used in the calculation of IDs. They are usually expressed as the number of first reports of an event per 1000 patient-weeks. This assumes the pattern of use is continuous. The numerator will be the first reports of events reported as occurring after the index date and during treatment.[2] For this study, IDs will be calculated for each event for each week as follows:

$$ID_t = \frac{\text{Number of first reports of an event during treatment for period t} \times 1000}{\text{Number of patient-weeks of treatment for period t}}$$

$$\text{Thus, } ID_t = \frac{N_t \times 1000}{D_t}$$

where: N_t = Number of first reports of an event during treatment for period t,

and D_t = Number of patient-days of treatment for period t / 7

IDs will also be calculated for each event for all 12 weeks during treatment combined (ID_A), and the first week after stopping (ID_{SW1}) if patient stopped (and where patients are recorded as remaining on treatment for at least 1 week) after index date.

Sensitivity analyses will examine any under-reporting by including events of interest recorded in primary care medical charts and confirmed on follow-up for those patients discharged to primary care, during the 12 week observation period.

As IDs for the overall cohort may sometimes mask significant signals in specific risk groups, the subgroups defined by specific characteristics (e.g. previous history of ACS or haemorrhage, previous/concurrent use of selected medications, off-label indication

[1] It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

[2] Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.

groups, rivaroxaban naïve or past user) will have IDs calculated and compared according to strata for relevant events, where appropriate.

It is possible to explore the time taken for an event of interest using parametric time to event models (e.g. Weibull) as described previously, thus providing an additional tool for signal generation purposes. This approach will be explored for events of interest, where counts $\geq$ 5. If undertaken, a sensitivity analysis will be performed to include in the numerator events reported within seven days of stopping, and extend the denominator by seven days.

9.7.5 To describe clinical features and management of cases of overdose, major bleeding (including bleeding sites specified in the primary objective, in addition to other major bleeds identified) (Tables 1 and 2) during observation of the cohort exposed to rivaroxaban.

The following relates to Section 8.2 exploratory objective 2) for the rivaroxaban cohort only. A qualitative assessment of these cases will include evaluation of patient demographic characteristics, treatment details, the detection and clinical features and management of events of interest, resolution, relevant investigations prior to and during therapy, the patient's relevant medical history and concurrent medication and any sequelae. Data will be derived from the SCEM and follow up questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table.

Selected events of interest (Table 3) that require further characterisation and evaluation may be followed-up via a questionnaire sent to the responsible specialist HCP or patient's GP seeking further information. The information received at follow-up for events of medical significance or those which require further clarification will facilitate further evaluation at the aggregate level. Where it is appropriate to do so, drug relatedness assessments may be performed on selected events. The aim of the collective drug-relatedness assessment for groups of events during the analysis of the interim and final reports, is to put events in context regarding temporality co-morbidity, pre-existing disease and concomitant medications. This aggregate assessment of event data occurs at interim or final report for cases for which all requested information (i.e. baseline questionnaire, 12 week end of observation questionnaire and follow-up questionnaire if applicable) has been received. In the process of aggregate assessment of event data, the application of elements of the Austin Bradford Hill criteria, when the necessary information is available and the use of the method is considered appropriate, will be used (see Box 1).(18)

Box 1. Points for consideration in collective evaluation of reported events

- *The distribution of time to onset (temporal relationship);*
- *The principle clinical and pathological characteristics of the group of events;*
- *The pharmacological plausibility based on previous knowledge of the drug and the therapeutic class if appropriate;*
- *Similar reports in medical literature*
- *patient's clinical characteristics, including:*

- previous medical history, such as history of drug allergies, presence of renal or hepatic impairment, etc.

-concomitant medications or medications taken prior to and during treatment;

- *Management and remedial action;*

Where undertaken, the collective drug-relatedness of selected groups of events of interest will be categorised in terms of proportions of reports assessed within the following four categories: 1) probable[1], 2) possible[2], 3) unlikely[3] and 4) not assessable[4].(19)

9.7.6 Missingness

Missing data are those where a variable is directly reported as missing or unavailable, where a variable observation is blank, where the reported data may not be interpretable, or where the value must be imputed to be missing because of data inconsistency or out-of-range results. It is not possible to fully predict the pattern of missingness for each study variable; however several approaches will be initially undertaken to mitigate the potential for missingness in the process of data collection:

[1] Events are assessed as 'probable' if the event is well defined clinically and pathologically, if there is a reasonable time sequence, if it is more likely to be attributed to the study drug rather than to a concurrent disease or concomitant medication, if there is a positive dechallenge, rechallenge or response to dose increase, and if there are other supporting criteria (e.g. on the basis of lab tests or histological findings).

[2] Events are assessed as 'possible' if the event has a reasonable clinical and pathological definition, if there is a reasonable time sequence, if it could also be explained by concurrent disease or concomitant medication, but dechallenge, rechallenge and confirmatory investigations are inconclusive or not fully available. Medical judgement will be necessary in some cases.

[3] Events are assessed as unlikely if the event had a temporal relationship to the study drug administration that made a causal relationship improbable, or if concurrent disease or concomitant medication provided a far more plausible explanation.

[4] Events are unassessable if insufficient information about the event has been provided and an appropriate evaluation is therefore not possible.

1. Collection of data within questionnaires will be through use of closed questions with binary response (Y/N) where possible. Responders who are uncertain will be encouraged to review available information to provide suitable response.
2. Returned questionnaires will be examined upon receipt for data completeness. The responder will be contacted to obtain the missing or correct information and data revised as appropriate on source document when possible.
3. Reminders will be sent for those questionnaires where the document has not been received as anticipated in accordance with return dates.
4. Each patients' GP will be contacted to obtain information on key study variables – this supplementary information will contribute to identification of relevant cases, where information may be missing from questionnaires completed by specialists

Specific methods to handle issues of missing or conflicting data, will be summarised within the detailed study specific Data Management Plan (DMP) which will be constructed to assist database development and data analysis. In brief, the missingness pattern of primary covariates and proportions thereof in the study subjects will be presented to explore plausibility of missing at random (MAR) assumption to justify subsequent regression analysis. Multiple imputation is planned. However, we will compare the results of this to a complete case analysis. If the two are substantially different we will evaluate what the reasons may be. Thus, imputation will be performed using STATA SE 12 ICE imputation for exposure variables with less than 20% missing data and a sensitivity analysis conducted to determine magnitude and direction of bias arising from missing data from complete case analysis as relevant to Section 8.2 primary and secondary objectives.

9.8 Quality Control

Good clinical data management is a high priority at the DSRU. A number of strategies exist to minimise biased study results. The DSRU has a set of rules and processes associated with the conduct of pharmacoepidemiological studies. Data quality is assured through a number of methods based on error-prevention, data monitoring, data cleaning and documentation. These include:

- Operator training
- Vigilance of operators at the various stages of processing
- On screen validation during data entry
- Adoption of and adherence to study-specific data coding conventions
- Coding review meetings
- Code list and algorithms

- Double entry (random sample of 10% of questionnaires), error reporting and correction of discrepancies between the entries by quality assurance staff
- Coding of questionnaires are randomly reviewed by a quality assurance assessor
- Routine data cleaning to screen for errors, missing values and extreme values, and diagnose their cause; this being supported by bespoke software with objective, standardised logical checks and undertaken by the DSRU data manager or allocated staff
- Relevant maintenance of reference tables
- Pilot testing of study documentation

9.9 Limitations of the Research Methods

- Possible delay in new user cohort accrual if adoption by secondary care hospital trusts and specialists is low.
- Since this is an observational epidemiological study, we recognise several potential sources of bias. The most important is selection bias and the possibility that the cohorts will not be representative of the population for who anticoagulation is clinically desirable for ACS. Because of the nature of patient recruitment, bias in recruitment may be introduced by some participating specialists through awareness of some form of remuneration (regardless of how and when payment is made). The same number of patients treated with other treatment combinations for ACS will be collected to explore factors which may contribute to selection bias. We have deviated from the new user design for antiplatelet treatment. This was done to allow inclusion of patients who might already be antiplatelet users for primary or secondary prevention of ACS. Although this deviation may have implications for the bleeding risk because these patients may have a higher baseline risk at start of rivaroxaban use, this allows inclusion of rivaroxaban patients that would otherwise be excluded based on a new user design.
- Knowledge of which patients will be participating may affect the non-interventional nature of observational research, however this will probably be minimised by the fact that they are members of broad research networks within the UK healthcare system. It is also possible that specialists who participate in the study will be a self-selected group, but we do not believe that this selection bias will affect the types or number of events experienced and reported by a patient after treatment has been initiated.
- Confounding by indication is a form of selection bias where the disease that forms the indication being treated (irrespective of severity) is not only associated with treatment but also an independent risk factor for selected outcomes (events of interest) in patients not exposed to antithrombotic agents. This needs to be examined since such channelling may result in apparent association of increased

risk of such events in this population. It may be introduced through prescribing of treatment based on certain characteristics of a patient. For this study, patients for whom prior alternative treatment was poorly tolerated or ineffective may be selectively prescribed the new treatment.

- Confounding by severity is possible and needs to be accounted for.
- Under- and mis- reporting of outcomes is possible; specialist HCPs' notes may be incomplete with regard to medical history and non-cardiovascular related outcomes of interest associated with current treatment. The two-phase data capture approach could facilitate compliance with data reporting as well as spreading workload for specialist HCPs. By obtaining information from all patients GPs and access to primary medical charts, under ascertainment of outcomes can be minimised. In contrast, over-recording of health related events in the period following the administration of the baseline questionnaire are possible due to increased specialist HCP attention to special populations of interest (patients with concomitant complications) as detailed in the questionnaire, however since information is being abstracted from medical charts such bias is unlikely. However, this is likely to be similar in the contextual cohort.
- Regarding the definition of bleeding, in this study case definitions are based on acceptable agreed clinical standards and aim to address specific regulatory questions in the context of the risk management plan for the product.
- Immortal time bias is possible arising from misclassification of exposure to the study drug.
- With this patient population, patient attrition and loss to follow-up may introduce selection bias, however, the relatively short period of observation should mitigate this possibility at least to some extent.
- Misclassification bias will be minimised by well defined outcome and follow-up of medically important events. Patients with selected events of interest will be followed-up with regard to co-prescribed medicines and concurrent illness. Events that represent features of the respective indications will be taken into account when safety signals are investigated (i.e. confounding by indication).
- Furthermore unidentified poor adherence may also lead to misclassification of exposure. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be ascertained. Whilst it is not possible to be sure the patient used the medication, it is almost certain that the patient received it since starting treatment is required for study participation. This is unlikely to be significant in this patient population, and for the 12 week period of observation.
- The potential exists for misclassification of mild renal failure since severe forms of renal failure will be more readily identified. However, to limit this, specific information about renal function (e.g. eGFR and serum creatinine levels) will be

collected during the course of the observation period to provide details of renal function.

9.10 Other aspects

Not applicable

10 Protection of Human Subjects

10.1 Good pharmacovigilance practices

Studies conducted by the DSRU are undertaken according to national and international guidelines for ethical conduct ofresearch involving human subjects (20-23). Following the principles of good pharmacovigilance practice (17;24;25), a full protocol is written for each study to monitor and research the safety of medicines.

10.2 Confidentiality

Patient information security is assured through strict measures as laid out in the DSRU Information Governance Policy.

10.3 Patient consent

For this cohort study, ethics approval via IRAS (integrated research application system) in the UK will be required. Participating specialist HCPs will be asked to provide patients with documentation (with a unique study reference code). Patient study documentation will include a patient information sheet about the study which will describe that their primary and secondary care medical charts will be accessed during the time-frame of active study data collection by the HCP and/or DSRU research staff in order to extract exposure and outcome data relevant to the 12 week observation period[1]. It will also provide contact details of the DSRU study team if they have any questions.

Specialist HCPs will provide patients with a consent form so that patients can consider and give consent for their participation within this project. The consent form will stress confidentiality, that no specific details of their treatment will be released to external parties, that the patient may withdraw consent at any time by contacting either the specialist HCP or the DSRU study research team directly, and that the patient will not be asked to attend clinics more than usual or undergo any additional treatment or questioning. The consent form will also request information to be provided on patient ethnicity, current marital status, current employment status, smoking and alcohol use. This is optional and will be used to inform on representativeness of study cohort. Three

[1] The exception will be if a female patient becomes pregnant, the outcome of the birth will be requested.

signed copies are required. Those patients who wish to inform the DSRU immediately of their decision will give the signed consent form to the specialist HCP. They in turn will send the original to the DSRU, retain one copy for their records and issue a copy to the patient.

For those patients who wish to have a further opportunity to reflect on their participation, the specialist HCP will ask the patient to complete a 'consent to contact' form, which will enable DSRU study research staff to contact the patient through their preferred route of contact (surface post, email, or telephone) after a period of at least two days to obtain consent. This will be the only point at which DSRU research staff will contact the eligible patients directly. If the patient agrees to participate, they will sign the consent form , retain a copy and send the original and one further copy via surface mail to the DSRU study coordinating centre, or, if preferred, to the specialist HCP (who will then submit the original form to the DSRU). Receipt of the signed consent to contact form or the fully completed consent form (if patient provides immediate consent) by the DSRU study team should be within four weeks after index date, if possible.

In addition, within the same time frame, the specialist HCP will be asked to summarise selected data from the medical charts (non-clinical reasons for prescribing, demographic and treatment details) using a simple questionnaire (anonymised using the patient's allocated study reference number) and send these data to the DSRU coordinating centre either through a secure electronic website, or via surface mail.

11 Management and Reporting of Adverse Events/ Adverse Reactions

For SCEM, study data are derived through secondary use of medical records information as abstracted onto study specific questionnaires by specialist HCPs in England and Wales. For observational studies based on secondary data collection, individual adverse reaction reporting is not required. Reports of adverse events/reactions should only be summarized in the observational study report, where applicable. As a consequence, the DSRU does not have any direct reporting requirements to the competent regulatory authorities. The DSRU shall on an ongoing basis notify the Marketing Authorisation Holder (MAH) when they consider, based on their evaluation, that any issues or matters of interest relating to the Study or its outcomes are of importance and shall provide the MAH with related results of the study and analyses thereof. The DSRU will comply with the requirements of GVP Module VI in the appropriate way that it applies to our study.

Aggregate event data is collated during the course of this study. Since the clinicians are prescribing a licensed product, it is their responsibility to report any suspected adverse reactions (including serious adverse drug reactions) to the company and/or to the MHRA using Yellow Cards as they would normally do in their practice. Reports received by the DSRU in error are forwarded to the MHRA and/or the MAH as appropriate.

12 Plans for Disseminating and Communicating Study Results

12.1 Communications

Progress reports (relevant to specialist and patient cohort accrual) will be produced in time for inclusion in the scheduled regular updates of the RMP for and Periodic Safety Update Reports for the product as long as the study continues. Examination of aggregate event data will be limited to one interim report on the valid cohort achieved at approximately 18 months post date of first patient recruited; and a detailed final report based on a study cohort of per protocol evaluable patients or on the valid cohort achieved at approximately 36 months post date of first patient recruited, whichever is the sooner (unless an extension to study period is required).

12.1.1 Reporting

The DSRU shall on an ongoing basis notify the MAH when they consider, based on their evaluation, that any issues or matters of interest relating to the study or its outcomes are of importance and shall provide the MAH with related results of the study and analyses thereof. The DSRU shall deliver interim and final reports in accordance with the Protocol and with content sufficient for the MAH to meet its regulatory obligations. The DSRU will comply with the requirements of GVP Module VI in the appropriate way that it applies to our study.

12.1.2 Study sponsorship

This study is being undertaken by the DSRU as part of the Risk Management Plan for the product at the request of the Committee for Medicinal Products for Human Use (CHMP). The Drug Safety Research Trust is a registered independent charity (No, 327206) operating in association with the University of Portsmouth and is the sponsor of the study. For this study, the DSRU (the academic sponsor) will receive support from Bayer.

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Annex 1 List of Stand-alone documents

Number	Document reference number	Date	Title
1	1	16/4/2015	DSRU RAIDAR list

Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales.

Study reference number:
SCEM ACS (SN 17542)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☒	☐	
1.1.2 End of data collection[2]	☐	☒	☐	
1.1.3 Study progress report(s)	☒	☐	☐	47
1.1.4 Interim progress report(s)	☒	☐	☐	47
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	47

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Dates to be confirmed following outcome of ethics application; study to be registered post approval

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	14
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	14
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

There are no formal hypotheses to be tested in this study

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	28
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	31

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	21
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	21
4.2.2 Age and sex?	☒	☐	☐	21
4.2.3 Country of origin?	☒	☐	☐	21
4.2.4 Disease/indication?	☒	☐	☐	21
4.2.5 Co-morbidity?	☒	☐	☐	21
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	22

Comments:

Seasonality is not applicable in this study

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and	☒	☐	☐	28

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
categorising exposure)				
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	22
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Exposure is based on specialist prescription of rivaroxaban, as reported by the specialist from the patients medical charts

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	31
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	27
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	27
8.1.3 Covariates?	☒	☐	☐	28
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	27
8.2.2 Endpoints? (e.g. date of occurrence, multiple event,				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
severity measures related to event)	☒	☐	☐	27
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	27
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	30
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	27,28

Comments:

Events (diseases/outcomes) are reported as recorded in patient medical charts, then coded into MedDRA by the DSRU. Exposure on study drug and medications is based on prescription records. for analysis purposes, medications will be presented according to ATC classification system, not a classification system. Specailist, patient and questionnaires will be linked using unique study reference number in this study.

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	28

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	31
10.3 Are descriptive analyses included?	☒	☐	☐	31
10.4 Are stratified analyses included?	☒	☐	☐	31
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	33,36
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	36

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	41
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	30,31
11.3 Are methods of quality assurance described?	☒	☐	☐	42
11.4 Does the protocol describe possible quality issues	☒	☐	☐	43

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
related to the data source(s)?				
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	31

Comments:
project Advisory Committee

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	43
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	43
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	43
12.3 Does the protocol address other limitations?	☒	☐	☐	43

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	45
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	30

Comments:
Ethics application has been submitted but outcome is not available yet

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	47
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	47

Comments:

Name of the main author of the protocol: PPD

Date: 24/4/2015

Signature: PPD

Annex 3. Additional information

Not applicable

Appendix 2. Recruitment strategies

Drug Safety Research Unit (DSRU)

Rivaroxaban in Acute Coronary Syndrome

Recruitment Strategies

January 2019

PPD

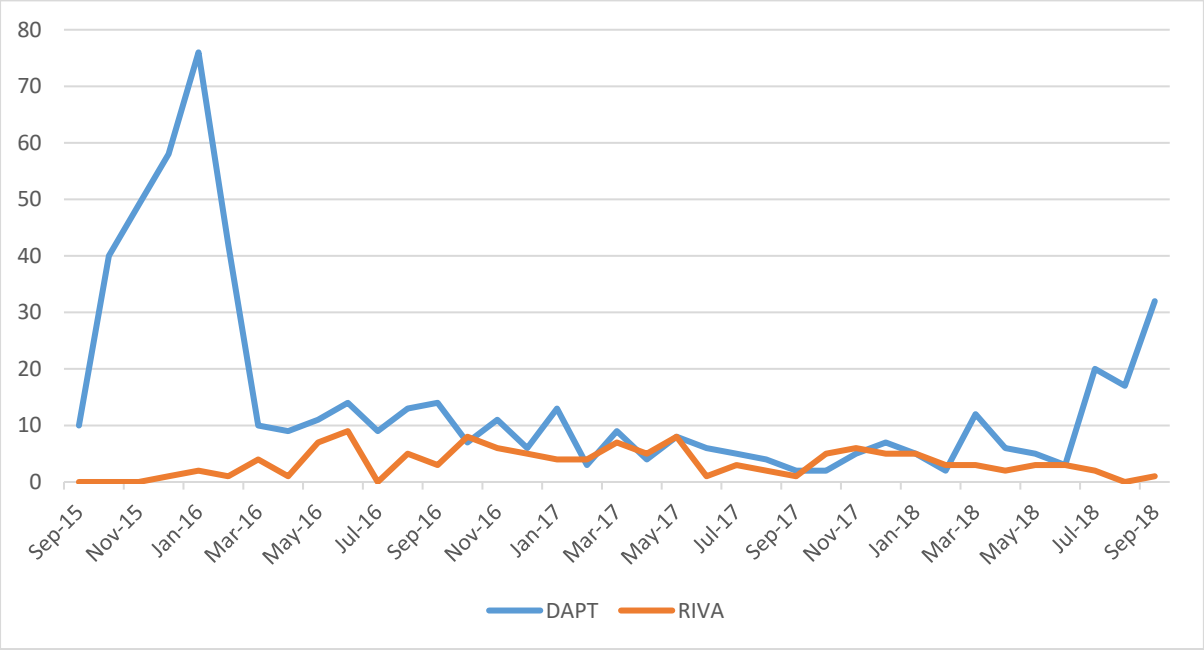
PPD

This report discusses the strategies which have been undertaken throughout the study to improve recruitment of rivaroxaban patients, these are detailed below.

Initiatives to Appropriately Maximise Recruitment and Raise Awareness

Given the current paucity of rivaroxaban patients that were being recruited to the ROSE-ACS study and the rate at which new rivaroxaban patients were being recruited (Figure 1), the study looked unlikely to achieve its recruitment target within the designated timeframe. The DSRU therefore proposed a number of strategies to increase the cohort size. These are detailed below and included broadening the inclusion criteria and minimizing exclusion criteria and implementing additional recruitment strategies with the aim of further improving identification of rivaroxaban patients.

Figure 1. Monthly recruitment of rivaroxaban and DAPT over the course of the study



1 Amendment to the Protocol Regarding Eligibility Criteria

In order to supplement the ROSE-ACS study with additional patients that reflected the current clinical practice being observed, the inclusion and exclusion criteria were amended such that:

- Patients prescribed rivaroxaban plus a single antiplatelet were included, as opposed to the requirement for rivaroxaban plus at least dual therapy;

- Patients could have previously received rivaroxaban for the indication of secondary prevention after ACS provided it wasn't within 6 months prior to study start, as opposed to the exclusion of any patients for whom any past use of rivaroxaban was recorded for secondary prevention after ACS.

The protocol amendment was accepted by the Pharmacovigilance Risk Assessment Committee (PRAC) 30th November 2017 and resulted in the inclusion of an additional five patients.

2 General recruitment strategies

The DSRU maintained active channels of communication with NHS Trusts throughout the duration of the study via regular contact by email and phone calls however feedback continuously suggested that the use of rivaroxaban for the indication of secondary prevention in patients after ACS was low. The majority of trusts who declined to take part indicated that rivaroxaban for the indication of ACS was currently not on their formulary, not included within Trust guidelines, or was not considered to be standard practice.

A total of 120 sites were granted Health Research Authority (HRA) approval in England i.e. they were potential recruitment sites for the study. This encompassed all the potential sites in England i.e. did not include specialist sites such as Children's, Community or Mental Health Trusts. A total of 29 Trusts underwent their local approval; 15 of these Trusts recruited patients during 2017 however only eight Trusts were still actively recruiting in 2018. In addition two further sites were approved in Wales, however only one of these recruited to the study. Within these sites in England and Wales, a total of 34 HCPs were engaged in the study[1]. The majority of the sites who stopped recruiting did so due to the fact that they could not recruit rivaroxaban patients for the ACS indication.

During the study, the DSRU also received information from Bayer on the current use of rivaroxaban for the indication of ACS and were provided with a list of the centres which had ordered the 2.5mg rivaroxaban tablet. All these trusts were contacted; of the top six centres from where 80% of orders came from, only two participated, three declined to take part and one site did not respond.

The DSRU continued to enlist the support of the Clinical Research Network in disseminating details of the study to all their local research networks and engaging with the Research Delivery Manager to raise the study's profile at meetings and via the Cardiovascular Specialty Group. Throughout the duration of the study, the DSRU also undertook additional generalised

[1] This is correct at the time of the Interim report (October 2017)

recruitment strategies to further improve patient recruitment to the study. These are detailed below:

Study promotion

- Via consultant meetings, local study/research team meetings, investigator meetings, local research conferences (including British Cardiovascular Society and British Cardiovascular Intervention Society) and a regular study newsletter
- ROSE-ACS Study poster was provided to and made visible by healthcare staff in order to heighten awareness of the study amongst healthcare professionals
- Study remuneration reminders were sent to ensure return of completed questionnaires
- Letters were sent to the prescribers to thank them for their contribution and encourage their continued involvement in recruiting patients

Recruiting new investigators

- All trusts not previously involved were approached or re-approached to request participation in the study.
- Principal Investigators and Trust Research and Development departments were contacted to request assistance and advice on recruitment in their trust.
- All cardiologists in the trusts were contacted to invite them to participate in the study, with face-to –face meetings where possible.
- Contacted nurse prescribers and other non-clinicians and members of the care team who had the potential to recruit eligible patients.
- Correspondence letter communicated from the Co-Principal Investigators (Dr Mark de Belder and Professor John Camm) to other cardiologists requesting their support of the study and help in identifying patients.

Incentives to investigators

- Research capacity building
  - To provide evidence of participation in research (e.g. certificate) for all study investigators who recruited and completed at least one patient, for professional portfolios.
  - To enhance local research collaborations by enabling secondary use of site specific study data for prescribing service evaluation

Communication

- Provided regular updates to investigators/research staff on trust recruitment, including end of month updates to investigators to summarise regional recruitment.

- Emailed each new registered prescriber, offering support.

Prescription data from M-PEM study

Table 1 presents data on the 2.5mg rivaroxaban dose for the DSRU's complementary M-PEM study conducted in primary care. This data represents the number of dispensed 2.5 mg rivaroxaban prescriptions in primary care per month from October 2014 to June 2016 and the corresponding number of new patients. As can be seen from the table, the number of patients per month with a 2.5mg prescription is very low and these patients may not necessarily have had a reported ACS indication. Of the 154 patients where evaluable data was provided, only 100 were reported by the GP to have been initiated on a 2.5mg tablet. In addition, only 25 of these patients had an indication associated with ACS. Based on these results, the MPEM data does appear to reflect the low usage and therefore recruitment seen in the SCEM study.

Table 1. Prescription data for 2.5mg rivaroxaban from the M-PEM study[2]

Time Period	No. of Prescriptions	No. of Patients
Oct-14	2	2
Nov-14	1	1
Dec-14	11	11
Jan-15	16	11
Feb-15	33	17
Mar-15	42	21
Apr-15	39	12
May-15	53	25
Jun-15	54	14
Jul-15	40	12
Aug-15	74	22
Sep-15	79	17
Oct-15	60	14
Nov-15	88	19
Dec-15	66	22
Jan-16	60	21
Feb-16	190	59
Mar-16	221	49
Apr-16	208	39
May-16	227	39
Jun-16	241	39

[2] Data captured up to June 2016

ROSE ACS
Rivaroxaban Observational Safety Evaluation post Acute Coronary Syndrome

BASELINE CASE REPORT FORM

IMPORTANT ▶

Patient Study Identification Code

PSIC				

Investigator Study Identification Code

ISIC				

PATIENT DETAILS

1. Provide the following demographic characteristics for the patient

Year of Birth (yyyy)					Sex	Female ☐	Male ☐

CURRENT CONDITION AND TREATMENT

2. Specify the indication requiring oral antiplatelet / anticoagulant treatment (Tick ✓all that apply)

Prevention of atherothrombotic events in adults after an Acute Coronary Syndrome (ACS)	☐
Other	☐
If Other, specify:	

3. Give details of the type of ACS and date of hospital admission (Tick ✓all that apply)

		Date of admission (dd/mm/yyyy)
ST-segment elevation myocardial infarction (STEMI)	☐	/ /
Non-ST segment elevation myocardial infarction (NSTEMI) with raised biomarkers	☐	/ /
Unstable angina	☐	/ /
Other	☐	/ /
If Other, specify:		

4. Indicate which of the following medications were prescribed for secondary prevention of atherothrombotic events either <u>during or following the admission with ACS</u> and whether the patient was already taking the drug on admission (Tick ✓yes or no for each drug)

	Total daily dose (mg)		Prescribed for secondary prevention		Already taking on admission	
	Dose	If Other dose, specify	Yes	No	Yes	No
Aspirin	75 ☐	Other ☐	☐	☐	☐	☐
Clopidogrel	75 ☐	Other ☐	☐	☐	☐	☐
Prasugrel	10 ☐	Other ☐	☐	☐	☐	☐
Ticagrelor	180 ☐	Other ☐	☐	☐	☐	☐
Rivaroxaban	5 ☐	Other ☐	☐	☐	☐	☐
Other	☐		☐	☐	☐	☐
If Other, specify drug name and dose:						

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BASELINE CASE REPORT FORM

(Note: there is no need to provide details relating to secondary prevention medication already being taken on admission)

5. Indicate the setting in which medications were initiated for secondary prevention either during or following the admission with ACS and provide date prescribed (Tick ✓all that apply)

	In patient ward	Outpatient clinic	GP	Date prescribed (dd/mm/yyyy)
Aspirin	☐	☐	☐	/ /
Clopidogrel	☐	☐	☐	/ /
Prasugrel	☐	☐	☐	/ /
Ticagrelor	☐	☐	☐	/ /
Rivaroxaban	☐	☐	☐	/ /
Other	☐	☐	☐	/ /
If Other, specify:				

6. Has the patient received any of the following direct factor Xa or direct thrombin inhibitors (oral anticoagulant treatment(s)) at any time prior to this admission with ACS?

a) Ever (Tick ✓ yes or no for each drug)

Name	Ever		Indication for treatment
	Yes	No	
Rivaroxaban	☐	☐	
Apixaban	☐	☐	
Dabigatran	☐	☐	
Other	☐	☐	
If Other, specify:			

b) Within the 6 months prior to admission (Tick ✓yes or no for each drug)

Name	Within last 6 months		Indication for treatment
	Yes	No	
Rivaroxaban	☐	☐	
Apixaban	☐	☐	
Dabigatran	☐	☐	
Other	☐	☐	
If Other, specify:			

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BASELINE CASE REPORT FORM

REASONS FOR PRESCRIBING

7. Give reasons for prescribing the current secondary prevention regimen selected in Q4 above. (Tick ✓all that apply)

Clinical judgement	☐
Recommendation from NICE	☐
Expert Committee Guidelines	☐
Trust formulary committee guidelines	☐
Patient choice	☐
Other	☐
If Other, specify:	

BLEEDING RISK ASSESSMENT

8. Confirm the results of the following blood tests performed on admission with ACS (Tick ✓all that apply)

Serum Creatinine (μmol/L) on admission						
<88 ☐	88-106 ☐	107-124 ☐	125-141 ☐	142-159 ☐	160-177 ☐	>177 ☐

White blood cell count on admission (10^9/L)						
<10.0 ☐	10.0-11.9 ☐	12.0-13.9 ☐	14.0-15.9 ☐	16.0-17.9 ☐	18.0-19.9 ☐	≥20 ☐

Haemoglobin on admission (g/L)						
<80 ☐	80-89 ☐	90-99 ☐	100-109 ☐	110-119 ☐	120-129 ☐	>130 ☐

Thank you for completing the case report form
Please return to:

PPD
PPD Tel: PPD

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SO31 1AA

Form Study Identification Code

FSIC				

ROSE ACS
Rivaroxaban Observational Safety Evaluation post Acute Coronary Syndrome

Patient Information Sheet

You are being invited to take part in a research study. This is a safety study and not a clinical trial. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Please ask us if there is anything that is not clear or if you would like more information.

What is Acute Coronary Syndrome (ACS)?

ACS can be caused by a blood clot that forms within a blood vessel in the heart. This can lead to either chest pain (angina) or a heart attack, and requires immediate hospital admission.

The purpose of the study

Rivaroxaban (Xarelto®) is a relatively newly introduced medication which reduces the formation of blood clots. It is used for the following:

- To prevent further blood clots in patients who have already had ACS. It would be used in combination with other blood thinning agents (antiplatelet therapy)
- To prevent blood clots in the brain or in other blood vessels in the body in patients with an irregular heart beat
- To prevent and treat blood clots in the legs and lungs

All drugs undergo extensive study before being made available on the market. In addition, all new drugs undergo routine surveillance by the regulatory body that is responsible for the use and safety of medicines in the UK.

This study aims to collect more information on the use of rivaroxaban and its safety when used by patients following ACS, for the first three months after starting. This study was requested by the European regulatory body (The EMA) which is responsible for the use and safety of medicines. It will last for approximately three years and is a national study covering the whole of England and Wales.

Who can take part?

Any patient aged 18 years or more who is started by their consultant care team on rivaroxaban and antiplatelet therapy (e.g. clopidogrel, aspirin) or dual antiplatelet therapy without rivaroxaban will be eligible to take part. Not everyone that participates in the study will be prescribed rivaroxaban; you may have been prescribed aspirin and clopidogrel, for example.

Each patient will only be monitored for the first 13 weeks after hospital admission for ACS.

Why have you been chosen?

You have been chosen because your care team have decided, based on their clinical opinion, that either rivaroxaban and antiplatelet therapy or dual antiplatelet therapy only is the most appropriate treatment for your condition.

What is the difference between the ROSE study and the ROSE-ACS study?

You may have heard of the ROSE study or know somebody involved in it. This is another study conducted by the DSRU that monitors the use and safety of rivaroxaban in patients compared to warfarin. The ROSE study focuses on patients who have been prescribed rivaroxaban, at higher doses (for example, 15mg twice daily), for the prevention or treatment of blood clots in other parts of the body. ROSE ACS, however, will only involve patients who have been prescribed rivaroxaban, at a lower dose (2.5mg twice daily), plus antiplatelet therapy or dual antiplatelet therapy for the prevention of blood clots in the heart following an ACS event.

Do you have to take part?

It is up to you to decide whether or not to take part once you have read this sheet, spoken to your care team and/or seen or spoken to a member of our study team. This will not affect the medical care and treatment that you receive. If you do decide to take part you will keep this information sheet and be asked to complete and sign a consent form. You are still free to withdraw at any time by writing to your specialist or the study research team without giving a reason and your medical care will not be affected.

Do you have to decide right now?

No. You may take away this documentation and think about it. If you do, we only ask that you complete and sign the 'Consent to Contact' form and return it to a member of your care team. This form does not commit you in any way to take part in the study, but allows the study research staff to contact you within the next few days to ask for your decision. This will be the ONLY time that you will be contacted directly by the research staff in this study. There is a telephone number you can ring PPD or you can email any queries to: PPD during this time.

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What will happen to you if you take part?

If you choose to take part and give your consent, we ask that you answer a few simple questions on the back of the consent form. The study team will also ask your care team to answer some simple questions about you (about the dose of medication you are taking, other medications you are taking or have taken, other illnesses you have or have had in the past, and your general health). This information will be obtained from your healthcare charts between the time you start your medication and 13 weeks later (specifically asking about your experiences whilst on the medication). If anything unusual is noted in your medical charts during that 13 week period, we may ask your care team to fill out a further follow-up questionnaire at a later date.

Will your GP be informed?

We would like to inform your GP that you are participating in the study, if you give your consent to do so. We can do this only if you provide your GP's address on the consent form. We will also send your GP a short questionnaire to see if you are still taking the medication and if anything unusual was noted in your primary care medical charts.

Do you have to have any additional tests?

No other examinations or tests will be performed as part of this research. You will NOT be given any experimental treatment or medication as part of this study.

What do you do if you decide you don't want to take part anymore?

You can contact your care team or the study research team at any time during the study (address is at the end of this letter). This is best done in writing or by email.

In the unlikely event of a loss of your present ability to provide informed consent, the research team will retain any data collected and continue to use it confidentially for this study.

Will your taking part in this study be kept confidential?

The information you give is entirely confidential and will not be disclosed to anyone outside the research team without your permission, although we will inform your GP that you are participating, if you give your consent to do so.

What will happen to the results of the research study?

We expect the results of the research will be submitted for publication in a medical journal in a few years time. A copy of the publication will be obtainable from the Drug Safety Research Unit (DSRU). You will not be identified in any publication, and no personal information will be used.

Who is organising and funding the research?

The study is to be carried out independently by the DSRU in Southampton, although it receives financial support from Bayer, the manufacturers of Xarelto®.

Who has reviewed the study?

The National Research Ethics Service South Central Hampshire A Research Ethics Committee has reviewed the study.

Contact for Further Information

PPD Study Manager,
PPD
PPD

Independent information about taking part in health research is available from the Association of Research Ethics Committees at www.arec.org.uk.

Thank you for considering participation in this study. If you agree you will be given a copy of the information sheet and a signed consent form to keep.

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Local Information

ROSE ACS
Rivaroxaban Observational Safety Evaluation post Acute Coronary Syndrome

Main Consent Form

IMPORTANT ▶

Patient Study Identification Code

PSIC				

Investigator Study Identification Code

ISIC				

PATIENT DETAILS

Patient Name

Patient Date of Birth | | | / | | | / | | | | |

Patient Address

Post code

NHS number | | | | | | | | | | |

Hospital number | | | | | | | | | | |

Please initial here ▼

PATIENT CONSENT

1.	I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3.	I give permission for relevant parts of my hospital notes and GP medical charts to be accessed in connection with this study.	
4.	I agree to my GP being contacted to find out more information about my treatment in connection with this study.	

GP CONTACT DETAILS

Name

Address

Postcode Telephone No.

5.	I agree to information, from which I can be identified, being held by the research team at the Drug Safety Research Unit together with data collected during the study.	
6.	I agree to take part in the ROSE-ACS study.	
7.	I agree for the research team to contact me in the future about further Drug Safety Research studies.	

....
Name of Patient (PRINT) Date Signature

....
Name of Person taking consent (PRINT) Date Signature

Please answer the questions overleaf

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Please return to:

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Form Study Identification Code

FSIC				

ROSE ACS
Rivaroxaban Observational Safety Evaluation post Acute Coronary Syndrome

Main Consent Form

IMPORTANT ▶

Patient Study Identification Code

PSIC				

Investigator Study Identification Code

ISIC				

*These questions are **optional. You do not have to complete this section.** Your answers to the following questions will help us to evaluate how successfully we are gathering information from all sections of society.*
You do not have to answer every question.

1. Please tell us how you would describe your gender:

Male ☐	Female ☐	Prefer not to say ☐

2. Please tell us what your current marital status is:

Married ☐	Co-habiting ☐	Single ☐
Separated ☐	Divorced ☐	Widowed ☐
Other ☐	Please describe	

3. Please tell us what your current employment status is:

Full-time employment ☐	Part-time employment ☐	Unemployed ☐
Student ☐	House husband/wife ☐	Self-employed ☐
Other ☐	Please describe	

4. Please tell us what your ethnic background is:

White ☐	Black African ☐	Black Caribbean ☐
Black - other ☐	Please describe	
Indian ☐	Pakistani ☐	Bangladeshi ☐
Chinese ☐		
Any other ethnic group ☐	Please describe	

5. Please tell us what your current weight and height:

If you don't know please ✓ tick ☐	
Height - metres & centimetres	OR feet & inches
Weight - kilogrammes	OR stones & pounds

6. Please tell us about your smoking habits (if any)

Current smoker [a] ☐	Never smoked ☐
Ex-smoker [b] ☐	Ex-occasional smoker [b] ☐
Exposed regularly to second-hand smoke at own/others' home, work, public place ☐	

[a] smoked within past year;
[b] smoked more than 1 year ago

7. Please tell us how often you have a drink containing alcohol

Never ☐	Monthly or less ☐	2-4 times a month ☐
2-3 times a week ☐	4 or more times a week ☐	

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GP OUTCOME DATA CASE REPORT FORM

IMPORTANT ▶ Patient Study Identification Code

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All questions must be answered in full, to the best of your knowledge.
Where appropriate, yes or no tick boxes must be checked
Many thanks for your cooperation

PATIENT DETAILS

1. Is the patient currently registered with the practice?

Yes ☐	No ▼ ☐
If **NO**, date deregistered (dd/mm/yyyy)	/ /

2. Has the patient died?

Yes ▼ ☐	No ☐
If **YES**, date of death (dd/mm/yyyy)	/ /
Immediate cause of death:	
Underlying cause/condition(s):	

CURRENT ANTIPLATELET TREATMENT

3. Have one or both of the antiplatelets been stopped for any reason?

Yes	☐	Give details below
No	☐	

Drug name	
Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
Number of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping:	

Drug name	
Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
Number of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping:	

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4. If one or both of the antiplatelets HAVE been stopped, have they subsequently been restarted?

Yes	☐	Give details below
No	☐	

Drug name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted treatment	
Dose	
Frequency	
OR Total daily dose	

Drug name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted treatment	
Dose	
Frequency	
OR Total daily dose	

5. If one or both of the antiplatelet therapies HAVE been stopped, has the patient been prescribed an alternative antiplatelet therapy?

Yes	☐	Give details below
No	☐	

Drug Name	
Date started (dd/mm/yyyy)	/ /
Treatment details of new antiplatelets	
Dose	
Frequency	
OR Total daily dose	

Drug Name	
Date started (dd/mm/yyyy)	/ /
Treatment details of new antiplatelets	
Dose	
Frequency	
OR Total daily dose	

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6. If treatment with initial dual antiplatelet agents has NOT been stopped, have any changes been made to the treatment regimen?

Yes	☐	Give details below
No	☐	

Drug name	
Date changed (dd/mm/yyyy)	/ /
Details of revised treatment	
Dose	
Frequency	
OR Total daily dose	

Drug name	
Date changed (dd/mm/yyyy)	/ /
Details of revised treatment	
Dose	
Frequency	
OR Total daily dose	

CONCURRENT MEDICATION USE

7. Has the patient taken any OTHER prescribed medications (including Over-The-Counter) for any condition following their admission with ACS?

Yes	☐	Give details below
No	☐	

Prescribed medication	
Drug name	Date started (dd/mm/yyyy)
	/ /
	/ /
	/ /
	/ /
	/ /

Over-the-counter	
Drug name	Date started (dd/mm/yyyy)
	/ /
	/ /
	/ /
	/ /
	/ /

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GP OUTCOME DATA CASE REPORT FORM

EVENTS*/ MEDICAL CONDITIONS

8. Has the patient experienced a bleed following their admission with ACS?
(Please tick ✓ all that apply and provide a date)

Bleeding Event*		Date first reported (dd/mm/yyyy)
Intracranial bleed	☐	/ /
Gastrointestinal bleed	☐	/ /
Urogenital bleed	☐	/ /
Coronary Artery Bypass Graft (CABG) related bleed	☐	/ /
Other bleed	☐	/ /
If Other bleed, specify site:		
Other bleed	☐	/ /
If Other bleed, specify site:		
Other bleed	☐	/ /
If Other bleed, specify site:		

9. Has the patient had any of the following events*/conditions following their admission with ACS?
(Please tick ✓ all that apply and provide a date)

Event*		Date first reported (dd/mm/yyyy)
Injury/Trauma[a]	☐	/ /
Overdose[a]	☐	/ /
Stopping of anticoagulation therapy for bleeding [a]	☐	/ /
Reversal of anticoagulation therapy for bleeding [a]	☐	/ /
Abnormal liver function tests [b]	☐	/ /
Pregnancy	☐	/ /
Breastfeeding	☐	/ /

[a] of clinical medical importance which required acute medical/ surgical treatment (with/ without) hospitalisation

[b] Bilirubin/AST/ALT/ ALP/GGT

***DEFINITION OF AN EVENT:**

"any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's medical charts"

Thank you for completing the case report form
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GP OUTCOME DATA CASE REPORT FORM

All questions must be answered in full, to the best of your knowledge.
Where appropriate, yes or no tick boxes must be checked
Many thanks for your cooperation

PATIENT DETAILS

1. Is the patient currently registered with the practice?

Yes ☐	No ▼ ☐
If **NO**, date deregistered (dd/mm/yyyy)	/ /

2. Has the patient died?

Yes ▼ ☐	No ☐
If **YES**, date of death (dd/mm/yyyy)	/ /
Immediate cause of death:	
Underlying cause/condition(s):	

CURRENT ANTICOAGULANT/ ANTIPLATELET TREATMENT

3. If the patient was started on RIVAROXABAN, has this been stopped for any reason?

Yes	☐	Give details below
No	☐	

Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
Number of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping:	

4. If RIVAROXABAN was stopped, has it subsequently been restarted?

Yes	☐	Give details below
No	☐	

Date restarted (dd/mm/yyyy)	/ /
Details of restarted treatment	
Dose	
Frequency	
OR Total daily dose	

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GP OUTCOME DATA CASE REPORT FORM

5. If treatment with RIVAROXABAN was NOT stopped, have there been any changes made to the prescribed dose(s) and frequency of treatment?

Yes	☐	Give details below
No	☐	

Date changed (dd/mm/yyyy)	/ /
Revised Treatment details	
Dose	
Frequency	
OR Total daily dose	
Reason for change:	

6. Has the patient's antiplatelet therapy been stopped for any reason?

Yes	☐	Give details below
No	☐	

Drug Name	
Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
No. of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping:	

Drug Name	
Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
No. of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping:	

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7. If antiplatelet therapy has been stopped has it subsequently been restarted?

Yes	☐	Give details below
No	☐	

Drug Name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted medication	
Dose	
Frequency	
OR Total daily dose	

Drug Name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted medication	
Dose	
Frequency	
OR Total daily dose	

CONCURRENT MEDICATION USE

8. Has the patient taken any OTHER prescribed medications (including Over-The-Counter) for any condition following their admission with ACS?

Yes	☐	Give details below
No	☐	

Prescribed medication	
Drug name	Date started (dd/mm/yyyy)
	/ /
	/ /
	/ /
	/ /
	/ /

Over-the-counter	
Drug name	Date started (dd/mm/yyyy)
	/ /
	/ /
	/ /
	/ /
	/ /

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GP OUTCOME DATA CASE REPORT FORM

EVENTS*/ MEDICAL CONDITIONS

9. Has the patient experienced a bleed following their admission with ACS?
(Please tick ✓ all that apply and provide a date)

Bleeding Event*		Date first reported (dd/mm/yyyy)
Intracranial bleed	☐	/ /
Gastrointestinal bleed	☐	/ /
Urogenital bleed	☐	/ /
Coronary Artery Bypass Graft (CABG) related bleed	☐	/ /
Other bleed	☐	/ /
If Other bleed, specify site:		
Other bleed	☐	/ /
If Other bleed, specify site:		
Other bleed	☐	/ /
If Other bleed, specify site:		

10. Has the patient had any of the following events*/conditions following their admission with ACS?
(Please tick ✓ all that apply and provide a date)

Event*		Date first reported (dd/mm/yyyy)
Injury/Trauma[a]	☐	/ /
Overdose[a]	☐	/ /
Stopping of anticoagulation therapy for bleeding [a]	☐	/ /
Reversal of anticoagulation therapy for bleeding [a]	☐	/ /
Abnormal liver function tests [b]	☐	/ /
Pregnancy	☐	/ /
Breastfeeding	☐	/ /

[a] *of clinical medical importance which required acute medical/ surgical treatment (with/ without) hospitalisation*

[b] *Bilirubin/AST/ALT/ ALP/GGT*

***DEFINITION OF AN EVENT:**

"any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's medical charts"

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Investigator Study Identification Code

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OUTCOME DATA CASE REPORT FORM

All questions must be answered in full, to the best of your knowledge.
Where appropriate, yes or no tick boxes must be checked
Many thanks for your cooperation

CLINICAL CARE TEAM

1. Provide details of the person completing the case report form

Title
Surname
Forename
Job Title
Speciality
Professional Body Registration Number (e.g. GMC, GPhC or NMC)
Age
Telephone No.
Email

2. Provide the date the case report form was completed

Date form completed (dd/mm/yyyy)			/			/				

3. Provide details of the prescriber (i.e. who made the decision to treat) if different from above

Title
Surname
Forename
Job Title
Speciality
Professional Body Registration Number (e.g. GMC, GPhC or NMC)
Age
Telephone No.
Email

PATIENT CONSENT AND CONTACT

4. Has the patient withdrawn consent to continue participation in this study?

Yes	☐	**PLEASE CONTACT A MEMBER OF THE DSRU RESEARCH TEAM**
No	☐	

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OUTCOME DATA CASE REPORT FORM

5. Does the patient continue to be under the care of the specialist team responsible for initiating oral antiplatelet /anticoagulant treatment?

Yes	☐	Continue to complete the case report form
No	☐	Give reason(s) and date(s) below for transferring the care or discontinuation of contact **and continue to complete the case report form**

Reason	Yes	Date (dd/mm/yyyy)
Discharged to GP	☐	/ /
Care transferred to other specialist	☐	/ /
Lost contact (did not re-attend)	☐	/ /
Died	☐	/ /
If **Died**, specify immediate cause of death:		
Underlying cause/condition(s):		
Other	☐	/ /
If **Other**, specify:		

ACUTE MANAGEMENT OF ACS

6. Indicate which of the following medications were prescribed for the acute treatment of ACS (Tick ✓ all that apply and provide date prescribed)

		Date prescribed (dd/mm/yyyy)
Aspirin	☐	/ /
Clopidogrel	☐	/ /
Prasugrel	☐	/ /
Ticagrelor	☐	/ /
Unfractionated Heparin[a]	☐	/ /
Low Molecular Weight Heparin[b]	☐	/ /
Fondaparinux	☐	/ /
Bivalirudin	☐	/ /
Eptifibatide	☐	/ /
Tirofiban	☐	/ /
Abciximab	☐	/ /
Streptokinase	☐	/ /
Alteplase	☐	/ /
Reteplase	☐	/ /
Tenecteplase	☐	/ /

[a] including Monoparin, MonoparinCalcium and Multiparin

[b] including Bemiparin, Enoxaparin, Tinzaparin and Dalteparin

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OUTCOME DATA CASE REPORT FORM

INVASIVE PROCEDURES FOLLOWING THE EVENT OF ACS

7. Has the patient undergone a primary coronary intervention (PCI) during their admission? (e.g coronary angioplasty, thrombus extraction catheter, stenting).

Yes	☐	Give details below
No	☐	

Procedure	Date of procedure (dd/mm/yyyy)	Comment
	/ /	
	/ /	
	/ /	

8. Has the patient undergone a coronary artery bypass graft (CABG) during their admission?

Yes	☐	Give details below of date of procedure, and whether any antiplatelet medication had been stopped prior to the procedure
No	☐	

Date of procedure (dd/mm/yyyy)	/ /		
Was antiplatelet therapy (e.g. clopidogrel, aspirin) stopped prior to the procedure?			
Yes ☐	If **YES** give details below ▼	No ☐	
Drug name:			
Date stopped (dd/mm/yyyy)	/ /		
Date restarted (dd/mm/yyyy)	/ /		
Drug name:			
Date stopped (dd/mm/yyyy)	/ /		
Date restarted (dd/mm/yyyy)	/ /		

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OUTCOME DATA CASE REPORT FORM

CURRENT ANTIPLATELET/ ANTICOAGULANT TREATMENT

For patients started ON RIVAROXABAN and antiplatelet therapy ▶Go to QUESTION 9

For patients started on DUAL ANTIPLATELET THERAPY (i.e. not taking rivaroxaban) ▶Go to QUESTION 10

QUESTION 9 ▶ RIVAROXABAN AND ANTIPLATELET THERAPY

9.1 If the patient was started on RIVAROXABAN, has this been stopped for any reason?

Yes ☐	Give details below
No ☐	

Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
Number of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping	

9.2 If RIVAROXABAN was stopped, has it subsequently been restarted?

Yes ☐	Give details below
No ☐	

Date restarted (dd/mm/yyyy)	/ /
Details of restarted medication	
Dose	
Frequency	
OR Total daily dose	

9.3 If treatment with RIVAROXABAN was NOT stopped, have there been any changes made to the prescribed dose(s) and frequency of treatment?

Yes ☐	Give details below
No ☐	

Date changed (dd/mm/yyyy)	/ /
Revised Treatment details	
Dose	
Frequency	
OR Total daily dose	
Reason for change:	

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9.4 Has the patient's antiplatelet therapy been stopped for any reason?

Yes ☐	Give details below
No ☐	

Drug name	
Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
No. of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping	

Drug name	
Date stopped (dd/mm/yyyy)	/ /
OR Date of last prescription (dd/mm/yyyy)	/ /
No. of days duration	
Details of stopped medication	
Dose	
Frequency	
OR Total daily dose	
Reason for stopping	

9.5 If antiplatelet therapy has been stopped has it subsequently been restarted?

Yes ☐	Give details below
No ☐	

Drug name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted medication	
Dose	
Frequency	
OR Total daily dose	

Drug name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted medication	
Dose	
Frequency	
OR Total daily dose	

▶ **GO TO QUESTION 11** (Page 9)

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OUTCOME DATA CASE REPORT FORM

QUESTION 10 ▶ DUAL ANTIPLATELET THERAPY

10.1 Have one or both of the antiplatelets been stopped for any reason?

Yes	☐	Give details below
No	☐	

Drug name			/			/				
Date stopped (dd/mm/yyyy)			/			/				
OR Date of last prescription (dd/mm/yyyy)			/			/				
Number of days duration										
Details of stopped medication										
Dose										
Frequency										
OR Total daily dose										
Reason for stopping										

Drug name			/			/				
Date stopped (dd/mm/yyyy)			/			/				
OR Date of last prescription (dd/mm/yyyy)			/			/				
Number of days duration										
Details of stopped medication										
Dose										
Frequency										
OR Total daily dose										
Reason for stopping										

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10.2 If one or both of the antiplatelets HAVE been stopped, have they subsequently been restarted?

Yes	☐	Give details below
No	☐	

Drug name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted medication	
Dose	
Frequency	
OR Total daily dose	

Drug name	
Date restarted (dd/mm/yyyy)	/ /
Details of restarted medication	
Dose	
Frequency	
OR Total daily dose	

10.3 If one or both of the antiplatelet therapies HAVE been stopped, has the patient been prescribed an alternative antiplatelet therapy?

Yes	☐	Give details below
No	☐	

Drug name	
Date started (dd/mm/yyyy)	/ /
Treatment details of new antiplatelets	
Dose	
Frequency	
OR Total daily dose	

Drug name	
Date started (dd/mm/yyyy)	/ /
Treatment details of new antiplatelets	
Dose	
Frequency	
OR Total daily dose	

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OUTCOME DATA CASE REPORT FORM

10.4. If treatment with initial dual antiplatelet agents has NOT been stopped, have any changes been made to the treatment regimen?

Yes	☐	Give details below
No	☐	

Drug name	
Date changed (dd/mm/yyyy)	/ /
Revised treatment details	
Dose	
Frequency	
OR Total daily dose	

Drug name	
Date changed (dd/mm/yyyy)	/ /
Revised treatment details	
Dose	
Frequency	
OR Total daily dose	

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OUTCOME DATA CASE REPORT FORM

PRIOR ANTIPLATELET / ANTICOAGULANT TREATMENT

QUESTION 11

11. Has the patient received antiplatelet or anticoagulant therapy within 12 months prior to their admission with ACS? Include details of parenteral treatment, if received.

(Please tick ✓ all that apply. If stopped prior to admission with ACS, provide date stopped and reason for stopping)

Drug	Started within 12 months prior to admission with ACS	Drug taken within 4 weeks prior to admission with ACS	If stopped, give date stopped and reason for stopping	
			Date of stopping (dd/mm/yyyy)	Reason for stopping
Oral Antiplatelets				
Aspirin (≤300mg/day)	☐	☐	/ /	
Clopidogrel	☐	☐	/ /	
Dipyridamole	☐	☐	/ /	
Prasugrel	☐	☐	/ /	
Ticagrelor	☐	☐	/ /	
Other	☐	☐	/ /	
If Other, specify				
Other	☐	☐	/ /	
If Other, specify				
Oral Anticoagulants				
Warfarin	☐	☐	/ /	
Phenindione	☐	☐	/ /	
Nicoumalone	☐	☐	/ /	
Dabigatran (Pradaxa)	☐	☐	/ /	
Apixaban (Eliquis)	☐	☐	/ /	
Other	☐	☐	/ /	
If Other, specify				
Other	☐	☐	/ /	
If Other, specify				
Glycoprotein IIb/IIIa inhibitors				
Abciximab	☐	☐	/ /	
Eptifibatide	☐	☐	/ /	
Tirofiban	☐	☐	/ /	
Other	☐	☐	/ /	
If Other, specify				
Other	☐	☐	/ /	
If Other, specify				

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OUTCOME DATA CASE REPORT FORM

Drug	Started within 12 months prior to admission with ACS	Drug taken within 4 weeks prior to admission with ACS	If stopped, give date stopped and reason for stopping	
			Date of stopping (dd/mm/yyyy)	Reason for stopping
Antithrombin Therapy				
Bivalirudin	☐	☐	/ /	
Unfractionated Heparin [c]	☐	☐	/ /	
Low Molecular Weight Heparin [d]	☐	☐	/ /	
Fondaparinux	☐	☐	/ /	
Other	☐	☐	/ /	
If Other, specify				
Other	☐	☐	/ /	
If Other, specify				
Fibrinolytics				
Streptokinase	☐	☐	/ /	
Alteplase	☐	☐	/ /	
Reteplase	☐	☐	/ /	
Tenecteplase	☐	☐	/ /	
Other	☐	☐	/ /	
If Other, specify				
Other	☐	☐	/ /	
If Other, specify				

[c] *including Monoparin, Monoparin Calcium and Multiparin*
[d] *including Bemiparin, Enoxaparin, Tinzaparin and Dalteparin*

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OUTCOME DATA CASE REPORT FORM

RECENT AND CONCURRENT MEDICATION USE

12. Has the patient taken any OTHER prescribed medications (including Over-The-Counter and herbals) for any condition within 4 weeks prior to, during or following their admission with ACS? (Please ✓ tick all that apply and date started, if prescribed during or following admission with ACS)

Please tick all that apply	Within 4 weeks prior to day of admission with ACS	**PRESCRIBED** during or following admission with ACS	If **prescribed** during or following admission with ACS, give date medication started (dd/mm/yyyy)
Analgesics / anti-inflammatory			
Paracetamol	☐	☐	/ /
Aspirin (>300mg/day)	☐	☐	/ /
NSAID	☐	☐	/ /
Other Analgesics / anti-inflammatory			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
Anti-convulsants			
Phenytoin	☐	☐	/ /
Phenobarbital	☐	☐	/ /
Carbamazepine	☐	☐	/ /
Primidone	☐	☐	/ /
Other Anti-convulsants			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
Anti-infective			
Ketoconazole	☐	☐	/ /
Itraconazole	☐	☐	/ /
Posaconazole	☐	☐	/ /
Ritonavir	☐	☐	/ /
Clarithromycin	☐	☐	/ /
Erythromycin	☐	☐	/ /
Rifampicin	☐	☐	/ /
Sulfamethoxazole	☐	☐	/ /
Metronidazole	☐	☐	/ /
Griseofulvin	☐	☐	/ /
Other Anti-infective			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /

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ROSE ACS
Rivaroxaban Observational Safety Evaluation post Acute Coronary Syndrome

OUTCOME DATA CASE REPORT FORM

Please tick all that apply	Within 4 weeks prior to day of admission with ACS	**PRESCRIBED** during or following admission with ACS	If **prescribed** during or following admission with ACS, give date medication started (dd/mm/yyyy)
Antidepressants			
Tricyclic and related (e.g. amitriptyline)	☐	☐	/ /
MAOI	☐	☐	/ /
SSRI	☐	☐	/ /
St John's Wort	☐	☐	/ /
Other Antidepressants			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
Female hormone products (if applicable)			
Oestrogen and /or progestogen containing contraceptive products	☐	☐	/ /
Hormone replacement therapies	☐	☐	/ /
Other Female hormone products			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
Oral corticosteroids			
Prednisolone	☐	☐	/ /
Other Corticosteroid			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
Other medication			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /

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OUTCOME DATA CASE REPORT FORM

Please tick all that apply	Within 4 weeks prior to day of admission with ACS	**PRESCRIBED** during or following admission with ACS	If **prescribed** during or following admission with ACS, give date medication started (dd/mm/yyyy)
OTC			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
Herbal/Food supplements			
Specify name(s):	☐	☐	/ /
	☐	☐	/ /
	☐	☐	/ /
Grapefruit Juice	☐	☐	/ /

***Definition of an event:**
"any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's medical charts"

PRIOR AND CONCURRENT MEDICAL CONDITIONS

13. Has the patient experienced a bleed either prior to, during or following their admission with ACS? (Please tick ✓ all that apply and provide a date if during or following admission with ACS)

For Each Event*/Condition Tick All That Apply**	Prior to day of admission with ACS		During or following admission with ACS	Date EVENT reported (dd/mm/yyyy)
	PAST (>3 months)	RECENT (<3 months)		
Intracranial Bleed	☐	☐	☐	/ /
Gastrointestinal Bleed	☐	☐	☐	/ /
Urogenital Bleed	☐	☐	☐	/ /
Other Bleed	☐	☐	☐	/ /
If Other bleed, specify site:				
Other Bleed	☐	☐	☐	/ /
If Other bleed, specify site:				
Other Bleed	☐	☐	☐	/ /
If Other bleed, specify site:				

**If uncertain about events listed above, provide comments:

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OUTCOME DATA CASE REPORT FORM

14. For any bleeds ticked in Q13, were any of the following criteria met?
(Please tick ✓ all that apply and provide a date if during or following admission with ACS)

For Each Event*/Condition Tick All That Apply**	Prior to day of admission with ACS		During or following admission with ACS	Date EVENT reported (dd/mm/yyyy)
	PAST (>3 months)	RECENT (<3 months)		
MAJOR BLEED CRITERIA				
Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL	☐	☐	☐	/ /
Specify Site:				
Any symptomatic intracranial haemorrhage	☐	☐	☐	/ /
Fatal bleeding (bleeding that directly results in death within 7 days)	☐	☐	☐	/ /
Specify Site:				
Clinically overt sign of haemorrhage associated with a drop in haemoglobin concentration of 3 to <5 g/dL	☐	☐	☐	/ /
Specify Site:				

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OUTCOME DATA CASE REPORT FORM

15. If the patient has had a coronary artery bypass graft (CABG) during their admission with ACS, has the patient experienced any of the following CABG related haemorrhagic events? (Please tick ✓ all that apply and provide a date if during or following admission with ACS)

For Each Event*/Condition Tick All That Apply**	Prior to day of admission with ACS		During or following admission with ACS	Date EVENT reported (dd/mm/yyyy)
	PAST (>3 months)	RECENT (<3 months)		
MAJOR BLEED CRITERIA				
Fatal bleeding (bleeding that directly results in death)			☐	/ /
Perioperative intracranial bleeding	☐	☐	☐	/ /
Reoperation following closure of the sternotomy incision to control bleeding	☐	☐	☐	/ /
Transfusion of greater than or equal to 5 units of whole blood or PRBCs within a 48 hour period	☐	☐	☐	/ /
Chest tube output >2L within a 24 hour period	☐	☐	☐	/ /
**If uncertain about events listed above, provide comments:				

16. Has the patient had any of the following events*/conditions prior to, during or following their admission with ACS? (Please tick ✓ all that apply and provide a date if during or following admission with ACS)

For Each Event*/Condition Tick All That Apply**	Prior to day of admission with ACS		During or following admission with ACS	Date EVENT reported (dd/mm/yyyy)
	PAST (>3 months)	RECENT (<3 months)		
Injury/Trauma[e]	☐	☐	☐	/ /
Specify:				
Overdose[e]	☐	☐	☐	/ /
Provide details:				
Stopping of anticoagulation therapy for bleeding [e]	☐	☐	☐	/ /
Reversal of anticoagulation therapy for bleeding [e]	☐	☐	☐	/ /
**If uncertain about events listed above, provide comments:				

[e] *of clinical medical importance which required acute medical/ surgical treatment (with/ without) hospitalisation*

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OUTCOME DATA CASE REPORT FORM

17. Has the patient had any of the following events*/conditions prior to, during or following their admission with ACS? (Please tick ✓ all that apply and provide a date if during or following admission with ACS)

For Each Event*/Condition Tick All That Apply**	Prior to day of admission with ACS		During or following admission with ACS	Date EVENT reported (dd/mm/yyyy)
	PAST (>3 months)	RECENT (<3 months)		
STEMI	☐	☐	☐	/ /
NSTEMI	☐	☐	☐	/ /
Angina	☐	☐	☐	/ /
Congestive heart failure	☐	☐	☐	/ /
Peripheral arterial disease	☐	☐	☐	/ /
Cardiac Arrhythmias [f]	☐	☐	☐	/ /
**If uncertain about conditions listed above, provide comments:				

[f] *includes events such as bradyarrhythmias, tachyarrhythmias and history of QT prolongation*

18. Has the patient had any of the following events*/conditions prior to, during or following their admission with ACS? (Please tick ✓ all that apply and provide a date if during or following admission with ACS)

For Each Event*/Condition Tick All That Apply**	Prior to day of admission with ACS		During or following admission with ACS	Date EVENT reported (dd/mm/yyyy)
	PAST (>3 months)	RECENT (<3 months)		
Liver disorder [g]	☐	☐	☐	/ /
Abnormal liver function tests [h]	☐	☐	☐	/ /
Renal failure (Stage 5 CKD)	☐	☐	☐	/ /
Renal impairment (Stage 3-4 CKD)	☐	☐	☐	/ /
Renal impairment (Stage 1-2 CKD)	☐	☐	☐	/ /
Pregnancies (with the last 12 months)	☐	☐	☐	/ /
Breastfeeding	☐	☐	☐	/ /
**If uncertain about any of these other conditions listed above, provide comments:				

[g] *includes events such as cholestasis and jaundice, hepatic failure and associated disorders, hepatic fibrosis and cirrhosis, and hepatic viral infections*

[h] *Bilirubin/AST/ALT/ALP/GGT*

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OUTCOME DATA CASE REPORT FORM

19. Has the patient had any OTHER events*/conditions prior to day of admission with ACS which are not listed above? (Please tick ✓ all that apply)

Events*/conditions prior to day of admission with ACS	PAST (>3 months)	RECENT (<3 months)
	☐	☐
	☐	☐
	☐	☐
	☐	☐
	☐	☐

20. Has the patient had any OTHER NEW events*/conditions or events DURING OR FOLLOWING their admission with ACS which are not listed above?

NEW events*/conditions during or following hospital admission with ACS	Date NEW EVENT reported (dd/mm/yyyy)
	/ /
	/ /
	/ /
	/ /

21. To your knowledge has the patient ever had any of the following behaviours prior to, during or following their admission with ACS? (Please tick ✓all that apply)

Behaviour	Prior to day of admission with ACS	During or following admission with ACS
Smoking (cigar/cigarette/pipe)	☐	☐
Alcohol misuse [l]	☐	☐
Substance misuse [m]	☐	☐
If yes to any of the above, provide details below:		

[l] includes alcohol abuse problems, withdrawal syndrome and alcoholism

[m] includes substance dependence, abuse, evidence of withdrawal syndrome

PATIENT COMPLIANCE/ CONCORDANCE

22. Are you aware of the patient demonstrating any of the following behaviours regarding anticoagulation treatment adherence following their admission with ACS? (Please tick ✓all that apply)

Patient behaviours	
Overall general poor-medication taking behaviour	☐
Missed clinical review appointments	☐
Missed anticoagulant doses	☐
Extra anticoagulant doses	☐
Demonstrated poor understanding of need for regular use	☐

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OUTCOME DATA CASE REPORT FORM

23. Provide any known values for the following health parameters during or following admission with ACS. (Specify dates parameters measured)

BMI (kg/m^2)	Weight (kg)	Date parameter measured: (dd/mm/yyyy)
		/ /
		/ /
		/ /

LABORATORY TESTS

24. Provide results of the <u>baseline</u> clotting screen, if performed, during admission with ACS. (Specify date measured)

Test	Result (Units)	Date of Test (dd/mm/yyyy)
PT		/ /
APTT		/ /
Fibrinogen Derived		/ /

25. Provide haemoglobin, platelets, eGFR and serum creatinine test results, if performed, during or following admission with ACS. (Specify date measured)

If preferred, attach a copy of relevant test results, if available.

Haemoglobin (Hb) (g/L)	Platelets (x 10^9/L)	eGFR (ml/min)	Creatinine (µmol/L)	Date measured (dd/mm/yyyy)
				/ /
				/ /
				/ /
				/ /
				/ /
				/ /
				/ /

Thank you for completing the case report form
Please return to:

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Tel: PPD

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Appendix 4. Other Medical History Prior to Admission

Rivaroxaban N=124								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Hypertension	16	12.9	Angina pectoris	1	0.8	Meniscus operation	1	0.8
Type 2 diabetes mellitus	8	6.5	Chest pain	1	0.8			
Hypercholesterolaemia	7	5.6	Dyspnoea exertional	1	0.8			
Asthma	5	4.0	Endoscopy	1	0.8			
Coronary artery bypass	4	3.2	Faeces discoloured	1	0.8			
Coronary arterial stent insertion	3	2.4	Gastritis	1	0.8			
Depression	3	2.4	Hiatus hernia	1	0.8			
Obesity	3	2.4	Hypothyroidism	1	0.8			
Acute myocardial infarction	2	1.6	Malaise	1	0.8			
Arthroscopy	2	1.6	Melaena	1	0.8			
Hypothyroidism	2	1.6	Obesity	1	0.8			
Left ventricular dysfunction	2	1.6	Pulmonary oedema	1	0.8			
Nephrolithiasis	2	1.6	Rectal adenocarcinoma	1	0.8			
Type 1 diabetes mellitus	2	1.6	Type 2 diabetes mellitus	1	0.8			
Acute coronary syndrome	1	0.8	Viral infection	1	0.8			
Aneurysm	1	0.8						
Anxiety	1	0.8						
Aphasia	1	0.8						
Arterial bypass operation	1	0.8						
Atrial flutter	1	0.8						
Back injury	1	0.8						
Back pain	1	0.8						
Benign prostatic hyperplasia	1	0.8						
Biopsy	1	0.8						
Blood cholesterol increased	1	0.8						
Breast mass	1	0.8						
Bronchiectasis	1	0.8						
Bronchitis	1	0.8						
Cardiac failure	1	0.8						
Chronic kidney disease	1	0.8						

Rivaroxaban N=124								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Chronic obstructive pulmonary disease	1	0.8						
Constipation	1	0.8						
Coronary angioplasty	1	0.8						
Cough	1	0.8						
Diabetic retinopathy	1	0.8						
Dyspepsia	1	0.8						
Dyspnoea exertional	1	0.8						
Essential hypertension	1	0.8						
Gastritis	1	0.8						
Glomerulonephritis membranous	1	0.8						
Hip arthroplasty	1	0.8						
Hospitalisation	1	0.8						
Hyperlipidaemia	1	0.8						
Interstitial lung disease	1	0.8						
Ischaemic cardiomyopathy	1	0.8						
Left ventricular failure	1	0.8						
Malignant neoplasm of eye	1	0.8						
Mental disorder	1	0.8						
Myocardial infarction	1	0.8						
Myocardial ischaemia	1	0.8						
Neck pain	1	0.8						
Normocytic anaemia	1	0.8						
Pancreatitis chronic	1	0.8						
Pneumonia	1	0.8						
Prostatic specific antigen increased	1	0.8						
Psoriasis	1	0.8						
Raynaud's phenomenon	1	0.8						
Scleroderma	1	0.8						
Skin ulcer	1	0.8						
Stent placement	1	0.8						
Toe amputation	1	0.8						
Transient ischaemic attack	1	0.8						

Rivaroxaban N=124								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Vasectomy	1	0.8						

[a] Unknown whether prior event was past or recent

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Hypertension	81	15.3	Hypertension	7	1.3	Hypertension	4	0.8
Type 2 diabetes mellitus	39	7.4	Chronic obstructive pulmonary disease	4	0.8	Chronic obstructive pulmonary disease	2	0.4
Asthma	30	5.7	Chest pain	3	0.6	Gout	2	0.4
Blood cholesterol increased	23	4.4	Dyspnoea	3	0.6	Hypothyroidism	2	0.4
Osteoarthritis	18	3.4	Type 2 diabetes mellitus	3	0.6	Anxiety	1	0.2
Chronic obstructive pulmonary disease	17	3.2	Angina pectoris	2	0.4	Arthritis	1	0.2
Hypercholesterolaemia	16	3.0	Blood cholesterol increased	2	0.4	Asthma	1	0.2
Diabetes mellitus	14	2.7	Left ventricular dysfunction	2	0.4	Atrial fibrillation	1	0.2
Depression	12	2.3	Nausea	2	0.4	Blood cholesterol increased	1	0.2
Prostate cancer	12	2.3	Asthma	1	0.2	Depression	1	0.2
Hypothyroidism	10	1.9	Back pain	1	0.2	Gastrooesophageal reflux disease	1	0.2
Gastrooesophageal reflux disease	9	1.7	Biopsy prostate	1	0.2	Hiatus hernia	1	0.2
Myocardial infarction	9	1.7	Cardiac resynchronisation therapy	1	0.2	Hyperlipidaemia	1	0.2
Percutaneous coronary intervention	9	1.7	Cerebrovascular accident	1	0.2	Hyperthyroidism	1	0.2
Anxiety	8	1.5	Chest discomfort	1	0.2	Intervertebral disc operation	1	0.2
Coronary artery bypass	8	1.5	Cholelithiasis	1	0.2	Myocardial ischaemia	1	0.2
Gout	8	1.5	Cold sweat	1	0.2	Sinus polyp	1	0.2
Irritable bowel syndrome	8	1.5	Coronary angioplasty	1	0.2	Thrombosis	1	0.2
Transient ischaemic attack	8	1.5	Coronary arterial stent insertion	1	0.2	Vertigo	1	0.2
Angina pectoris	7	1.3	Dyspepsia	1	0.2			
Hiatus hernia	7	1.3	Fall	1	0.2			
Hip arthroplasty	7	1.3	Gastrooesophageal reflux disease	1	0.2			
Osteoporosis	7	1.3	Haemodialysis	1	0.2			
Cerebrovascular accident	6	1.1	Hospitalisation	1	0.2			
Diverticulum	6	1.1	Hypothyroidism	1	0.2			
Glaucoma	6	1.1	Lower respiratory tract infection	1	0.2			

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Inguinal hernia repair	6	1.1	Migraine	1	0.2			
Peripheral vascular disorder	6	1.1	Muscular weakness	1	0.2			
Acute myocardial infarction	5	0.9	Myocardial infarction	1	0.2			
Diabetic retinopathy	5	0.9	Nerve block	1	0.2			
Sciatica	5	0.9	Osteoarthritis	1	0.2			
Appendicectomy	4	0.8	Pain in jaw	1	0.2			
Arthritis	4	0.8	Parkinson's disease	1	0.2			
Breast cancer	4	0.8	Percutaneous coronary intervention	1	0.2			
Cholecystectomy	4	0.8	Pituitary tumour benign	1	0.2			
Chronic kidney disease	4	0.8	Polyarthritis	1	0.2			
Knee arthroplasty	4	0.8	Prostate cancer	1	0.2			
Myocardial ischaemia	4	0.8	Pulmonary fibrosis	1	0.2			
Nephrolithiasis	4	0.8	Sleep apnoea syndrome	1	0.2			
Sleep apnoea syndrome	4	0.8	Spinal decompression	1	0.2			
Spinal osteoarthritis	4	0.8	Tooth abscess	1	0.2			
Type 1 diabetes mellitus	4	0.8	Transient global amnesia	1	0.2			
Arthralgia	3	0.6	Urethral dilatation	1	0.2			
Carpal tunnel syndrome	3	0.6	Urethral stenosis	1	0.2			
Cataract	3	0.6	Urinary tract infection	1	0.2			
Coronary arterial stent insertion	3	0.6						
Epilepsy	3	0.6						
Haemorrhoids	3	0.6						
Hernia repair	3	0.6						
Pulmonary fibrosis	3	0.6						
Rheumatoid arthritis	3	0.6						
Seasonal allergy	3	0.6						
Stent placement	3	0.6						
Transurethral prostatectomy	3	0.6						
Adenotonsillectomy	2	0.4						
Angina unstable	2	0.4						

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Ankle fracture	2	0.4						
Aortic stenosis	2	0.4						
Aortic valve incompetence	2	0.4						
Arthroscopy	2	0.4						
Atrial fibrillation	2	0.4						
Barrett's oesophagus	2	0.4						
Basal cell carcinoma	2	0.4						
Bronchiectasis	2	0.4						
Cardiac pacemaker insertion	2	0.4						
Cholelithiasis	2	0.4						
Clavicle fracture	2	0.4						
Colitis	2	0.4						
Colitis ulcerative	2	0.4						
Deep vein thrombosis	2	0.4						
Dyspepsia	2	0.4						
Emphysema	2	0.4						
Essential hypertension	2	0.4						
Gastric ulcer	2	0.4						
Gastritis	2	0.4						
Hepatic steatosis	2	0.4						
Hernia	2	0.4						
Hospitalisation	2	0.4						
Hydronephrosis	2	0.4						
Hyperlipidaemia	2	0.4						
Hyperthyroidism	2	0.4						
Hysterectomy	2	0.4						
Laparoscopic surgery	2	0.4						
Mastectomy	2	0.4						
Meniscus removal	2	0.4						
Migraine	2	0.4						
Neuropathy peripheral	2	0.4						
Palpitations	2	0.4						
Pneumonia	2	0.4						
Polymyalgia rheumatica	2	0.4						
Prostatectomy	2	0.4						
Prostatism	2	0.4						

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Prostatomegaly	2	0.4						
Radiotherapy	2	0.4						
Radius fracture	2	0.4						
Raynaud's phenomenon	2	0.4						
Skin ulcer	2	0.4						
Spinal operation	2	0.4						
Ureterolithiasis	2	0.4						
Varicose vein	2	0.4						
Vertigo	2	0.4						
Abnormal loss of weight	1	0.2						
Acute coronary syndrome	1	0.2						
Adenoma benign	1	0.2						
Alcohol abuse	1	0.2						
Alcoholism	1	0.2						
Angiogram	1	0.2						
Angiogram normal	1	0.2						
Angioplasty	1	0.2						
Anxiety disorder	1	0.2						
Aortic aneurysm	1	0.2						
Aortic aneurysm repair	1	0.2						
Aortic occlusion	1	0.2						
Aortic valve replacement	1	0.2						
Arrhythmia	1	0.2						
Arthrodesis	1	0.2						
Atrioventricular block	1	0.2						
Back pain	1	0.2						
Benign prostatic hyperplasia	1	0.2						
Bladder cancer	1	0.2						
Bladder catheterisation	1	0.2						
Blepharitis	1	0.2						
Blindness unilateral	1	0.2						
Blood testosterone decreased	1	0.2						
Bowen's disease	1	0.2						
Breast conserving surgery	1	0.2						
Bundle branch block left	1	0.2						

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Caesarean section	1	0.2						
Cardiac ablation	1	0.2						
Cardiac arrest	1	0.2						
Cardiac failure	1	0.2						
Cardiac failure chronic	1	0.2						
Cardiac valve disease	1	0.2						
Carotid endarterectomy	1	0.2						
Central nervous system vasculitis	1	0.2						
Cerebrovascular disorder	1	0.2						
Cervical polypectomy	1	0.2						
Cervicogenic headache	1	0.2						
Change of bowel habit	1	0.2						
Chest pain	1	0.2						
Cholecystitis	1	0.2						
Cluster headache	1	0.2						
Coeliac disease	1	0.2						
Colitis microscopic	1	0.2						
Connective tissue disorder	1	0.2						
Continuous positive airway pressure	1	0.2						
Cutaneous lupus erythematosus	1	0.2						
Diabetic neuropathy	1	0.2						
Diabetic retinal oedema	1	0.2						
Diverticulitis	1	0.2						
Dizziness	1	0.2						
Duodenal ulcer	1	0.2						
Duodenitis	1	0.2						
Endometrial ablation	1	0.2						
Endometriosis	1	0.2						
Epistaxis	1	0.2						
Erectile dysfunction	1	0.2						
Ex-tobacco user	1	0.2						
Facial bones fracture	1	0.2						
Facial paralysis	1	0.2						
Fall	1	0.2						
Familial risk factor	1	0.2						

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Fibroadenoma of breast	1	0.2						
Focal segmental glomerulosclerosis	1	0.2						
Fracture	1	0.2						
Gastrectomy	1	0.2						
Gastric banding	1	0.2						
Gastric cancer	1	0.2						
Gastrointestinal carcinoma	1	0.2						
Gilbert's syndrome	1	0.2						
Glomerulonephritis	1	0.2						
Glucose tolerance impaired	1	0.2						
Guillain-Barre syndrome	1	0.2						
Haematuria	1	0.2						
Haemodialysis	1	0.2						
Hand fracture	1	0.2						
Hepatic cyst	1	0.2						
Hepatitis C	1	0.2						
Hernia hiatus repair	1	0.2						
Herpes zoster	1	0.2						
Hip fracture	1	0.2						
Hypertrophic cardiomyopathy	1	0.2						
Hyponatraemia	1	0.2						
Injection	1	0.2						
Injury	1	0.2						
Interstitial lung disease	1	0.2						
Intervertebral disc degeneration	1	0.2						
Intervertebral disc operation	1	0.2						
Intestinal polyp	1	0.2						
Investigation	1	0.2						
Joint dislocation	1	0.2						
Kyphoscoliosis	1	0.2						
Lacunar infarction	1	0.2						
Laparoscopy	1	0.2						
Large intestinal polypectomy	1	0.2						

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Left ventricular dysfunction	1	0.2						
Left ventricular hypertrophy	1	0.2						
Lens extraction	1	0.2						
Lichen planus	1	0.2						
Ligament injury	1	0.2						
Ligament operation	1	0.2						
Lower respiratory tract infection	1	0.2						
Lung disorder	1	0.2						
Lymphocytosis	1	0.2						
Macroangiopathy	1	0.2						
Macular degeneration	1	0.2						
Malignant melanoma	1	0.2						
Medical diet	1	0.2						
Meniere's disease	1	0.2						
Metastatic squamous cell carcinoma	1	0.2						
Mitral valve repair	1	0.2						
Multiple sclerosis	1	0.2						
Muscle rupture	1	0.2						
Nasal polypectomy	1	0.2						
Nasal polyps	1	0.2						
Neovascular age-related macular degen..	1	0.2						
Nephrotic syndrome	1	0.2						
Nerve compression	1	0.2						
Neuralgia	1	0.2						
Neurodermatitis	1	0.2						
Neurogenic bladder	1	0.2						
Obesity	1	0.2						
Ocular hypertension	1	0.2						
Oesophageal spasm	1	0.2						
Oesophagogastroduodenoscopy	1	0.2						
Orthostatic hypotension	1	0.2						
Osteonecrosis	1	0.2						
Osteopenia	1	0.2						
Pain	1	0.2						

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Pain in extremity	1	0.2						
Pancreatitis	1	0.2						
Paraparesis	1	0.2						
Parkinson's disease	1	0.2						
Pelvic fracture	1	0.2						
Pernicious anaemia	1	0.2						
Peroneal nerve palsy	1	0.2						
Pituitary tumour	1	0.2						
Pituitary tumour benign	1	0.2						
Pityriasis rosea	1	0.2						
Plantar fasciitis	1	0.2						
Poliomyelitis	1	0.2						
Pollakiuria	1	0.2						
Polyarteritis nodosa	1	0.2						
Postinfarction angina	1	0.2						
Presyncope	1	0.2						
Proctitis	1	0.2						
Protein S deficiency	1	0.2						
Psoriasis	1	0.2						
Psoriatic arthropathy	1	0.2						
Pulmonary embolism	1	0.2						
Pyelonephritis	1	0.2						
Renal cancer	1	0.2						
Renal vein thrombosis	1	0.2						
Restless legs syndrome	1	0.2						
Retinal vein occlusion	1	0.2						
Road traffic accident	1	0.2						
Rotator cuff syndrome	1	0.2						
Salpingo-oophorectomy	1	0.2						
Skin graft	1	0.2						
Skin neoplasm excision	1	0.2						
Spinal column stenosis	1	0.2						
Stress	1	0.2						
Subarachnoid haemorrhage	1	0.2						
Subdural haemorrhage	1	0.2						
Syncope	1	0.2						
Tendon rupture	1	0.2						

Contextual N=528								
Past Prior Other Events (>3 months)			Recent Prior Other Events (<3 months)			Period Unknown[a]		
Preferred Term	n	%	Preferred Term	n	%	Preferred Term	n	%
Tension headache	1	0.2						
Thrombophlebitis superficial	1	0.2						
Tonsillectomy	1	0.2						
Tumour excision	1	0.2						
Type V hyperlipidaemia	1	0.2						
Umbilical hernia	1	0.2						
Upper limb fracture	1	0.2						
Ureteric stenosis	1	0.2						
Urethral stenosis	1	0.2						
Urinary incontinence	1	0.2						
Uvulectomy	1	0.2						
Varices oesophageal	1	0.2						
Vasectomy	1	0.2						
Ventricular dysfunction	1	0.2						
Ventricular fibrillation	1	0.2						
Vitreous detachment	1	0.2						

[a] Unknown whether prior event was past or recent

Appendix 5. Medications with unknown time period

ATC Code	Drug class.name	Rivaroxaban (N=124)		Contextual (N=528)	
		n	%	n	%
Analgesics					
M01	Oral NSAIDs	0	0.0	1	0.2
N02	Opioids	0	0.0	2	0.4
Antidepressants					
N06	Tricyclic	0	0.0	1	0.2
N06	SSRI	1	0.8	0	0.0
Systemic steroids					
H02	Prednisolone	1	0.8	0	0.0
Other Medications					
A02	Drugs For Acid Related Disorders	1	0.8	3	0.6
A03	Drugs For Functional Gastrointestinal Disorders	0	0.0	1	0.2
A06	Laxatives	0	0.0	1	0.2
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	0	0.0	1	0.2
A10	Drugs Used In Diabetes	2	1.6	1	0.2
A12	Mineral Supplements	0	0.0	1	0.2
B01	Aspirin	0	0.0	1	0.2
B01	Clopidogrel	1	0.8	1	0.2
B01	Rivaroxaban	1	0.8	0	0.0
B03	Antianemic Preparations	1	0.8	1	0.2
C01	Cardiac Therapy	3	2.4	5	0.9
C02	Antihypertensives	0	0.0	1	0.2
C03	Diuretics	0	0.0	4	0.8
C05	Vasoprotectives	0	0.0	1	0.2
C07	Beta Blocking Agents	1	0.8	3	0.6
C09	Agents Acting On The Renin-Angiotensin System	0	0.0	6	1.1
C10	Lipid Modifying Agents	3	2.4	6	1.1
G04	Urologicals	0	0.0	1	0.2
H03	Thyroid Therapy	0	0.0	1	0.2
M04	Antigout Preparations	0	0.0	1	0.2
N04	Anti-Parkinson Drugs	0	0.0	1	0.2
NS	Not Specified	0	0.0	1	0.2
R01	Nasal Preparations	0	0.0	1	0.2
R03	Drugs For Obstructive Airway Diseases	0	0.0	2	0.4
R05	Cough And Cold Preparations	0	0.0	1	0.2
R06	Antihistamines For Systemic Use	0	0.0	1	0.2
Over-the-counter medications					
A02	Drugs For Acid Related Disorders	0	0.0	1	0.2
R01	Nasal Preparations	0	0.0	1	0.2
S01	Ophthalmologicals	0	0.0	1	0.2

Appendix 6. Other medication history prior to admission (within 4 weeks prior)

ATC code	Drug class/name	Rivaroxaban (N=124)		Contextual (N=528)	
		n	%	n	%
Other medication (by ATC)					
A02	Drugs For Acid Related Disorders	15	12.1	134	25.4
A03	Drugs For Functional Gastrointestinal Disorders	0	0.0	2	0.4
A04	Antiemetics And Antinauseants	0	0.0	1	0.2
A06	Laxatives	1	0.8	17	3.2
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	0	0.0	1	0.2
A10	Drugs Used In Diabetes	14	11.3	59	11.2
A11	Vitamins	4	3.2	14	2.7
A12	Mineral Supplements	1	0.8	15	2.8
B01	Aspirin	1	0.8	8	1.5
B01	Clopidogrel	0	0.0	3	0.6
B03	Antianemic Preparations	2	1.6	14	2.7
C01	Cardiac Therapy	10	8.1	53	10.0
C02	Antihypertensives	3	2.4	15	2.8
C03	Diuretics	8	6.5	37	7.0
C04	Peripheral Vasodilators	0	0.0	1	0.2
C05	Vasoprotectives	0	0.0	4	0.8
C07	Beta Blocking Agents	14	11.3	76	14.4
C08	Calcium Channel Blockers	8	6.5	53	10.0
C09	Agents Acting On The Renin-Angiotensin System	16	12.9	129	24.4
C10	Lipid Modifying Agents	21	16.9	146	27.7
D02	Emollients And Protectives	1	0.8	3	0.6
D07	Corticosteroids, Dermatological Preparations	1	0.8	8	1.5
G03	Sex Hormones And Modulators Of The Genital System	0	0.0	1	0.2
G04	Urologicals	4	3.2	29	5.5
H02	Corticosteroids For Systemic Use	0	0.0	1	0.2
H03	Thyroid Therapy	3	2.4	16	3.0
L01	Antineoplastic Agents	0	0.0	1	0.2
L02	Endocrine Therapy	0	0.0	4	0.8
L04	Immunosuppressive Agents	0	0.0	7	1.3
M03	Muscle Relaxants	0	0.0	1	0.2
M04	Antigout Preparations	0	0.0	13	2.5
M05	Drugs For Treatment Of Bone Diseases	1	0.8	9	1.7
M09	Other Drugs For Disorders Of The Musculo-Skeletal System	1	0.8	6	1.1
N04	Anti-Parkinson Drugs	0	0.0	4	0.8
N05	Psycholeptics	2	1.6	7	1.3

ATC code	Drug class/name	Rivaroxaban (N=124)		Contextual (N=528)	
		n	%	n	%
N07	Other Nervous System Drugs	0	0.0	2	0.4
NS	Not Specified	0	0.0	1	0.2
P01	Antiprotozoals	1	0.8	7	1.3
R01	Nasal Preparations	0	0.0	2	0.4
R03	Drugs For Obstructive Airway Diseases	5	4.0	45	8.5
R05	Cough And Cold Preparations	0	0.0	3	0.6
R06	Antihistamines For Systemic Use	0	0.0	12	2.3
S01	Ophthalmologicals	1	0.8	18	3.4
S02	Otologicals	0	0.0	2	0.4
V03	All Other Therapeutic Products	0	0.0	1	0.2
V06	General Nutrients	0	0.0	2	0.4
Over-the-counter medication					
A02	Drugs For Acid Related Disorders	0	0.0	9	1.7
A06	Drugs For Constipation	0	0.0	1	0.2
A06	Laxatives	0	0.0	4	0.8
R05	Cough And Cold Preparations	0	0.0	1	0.2
S01	Ophthalmologicals	0	0.0	1	0.2
S02	Otologicals	0	0.0	1	0.2

Appendix 7. Other medication use during or following admission

ATC code	Drug class/name	Rivaroxaban (N=124)		Contextual (N=528)	
		n	%	n	%
Other medication*					
A01	Stomatological Preparations	1	0.8	1	0.2
A02	Drugs For Acid Related Disorders	42	33.9	194	36.7
A03	Drugs For Functional Gastrointestinal Disorders	16	12.9	29	5.5
A04	Antiemetics And Antinauseants	8	6.5	14	2.7
A06	Laxatives	5	4.0	37	7.0
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	1	0.8	5	0.9
A08	Antiobesity Preparations, Excl. Diet Products	0	0.0	1	0.2
A10	Drugs Used In Diabetes	12	9.7	40	7.6
A11	Vitamins	2	1.6	7	1.3
A12	Mineral Supplements	8	6.5	21	4.0
B01	Abciximab	1	0.8	1	0.2
B01	Apixaban	0	0.0	7	1.3
B01	Aspirin	32	25.8	72	13.6
B01	Clopidogrel	15	12.1	50	9.5
B01	Edoxaban	1	0.8	1	0.2
B01	Fondaparinux Sodium	0	0.0	6	1.1
B01	Heparin	1	0.8	15	2.8
B01	LMWH	9	7.3	74	14.0
B01	Rivaroxaban	7	5.6	3	0.6
B01	Ticagrelor	18	14.5	35	6.6
B01	Tirofiban	0	0.0	4	0.8
B01	Warfarin	0	0.0	3	0.6
B03	Antianemic Preparations	0	0.0	24	4.5
B05	Blood Substitutes And Perfusion Solutions	0	0.0	5	0.9
C01	Cardiac Therapy	38	30.6	214	40.5
C02	Antihypertensives	3	2.4	9	1.7
C03	Diuretics	16	12.9	76	14.4
C04	Peripheral Vasodilators	0	0.0	1	0.2
C05	Vasoprotectives	0	0.0	4	0.8
C07	Beta Blocking Agents	83	66.9	362	68.6
C08	Calcium Channel Blockers	13	10.5	54	10.2
C09	Agents Acting On The Renin-Angiotensin System	85	68.5	341	64.6
C10	Lipid Modifying Agents	84	67.7	369	69.9
D02	Emollients And Protectives	1	0.8	7	1.3
D05	Antipsoriatics	0	0.0	1	0.2
D07	Corticosteroids, Dermatological Preparations	1	0.8	7	1.3
D08	Antiseptics And Disinfectants	0	0.0	4	0.8
G03	Sex Hormones And Modulators Of The Genital System	0	0.0	1	0.2
G04	Urologicals	5	4.0	27	5.1
H02	Corticosteroids For Systemic Use	0	0.0	2	0.4
H03	Thyroid Therapy	6	4.8	11	2.1
L01	Antineoplastic Agents	0	0.0	1	0.2
L02	Endocrine Therapy	1	0.8	5	0.9

ATC code	Drug class/name	Rivaroxaban (N=124)		Contextual (N=528)	
		n	%	n	%
L04	Immunosuppressive Agents	2	1.6	8	1.5
M03	Muscle Relaxants	0	0.0	2	0.4
M04	Antigout Preparations	0	0.0	10	1.9
M05	Drugs For Treatment Of Bone Diseases	1	0.8	7	1.3
M09	Other Drugs For Disorders Of The Musculo-Skeletal System	1	0.8	5	0.9
N01	Anesthetics	0	0.0	11	2.1
N04	Anti-Parkinson Drugs	0	0.0	2	0.4
N05	Psycholeptics	12	9.7	38	7.2
N07	Other Nervous System Drugs	5	4.0	19	3.6
P01	Antiprotozoals	0	0.0	2	0.4
R01	Nasal Preparations	1	0.8	6	1.1
R03	Drugs For Obstructive Airway Diseases	6	4.8	37	7.0
R05	Cough And Cold Preparations	0	0.0	8	1.5
R06	Antihistamines For Systemic Use	3	2.4	23	4.4
S01	Ophthalmologicals	2	1.6	16	3.0
S02	Otologicals	0	0.0	2	0.4
V03	All Other Therapeutic Products	3	2.4	4	0.8
V06	General Nutrients	1	0.8	1	0.2
V08	Contrast Media	0	0.0	8	1.5
Over-the-counter medication					
A02	Drugs For Acid Related Disorders	0	0.0	7	1.3
A06	Laxatives	0	0.0	7	1.3
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	0	0.0	2	0.4
N07	Other Nervous System Drugs	1	0.8	4	0.8
R01	Nasal Preparations	0	0.0	1	0.2

* HCPs may have included medications prescribed for the acute treatment and secondary prevention

Appendix 8. All reasons for stopping for both cohorts

All reported reasons for stopping rivaroxaban within 12 weeks and after 12 weeks					
Within 12 weeks	N= 24		After 12 weeks	N=13	
Reason for stopping	n	% reasons	Reason for stopping	n	% reasons
Therapy change	3	12.5	Cardiovascular evaluation	1	7.7
Drug course complete	2	8.3	Doctor decision	1	7.7
Haemorrhage	2	8.3	Drug course complete	6	46.2
Hospitalisation	2	8.3	Epistaxis	1	7.7
Percutaneous coronary intervention	2	8.3	Haemoptysis	1	7.7
Secondary care advice, formulary or guidelines	2	8.3	Local Health Authority advice, formulary or guidelines	2	15.4
Acute coronary syndrome	1	4.2	Patient decision to not take drug	1	7.7
Acute kidney injury	1	4.2	Planned duration R for stopping	1	7.7
Angiocardiogram	1	4.2	Secondary care advice, formulary or guidelines	3	23.1
Atrial fibrillation	1	4.2			
Cardiovascular evaluation	1	4.2			
Chest pain	1	4.2			
Contusion	1	4.2			
Coronary artery bypass	1	4.2			
Death	1	4.2			
Diarrhoea	1	4.2			
Epistaxis	1	4.2			
Faeces discoloured	1	4.2			
Haematuria	1	4.2			
Haemoglobin decreased	1	4.2			
Increased tendency to bruise	1	4.2			
Local Health Authority advice, formulary or guidelines	1	4.2			
Melaena	1	4.2			
Menorrhagia	1	4.2			
Patient concerns with drug	1	4.2			
Preoperative care	1	4.2			
Product dose omission	1	4.2			
Refusal of treatment by patient	1	4.2			
Sinus rhythm	1	4.2			
Stent placement	1	4.2			
Vascular graft	1	4.2			
Vascular stent thrombosis	1	4.2			

All reported reasons for stopping contextual treatment within 12 weeks and after 12 weeks					
Within 12 weeks	N=76		After 12 weeks	N=18	
Reason for stopping	n	% reasons	Reason for stopping	n	% reasons
Coronary artery bypass	13	10.2	Angiogram	1	5.6
Therapy change	13	10.2	Angiogram normal	1	5.6
Pre-existing condition improved	7	5.5	Atrial fibrillation	3	16.7
Angiogram normal	5	3.9	Atrial flutter	1	5.6
Preoperative care	5	3.9	Cardiac pacemaker insertion	1	5.6
Rectal haemorrhage	5	3.9	Cardiovascular evaluation	4	22.2
Secondary care advice, formulary or guidelines	5	3.9	Cardioversion	1	5.6
Atrial fibrillation	4	3.1	Colitis	1	5.6
Cardiovascular evaluation	4	3.1	Contusion	1	5.6
Review of diagnosis	4	3.1	Drug course complete	2	11.1
Drug course complete	3	2.3	Dyspnoea	6	33.3
Dyspnoea	3	2.3	Haemorrhage prophylaxis	1	5.6
Supraventricular tachycardia	3	2.3	Nuclear magnetic resonance imaging heart	1	5.6
Surgery	3	2.3	Practice advice, formulary or guidelines	1	5.6
Angiocardiogram	2	1.6	Product dose omission	1	5.6
Cardiac monitoring	2	1.6	Refusal of treatment by patient	1	5.6
Death	2	1.6	Secondary care advice, formulary or guidelines	2	11.1
Troponin increased	2	1.6	Therapy change	4	22.2
Vascular graft	2	1.6			
Acute kidney injury	1	0.8			
Angina unstable	1	0.8			
Angiogram	1	0.8			
Angiogram abnormal	1	0.8			
Arteriogram coronary normal	1	0.8			
Asthenia	1	0.8			
Cardiac failure	1	0.8			
Cardiac operation	1	0.8			
Cardiac resynchronisation therapy	1	0.8			
Contusion	1	0.8			
Coronary arterial stent insertion	1	0.8			
Coronary artery disease	1	0.8			
Doctor decision	1	0.8			
Drug intolerance	1	0.8			
Ear, nose and throat examination	1	0.8			
Epistaxis	1	0.8			

All reported reasons for stopping contextual treatment within 12 weeks and after 12 weeks					
Within 12 weeks	N=76		After 12 weeks	N=18	
Reason for stopping	n	% reasons	Reason for stopping	n	% reasons
Gastrointestinal haemorrhage	1	0.8			
Haematuria	1	0.8			
Hospitalisation	1	0.8			
Implantable defibrillator insertion	1	0.8			
Investigation	1	0.8			
Local Health Authority advice, formulary or guidelines	1	0.8			
Malaise	1	0.8			
Melaena	1	0.8			
Multiple drug therapy	1	0.8			
Myalgia	1	0.8			
Nasal cavity packing	1	0.8			
Nausea	1	0.8			
Non-cardiac chest pain	1	0.8			
Oesophagogastroduodenoscopy	1	0.8			
Palliative care	1	0.8			
Percutaneous coronary intervention	1	0.8			
Pulmonary embolism	1	0.8			
Rash pruritic	1	0.8			
Referred to specialist	1	0.8			
Refusal of treatment by patient	1	0.8			
Respiration abnormal	1	0.8			
Scan myocardial perfusion normal	1	0.8			
Short term use only	1	0.8			
Thrombolysis	1	0.8			
Upper gastrointestinal haemorrhage	1	0.8			

Appendix 9. Events reported on treatment including wash-out period within 12 weeks observation period

Cumulative incidence of bleeding events in the rivaroxaban cohort reported during 12 week observation period, by TIMI category, including wash-out period

N=124															
Bleeding event	All			Intracranial			Gastrointestinal			Urogenital			Other		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Non-CABG major	1	0.8	0.0, 4.4	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	0	0.0	n/a
Non-CABG minor	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Non-CABG requiring medical attention	13	10.5	5.7, 17.3	0	0.0	n/a	4	3.2	0.9, 8.1	4	3.2	0.9, 8.1	7[a]	5.6	2.3, 11.3
Non-CABG minimal	2	1.6	0.2, 5.7	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	1	0.8	0.0, 4.4
CABG related major	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	2	1.6	0.2, 5.7	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	1	0.8	0.0, 4.4

[a] one patient had bleeding within respiratory site and skin

Cumulative incidence of bleeding events in the contextual cohort reported during 12 week observation period, by TIMI category, including wash-out period

N=528															
Bleeding event	All			Intracranial			Gastrointestinal			Urogenital			Other		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Non-CABG major	5	0.9	0.3, 2.2	0	0	n/a	4	0.8	0.2, 1.9	0	0.0	n/a	1	0.2	0.0, 1.1
Non-CABG minor	3	0.6	0.1, 1.7	0	0	n/a	2	0.4	0.0, 1.4	0	0.0	n/a	1	0.2	0.0, 1.1
Non-CABG requiring medical attention	20	3.8	2.3, 5.8	0	0	n/a	9[a]	1.7	0.8, 3.2	1	0.2	0.0, 1.1	11[b]	2.1	1.0, 3.7
Non-CABG minimal	0	0.0	n/a	0	0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
CABG major	0	0.0	n/a	0	0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	1	0.2	0.0, 1.1	0	0	n/a	0	0.0	n/a	0	0.0	n/a	1	0.2	0.0, 1.1

[a] One patient had two gastrointestinal bleeding events within different anatomical sites
[b] one patient had bleeding within respiratory site and skin

Count of number of targeted events within 12 week observation period including wash-out period*

	Rivaroxaban (N=124)		Contextual (N=528)	
Event[a]	**n**	%	n	%
Injury/Trauma	0	0.0	1	0.2
Overdose	0	0.0	0	0.0
Cardiovascular Disorders				
STEMI	6	4.8	81	15.3
NSTEMI	9	7.3	86	16.3
Angina	3	2.4	26	4.9
Congestive heart failure	4	3.2	10	1.9
Peripheral arterial disease	0	0.0	0	0.0
Cardiac Arrhythmias	7	5.6	19	3.6
Other Conditions				
Liver Disorder	0	0.0	0	0.0
Abnormal liver function test	4	3.2	13	2.5
Renal Failure (Stage 5 CKD)	0	0.0	1	0.2
Renal Impairment (Stage 3-4 CKD)	4	3.2	4	0.8
Renal Impairment (Stage 1-2 CKD)	2	1.6	10	1.9
Pregnancies (within the last 12 months)	0	0.0	0	0.0
Breastfeeding	0	0.0	0	0.0

* Responses provided as "tick all that apply". Where no response was provided for each medical condition listed, the patient was assumed not to have had the condition. This approach was justified in that physicians are more likely to record presence of a condition rather than confirm absence.

[a] Events reported by GP: rivaroxaban cohort: Injury/Trauma (n=1), abnormal liver function test (n=3); contextual cohort: Injury/Trauma (n=5), abnormal liver function test (n=9).

Count of number of events of abnormal LFTs (greater than 3 X upper limit of normal) within 12 week observation period including wash-out period

Rivaroxaban N=124		Contextual N=528	
n	%	n	%
3	2.4	4	0.8

Appendix 10. Events reported on treatment outside of the 12 weeks observation period

Cumulative incidence of bleeding events in the rivaroxaban cohort reported outside of the 12 week observation period, by TIMI category

N=124															
	All[a]			Intracranial			Gastrointestinal			Urogenital			Other		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Non-CABG major	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Non-CABG minor	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Non-CABG requiring medical attention	1	0.8	0.0, 4.4	0	0.0	n/a	1	0.8	0.0, 4.4	0	0.0	n/a	0	0.0	n/a
Non-CABG minimal	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
CABG related major	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	1	0.8	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	1	0.8	0.0, 4.4

[a] Number of patients with at least one bleeding event (NB. This may not equal the row total if patients experienced more than one bleed of the same classification at different sites)

Cumulative incidence of bleeding events in the contextual cohort reported outside of the 12 week observation period, by TIMI category

N=528															
	All[a]			Intracranial			Gastrointestinal			Urogenital			Other		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Non-CABG major	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Non-CABG minor	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Non-CABG requiring medical attention	2	0.4	0.0, 1.4	0	0.0	n/a	1	0.2	0.0, 1.1	1	0.2	0.0, 1.1	1	0.2	0.0, 1.1
Non-CABG minimal	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
CABG related major	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a
Unclassifiable	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a	0	0.0	n/a

[a] Number of patients with at least one bleeding event (NB. This may not equal the row total if patients experienced more than one bleed of the same classification at different sites)

Count of number of targeted events reported outside of the 12 week observation period*

	Rivaroxaban (N=124)		Contextual (N=528)	
Event[a]	n	%	n	%
Injury/Trauma	0	0.0	2	0.4
Overdose	0	0.0	0	0.0
Cardiovascular Disorders				
STEMI	0	0.0	0	0.0
NSTEMI	0	0.0	0	0.0
Angina	0	0.0	1	0.2
Congestive heart failure	0	0.0	0	0.0
Peripheral arterial disease	0	0.0	0	0.0
Cardiac Arrhythmias	0	0.0	1	0.2
Other Conditions				
Liver Disorder	0	0.0	0	0.0
Abnormal liver function test	0	0.0	1	0.2
Renal Failure (Stage 5 CKD)	0	0.0	0	0.0
Renal Impairment (Stage 3-4 CKD)	1	0.8	0	0.0
Renal Impairment (Stage 1-2 CKD)	0	0.0	1	0.2
Pregnancies (within the last 12 months)	0	0.0	0	0.0
Breastfeeding	0	0.0	0	0.0

* Responses provided as "tick all that apply". Where no response was provided for each medical condition listed, the patient was assumed not to have had the condition. This approach was justified in that physicians are more likely to record presence of a condition rather than confirm absence.

[a] Events reported by GP: rivaroxaban cohort: Injury/Trauma (n=1), abnormal liver function test (n=3); contextual cohort: Abnormal liver function test (n=9).

Count of number of events of abnormal LFTs (greater than 3 X upper limit of normal) reported outside of the 12 week observation period

Rivaroxaban N=124		Contextual N=528	
n	%	n	%
0	0.0	2	0.4

Appendix 11. Comparison of TIMI/BARC classifications

Rivaroxaban cohort N=124										
BARC by TIMI classification	All sites combined		Stratified by site							
			Intracranial		Gastrointestinal		Urogenital		Other	
	n	% of TIMI category	n	% of TIMI category	n	% of TIMI category	n	% of TIMI category	n	% of TIMI category
TIMI Non-CABG related major bleeding										
BARC Type 3b	1	100.0	0	0.0	1	100.0	0	0.0	0	0.0
TIMI Non-CABG related bleeding requiring medical attention										
BARC Type 2	12	92.3	0	0.0	3	23.1	4	30.8	7	53.8
BARC Type 3b	1	7.7	0	0.0	1	7.7	0	0.0	0	0.0
TIMI Non-CABG related minimal bleeding										
BARC Type 1	2	100.0	0	0.0	1	50.0	0	0.0	1	50.0
TIMI Unclassifiable										
BARC unclassifiable	2	100.0	0	0.0	1	50.0	0	0.0	1	50.0

Contextual cohort N=528										
BARC by TIMI classification	All sites combined		Stratified by site							
			Intracranial		Gastrointestinal		Urogenital		Other	
	n	% of TIMI category	n	% of TIMI category	n	% of TIMI category	n	% of TIMI category	n	% of TIMI category
TIMI Non-CABG related major bleeding										
BARC Type 3b	5	100.0	0	0.0	4	80.0	0	0.0	1	20.0
TIMI Non-CABG related minor bleeding										
BARC Type 3a	2	66.7	0	0.0	1	33.3	0	0.0	1	33.3
BARC Type 3b	1	33.3	0	0.0	1	33.3	0	0.0	0	0.0
TIMI Non-CABG related bleeding requiring medical attention										
BARC Type 2	19	95.0	0	0.0	9	45.0	1	5.0	10	50.0
BARC Type 3b	1	5.0	0	0.0	0	0.0	0	0.0	1	5.0
TIMI Unclassifiable										
BARC unclassifiable	1	100.0	0	0.0	0	0.0	0	0.0	1	100.0

Appendix 12. Event surveillance ("free text" events)

Count of number of free-text events within 12 week observation period for the rivaroxaban cohort

	Rivaroxaban (N=124)	
Preferred Term	n	%
Hospitalisation	6	4.8
Angiocardiogram	3	2.4
Palpitations	2	1.6
Percutaneous coronary intervention	2	1.6
Angina pectoris	1	0.8
Angiogram	1	0.8
Antiphospholipid antibodies positive	1	0.8
Atrial fibrillation	1	0.8
Breast mass	1	0.8
Cardiac failure	1	0.8
Cardiovascular evaluation	1	0.8
Chest X-ray abnormal	1	0.8
Chest pain	1	0.8
Drug therapy	1	0.8
Effusion	1	0.8
Epistaxis	1	0.8
Faeces discoloured	1	0.8
Fractional flow reserve	1	0.8
Haematuria	1	0.8
Hypertension	1	0.8
Hypothyroidism	1	0.8
Left ventricular dysfunction	1	0.8
Mammogram	1	0.8
Musculoskeletal chest pain	1	0.8
Paroxysmal arrhythmia	1	0.8
Pericarditis	1	0.8
Pneumonia	1	0.8
Ventricular fibrillation	1	0.8
Weight decreased	1	0.8

There were no reports by the GP for the rivaroxaban cohort

Count of number of free-text events within 12 week observation period for the rivaroxaban cohort including wash-out period

	Rivaroxaban (N=124)	
Preferred Term	n	%
Hospitalisation	6	4.8
Angiocardiogram	3	2.4
Palpitations	2	1.6
Percutaneous coronary intervention	2	1.6
Acute myocardial infarction	1	0.8
Angina pectoris	1	0.8
Angiogram	1	0.8
Antiphospholipid antibodies positive	1	0.8
Atrial fibrillation	1	0.8
Breast mass	1	0.8
Cardiac failure	1	0.8
Cardiovascular evaluation	1	0.8
Chest X-ray abnormal	1	0.8
Chest pain	1	0.8
Drug therapy	1	0.8
Effusion	1	0.8
Epistaxis	1	0.8
Faeces discoloured	1	0.8
Fractional flow reserve	1	0.8
Haematuria	1	0.8
Hypertension	1	0.8
Hypothyroidism	1	0.8
Left ventricular dysfunction	1	0.8
Mammogram	1	0.8
Musculoskeletal chest pain	1	0.8
Paroxysmal arrhythmia	1	0.8
Pericarditis	1	0.8
Pneumonia	1	0.8
Stent placement	1	0.8
Ventricular fibrillation	1	0.8
Weight decreased	1	0.8

There were no reports by the GP for the rivaroxaban cohort

Count of number of free-text events reported outside of the 12 week observation period for the rivaroxaban cohort

	Rivaroxaban (N=124)	
Preferred Term	n	%
Chronic kidney disease	1	0.8
Fall	1	0.8
Rib fracture	1	0.8

Events reported by GP	Rivaroxaban (N=124)	
Preferred Term	n	%
Lower respiratory tract infection	1	0.8

Count of number of free-text events within 12 week observation period for the contextual cohort

	Contextual (N=528)	
Preferred Term	n	%
Hospitalisation	16	3.0
Percutaneous coronary intervention	15	2.8
Chest pain	9	1.7
Angioplasty	8	1.5
Lower respiratory tract infection	6	1.1
Nuclear magnetic resonance imaging heart	6	1.1
Atrial fibrillation	5	0.9
Dyspnoea	5	0.9
Stent placement	5	0.9
Acute kidney injury	4	0.8
Angiocardiogram	4	0.8
Angiogram	4	0.8
Pleural effusion	4	0.8
Unevaluable event	4	0.8
Acute myocardial infarction	3	0.6
Chronic obstructive pulmonary disease	3	0.6
Diarrhoea	3	0.6
Gastrooesophageal reflux disease	3	0.6
Palpitations	3	0.6
Pericarditis	3	0.6
Platelet count decreased	3	0.6
Urinary tract infection	3	0.6
Abdominal pain	2	0.4
Abdominal pain upper	2	0.4
Alanine aminotransferase increased	2	0.4
Anaemia	2	0.4
C-reactive protein increased	2	0.4
Cardiac failure congestive	2	0.4
Cardiac pacemaker insertion	2	0.4
Contusion	2	0.4
Coronary arterial stent insertion	2	0.4
Echocardiogram	2	0.4
Emergency care	2	0.4
Epigastric discomfort	2	0.4
Fractional flow reserve	2	0.4
Haematocrit decreased	2	0.4

	Contextual (N=528)	
Preferred Term	n	%
Haemoglobin decreased	2	0.4
Hypotension	2	0.4
Myocardial ischaemia	2	0.4
Non-cardiac chest pain	2	0.4
Pneumonia	2	0.4
Rectal haemorrhage	2	0.4
Red blood cell count decreased	2	0.4
Troponin increased	2	0.4
White blood cell count increased	2	0.4
Anaemia macrocytic	1	0.2
Angina pectoris	1	0.2
Angina unstable	1	0.2
Angioedema	1	0.2
Atrioventricular block	1	0.2
Blood bilirubin increased	1	0.2
Blood creatinine increased	1	0.2
Blood fibrinogen increased	1	0.2
Blood phosphorus decreased	1	0.2
Blood sodium decreased	1	0.2
Blood test normal	1	0.2
Blood urea increased	1	0.2
Cardiac arrest	1	0.2
Cardiac murmur	1	0.2
Cardiac ventricular scarring	1	0.2
Cardiac ventricular thrombosis	1	0.2
Chest discomfort	1	0.2
Colonoscopy	1	0.2
Constipation	1	0.2
Coronary angioplasty	1	0.2
Coronary artery stenosis	1	0.2
Ejection fraction decreased	1	0.2
Electrocardiogram	1	0.2
Electrocardiogram ST segment elevation	1	0.2
Electrocardiogram abnormal	1	0.2
Electrocardiogram normal	1	0.2
End stage renal disease	1	0.2
Eosinophil count decreased	1	0.2
Fatigue	1	0.2
Folliculitis	1	0.2

	Contextual (N=528)	
Preferred Term	n	%
Gastritis	1	0.2
Haematemesis	1	0.2
Hypercholesterolaemia	1	0.2
Hyperhidrosis	1	0.2
Hypokinesia	1	0.2
Hyponatraemia	1	0.2
Intensive care	1	0.2
Iron deficiency anaemia	1	0.2
Left ventricular dysfunction	1	0.2
Lipoma	1	0.2
Liver scan normal	1	0.2
Lung consolidation	1	0.2
Lymphocyte count decreased	1	0.2
Malaise	1	0.2
Monocyte count increased	1	0.2
Myocarditis	1	0.2
Nausea	1	0.2
Neck pain	1	0.2
Nephrolithiasis	1	0.2
Neutrophil count increased	1	0.2
Oedema peripheral	1	0.2
Oesophagogastroduodenoscopy	1	0.2
Oral herpes	1	0.2
Osteoporosis	1	0.2
Packed red blood cell transfusion	1	0.2
Pain in jaw	1	0.2
Paronychia	1	0.2
Periarthritis	1	0.2
Pleural thickening	1	0.2
Pneumothorax	1	0.2
Presyncope	1	0.2
Prostate cancer	1	0.2
Protein total decreased	1	0.2
Pulmonary function test	1	0.2
Pulmonary oedema	1	0.2
Rash	1	0.2
Refusal of treatment by patient	1	0.2
Respiratory tract infection	1	0.2
Retroperitoneal haemorrhage	1	0.2

	Contextual (N=528)	
Preferred Term	n	%
Spinal compression fracture	1	0.2
Supraventricular tachycardia	1	0.2
Swollen tongue	1	0.2
Syncope	1	0.2
Tooth extraction	1	0.2
Transfusion	1	0.2
Troponin	1	0.2
Type 2 diabetes mellitus	1	0.2
Urinary retention	1	0.2
Ventricular tachycardia	1	0.2
Vomiting	1	0.2
Weight decreased	1	0.2
Wound infection	1	0.2

Events reported by GP	Contextual (N=528)	
Preferred Term	n	%
Hospitalisation	3	0.6
Acute myocardial infarction	2	0.4
Alanine aminotransferase abnormal	2	0.4
Blood alkaline phosphatase increased	2	0.4
Skin laceration	2	0.4
Angina pectoris	1	0.2
Blood pressure measurement	1	0.2
Chest discomfort	1	0.2
Chest pain	1	0.2
Cough	1	0.2
Dyspnoea	1	0.2
Echocardiogram abnormal	1	0.2
Haemorrhoids	1	0.2
Iron deficiency anaemia	1	0.2
Liver function test normal	1	0.2
Nasal cavity packing	1	0.2
Nausea	1	0.2
Peripheral artery thrombosis	1	0.2
Postoperative wound infection	1	0.2
Pre-existing condition improved	1	0.2
QRS axis abnormal	1	0.2

Events reported by GP	Contextual (N=528)	
Preferred Term	n	%
Sinus rhythm	1	0.2
Spinal compression fracture	1	0.2
Unevaluable event	1	0.2
Vitreous floaters	1	0.2
Vitreous opacities	1	0.2

Count of number of free-text events within 12 week observation period for the contextual cohort including wash-out period

	Contextual (N=528)	
Preferred Term	n	%
Hospitalisation	16	3.0
Percutaneous coronary intervention	15	2.8
Chest pain	9	1.7
Angioplasty	8	1.5
Lower respiratory tract infection	6	1.1
Nuclear magnetic resonance imaging heart	6	1.1
Atrial fibrillation	5	0.9
Dyspnoea	5	0.9
Stent placement	5	0.9
Acute kidney injury	4	0.8
Angiocardiogram	4	0.8
Angiogram	4	0.8
Pleural effusion	4	0.8
Unevaluable event	4	0.8
Acute myocardial infarction	3	0.6
Chronic obstructive pulmonary disease	3	0.6
Diarrhoea	3	0.6
Gastrooesophageal reflux disease	3	0.6
Palpitations	3	0.6
Pericarditis	3	0.6
Platelet count decreased	3	0.6
Urinary tract infection	3	0.6
Abdominal pain	2	0.4
Abdominal pain upper	2	0.4
Alanine aminotransferase increased	2	0.4
Anaemia	2	0.4
C-reactive protein increased	2	0.4
Cardiac failure congestive	2	0.4
Cardiac pacemaker insertion	2	0.4
Contusion	2	0.4
Coronary arterial stent insertion	2	0.4
Echocardiogram	2	0.4
Emergency care	2	0.4
Epigastric discomfort	2	0.4
Fractional flow reserve	2	0.4
Haematocrit decreased	2	0.4

	Contextual (N=528)	
Preferred Term	n	%
Haemoglobin decreased	2	0.4
Hypotension	2	0.4
Myocardial ischaemia	2	0.4
Non-cardiac chest pain	2	0.4
Pneumonia	2	0.4
Rectal haemorrhage	2	0.4
Red blood cell count decreased	2	0.4
Troponin increased	2	0.4
White blood cell count increased	2	0.4
Anaemia macrocytic	1	0.2
Angina pectoris	1	0.2
Angina unstable	1	0.2
Angioedema	1	0.2
Atrioventricular block	1	0.2
Blood bilirubin increased	1	0.2
Blood creatinine increased	1	0.2
Blood fibrinogen increased	1	0.2
Blood phosphorus decreased	1	0.2
Blood sodium decreased	1	0.2
Blood test normal	1	0.2
Blood urea increased	1	0.2
Cardiac arrest	1	0.2
Cardiac murmur	1	0.2
Cardiac ventricular scarring	1	0.2
Cardiac ventricular thrombosis	1	0.2
Chest discomfort	1	0.2
Colonoscopy	1	0.2
Constipation	1	0.2
Coronary angioplasty	1	0.2
Coronary artery stenosis	1	0.2
Ejection fraction decreased	1	0.2
Electrocardiogram	1	0.2
Electrocardiogram ST segment elevation	1	0.2
Electrocardiogram abnormal	1	0.2
Electrocardiogram normal	1	0.2
End stage renal disease	1	0.2
Eosinophil count decreased	1	0.2
Fatigue	1	0.2
Folliculitis	1	0.2

	Contextual (N=528)	
Preferred Term	n	%
Gastritis	1	0.2
Haematemesis	1	0.2
Hypercholesterolaemia	1	0.2
Hyperhidrosis	1	0.2
Hypokinesia	1	0.2
Hyponatraemia	1	0.2
Intensive care	1	0.2
Iron deficiency anaemia	1	0.2
Left ventricular dysfunction	1	0.2
Lipoma	1	0.2
Liver scan normal	1	0.2
Lung consolidation	1	0.2
Lymphocyte count decreased	1	0.2
Malaise	1	0.2
Monocyte count increased	1	0.2
Myocarditis	1	0.2
Nausea	1	0.2
Neck pain	1	0.2
Nephrolithiasis	1	0.2
Neutrophil count increased	1	0.2
Oedema peripheral	1	0.2
Oesophagogastroduodenoscopy	1	0.2
Oral herpes	1	0.2
Osteoporosis	1	0.2
Packed red blood cell transfusion	1	0.2
Pain in jaw	1	0.2
Paronychia	1	0.2
Periarthritis	1	0.2
Pleural thickening	1	0.2
Pneumothorax	1	0.2
Presyncope	1	0.2
Prostate cancer	1	0.2
Protein total decreased	1	0.2
Pulmonary function test	1	0.2
Pulmonary oedema	1	0.2
Rash	1	0.2
Refusal of treatment by patient	1	0.2
Respiratory tract infection	1	0.2
Retroperitoneal haemorrhage	1	0.2

	Contextual (N=528)	
Preferred Term	n	%
Spinal compression fracture	1	0.2
Supraventricular tachycardia	1	0.2
Swollen tongue	1	0.2
Syncope	1	0.2
Tooth extraction	1	0.2
Transfusion	1	0.2
Troponin	1	0.2
Type 2 diabetes mellitus	1	0.2
Urinary retention	1	0.2
Ventricular tachycardia	1	0.2
Vomiting	1	0.2
Weight decreased	1	0.2
Wound infection	1	0.2

Events reported by GP	Contextual (N=528)	
Preferred Term	**n**	%
Hospitalisation	3	0.6
Acute myocardial infarction	2	0.4
Alanine aminotransferase abnormal	2	0.4
Blood alkaline phosphatase increased	2	0.4
Skin laceration	2	0.4
Angina pectoris	1	0.2
Blood pressure measurement	1	0.2
Chest discomfort	1	0.2
Chest pain	1	0.2
Cough	1	0.2
Dyspnoea	1	0.2
Echocardiogram abnormal	1	0.2
Haemorrhoids	1	0.2
Iron deficiency anaemia	1	0.2
Liver function test normal	1	0.2
Nasal cavity packing	1	0.2
Nausea	1	0.2
Peripheral artery thrombosis	1	0.2
Postoperative wound infection	1	0.2
Pre-existing condition improved	1	0.2
QRS axis abnormal	1	0.2
Sinus rhythm	1	0.2

Spinal compression fracture	1	0.2
Unevaluable event	1	0.2
Vitreous floaters	1	0.2
Vitreous opacities	1	0.2

Count of number of free-text events reported outside of the 12 week observation period for the contextual cohort

	Contextual (N=528)	
Preferred Term	**n**	%
Angiogram	2	0.4
Hospitalisation	2	0.4
Angina pectoris	1	0.2
Angiocardiogram	1	0.2
Angioplasty	1	0.2
Aortic aneurysm	1	0.2
Cardiovascular evaluation	1	0.2
Chronic obstructive pulmonary disease	1	0.2
Coronary artery bypass	1	0.2
Depression	1	0.2
Electrocardiogram normal	1	0.2
Ex-tobacco user	1	0.2
Exercise electrocardiogram	1	0.2
Gastroenteritis viral	1	0.2
Gout	1	0.2
Impaired work ability	1	0.2
Infection	1	0.2
Intervertebral disc degeneration	1	0.2
Mitral valve incompetence	1	0.2
Myocardial infarction	1	0.2
Orthostatic hypotension	1	0.2
Percutaneous coronary intervention	1	0.2
Pericardial effusion	1	0.2
Pleural effusion	1	0.2
Sigmoidoscopy normal	1	0.2
Unevaluable event	1	0.2

Events reported by GP	Contextual (N=528)	
Preferred Term	n	%
Blood alkaline phosphatase increased	2	0.4
Hospitalisation	2	0.4
Alanine aminotransferase increased	1	0.2
Blood bilirubin increased	1	0.2
Blood test	1	0.2
Coronary artery bypass	1	0.2
Ileus	1	0.2

Lipids	1	0.2
Orthostatic hypotension	1	0.2
Pneumonia	1	0.2
Unevaluable event	1	0.2

Appendix 13. Deaths

Number of deaths reported during the 12-week observation period in the rivaroxaban and contextual cohorts including wash-out period

	Rivaroxaban N=124		Contextual N=528	
Treatment status	n	%	n	%
Deaths on treatment including washout	3	2.4	9	1.7

Number of deaths reported outside of the 12 week observation period in the rivaroxaban and contextual cohorts

	Rivaroxaban N=124		Contextual N=528	
Treatment status	n	%	n	%
Deaths on treatment	0	0.0	0	0.0
Deaths off treatment	0	0.0	1	0.2

Immediate cause of death reported on treatment during the 12-week observation period including wash-out period*

Rivaroxaban N=124	n	%	Contextual N=528	n	%
Myocardial infarction	3	2.4	Acute myocardial infarction	2	0.4
			Cardiogenic shock	2	0.4
			Cardiac arrest	1	0.2
			Cardiac failure congestive	1	0.2
			Death	1	0.2
			Myocardial infarction	1	0.2
			Pneumonia	1	0.2

* cause of death events may not be included in the events on treatment tables

Immediate cause of death reported off treatment during the 12-week observation period

Rivaroxaban N=124	n	%	Contextual N=528	n	%
Death	1	0.8	Cerebral infarction	1	0.2
			Pneumonia	1	0.2
			Ventricular fibrillation	1	0.2

Appendix 13. Deaths

Underlying cause/conditions of death reported on treatment during the 12-week observation period including, wash-out period*

Rivaroxaban (N=124)	n	%	Contextual (N=528)	n	%
Cardiac failure	1	0.8	Acute kidney injury	3	0.6
Diabetes mellitus	1	0.8	Acute myocardial infarction	2	0.4
Hypertension	1	0.8	Hypertension	2	0.4
Myocardial ischaemia	1	0.8	Myocardial ischaemia	2	0.4
			Arteriosclerosis coronary artery	1	0.2
			Cardiac failure	1	0.2
			Cardiac failure congestive	1	0.2
			Carotid artery stenosis	1	0.2
			Chronic kidney disease	1	0.2
			Coronary artery disease	1	0.2
			Coronary artery occlusion	1	0.2
			Ischaemic cardiomyopathy	1	0.2
			Left ventricular dysfunction	1	0.2
			Myocardial infarction	1	0.2
			Pleural effusion	1	0.2
			Pneumonia	1	0.2
			Pulmonary oedema	1	0.2
			Type 2 diabetes mellitus	1	0.2
			Ventricular fibrillation	1	0.2

* Underlying cause/conditions of death events may not be included in the events on treatment tables

Underlying cause/conditions of death reported off treatment during the 12-week observation period

Rivaroxaban (N=124)	n	%	Contextual (N=528)	n	%
Chronic kidney disease	1	0.8	Acute myocardial infarction	2	0.4
Coronary artery disease	1	0.8	Myocardial ischaemia	2	0.4
Diabetes mellitus	1	0.8	Acute kidney injury	1	0.2
Renal impairment	1	0.8	Cardiac failure	1	0.2
			Coronary artery bypass	1	0.2
			Left ventricular failure	1	0.2
			Mitral valve replacement	1	0.2

Signature Page – Principal Investigator

Title	An Observational Post-authorization Safety Specialist Cohort Event Monitoring Study (SCEM) to Monitor the Safety and Utilization of rivaroxaban (XARELTO®) initiated in secondary care for the prevention of atherothrombotic events in patients who have had acute coronary syndrome in England and Wales
Report version and date	Version 1.0 Oct 2019
IMPACT study number	17542
Study type / Study phase	Observational, Phase IV
EU PAS register number	EUPAS9977
Medicinal product	Xarelto 2.5mg Tablets
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

PPD

03/12/2019

Date, Signature: _____, _____