Marketing Authorisation Holder(s)

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PASS INFORMATION

Title	Health outcomes of patients with acute coronary syndromes prescribed ticagrelor in UK primary care: a retrospective cohort study
Version identifier of the final study report	*V0.4*
Date of last version of the final study report	14 March 2019
EU PAS register number	EUPAS17107
Active substance	Ticagrelor
Medicinal product	*Brilique*
Product reference	Brilique 90 mg film-coated tablet oral: EU/1/10/655/001; EU/1/10/655/002; EU/1/10/655/003; EU/1/10/655/004; EU/1/10/655/005; EU/1/10/655/006 Brilique 90 mg orodispersible tablet oral: EU/1/10/655/012; EU/1/10/655/013; EU/1/10/655/014
Procedure number	*N/A*
Marketing authorisation holder(s)	AstraZeneca
Joint PASS	No

Research question and objectives	**Primary Objectives** To assess the incidence and time to event for the following in patients treated with ticagrelor in primary care following ACS events: • composite outcome of MI, stroke or death from vascular causes • individual vascular events (MI, stroke, and death from vascular causes) • all cause death **Secondary Objectives** To estimate the rates of vascular events stratified by the following factors: • Aged <75 and 75 or older • MI vs UA or unspecified (Index ACS) • Medically managed vs interventionally managed • Diabetic vs non-diabetic • Presence/absence of other CV co-morbidities (prior stroke, heart failure, peripheral artery disease, atrial fibrillation) To assess the incidence and time to event for the following in patients treated with ticagrelor in primary care following ACS events: • Bleeding events and stratified by presence/absence of bleeding risk factors (prior bleed, peptic ulcers, warfarin) • Dyspnoea and stratified by presence/absence of dyspnoea risk factors (prior history of respiratory disease or heart failure)
Country (-ies) of study	UK
[redacted]	[redacted]

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1. ABSTRACT

Title

Health outcomes of patients with acute coronary syndromes prescribed ticagrelor in UK primary care: a retrospective cohort study

Keywords

Ticagrelor, Acute Coronary Syndrome, Clinical Practice Research Datalink, retrospective study, bleeding, dyspnoea

Background

The PLATO study showed that ticagrelor compared with clopidogrel, as dual antiplatelet treatment with aspirin, in patients with acute coronary syndrome (ACS) significantly reduced the rate of death from vascular causes, myocardial infarction (MI), or stroke without an increase in the rate of overall major bleeding, but with an increase in the rate of non-procedure-related bleeding. In view of the findings of the PLATO trial, an observational study was considered appropriate to develop evidence on the health outcomes following first use of ticagrelor in the UK outpatient setting.

Purpose

To describe the characteristics and quantify the incidence of efficacy and safety outcomes, following ACS, in a real-world English patient population prescribed ticagrelor.

Methods

The study was a longitudinal cohort study of patients prescribed ticagrelor in primary care, following ACS, with a first prescription between December 2010 and March 2015. Patients were followed for up to 12 months on-treatment. The study used the Clinical Practice Research Datalink which consists of English linked multi-source data from primary and secondary care (Hospital Episode Statistics), and Office for National Statistics Mortality data. The primary outcome was a composite of hospitalised MI, hospitalised stroke and vascular death. Secondary outcomes included individual vascular events, bleeds (based on BARC type ≥2**)** and dyspnoea. Crude incidence rates were presented per 100 person-years (95% CI) and Kaplan-Meier survival curves were generated showing the probability (95% CI) of being event free at one month intervals. No adjustments were made due to limited study population and low number of events and thus insufficient statistical power for any such analyses.

Results

Altogether, 1650 patients were included. Of these 72.4% were men, 23.5% aged ≥75 years, and 85.0% received revascularisation (PCI or CABG) at time of ACS. The incidence rate of the primary composite outcome per 100 person years was 5.3 (3.8–6.8), and for the individual vascular events MI 3.3 (2.1–4.5), stroke 0.9 (0.3-1.5) and vascular death 1.4 (0.6-2.2), respectively. For those with revascularisation, the incidence rate of the composite outcome (3.9 (2.6–5.3)) and MI (2.3 (1.3–3.4)) was lower than among those without revascularisation (15.1 (7.9–22.3) and 10.7 (4.6–16.7), respectively). However, non-revascularized patients were older (mean age 70.7 vs. 63.6 years), more likely to be women (36.7% vs. 26.0%), with a history of MI (23.0% vs 11.1%) and stroke (12.9% vs. 5.1%).

The overall incidence rate of bleeding per 100 person years was 6.6 (4.9–8.2), with no major difference between elderly (≥75) and younger patients (7.1 (3.4–10.8) vs. 6.4 (4.6–8.3), respectively). The incidence rate of hospitalised bleeds was 2.5 (1.5–3.5) and was similar in elderly and younger patients (3.5 (0.9–6.2) vs. 2.2 (1.1–3.3)). 32.4% of the overall cohort had respiratory disease or prior dyspnoea of unknown cause at baseline. During the study period the overall incidence rate of dyspnoea was 21.6 (18.6–24.6), it was higher among those aged ≥75 [34.3 (26.2-42.5) vs 18.1 (15.0-21.2)] and those with other prior cardiovascular disease [36.9 (28.3-45.5) vs 17.7 (14.6-20.7)]. The incidence rate of hospitalised dyspnoea was 1.7 (0.9-2.6).

Among those without respiratory disease or prior dyspnoea, the incidence rate of dyspnoea was 14.5 (11.6–17.5) and the incidence rate of hospitalised dyspnoea was 1.4 (0.5–2.3).

Conclusion

In this study the crude incidence rate of a composite of hospitalised MI, hospitalised stroke and vascular death was 5.3 (3.8-6.8) per 100 person years in this population. The crude incidence rates for bleeding with hospital care was 2.5 (1.5–3.5) and dyspnoea requiring hospital care 1.7 (0.9-2.6). The interpretation of this real-world study is limited due to survival bias, lack of a comparator and statistical modelling to assess the role of risk factors. Modelling of risk factors was not done because the number of events were considered too few for assessing hazard ratios with sufficient precision and statistical power.

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Names and affiliations of principal investigators

[redacted]

2. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACS	Acute Coronary Syndrome
ASA	Acetylsalicylic acid
AZ	AstraZeneca
BARC	Bleeding Academic Research Consortium
CABG	Coronary Artery Bypass Graft
CPRD	Clinical Practice Research Datalink
CPTP	Cyclopentyltriazolo-pyrimidine
CV	Cardiovascular
HES	Hospital Episode Statistics
MI	Myocardial Infarction
NICE	National Institute for Health and Care Excellence
NSTEMI	Non-ST elevation myocardial infarction
OAP	Oral anti-platelet
OPCS	Office of Population Censuses and Surveys (OPCS)
PCI	Percutaneous coronary intervention
STEMI	ST elevation myocardial infarction
UA	Unstable Angina

3. INVESTIGATORS

[redacted]

4. OTHER RESPONSIBLE PARTIES

[redacted]. This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol number: 14_243RA).

5. MILESTONES

Table 1 Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	*25 February 2015*	*25 February 2015*	<<>>
End of data collection	*31 March 2015*	*31 March 2015*	<<>>
Registration in the EU PAS register	*14 December 2016*	*27 April 2017*	<<>>
Final report of study results	*13 November 2018*	*14 March 2019*	<<>>

6. RATIONALE AND BACKGROUND

Patients who have an acute myocardial infarction (MI) or another acute coronary syndrome (ACS) event are at high risk of a recurrent event or cardiovascular (CV) death. Therefore, secondary prevention is critical [1-3]. Several antiplatelet therapies for secondary prevention are available, including ticagrelor, a direct-acting, reversible $P2Y_{12}$ antagonist [4-6]. After 12 months follow up in the phase III PLATO trial, the incidences of the primary composite endpoint and the three elements alone (MI, stroke or death from vascular causes) were lower in patients receiving ticagrelor compared to clopidogrel as dual antiplatelet treatment with aspirin but ticagrelor was associated with an increase in the rate of non-procedure-related bleeding and dyspnoea [7]. After PLATO a few studies have been performed in routinely treated patients but not on on-treatment outcomes. The results from a Swedish registry and a single Danish hospital are consistent with the PLATO study [8,9]. The Swedish prospective cohort study [8] followed ACS patients discharged on ticagrelor or clopidogrel for two years. At 24 months, the cumulative incidence of the primary outcome – a composite of all-cause mortality, readmission with MI or stroke – was 11.7% with ticagrelor and 22.3% with clopidogrel (adjusted HR=0.85; 95% CI 0.78–0.93). The risk of death at 24 months was significantly lower with ticagrelor than clopidogrel. There was a higher risk of readmission with bleeding in patients who received ticagrelor versus clopidogrel groups. The Danish [9] registry study found that ticagrelor reduced the rate of cardiac death by 40% in ACS patients compared with clopidogrel during a one-year follow up. Non-cardiac death did not differ significantly between the ticagrelor and clopidogrel groups but the rate of definite stent thrombosis was 69% lower in the ticagrelor than clopidogrel groups. However, these studies were limited by an absence of data on whether patients were on the treatment following discharge from hospital. In addition, the Danish study did not have access to information about bleeding events. A recent UK study showed results which were not consistent with PLATO [10]. This study focused on patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) between 2006-2016 and showed a lower risk of in hospital bleeds for patients receiving ticagrelor compared to those receiving clopidogrel. The study showed no difference in all-cause mortality at 30 days and 1 year between patients who received ticagrelor and prasugrel. The study didn't assess dyspnoea or whether patients were on treatment post discharge from hospital. There remains a need to understand the characteristics of patients treated with ticagrelor as

well as on treatment effectiveness and safety outcomes in routine clinical care and in subgroups with different risks, in particular, the elderly who are seen as being at higher risk of both bleeding and adverse CV outcomes.

7. RESEARCH QUESTION AND OBJECTIVES

Primary objectives

To assess the incidence and time to event for the following in patients treated with ticagrelor in primary care following ACS events:

- composite outcome of MI, Stroke or death from vascular causes
- individual vascular events (MI, Stroke, and death from vascular causes)
- death from all causes

Secondary objectives

To estimate the incidence of vascular events in the following stratified by the following factors:

- Aged <75 and 75 or older
- MI vs UA or ACS unspecified (Index ACS)
- Medically managed vs interventionally managed
- Diabetic vs non-diabetic
- Presence/absence of other cardiovascular (CV) co-morbidities (prior stroke, heart failure, peripheral artery disease, atrial fibrillation)

To assess the incidence and time to event for the following in patients treated with ticagrelor in primary care following ACS events:

- Bleeding events (by BARC class [11]) and stratified by presence/absence of bleeding risk factors (prior bleed, peptic ulcers, warfarin)
- Dyspnoea (minor or requiring treatment in secondary care) and stratified by presence/absence of dyspnoea risk factors (prior history of respiratory disease or heart failure)

8. AMENDMENTS AND UPDATES

The time period for selection of patients was extended to reflect the updated linked data available which increased the number of patient with linked data (secondary care, ONS mortality and deprivation data) and follow-up. As no new free text has been added to any CPRD GOLD build after September 2013, we were advised by CPRD that free text should only be used in a cut of CPRD data up to this point only. This would significantly impact patient numbers so we decided not to restrict to this version of data and therefore not use any free text. All analyses were restricted to those patients with linked data and we didn’t use free text to validate outcomes.

Amendments are described below and the original approved protocol with amendments are included in appendix.

Table 2 Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	29 February 2016	3. Study Design 4. Study Population 7. Sample size 8. Limitation	"First prescription for ticagrelor between Dec 2010 and March 2015" replaced "First prescription for ticagrelor between Dec 2010 and July 2014"	We extended the period for inclusion to reflect the most recent linked data available which increased patient numbers with linked data.
2	29 February 2016	5. Study Variables	Removal of reference to use of free text for event validation "Anonymised free text associated with dates of cardiovascular, fatal and bleeding events and hospitalizations without a recorded clinical reason will be requested from CPRD"	No new free text has been added to any CPRD GOLD build after September 2013. We had been advised by CPRD that free text should only be used in a cut of CPRD data up to this point only. This would significantly impact patient numbers so we decided not to restrict to this version of data and therefore not use any free text.

9. RESEARCH METHODS

A descriptive retrospective observational cohort study using primary care data from Clinical Practice Research Datalink (CPRD)

The study cohort consisted of all patients in CPRD who received at least one prescription for ticagrelor for the first time between December 2010 to March 2015 in the primary care setting after an ACS event, were registered for a minimum of 12 months with 'up-to-standard' data in a practice contributing to CPRD prior to the index prescription and had linkage to Hospital Episode Statistics data.

The date of the first prescription for ticagrelor was defined as the index date and patient characteristics were described at this date.

9.1 Study design

A descriptive retrospective observational cohort study using primary care data from Clinical Practice Research Datalink (CPRD). The study cohort consisted of all patients in CPRD who received at least one prescription for ticagrelor for the first time between December 2010 to Mar 2015 in the primary care setting after an ACS event, were registered for a minimum of 12 months with 'up-to-standard' data in a practice contributing to CPRD prior to the index prescription and had linkage to Hospital Episode Statistics data.

The date of the first prescription for ticagrelor registered in CPRD was defined as the index date and patient characteristics were described at this date. Patients were followed from index date for up to 12 months; until the earliest of death, discontinuation of ticagrelor or end of data available in different sources (primary care, secondary care and ONS mortality data).

Exposure was defined as ticagrelor on treatment for up to 12 months in patients with at least one prescription for ticagrelor and received for the first time in primary care between 1 December 2010 and 31 March 2015. Patients were followed from the index date until the date they transferred from the practice to a different practice, death, discontinuation of ticagrelor, end of data availability or 12 months after the initiation of ticagrelor.

9.2 Setting

This study used a secondary data source, the UK Clinical Practice Research Datalink (CPRD) (December 2015 version of primary care data and Hospital Episode Statistics Set 11) consisting of primary and secondary care data with linkages to other data sources including mortality and deprivation data. The inclusion period for selection of patients was 1 December 2010 and 31 March 2015 in the primary care data. Patients with a first prescription for ticagrelor during this time period were selected. For full detail on data sources and inclusion criteria see sections 9.3 (Subjects) and 9.5 (Data sources and measures).

9.3 Subjects

The study cohort was selected from CPRD according to the following criteria:

Inclusion Criteria

- First prescription for ticagrelor between Dec 2010 and Mar 2015
- At least 12 months 'up-to standard' history in database prior to first ticagrelor prescription
- Linkage to Hospital Episode Statistics (HES)
- ACS event in the three months prior to and including the index date

Exclusion Criteria

- Primary care prescription for clopidogrel or prasugrel between the ACS date and the index date

9.4 Variables

Exposure and follow-up
Exposure to ticagrelor for up to 12 months was assessed in patients with at least one prescription for ticagrelor and received for the first time in primary care between 1 December 2010 and 31 March 2015. Prescriptions for medication, including ticagrelor, were identified using gemscript codes. Exposure was defined as persistence to ticagrelor (time from initial prescription to end of period covered by final prescription. A patient was considered to have discontinued treatment if there is a period of greater than 30 days without coverage following the period covered by the final prescription). Individual prescription duration was calculated using days supply divided by daily dose and where dose information was missing, daily dose was assumed to be the licensed dose (ie, 2 tablets daily).

Patients follow-up was calculated from index date (first prescription for ticagrelor) for up to 12 months; until the earliest of death, discontinuation of ticagrelor or end of data available across data sources (primary care, secondary care and ONS mortality data). In primary care end of data availability was calculated based on earliest of transfer out date (if patient left practice) and date of last data collection.

Outcomes
The primary outcome was an efficacy endpoint of the composite of hospitalised MI, hospitalised stroke and vascular death. Secondary outcomes included vascular events, bleeding events and dyspnoea. To avoid the potential for re-entry of the same event in primary care, data for MI and stroke using ICD-10 were derived from HES only. The cause of death was determined using ICD-10 codes using ONS mortality data.

Bleeding events were identified from primary and secondary care sources using primary care Read codes, ICD-10 diagnoses codes and Office of Population Censuses and Surveys (OPCS) classification of interventions and procedures version 4 for transfusion (see appendix for details). Bleed ICD 10 codes captured in secondary care were identified as the primary diagnosis in an episode of care. Bleeding events in primary care were identified using Read codes and then restricted to Read codes which were closest to Bleeding Academic Research Consortium (BARC) class 2 and above [11].

Dyspnoea was captured in primary and secondary care data using Read codes and ICD-10 diagnoses codes. For hospitalised dyspnoea, ICD 10 codes identified in secondary care were identified as the primary diagnosis in an episode of care.

All codes for defining outcomes are presented in Annex 2.

Other variables

- Demographic (at index date)
    - Age (continuous and categorical)
    - Gender (male, female)
    - BMI (categorical)
    - Smoking status (current, past, never, unknown)
    - Socio-demographic status (Townsend score, catagorical)

- Prior CV history (ever and in prior 12 months)
    - ACS type (MI, UA or unspecified) and frequency
    - ACS interventions (eg PCI, CABG)
    - Other CV

- Prior OAP treatment
    - Treatment with aspirin, clopidogrel or prasugrel (in 12 months prior to index ACS event)

- Index ACS event
    - Type of index ACS (MI, UA or unspecified)
    - Interventions associated with index ACS (eg. PCI, CABG)

- Major comorbidities (ever and in prior 12 months)
    - CV risk factors (eg diabetes, hypertension, hyperlipidaemia)
    - Co-morbidities and medicines related to risk of bleeding (prior bleed, peptic ulcer, anticoagulants)
    - Co-morbidities related to breathlessness (heart failure, respiratory disease)

- Secondary prevention medicines
  Aspirin, statins, β-blockers, ACE-inhibitors

Co-morbidities as well as bleed and dyspnoea history were identified, using Read codes, any time in patients history prior to first ticagrelor prescription (index date) following ACS. Interventions at time of ACS were identified using Office of Population Censuses and Surveys (OPCS) procedure codes in Hospital Episode Statistics. Age was calculated at index date using year of birth, day and month of birth were set to June 30 for all patients as day and month of birth are not available in CPRD. The deprivation index, based on on aggregate Townsend deprivation score at the patient's postal code level, were represented as quintiles, ranging from 1 representing least deprived to 5, most deprived. No transformation was necessary.

9.5 Data sources and measurement

This linked multi-source electronic healthcare longitudinal cohort study used data from the Clinical Practice Research Datalink. CPRD consists of primary care data, secondary care Hospital Episode Statistics (HES) data, mortality data from the Office for National Statistics (ONS) and Townsend deprivation data. The CPRD primary care data contain the complete primary care medical records for more than 12 million people enrolled in more than 650 general practices. Approximately 6.9% of the UK population are included in the primary care data and patients are broadly representative in terms of age, sex and ethnicity [12]. Linkage of primary care data to the other sources restricted all data to patients registered in English practices.

9.6 Bias

The first month of medication after discharge from hospital is missing and we were unable to account for patients who discontinue after discharge and before receiving medication in primary care. A survival bias will have been introduced in this study if patients initiated ticagrelor in hospital but died before being able to receive medication in primary care.To avoid the potential for re-entry of the same event in primary care, data for MI and stroke were derived from HES only. This may have caused underestimation of events. Moreover, the CPRD records that a prescription was issued in primary care and not whether the patient collected the medicine from pharmacy, adhered with treatment or capture events in patients who were on ticagrelor supplied by the hospital. In addition, incomplete data, differences in recording and classification raises the prospect of misclassification of outcomes.

It was also difficult to be precise about the date of the index ACS if this was recorded in primary care data but not in HES. Case validation by writing to general practitioners was not performed and the limited availability of HES linkage reduced the patient numbers.

Finally, interpretation of this study is limited by lack of a comparator and statistical modelling to assess the role of risk factors independently.

9.7 Study size

It was anticipated that there would be approximately 1800 patients prescribed ticagrelor and with linked data for inclusion in the study. The final number of patients included was 1650. Modelling of risk factors was not done in this study because the number of events was anticipated to be too few for detecting hazard ratios (HRs) of importance. Power calculations were conducted and were based on a higher number of patients than we had in the final study (1800 vs 1650).

Based on PLATO trial results, the overall risk rate for MACE (MI, stroke or CV death) was expected to be 9.8%. In order to detect an HR of 0.80 (or 1.20) in favour of one of the two subgroups and assuming that one of the baseline covariates would divide a study population of 1800 patients in to two equally sized groups (50% of 1800 vs 50% of 1800) = 900 vs 900 patients, the test power would be 31% (instead of commonly desired 80%), implying that the risk for observing an HR in the wrong direction would be 7%.

Based on the assumption that another baseline covariate would divide the study population of 1800 patients in to 15% vs 85% of the population = 270 vs 1530 patients, and where the small group has

the worst outcome of the two subgroups. The test power would be 13% (instead of commonly desired 80%), implying that the risk for observing an HR in the wrong direction would be 20%. Altogether based on these assessments, the sample size was considered too small to do any adjusted analyses or comparisons by patient characteristics with sufficient precision and statistical power.

9.8 Data transformation

The subgroups were chosen on the basis of evidence for increased risk for outcomes.

- Aged <75 vs ≥75 years
- MI vs UA or ACS unspecified (Index ACS)
- Medically managed vs interventionally managed
- Diabetic vs non-diabetic
- Presence vs absence of other CV co-morbidities (prior stroke, heart Failure, peripheral artery disease, atrial fibrillation)
- Bleed history/ gastrointestinal ulcer/ warfarin use vs absence of bleed risk (bleed history/ gastrointestinal ulcer/ warfarin use)
- Prior dyspnoea, respiratory disease or heart failure vs absence of dyspnoea risk (prior dyspnoea, respiratory disease or heart failure

Data were extracted from CPRD GOLD December 2015 version and downloaded as tab delimited ASCII files. All data were analysed using SAS 9.2.

See section 9.4 for detailed description of variable definitions and transformations.

9.9 Statistical methods

9.9.1 Main summary measures

Descriptive analyses were conducted for the overall population and for the sub-groups of patients described in objectives (section 7). Baseline characteristics were reported as frequency and percent for categorical variables and means, standard deviations, medians and 95% confidence intervals for continuous variables. Outcomes were reported as crude incidence rates (per 100 person years) with 95% confidence intervals and Kaplan-Meier survival curves were generated showing the probability, with 95% confidence intervals, of being event free at 1 month intervals.

9.9.2 Main statistical methods

This was a descriptive study. Outcomes were reported as incidence rates (per 100 person years) with 95% confidence intervals and and Kaplan-Meier survival curves were generated showing the probability, with 95% confidence intervals, of being event free at 1 month intervals.. Outcomes were stratified by risk level. Modelling to assess the role of risk factors independently was not conducted. Modelling of risk factors was not done because the number of events were considered too few for detecting meaningful hazard ratios as outlined in 9.7 Study size.

The following baseline characteristics were presented:

- Demographic (at index date)
  - Age (continuous and categorical)
  - Gender (male, female)
  - BMI (categorical)
  - Smoking status (current, past, never, unknown)
  - Socio-demographic status* (Townsend score, catagorical)

- Prior CV history (ever and in prior 12 months)
  - ACS type (MI, UA or unspecified) and frequency
  - ACS interventions (eg PCI, CABG)
  - Other CV

- Prior OAP treatment
  - Treatment with aspirin, clopidogrel or prasugrel (in 12 months prior to index ACS event)

- Index ACS event
  - Type of index ACS (MI, UA or unspecified)
  - Interventions associated with index ACS (eg. PCI, CABG)

- Major comorbidities (ever and in prior 12 months)
  - CV risk factors (eg diabetes, hypertension, hyperlipidaemia)
  - Co-morbidities and medicines related to risk of bleeding (prior bleed, peptic ulcer, anticoagulants)
  - Co-morbidities related to breathlessness (heart failure, respiratory disease)
  - Other co-morbidities

- Secondary prevention medicines
  - Aspirin, statins, β-blockers, ACE-inhibitors)

Outcomes were stratified by:

- Aged <75 vs ≥75 years
- MI vs UA or ACS unspecified (Index ACS)
- Medically managed vs interventionally managed
- Diabetic vs non-diabetic
- Presence vs absence of other CV co-morbidities (prior stroke, heart failure, peripheral artery disease, atrial fibrillation)
- Bleed history/ gastrointestinal ulcer/ warfarin use vs absence of bleed risk (bleed history/ gastrointestinal ulcer/ warfarin use)
- Prior dyspnoea, respiratory disease or heart failure vs absence of dyspnoea risk (prior dyspnoea, respiratory disease or heart failure

9.9.3 Missing values

In this study the complete absence of data on medication whilst in hospital was the main limitation and is a major source of bias. This is highlighted in the discussion. As MI and stroke were only captured in secondary care data, it is likely to be incomplete. Restriction to secondary data capture was done to avoid duplication as clinicians record these events as part of the patients' management of historical events rather than reflecting new events. Outcome measures for bleeds and dyspnoea which were captured in both the primary and secondary care data are less likely to be incomplete.

Where variables were recorded in CPRD but incomplete, eg baseline clinical measures like body mass index and blood pressure, imputation was no conducted.

9.9.4 Sensitivity analyses

Sensitivity analyses were conducted for patients with record for dyspnoea or bleed following initiation of ticagrelor by checking for new prescription of ticagrelor following dates of dyspnoea/ bleed. The results of these analyses are described in section 10.4

9.9.5 Amendments to the statistical analysis plan

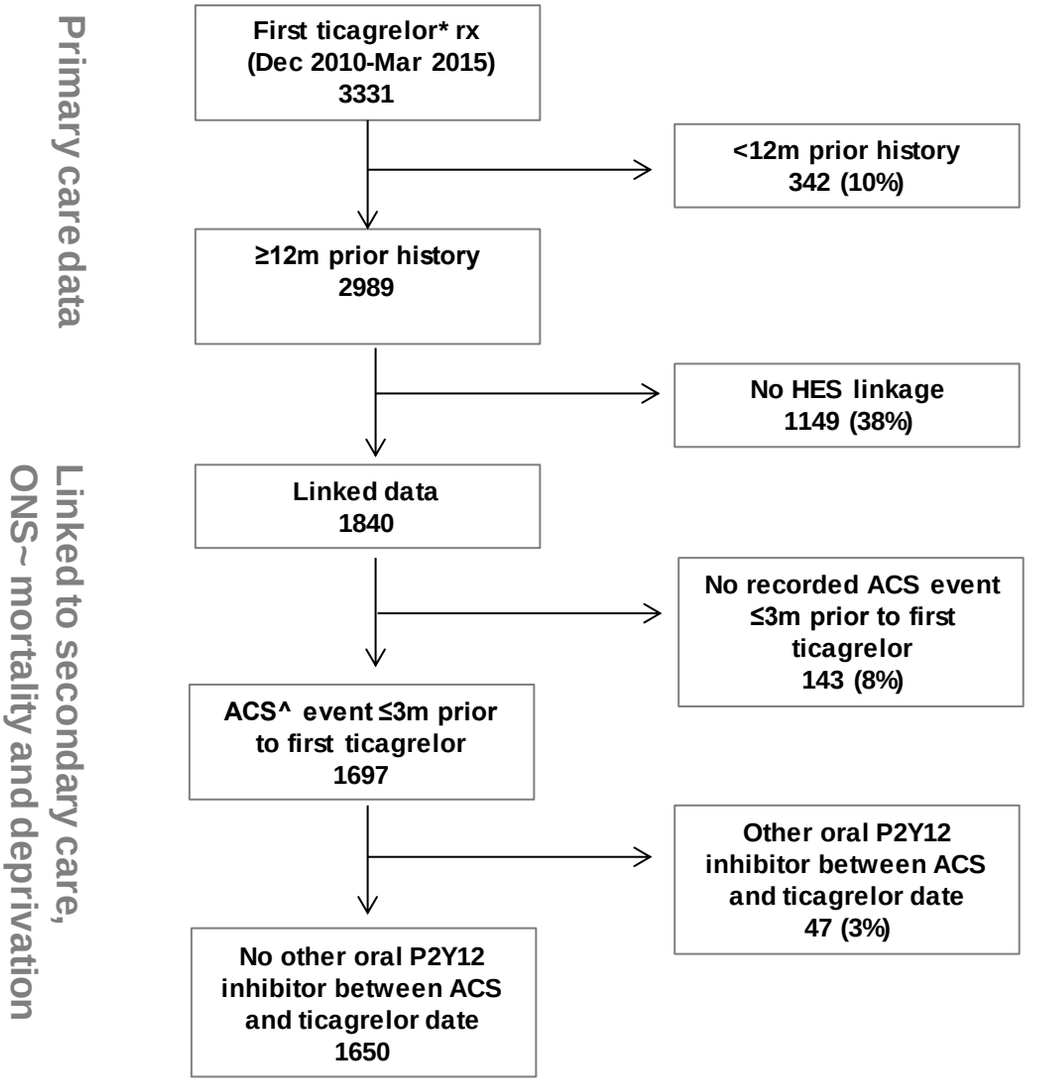
Sensitivity analyses were conducted which were not in the statistical analysis plan (see section 9.9.4). Persistence to secondary prevention medications (aspirin, statins, β-blockers, ACE-inhibitors) was not calculated. The proportion of patients with secondary medication was presented (Table 1). Efficacy outcomes were not stratified by type of ACS (ie, MI vs UA or ACS unspecified due to patient numbers. Similarly, bleed outcomes were not stratified by BARC class due to patient numbers.

9.10 Quality control

All codes (Read and ICD10) used in the study have been validated by a clinician. Programs have been thoroughly checked by the analyst but the study has not been double programmed using independent programmer.

10. RESULTS

10.1 Participants



**first ticagrelor in primary care, actual first ticagrelor administered in secondary care*
^ ACS event identified in primary or secondary care data (HES)
~Office of National Statistics (ONS)

10.2 Descriptive data

A total of 1650 patients initiating ticagrelor in primary care met the inclusion criteria for the study (Figure 1). Thirty eight percent of patients were excluded due to lack of linkage to other data sources (HES and ONS mortality data). Linkage is only available for practices in England and the initial cohort of patients initiating ticagrelor (N=3331) was selected from all practices in the UK

(England, Scotland, Wales and Northern Ireland). The median follow-up was 202.5 days. Most patients were male (72.4%, n=1195), the mean age was 64.7 years (median: 64.8, IQR: 54.6 – 74.4) with approximately a quarter (23.5%, n=388) aged ≥75 years (Table 1). About a quarter (25.5%, n=420) of patients were current smokers and almost half (46.6%, n=769) were ex-smokers.

Ninety-five per cent (95.1%, n=1569) had a MI at time of ACS event with a median 18 days (IQR: 11-26) between the recorded date of event and initiation of ticagrelor in primary care. Furthermore, 85.0% (n=1402) received either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) at the time of ACS and within 90 days before the first ticagrelor prescription. The mean age of the revascularized patients was 63.6 years (median: 63.7; IQR: 53.9 - 72.8) and a fifth (19.9% n=279) were aged ≥75 years.

About a fifth (22.5%, n=372) of patients had diabetes, 12.9% (n=213) a prior MI, 10.5% (n=174) heart failure, 6.3% (n=104) stroke, 6.4% (n=106) peripheral arterial disease and 3.6% (n=59) atrial fibrillation. Many patients seemed to be at potential risk for dyspnoea and bleeds following initiation of ticagrelor, such as a history of asthma or chronic obstructive pulmonary disease (COPD; 18.2%, n=300), dyspnoea without known underlying cause (25.9% n=428), heart failure (6.3% n=104), bleed (29%, n=479).

Most patients (96.1%, n=1585) had a prescription for aspirin within 90 days of ticagrelor initiation. Similarly, most patients received guideline-indicated secondary prevention pharmacotherapies including statins (96.7%, n=1596), ACE inhibitors (85.1%, n=1404) and β-blockers (91.3%, n=1507).

10.3 Outcome data

1650 patients were included in the overall analyses and the following patient numbers (n) were included for the key subpopulations of interest:

- Aged <75 (n=1262) vs ≥75 years (n=388)
- MI (n=1569) vs UA or ACS unspecified (n=56) (Index ACS)
- Medically managed (n=248) vs interventionally managed (n=1402)
- Diabetic (n=372) vs non-diabetic (n=1278)
- Presence (n=379) vs absence (n=1279) of other CV co-morbidities (prior stroke, heart failure, peripheral artery disease, atrial fibrillation)
- Bleed history/ gastrointestinal ulcer/ warfarin use (n=479) vs absence (n=1171) of bleed risk (bleed history/ gastrointestinal ulcer/ warfarin use)
- Prior dyspnoea, respiratory disease or heart failure (n=614) vs absence (n= 1036) of dyspnoea risk (prior dyspnoea, respiratory disease or heart failure

10.4 Main results

Efficacy outcomes
Overall, the incidence rate of the composite efficacy outcome was 5.3 (95% CI: 3.8–6.8) per 100 person years (PY) (Table 2a). Patients aged ≥75 years were more likely to exhibit the composite outcome than those <75 years: 11.6 per 100 PY (95% CI: 6.9–13.4 vs 3.6 per 100 PY 95% CI: 2.2–4.9 respectively). The difference in probability for the composite outcome between older and

younger patients was visible from 1 month (Figure 2a). The overall incidence rate of hospitalised MI was 3.3 per 100 PY (95% CI: 2.1–4.5). It was higher in older patients [7.6 (95% CI: 3.7-11.4) vs 2.2 (95% CI: 1.1-3.3) per 100 PY in those aged ≥75 years and <75 years respectively] and those with other cardiovascular diseases (11.4 vs 3.7 per 100 PY in patients with other CV disease vs those without). The overall incidence rate of all-cause death was 2.6 per 100 PY (95% CI: 2.1–4.5) and was higher in older patients [7.1 (95% CI: 3.4-10.8) vs 1.4 (95% CI: 0.5-2.2) per 100 PY in patients aged ≥75 years and <75 years respectively] and those with other cardiovascular diseases (6.2 vs 1.6 per 100 PY in patients with other CV disease vs those without).

In medically managed patients, the incidence rates of the composite outcome (14.9 per 100 PY; 95% CI: 7.8–22.0) and MI alone (10.5 per 100 PY, 95% CI 4.6–6.5) were higher than in patients with revascularization (composite 3.9 per 100 PY, 95% CI: 2.6 – 5.3; MI 2.3 per 100 PY 95% CI: 1.3 3.4) (Table 2a). Medically managed patients had a higher probability for outcome event from 1 month after ticagrelor first prescription (Fig 2b). Compared with revascularized patients, medically managed patients were older (mean age 70.7 vs 63.6 years), and more likely to: be female (36.7% vs 26.0%; n=91 vs n=364; have a history of MI (22.9% vs 11.3%; n=57 vs n=156), stroke (12.9% vs 5.1%; n=32 vs n=72, heart failure (18.5% vs 9.1%; n=46 vs n=128) or bleed (33.1% vs 28.3%; n=82 vs n=397).

Bleeding events

The incidence rate of any bleeding event was 6.6 per 100 PY (95% CI: 4.9–8.2) (Table 2). There was no difference in the probability of event over time (Fig 3a) or the incidence rate between patients aged ≥75 years and <75 years (7.1 per 100 PY, 95% CI 3.4–10.8 vs 6.4 per 100 PY, 95% CI 4.6–8.3 respectively). The incidence of bleeding events requiring hospital treatment was 2.5 per 100 PY (95% CI: 1.5–3.5) with no difference in rates between patients aged ≥75 years and <75 years (3.5 per 100 PY, 95% CI 0.9–6.2 vs 2.2 per 100 PY 95% CI 1.1–3.3 respectively). The incidence of a bleeding event while on ticagrelor was higher and evident from 1 month in patients who had a prior bleed or compared with patients without a prior bleed (Table 2b, Fig 3b): 11.9 per 100 PY (95% CI: 7.7–16.1) and 4.6 per 100 PY (95% CI: 2.9–6.2) respectively. Fifty-five of the 61 patients (90.1%) have no further prescription for ticagrelor after the date of bleed.

Dyspnoea

The overall incidence rate of dyspnoea was 21.6 per 100 PY (95% CI: 18.6–24.5) and for dyspnoea requiring hospital treatment it was 1.7 per 100 PY (95% CI: 0.9–2.6) (Table 2a). The incidence rate of all dyspnoea was higher in patients aged ≥75 years (34.3 per 100 PY (95% CI: 26.2–42.5) than in younger patients (18.1 per 100 PY (95% CI: 15.0–21.2) and there was a difference between age groups in the probability of having any dyspnoea event from 1 month (Fig 4a).

Thirty two percent (n=534) of all patients prescribed ticagrelor had a history of respiratory disease (asthma or COPD; 18.2%, n=300) or dyspnoea (25.9% n=428). Altogether 37.2% (n=614) had a history of respiratory disease, dyspnoea or heart failure (6.3% n=104). The incidence rate of dyspnoea was higher among patients with a history of respiratory disease, dyspnoea or heart failure compared to those without [all:36.5 (95% CI: 30.0-43.1) vs 13.2 (95% CI: 10.3-16.2) per 100 PY; hospital treated dyspnoea: 2.4 (95% CI: 0.7-4.1) vs 1.3 (0.4-2.3) per 100 PY] (Table 2b). For these different risk groups, a difference in the probability of having any dyspnoea event could be seen from 1 month onwards (Figure 4b).

Among patients without a history of respiratory disease or dyspnoea, the incidence rate of dyspnoea was 14.5 per 100 PY (95% CI: 11.6–17.5). In this group, the incidence rate of dyspnoea requiring hospital treatment was 1.4 per 100 PY (95% CI: 0.5–2.3).

For those patients with a record for any dyspnoea (n=200) after ticagrelor initiation, 89.5% (179) received a prescription for ticagrelor after the date of dyspnoea.

Table 1 Baseline characteristics

Patients (N)	1650
Follow-up person days* (N, mean, median)	338598 205.2 202.5
Gender	
Male (N, %)	1195 (72.4%)
Age (years)	
Mean, SD, median	64.7, 12.6, 64.8
Aged ≥75 years (N, %)	388 (23.5%)
BMI	
Mean, SD, median	28.2 5.1, 27.7
Systolic blood pressure (mm/Hg)	
Mean, SD, median	130.6 18.6, 130.0
Diastolic blood pressure (mm/Hg)	
Mean, SD, median	75.4 11.1, 76.0
Smoking (N, %)	
current smoker	420 (25.5%)
ex smoker	769 (46.6%)
Townsend social deprivation index (quintile)	
unknown	3 (0.2%)
1 (least deprived)	347 (21.0%)
2	347 (21.0%)
3	326 (19.8%)
4	306 (18.5%)
5 (most deprived)	321 (19.5%)
ACS event	
MI	1569 (95.1%)
Unstable angina	56 (3.4%)
Unspecified	25 (1.5%)
Time from ACS event to index prescription	
Mean, SD, median	19.5 11.6, 18.0
Surgical intervention ≤90 days of index prescripton (N, %)	1402 (85.0%)
Medical history (N, %)	
Atrial fibrilation	59 (3.6%)
Bleed	479 (29.0%)
Diabetes	372 (22.5%)
Dyspnoea	428 (25.9%)
Heart failure	174 (10.5%)
Hyperlipidemia	387 (23.5%)
Hypertension	770 (46.7%)
Peripheral Arterial Disease	106 (6.4%)
Respiratory (asthma or COPD)	300 (18.2%)
Myocardial Infarction	213 (12.9%)
Stroke	104 (6.3%)
Medication presribed within 12 month pre-index date (N, %)	
Ace inhibitors (N, %)	495 (30.0%)
Anti-coagulants	26 (1.6%)
Aspirin	486 (29.5%)
Beta blockers	465 (28.2%)
Clopidogrel	100 (6.1%)
Prasugrel	8 (0.5%)
Statins	711 (43.1%)
Medication presribed within 90 days post index date (N, %)	
Ace inhibitors	1404 (85.1%)
Anti-coagulants	35 (2.1%)
Aspirin	1585 (96.1%)
Beta blockers	1507 (91.3%)
Statins	1596 (96.7%)

Continuous data presented as mean, standard deviation (SD) and median unless otherwise stated. Dichotomous and ordinal data presented as N (%)

Table 2a Incidence rates per 100 person-years (95% confidence intervals) for all outcomes – stratified by age, presence of medical intervention (PCI/ CABG), diabetes, other cardiovascular (CV) disease

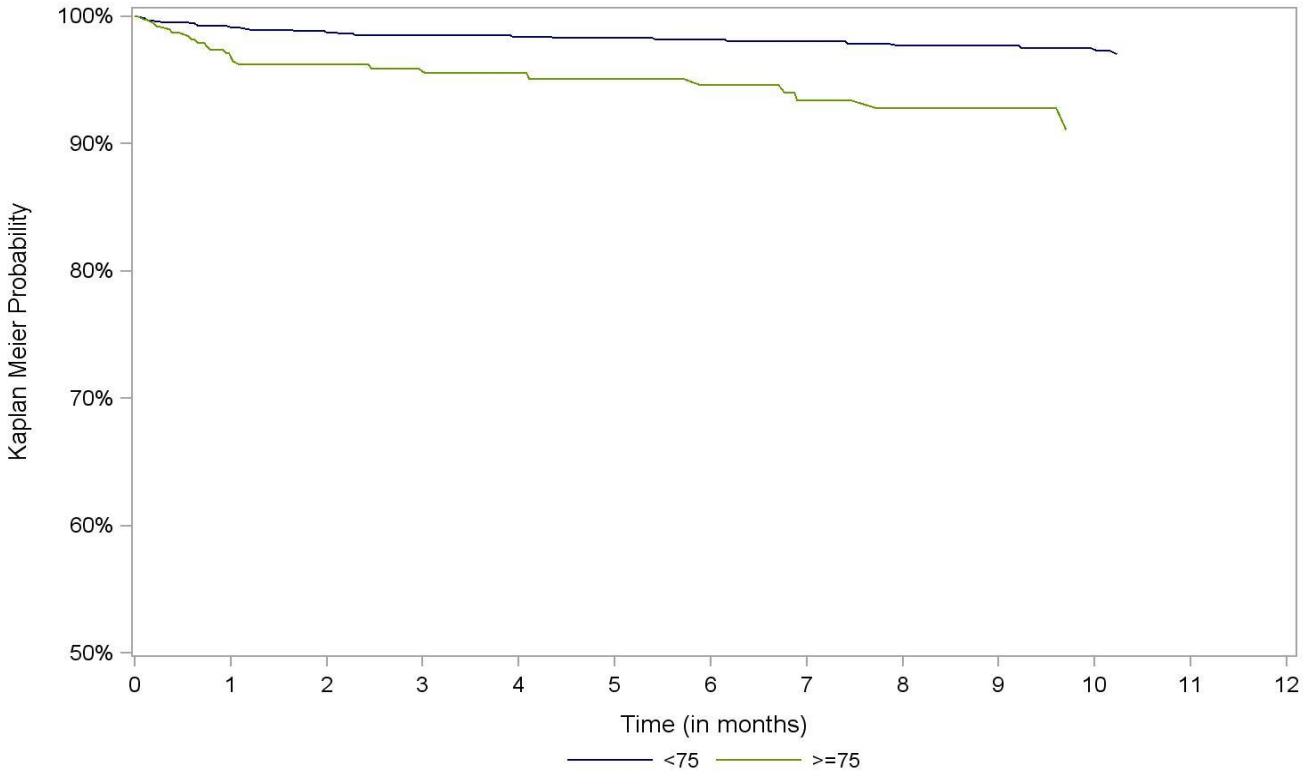
	All	age <75	age ≥75	No intervention	Intervention	No diabetes	Diabetes	No other CV	Other CV
Patient no.	**1650**	**1262**	**388**	**248**	**1402**	**1278**	**372**	**1279**	**371**
Follow-up person days (N, mean, median)	**338598** 205.2 202.5	**266304** 211.0 217.0	**72294** 186 168.5	**41029** 165.4 130.0	**297569** 212 217.0	**267728** 209.5 213.0	**70870** 190.5 166.5	**266373** 209.8 212.0	**70225** 189.3 170.0
MI, stroke or death from vascular causes	5.3 (3.8 - 6.8)	3.6 (2.2 - 4.9)	11.6 (6.9 - 16.4)	15.1 (7.9 - 22.3)	3.9 (2.6 - 5.3)	4.2 (2.7 - 5.7)	9.3 (5.0 - 13.6)	3.7 (2.3 - 5.1)	11.4(6.7 -16.2)
Hospitalised MI	3.3 (2.2 - 4.5)	2.2 (1.1 - 3.3)	7.6 (3.7 - 11.4)	10.7 (4.6 - 16.7)	2.3 (1.3 - 3.4)	2.6 (1.4 - 3.8)	6.2 (2.7 - 9.7)	2.5 (1.3 - 3.6)	6.8(3.1 -10.4)
Hospitalised stroke	0.9 (0.3 - 1.5)	0.5 (0.0 - 1.1)	2.0 (0.0 - 4.0)	0.9 (-0.9 - 2.6)	0.9 (0.2 - 1.5)	0.9 (-0.9 - 2.6)	1.0 (-0.4 - 2.5)	0.5 (0.0 - 1.1)	2.1(0.0 - 4.1)
Vascular death	1.4 (0.6 - 2.2)	1.1 (0.3 - 1.9)	2.5 (0.3 - 4.7)	3.6 (0.1 - 7.0)	1.1 (0.4 - 1.8)	1.2 (0.4 - 2.0)	2.1 (0.0 - 4.1)	1.0 (0.2 - 1.7)	3.1(0.6 - 5.6)
All cause death	2.6 (1.6 - 3.6)	1.4 (0.5 - 2.2)	7.1 (3.4 - 10.8)	5.3 (1.1 - 9.6)	2.2 (1.2 - 3.2)	2.2 (1.1 - 3.3)	4.1 (1.3 - 7.0)	1.6 (0.7 - 2.6)	6.2(2.7 - 9.8)
Hospitalised dyspnoea	1.7 (0.9 - 2.6)	1.5 (0.6 - 2.4)	2.5 (0.3 - 4.7)	3.6 (0.1 - 7.0)	1.5 (0.6 - 2.3)	1.8 (0.8 - 2.7)	1.5 (-0.2 - 3.3)	1.5 (0.6 - 2.4)	2.6(0.3 - 4.9)
All dyspnoea	21.6 (18.6 - 24.5)	18.1 (15.0 - 21.2)	34.3 (26.2 - 42.5)	26.7 (17.1 - 36.2)	20.9 (17.7 - 24.0)	20.6 (17.3 - 23.9)	25.2 (18.2 - 32.3)	17.7 (14.6 - 20.7)	36.9(28.3 -45.5)
Hospitalised bleed	2.5 (1.5 - 3.5)	2.2 (1.1 - 3.3)	3.5 (0.9 - 6.2)	4.4 (0.5 - 8.3)	2.2 (1.2 - 3.2)	2.2 (1.1 - 3.3)	3.6 (0.9 - 6.3)	2.2 (1.1 - 3.3)	3.6(0.9 - 6.3)
All bleeds	6.6 (4.9 - 8.2)	6.4 (4.6 - 8.3)	7.1 (3.4 - 10.8)	13.3 (6.6 - 20.1)	5.6 (4.0 - 7.3)	6.1 (4.3 - 7.9)	8.2 (4.2 - 12.3)	5.5 (3.8 - 7.2)	10.9(6.2 -15.6)

All bleeds includes hospitalised bleeds and BARC≥2 in primary care; Other CV: atrial fibrilation, heart failure, stroke, peripheral arterial disease

Table 2b Bleeds and dyspnoea – stratified by risk factors

	No prior bleed	Prior bleed
Patient no.	**1153**	**479**
Follow-up person days (total, mean median)	**240239** 208.4 215.0	**94925** 198.2 195.0
Hospitalised bleed	1.8 (0.8 - 2.9)	4.2 (1.7 - 6.7)
All bleeds	4.6 (2.9 - 6.2)	11.9 (7.7 - 16.1)
	No prior respiratory disease, dyspnoea or heart failure	**Prior respiratory disease, dyspnoea or heart failure**
Patient no.	**1036**	**614**
Follow-up person days (total, mean median)	**217732** 210.2 217.0	**120866** 196.9 189.0
Hospitalised dyspnoea	1.3 (0.4 - 2.3)	2.4 (0.7 - 4.1)
All dyspnoea	13.2 (10.3 - 16.2)	36.5 (30.0 - 43.1)

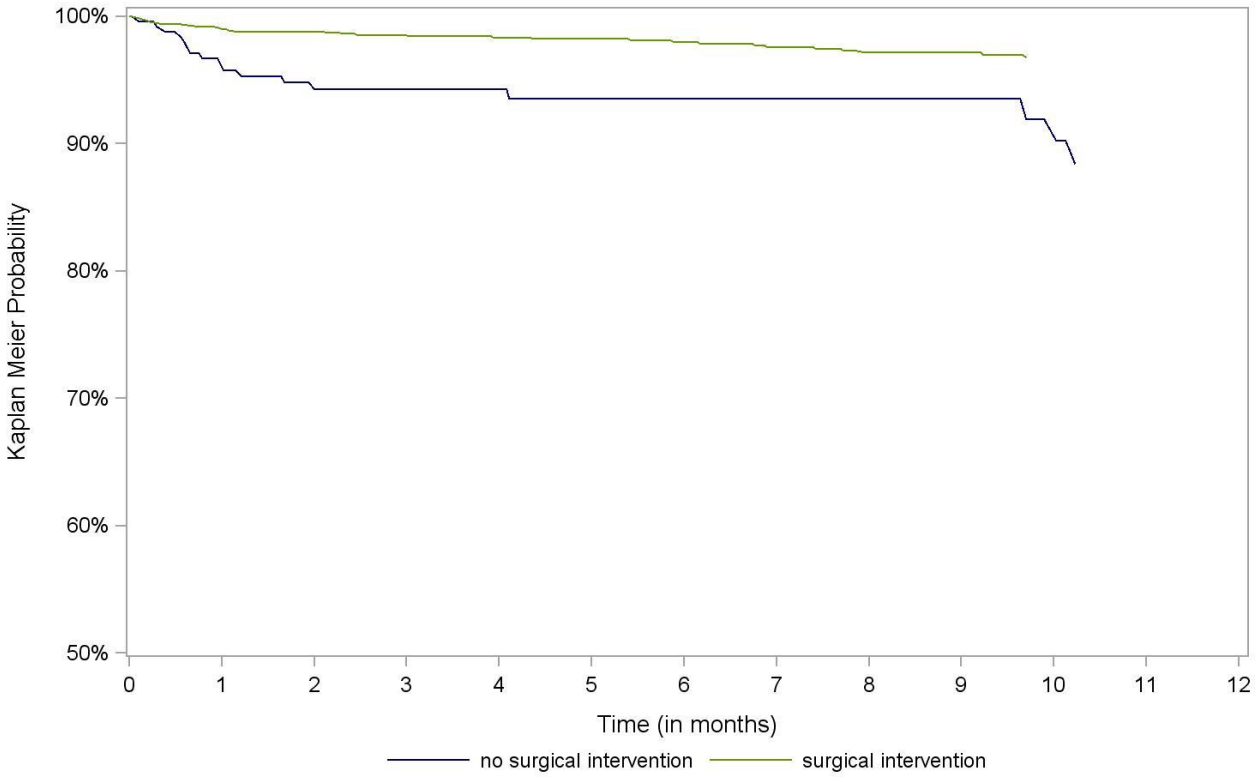
Figure 2a Kaplan-Meier Curve of time to the composite outcome (MI, stroke or vascular death) stratified by age



Probability of not having outcome by age group	N	1 month	3 months	6 months	9 months	12 months	Median (months)
<75	1262	99.2% [98.5% - 99.6%]	98.5% [97.6% - 99.1%]	98.2% [97.1% - 98.8%]	97.7% [96.5% - 98.5%]	NO	NO
<75	Number of patients still at risk*	1136	909	696	523	0	
>=75	388	97.1% [94.8% - 98.4%]	95.9% [93.3% - 97.5%]	94.6% [91.4% - 96.6%]	92.8% [88.8% - 95.4%]	NO	NO
>=75	Number of patients still at risk*	337	265	176	112	0	

[]: 95% Confidence Interval
NO: Not Observable
*: Number of patients still observable at a given time and for whom no events occurred

Figure 2b Kaplan-Meier Curve of time to the composite outcome (MI, stroke or vascular death) stratified by intervention (PCI or CABG)

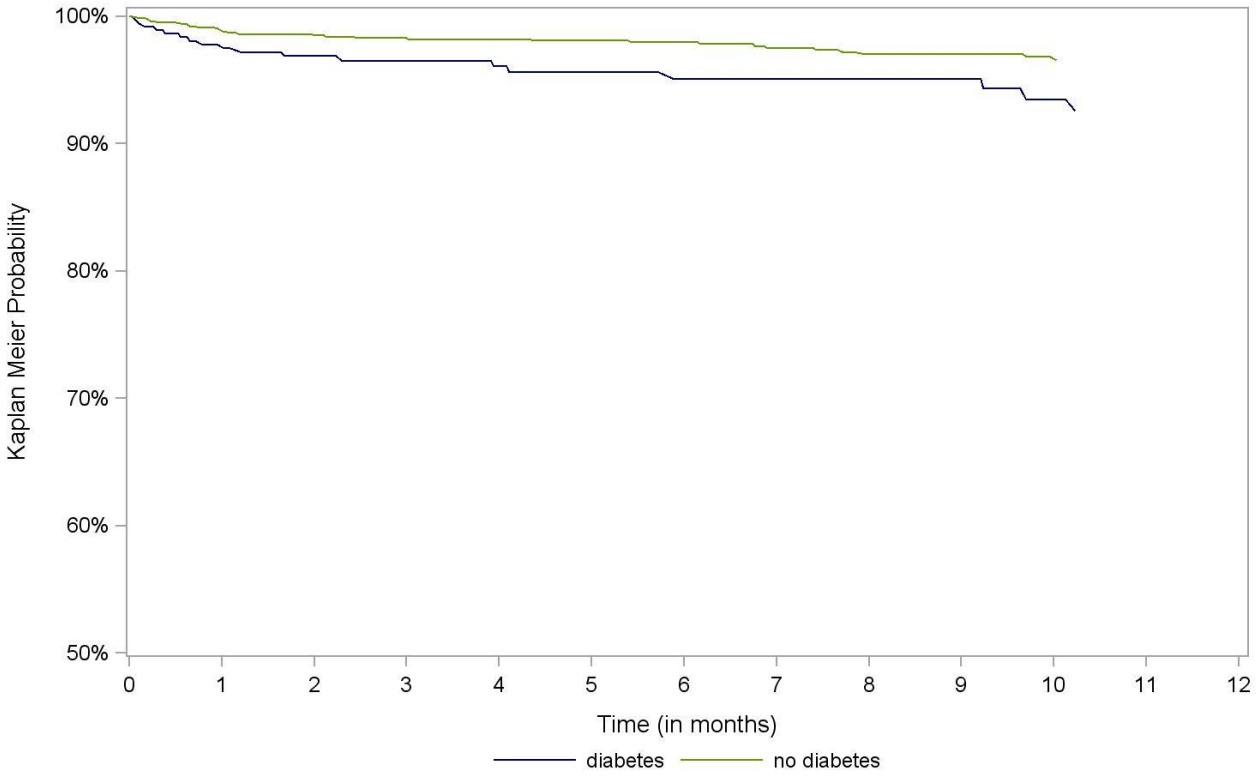


Probability of not having outcome by intervention	N	1 month	3 months	6 months	9 months	12 months	Median (months)
No intervention	248	96.7% [93.5% - 98.3%]	94.3% [90.3% - 96.6%]	93.5% [89.2% - 96.2%]	93.5% [89.2% - 96.2%]	NO	NO
No intervention	Number of patients still at risk*	211	145	98	66	0	
Intervention	1402	99.0% [98.4% - 99.4%]	98.5% [97.7% - 99.1%]	98.0% [97.0% - 98.7%]	97.1% [95.9% - 98.0%]	NO	NO
Intervention	Number of patients still at risk*	1262	1029	778	573	0	

[]: 95% Confidence Interval
NO: Not Observable

*: Number of patients still observable at a given time and for whom no events occurred

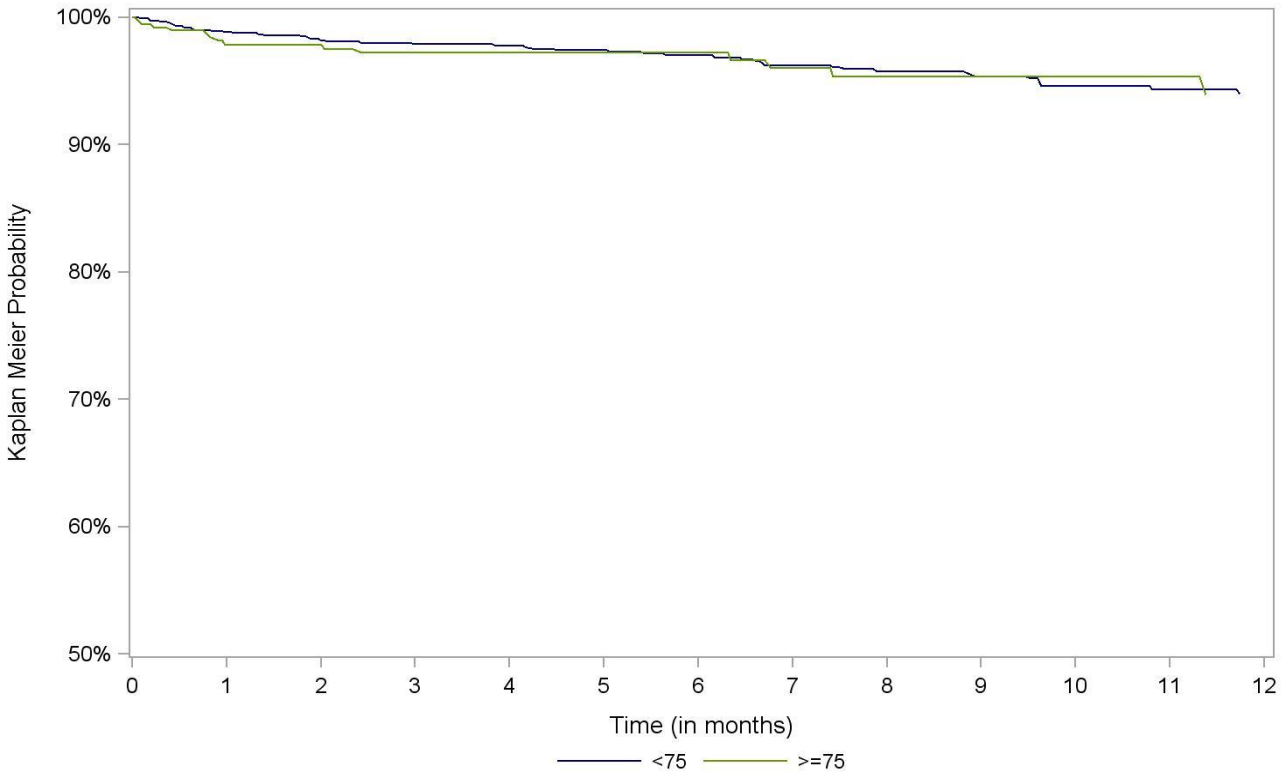
Figure 2c Kaplan-Meier Curve of time to thecomposite outcome (MI, stroke or vascular death) stratified by diabetes



Probability of not having outcome by diabetes	N	1 month	3 months	6 months	9 months	12 months	Median (months)
Diabetes	372	97.8% [95.6% - 98.9%]	96.5% [93.9% - 98.0%]	95.1% [91.9% - 97.1%]	95.1% [91.9% - 97.1%]	NO	NO
Diabetes	Number of patients still at risk*	323	248	172	123	0	
No diabetes	1278	98.9% [98.2% - 99.4%]	98.3% [97.4% - 98.9%]	98.0% [96.9% - 98.6%]	97.0% [95.6% - 97.9%]	NO	NO
No diabetes	Number of patients still at risk*	1150	926	700	512	0	

[]: 95% Confidence Interval
NO: Not Observable
*: Number of patients still observable at a given time and for whom no events occurred

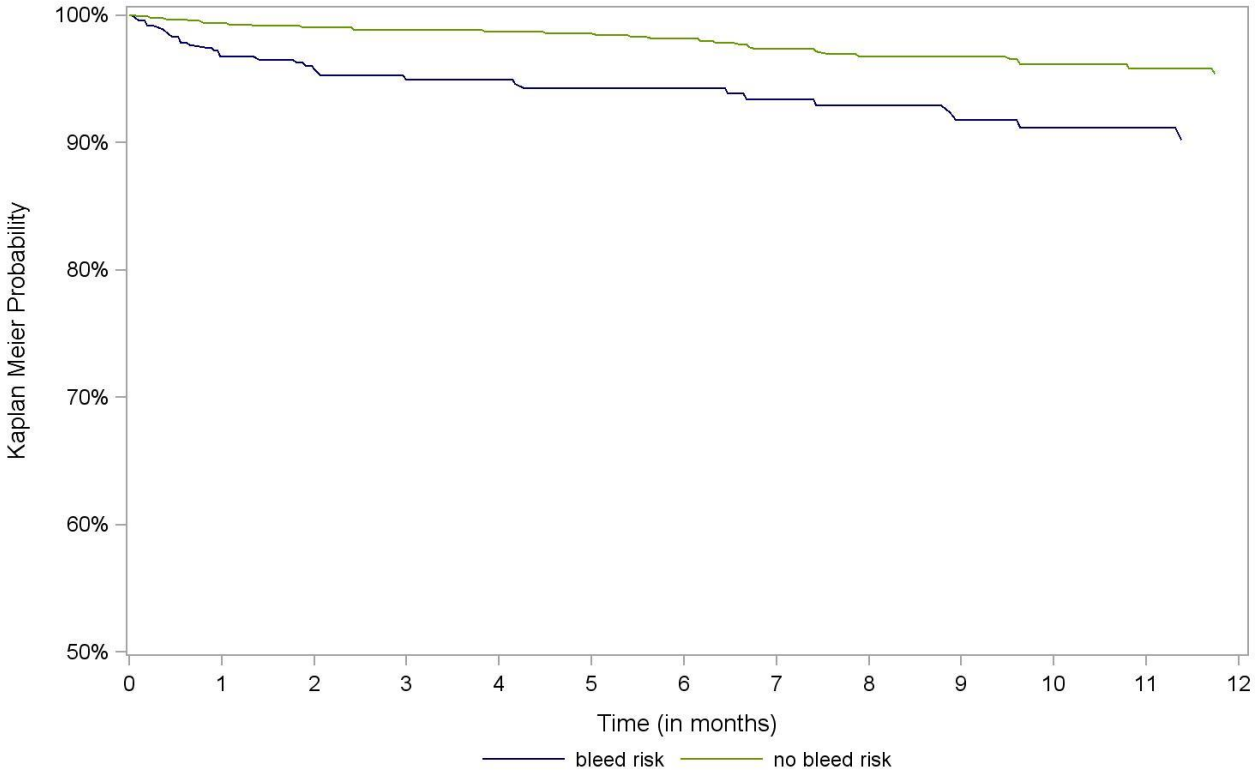
Figure 3a Kaplan-Meier Curve of time to bleed stratified by age



Probability of not having bleed by age	N	1 month	3 months	6 months	9 months	12 months	Median (months)
<75	1262	98.9% [98.1% - 99.3%]	97.9% [96.9% - 98.6%]	97.0% [95.7% - 97.9%]	95.4% [93.7% - 96.6%]	NO	NO
<75	Number of patients still at risk*	1131	898	680	507	0	
>=75	388	97.9% [95.8% - 98.9%]	97.2% [94.9% - 98.5%]	97.2% [94.9% - 98.5%]	95.4% [91.8% - 97.4%]	NO	NO
>=75	Number of patients still at risk*	338	265	178	112	0	

[]: 95% Confidence Interval
NO: Not Observable
*: Number of patients still observable at a given time and for whom no events occurred

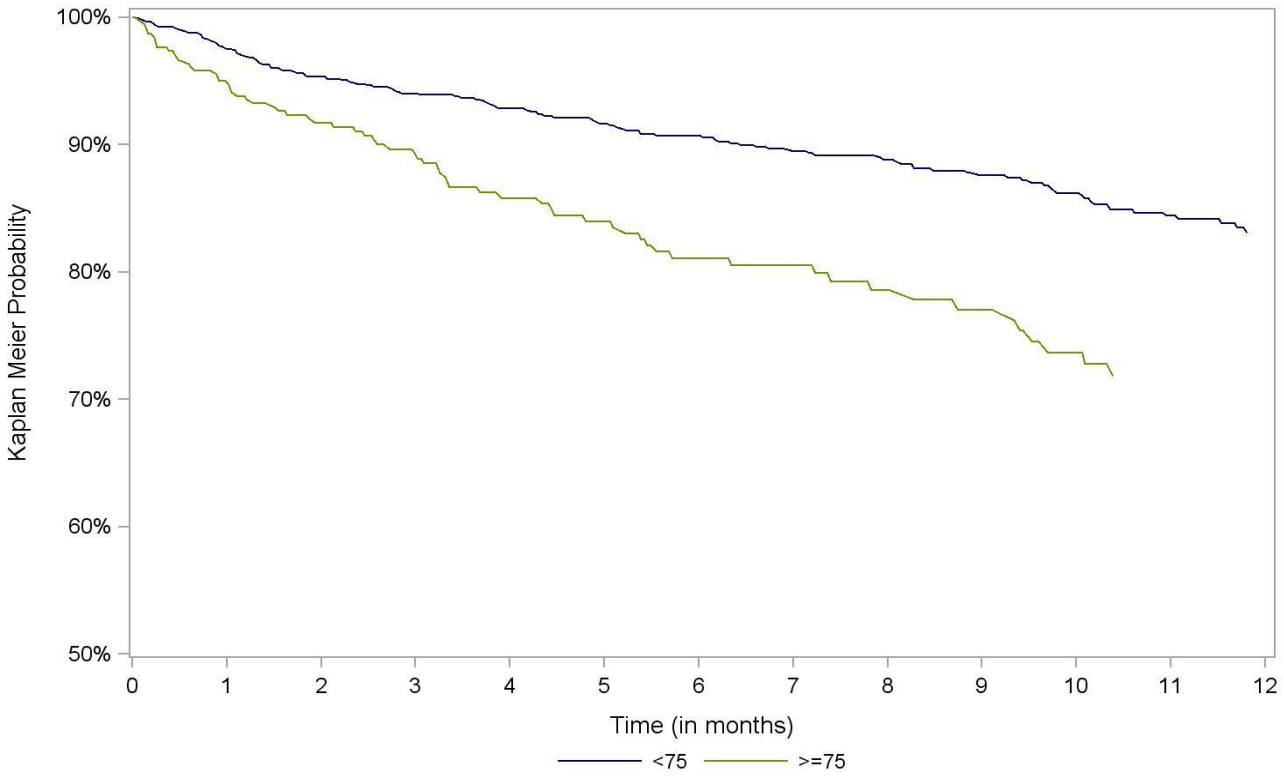
Figure 3b Kaplan-Meier Curve of time to bleed stratified by bleed history



Probability of not having bleed by prior bleed risk	N	1 month	3 months	6 months	9 months	12 months	Median (months)
No bleed risk	1171	99.4% [98.7% - 99.7%]	98.9% [98.0% - 99.4%]	98.2% [97.0% - 98.9%]	96.8% [95.2% - 97.9%]	NO	NO
No bleed risk	Number of patients still at risk*	1048	831	624	459	0	
Bleed risk	479	96.8% [94.7% - 98.0%]	95.0% [92.4% - 96.7%]	94.3% [91.6% - 96.2%]	91.8% [88.1% - 94.4%]	NO	NO
Bleed risk	Number of patients still at risk*	421	332	234	160	0	

[]: 95% Confidence Interval
NO: Not Observable
*: Number of patients still observable at a given time and for whom no events occurred
Bleed risk: prior bleed or gastrointestinal ulcer

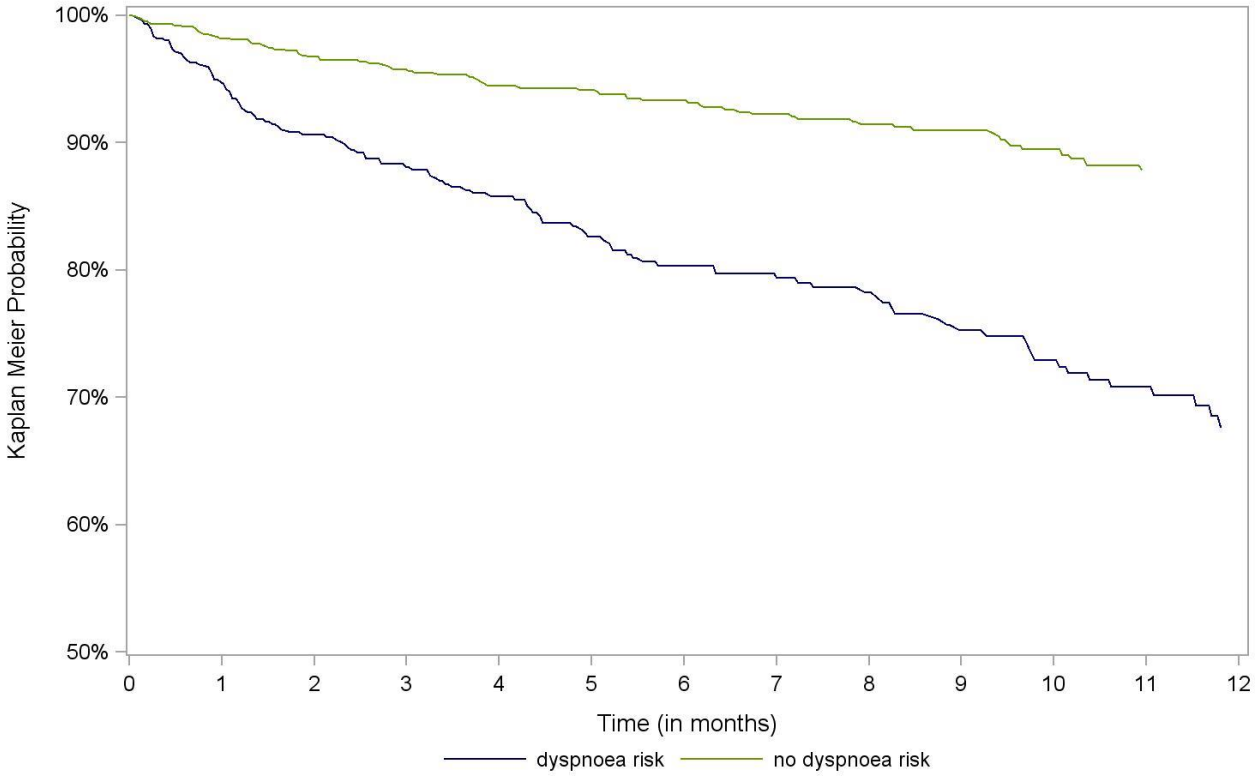
Figure 4a Kaplan-Meier Curve of time to dyspnoea stratified by age



Probability of not having dyspnoea by age	N	1 month	3 months	6 months	9 months	12 months	Median (months)
<75	1262	97.6% [96.6% - 98.3%]	94.0% [92.4% - 95.3%]	90.7% [88.7% - 92.4%]	87.6% [85.2% - 89.7%]	NO	NO
<75	Number of patients still at risk*	1115	861	640	465	0	
>=75	388	95.0% [92.3% - 96.8%]	89.3% [85.5% - 92.1%]	81.1% [75.9% - 85.2%]	77.1% [71.1% - 82.0%]	NO	NO
>=75	Number of patients still at risk*	324	242	153	93	0	

[]: 95% Confidence Interval
NO: Not Observable
*: Number of patients still observable at a given time and for whom no events occurred

Figure 4b Kaplan-Meier Curve of time to dyspnoea stratified by prior risk



Probability of not having dyspnoea by dyspnoea risk	N	1 month	3 months	6 months	9 months	12 months	Median (months)
dyspnoea risk	614	94.9% [92.9% - 96.4%]	88.1% [85.1% - 90.6%]	80.3% [76.4% - 83.7%]	75.3% [70.6% - 79.3%]	NO	NO
dyspnoea risk	Number of patients still at risk*	519	392	259	170	0	
no dyspnoea risk	1036	98.2% [97.2% - 98.9%]	95.7% [94.2% - 96.9%]	93.3% [91.3% - 94.8%]	91.0% [88.6% - 92.9%]	NO	NO
no dyspnoea risk	Number of patients still at risk*	920	711	534	388	0	

[]: 95% Confidence Interval
NO: Not Observable
*: Number of patients still observable at a given time and for whom no events occurred
Dyspnoea risk: history of respiratory disease, dyspnoea or heart failure

10.5 Other analyses

None

10.6 Adverse events/adverse reactions

This study assessed the incidence and time to bleed and dyspnoea in patients receiving ticagrelor prescription in primary care. The results of these analyses are presented in section 10.4 and the Read and ICD10 codes used to define are presented in the appendix. As this is a retrospective cohort study, causality assessment at the individual patient level is not possible.

11. DISCUSSION

11.1 Key results

In our study, the incidence rate of the composite efficacy outcome was 5.3 (95% CI: 3.8–6.8) per 100 PY. The overall incidence rates of hospitalised MI and all-cause mortality were 3.3 and 2.6 per 100 PY. In medically managed patients, the incidence rate of the composite of vascular events (14.9 per 100 PY; 95% CI: 7.8–22.0) and MI alone (10.5 per 100 PY, 95% CI 4.6–6.5) were higher than that in patients who underwent revascularization (composite outcome: 3.9 per 100 PY, 95% CI: 2.6–5.3; MI: 2.3 per 100 PY, 95% CI: 1.3–3.4). However, compared with patients who underwent revascularization, medically managed patients were older, more likely to be female and to have a history of MI, stroke, heart failure and bleed, suggesting greater frailty.

The incidence rate of all bleeds and hospital-treated bleeds were 6.6 (95% CI: 4.9–8.2) and 2.5 (95% CI: 1.5–3.5) per 100 PY respectively. The incidence rate of all dyspnoea was 21.6 (95% CI: 18.6–24.5) per 100 PY and dyspnoea requiring hospital treatment1.7 per 100 PY. Among all patients with dyspnoea 89.5% received a prescription for ticagrelor after the date of dyspnoea. 25.9% of patients in the current study had a history of dyspnoea. Older patients (aged ≥75 years) were more likely to develop dyspnoea.

11.2 Limitations

There is a number of study limitations, many of which are inherent in analyses that use observational and linked electronic health records data.

The first month of medication after discharge from hospital was missing for all patients included in this study and patients who discontinued medication after discharge and before receiving medication in primary care could not be included in the study. Medication is not captured in the Hospital Episode Statistics. As this study captured events after initiation of ticagrelor in primary care and not in hospital, it is likely to have introduced a survival bias. To avoid the potential for re-entry of the same event in primary care, data for MI and stroke were derived from HES only. This may have caused underestimation of events. Moreover, the CPRD records that a prescription was issued in primary care and not whether the patient collected the medicine from pharmacy, adhered with treatment or capture events in patients

who were on ticagrelor supplied by the hospital. In addition, incomplete data, differences in recording and classification raises the prospect of misclassification of outcomes. Hospitalised safety events (bleeding and dyspnea) were captured by primary diagnosis codes only in order to avoid misclassifying historical events but may have resulted in under representation. It was also difficult to be precise about the date of the index ACS if this was recorded in primary care data but not in HES. Case validation was not conducted and the limited availability of HES linkage reduced the patient numbers. Restricting analyses to patients with HES linkage may have introduced bias. However, previous comparisons of those included in the linkage scheme to the whole CPRD population found no significant differences in patient characteristics [13, 14].

Finally, interpretation if this study is limited by lack of a comparator and statistical modelling to assess the role of risk factors collectively and individually. Modelling of risk factors was not done because the number of events were considered too few for assessing hazard ratios with sufficient precision and statistical power.

11.3 Interpretation

The PLATO trial [7] reported that in patients hospitalised for ACS, ticagrelor lowered the risk of thrombotic cardiovascular events more effectively than clopidogrel, without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding. It is important, however, to assess the effectiveness and safety of new interventions in routine clinical care to determine whether the outcomes achieved are in line with those of a controlled, randomized clinical trial.

A few studies [8,9,10] have examined the effectiveness and safety of ticagrelor following ACS in European health systems. These studies did not, however, assess if patients were still on therapy after hospital discharge. This study used linked primary, secondary and mortality data to examine the usage and outcomes in patients treated with ticagrelor in routine clinical care within the English National Health Service.

In PLATO, during12 months follow up, 9.8% of patients had the primary composite endpoint (death from vascular causes:4.0%; MI: 5.8%; stroke:4.5%). The percentage of patients with events from PLATO are Kaplan-Meier estimates of the rate of the end point at 12 months. in this study, incidence rates were calculated based on follow-up time in the database from initiation of ticagrelor in primary care, accounting for time on treatment and censoring. The current study also estimated the probability of being event free at various time points from ticagrelor initiation via Kaplan-Meier estimator. Estimates at 12 months couldn't be displayed as patients were followed for maximum of 12 months from first prescription in primary care but only whilst patients were on therapy (patients are recommended to receive ticagrelor up to 12 months from initiation in secondary care). Neither of the types of estimates used in this study are directly comparable to the estimates from PLATO. These differences are important to consider when comparing PLATO results to this study. In our study, the incidence rate of the composite efficacy outcome was 5.3 (95% CI: 3.8–6.8) per 100 PY. The overall incidence rates of hospitalised MI and all-cause mortality were 3.3 and 2.6 per 100 PY respectively. In

medically managed patients, the incidence rate of the composite of vascular events (14.9 per 100 PY; 95% CI: 7.8–22.0) and MI alone (10.5 per 100 PY, 95% CI 4.6–6.5) were higher than that in patients who underwent revascularization (composite outcome: 3.9 per 100 PY, 95% CI: 2.6–5.3; MI: 2.3 per 100 PY, 95% CI: 1.3–3.4). However, compared with patients who underwent revascularization, medically managed patients were older, more likely to be female and have a history of MI, stroke, heart failure and bleed.

In PLATO, 2.8% of patients had major bleeds that were not related to CABG, defined according to the Thrombolysis In Myocardial Infarction (TIMI) criteria, and using the more comprehensive PLATO criteria 4.5% had bleeds. For the more comprehensive criteria in PLATO, major life-threatening bleeding was defined as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells. Other major bleeding was defined as bleeding that led to clinically significant disability (e.g., intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the hemoglobin level of at least 3.0 g per deciliter but less than 5.0 g per deciliter or requiring transfusion of 2 to 3 units of red cells. Minor bleeding was defined as any bleeding requiring medical intervention but not meeting the criteria for major bleeding.

In our study, the incidence rate of all bleeds and hospital-treated bleeds were 6.6 (95% CI: 4.9–8.2) and 2.5 (95% CI: 1.5–3.5) per 100 PY respectively. Although different definitions of bleeding were employed in our study hospital-treated bleeds as defined in this study are likely to capture all major bleeds as defined by PLATO. For hospital-treated bleeds, patients had to have a primary diagnosis code for a bleed. An additional check was conducted to determine if patients had a blood transfusion but no primary diagnosis code indicating a bleed. No patients had a blood transfusion without a primary diagnosis. This study could not assess bleeding associated with hemoglobin changes in hospital as secondary care laboratory data are not captured. No patients in this study had a fatal bleed, defined by bleeding as cause of death in ONS data, without having a hospital treated bleed. As well as looking at bleeds in secondary care, our study used Read codes to capture all events recorded in primary which were deemed to meet BARC 2 and above criteria, ie, any clinically overt sign of hemorrhage that “is actionable” and requires diagnostic studies, hospitalization, or treatment by a health care professional. However, without case validation via questionnaire to GPs it is difficult to ascertain if the events recorded meet these criteria.

The overall incidence rate of dyspnoea in our real-world population was 21.6 (95% CI: 18.6–24.5) per 100 PY. However, dyspnoea that required hospital treatment was infrequent (1.7 per 100 PY) and 89.5% of all patients with dyspnoea received a prescription for ticagrelor after the date of dyspnoea. By way of comparison, the incidence of dyspnoea in PLATO was 13.8% in the ticagrelor group. However, 25.9% of patients in the current study had a history of dyspnoea, compared with 15.1% in PLATO. Moreover, older patients (aged ≥75 years) were more likely to develop dyspnoea in our study. Therefore, differences in patient characteristics probably account for the apparently higher rate of dyspnoea in the real-world setting.
Few other studies have assessed ticagrelor in a real-world setting. A Danish [9] study of registry data found that ticagrelor (n=1134) significantly reduced the rate of cardiac death by

40% in ACS patients compared with clopidogrel (n=1201) during a one-year follow up (3.5% and 5.7% respectively; HR=0.60; 95% confidence interval [CI] 0.41–0.89]. Non-cardiac death (2.8% and 3.0% respectively) or MI rates (3.2% and 3.8%) did not differ significantly between the ticagrelor and clopidogrel groups. However, the rate of definite stent thrombosis was 69% lower in the ticagrelor than clopidogrel groups (0.5% and 1.4% respectively; HR=0.31; 95% CI 0.11–0.84).

A Swedish cohort study [8] followed ACS patients discharged on ticagrelor (n=11,954) or clopidogrel (n=33,119) for two years. The incidence of the primary outcome – a composite of all-cause mortality, readmission with MI or stroke – was 11.7% with ticagrelor and 22.3% with clopidogrel (adjusted HR=0.85; 95% CI 0.78–0.93). At 24 months, the risk of death (5.8% and 12.9%; adjusted HR=0.83; 95% CI 0.75–0.92) and MI (6.1% and 10.8%; adjusted HR=0.89; 95% CI 0.78–1.01) were significantly lower with ticagrelor than with clopidogrel. Readmission with bleeding occurred in 5.5% and 5.2% of the ticagrelor and clopidogrel groups, respectively (adjusted HR=1.20; 95% CI 1.04–1.4).

A recent UK study showed results which were not consistent with PLATO [10]. This study focused on patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) between 2006-2016 and showed a lower risk of in hospital bleeds for patients receiving ticagrelor compared to those receiving clopidogrel. The study also showed no difference in all-cause mortality at 30 days and 1 year between patients who received ticagrelor and prasugrel. The study didn't assess dsypnoea or whether patients were on treatment post discharge from hospital.

These different real-world studies are not directly comparable. For instance, the studies differed in duration of follow up and absence of data, such as medication following discharge [8,9,10] and about bleeding events [8]. Nonetheless, two of these real-world studies showed that the outcomes were in line with the benefit noted in the PLATO trial: patients discharged on ticagrelor had lower incidence of vascular events and mortality but were also a risk of bleeding.

11.4 Generalisability

Compared to randomised trials, the results of studies using real world settings without restrictions on types of patients included have the advantage of increased generalisability. This study also has the advantage over other real world studies assessing the effects of ticagrelor in that it reflects what happens to patients in both the primary and secondary care setting. Most other real world studies assessing ticagrelor have focused on secondary care settings only. However, this study has a number of limitations which have implications for its interpretation.

12. OTHER INFORMATION

None

13. CONCLUSION

In the present study the crude incidence rate of a composite of hospitalised MI, stroke (all) and vascular death was 5.3 (3.8-6.8) per 100 PY in this population of UK patients prescribed ticagrelor in primary care after an ACS event. The crude incidence rates for bleeding with hospital care was2.5 (1.5–3.5) and dyspnoea requiring hospital care 1.7 (0.9-2.6).

The interpretation if this study is limited due to survival bias, lack of a comparator and statistical modelling to assess the role of risk factors. Modelling of risk factors was not done because the number of events were considered too few for assessing hazard ratios with sufficient precision and statistical power

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15. ASTRAZENECA SIGNATURE

Health outcomes of patients with acute coronary syndromes prescribed ticagrelor in UK primary care: a retrospective cohort study

PASS Study Report

I have read this Study Report and I confirm that it describes the procedure and the results of the study.

[redacted]

APPENDICES

Annex 1. list of stand-alone documents

None

Annex 2. Additional information

Codes used in study

DYSPNOEA READ CODES

Medcode	Read code	Read description
101843	173a.00	Borg Breathlessness Score: 10 maximal
107410	173f.00	Anxiety about breathlessness
107939	38Gb.00	Dyspnoea,obstruction, smoking, exacerbation frequency index
108650	173g.00	Breathlessness causing difficulty eating
1429	173..00	Breathlessness
18116	173D.00	Nocturnal dyspnoea
19426	173J.00	MRC Breathlessness Scale: grade 3
19427	173I.00	MRC Breathlessness Scale: grade 2
19429	173L.00	MRC Breathlessness Scale: grade 5
19430	173K.00	MRC Breathlessness Scale: grade 4
19432	173H.00	MRC Breathlessness Scale: grade 1
21801	173Z.00	Breathlessness NOS
22094	173F.00	Short of breath dressing/undressing
24889	173G.00	Breathless - strenuous exertion
2575	173C.00	Short of breath on exertion
2931	1738	Difficulty breathing
3092	R060A00	[D]Dyspnoea
31143	1734	Breathless - at rest
40813	173b.00	Unable to complete a sentence in one breath
42287	173V.00	Borg Breathlessness Score: 6 severe (+)
4822	1739	Shortness of breath

5175	173..11	Breathlessness symptom
5349	173..13	Shortness of breath symptom
53771	173C.11	Dyspnoea on exertion
57193	173R.00	Borg Breathlessness Score: 3 moderate
57759	173Q.00	Borg Breathlessness Score: 2 slight
57903	388H.00	CLASP shortness of breath score
5896	173..12	Dyspnoea - symptom
59860	173S.00	Borg Breathlessness Score: 4 somewhat severe
60096	ZR3Q.00	CLASP shortness of breath score
6326	1732	Breathless - moderate exertion
64049	173T.00	Borg Breathlessness Score: 5 severe
6434	1736	Paroxysmal nocturnal dyspnoea
67566	173Y.00	Borg Breathlessness Score: 9 very, very sev (almost maximal)
68707	173P.00	Borg Breathlessness Score: 1 very slight
70061	173W.00	Borg Breathlessness Score: 7 very severe
72334	173X.00	Borg Breathlessness Score: 8 very severe (+)
735	R060D00	[D]Breathlessness
741	R060800	[D]Shortness of breath
7683	1735	Breathless - lying flat
7932	1733	Breathless - mild exertion

BLEED READ CODES

Medcode	Read code	Read description

100998	K592012	Heavy menstrual bleeding
10118	K19y400	Bleeding from urethra
101260	L10z100	Early pregnancy haemorrhage NOS - delivered
101824	C154211	Adrenocortical haemorrhage
102134	J08zD00	Angina bullosa haemorrhagica
102745	L362100	Secondary postpartum haemorrhage - deliv with postnatal prob
103474	S73A100	Perianal haematoma
103476	16R..00	Bleeding symptom
103810	L115z00	Antepartum haemorrhage with uterine leiomyoma NOS
103877	L361200	Other immediate postpartum haemorrhage with postnatal prob
1039	K59y300	Intermenstrual bleeding
104124	8HTE000	Referral to rectal bleeding clinic
10425	K59yx00	Dysfunctional uterine haemorrhage NOS
104283	S780500	Retroperitoneal haematoma
104636	Q201300	Massive epicranial subaponeurotic haemorrhage-birth trauma
104807	L361000	Other immediate postpartum haemorrhage unspecified
104829	L260000	Fetal-maternal haemorrhage unspecified
105425	L361100	Other immediate postpartum haemorrhage - deliv with p/n prob
105544	Q413y00	Other specified umbilical haemorrhage after birth
105654	L10y100	Other haemorrhage in early pregnancy - delivered
106330	J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
106481	L113100	Antepartum haemorrhage with coagulation defect - delivered
106491	L050100	Unspecified legal abortion + delayed/excessive haemorrhage

106524	L071100	Unspecified incomplete abortion + delayed/excess haemorrhage
106975	Gy51.00	Haemorrhage of dialysis arteriovenous fistula
107171	L042100	Complete spontaneous abortion +delayed/excessive haemorrhage
107440	G619.00	Lobar cerebral haemorrhage
10764	SE42011	Heel bruise
10779	F42y.11	Haemorrhage - retinal
108134	L37..12	Retained placenta without haemorrhage
1084	SE...00	Contusion (bruise) with intact skin
108601	Q20y100	Liver subcapsular haematoma due to birth trauma
108636	SP07R00	Bleeding due to intrauterine contraceptive device
108668	Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
108759	Gy5..00	Haemorrhage of dialysis vascular access
10984	SE22300	Haematoma of rectus sheath
1105	F4C7200	Conjunctival haemorrhage NOS
11061	D3z..00	Clotting or bleeding disorder NOS
11124	J110111	Bleeding acute gastric ulcer
1155	SE...11	Haematoma with intact skin
11698	196C.00	Painless rectal bleeding
11718	196B.00	Painful rectal bleeding
11725	K599.00	Mid-cycle bleeding
11950	B937400	Essential (haemorrhagic) thrombocythaemia
1201	F4K2800	Vitreous haemorrhage
12012	L36..11	Bleeding postpartum

12142	SE0..11	Bruise of face
12426	K587.00	Contact bleeding of cervix
12471	J68z.00	Gastrointestinal haemorrhage unspecified
12615	SE1..11	Bruise of eye
12729	SE30011	Shoulder bruise
13564	G613.00	Cerebellar haemorrhage
1372	16B3.00	Spontaneous bruising
14762	L11..00	Antepartum haemorrhage, abruptio placentae, placenta praevia
1492	L36..00	Postpartum haemorrhage (PPH)
14925	L10z.00	Early pregnancy haemorrhage NOS
15131	K595.00	Ovulation bleeding
15257	G845000	External bleeding haemorrhoids
15444	K31y000	Breast haematoma due to nontraumatic cause
15464	F436000	Unspecified choroidal haemorrhage
15517	J68z000	Gastric haemorrhage NOS
15540	1C6Z.00	Nose bleed symptom NOS
1583	K5A1.00	Postmenopausal bleeding
15925	K56y100	Haemorrhage of vagina
16114	J10y000	Haemorrhage of oesophagus
16419	K286w00	Male genital haemorrhage NOS
1642	J68z.11	GIB - Gastrointestinal bleeding
16445	D31z.00	Haemorrhagic condition NOS
16525	K575.00	Haematoma of vulva

16848	7H02200	Reopen chest reexplore intraabdom op site surg arr PO bleed
16949	F503100	Haematoma of pinna
17383	SC13.11	Late effect of bruising
17734	G622.00	Subdural haematoma - nontraumatic
17825	SP21.12	Haemorrhage - postoperative
1786	G60..00	Subarachnoid haemorrhage
179	K59z.11	Break - through bleeding
18001	J120100	Acute duodenal ulcer with haemorrhage
1819	G8y0.00	Haemorrhage NOS
18281	SP21300	Primary post tonsillectomy haemorrhage
183	158..12	Vaginal bleeding
18411	S62A.00	Traumatic extradural haematoma
18604	G61..12	Stroke due to intracerebral haemorrhage
18625	J121111	Bleeding chronic duodenal ulcer
18677	SK02.00	Secondary and recurrent haemorrhage
18912	G623.00	Subdural haemorrhage NOS
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
19221	SP21400	Secondary post tonsillectomy haemorrhage
19271	J573.00	Haemorrhage of rectum and anus
1941	K597.00	Postcoital bleeding
19412	G602.00	Subarachnoid haemorrhage from middle cerebral artery
20284	G62z.00	Intracranial haemorrhage NOS
20326	L345.11	Perineal haematoma

2044	J510900	Bleeding diverticulosis
20828	7M0U400	Reexploration of organ & surgical arrest postop bleeding NOC
20857	SP21.00	Peri-operative haemorrhage or haematoma
20946	SE24211	Bruise of scrotum
21161	SE11.11	Bruise of eyelids
21263	SE05.11	Bruise of ear
2150	J68z100	Intestinal haemorrhage NOS
21582	42Q3.00	Bleeding time
21739	D31X.00	Haemorrhagic condition, unspecified
21799	F4K7.00	Retrobulbar haemorrhage
21946	K5E1.00	Abnormal uterine bleeding, unspecified
22176	F4Ey000	Haemorrhage of eyelid
22651	G77z000	Capillary haemorrhage
22775	L11y.00	Other antepartum haemorrhage
23439	SP03216	Bleeding due to intrauterine contraceptive device
23447	Q200000	Cerebral haemorrhage unspecified, due to birth trauma
23580	G60z.00	Subarachnoid haemorrhage NOS
23601	K221.00	Prostatic congestion or haemorrhage
23695	16BZ.00	Bruising symptom NOS
23813	7619100	Gastrotomy and ligation of bleeding point of stomach
2384	K59yx11	Dysfunctional uterine bleeding
24324	K286100	Scrotal haemorrhage
24349	K286300	Testicular haematoma due to nontraumatic cause

24603	L10y.00	Other haemorrhage in early pregnancy
24981	16B4.00	Post-traumatic bruising
24989	G850.00	Oesophageal varices with bleeding
25124	K56y112	BPV - Vaginal bleeding
26065	F501G00	Haemorrhagic otitis externa
2629	F404500	Intra-ocular haemorrhage
26677	Q413.00	Umbilical haemorrhage after birth
27661	S62..11	Extradural haemorrhage following injury
27711	16B2.00	Bruises easily
27731	L345.12	Vulval and perineal haematoma during delivery
2787	L11..11	Antepartum haemorrhage
27956	TA0..11	Accidental haemorrhage during medical care
28077	S62..14	Traumatic cerebral haemorrhage
2814	J12y100	Unspecified duodenal ulcer with haemorrhage
28144	7H22600	Reopen abdo reexplore intraabd op site surg arr postop bleed
28242	K5E2.00	Abnormal vaginal bleeding, unspecified
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
2832	G848000	Bleeding haemorrhoids NOS
28366	J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
28511	SE4z.12	Intramuscular haematoma NOS
28652	SP21000	Intra-operative haemorrhage
2872	L371200	Retained products with no haemorrhage with postnatal problem
28763	F436100	Expulsive choroidal haemorrhage

28765	F42y400	Subretinal haemorrhage
28807	S62..12	Subarachnoid haemorrhage following injury
2883	S622.00	Closed traumatic subdural haemorrhage
28914	662o.00	Haemorrhagic stroke monitoring
29492	J150000	Acute haemorrhagic gastritis
29702	FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere
29903	K59yy00	Functional uterine haemorrhage NOS
30045	G616.00	External capsule haemorrhage
30054	J110100	Acute gastric ulcer with haemorrhage
30132	A774.00	Epidemic haemorrhagic conjunctivitis
3020	7M0G400	Evacuation of haematoma NEC
30202	G617.00	Intracerebral haemorrhage, intraventricular
3039	F42y500	Retinal haemorrhage NOS
30655	G851.00	Oesophageal varices without bleeding
3097	J68..00	Gastrointestinal haemorrhage
31002	K544.00	Haematometra
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
3122	7736000	Evacuation of perianal haematoma
31265	Q413200	Massive umbilical haemorrhage
31395	J670200	Acute haemorrhagic pancreatitis
31500	7004100	Evacuation of haematoma from temporal lobe of brain
31521	SP21200	Post-operative haematoma formation
31595	G610.00	Cortical haemorrhage

3170	SE33011	Subungual haematoma
31805	G62..00	Other and unspecified intracranial haemorrhage
31918	K5E0.00	Abnormal uterine bleeding unrelated to menstrual cycle
32339	L3X..00	Intrapartum haemorrhage, unspecified
32446	J573100	Anal haemorrhage
33360	F4G3200	Exophthalmos due to orbital haemorrhage
33676	K5Ez.00	Abnormal uterine and vaginal bleeding, unspecified
33895	7517500	Surgical arrest of postoperative bleeding from tooth socket
34125	7531400	Surgical arrest of postoperative bleeding from tonsillar bed
34284	SE06.00	Bruise of mandibular joint area
34466	14CD.00	H/O: upper GIT haemorrhage
34694	Q200.00	Subdural and cerebral haemorrhage due to birth trauma
34757	K566.00	Vaginal haematoma
3487	K59y.11	Metropathia haemorrhagica
3535	G61z.00	Intracerebral haemorrhage NOS
35767	K55y300	Haemorrhage of cervix
35867	S630.12	Intracranial haematoma following injury
3600	SE23111	Perianal haematoma
36070	S760100	Kidney haematoma without mention of open wound into cavity
36128	A080500	Haemorrhagic dysentery
36178	G620.00	Extradural haemorrhage - nontraumatic
36234	L370z11	Retained placenta without haemorrhage
36583	J111111	Bleeding chronic gastric ulcer

36703	L345.00	Vulval and perineal haematoma during delivery
36873	7303000	Drainage of haematoma of external ear
3707	7D05200	Evacuation of haematoma of vulva
37245	L345000	Vulval and perineal haematoma during delivery, unspecified
37249	K13y800	Perirenal haematoma
37250	K16y200	Bladder haemorrhage
37280	L36z.00	Postpartum haemorrhage NOS
3766	L10..00	Haemorrhage in early pregnancy
37742	Q416400	Perinatal superficial haematoma
37772	851..00	Haemorrhage control by packing
37853	ZA13700	Drainage of subungual haematoma with hot wire
37882	S760111	Renal haematoma without mention of open wound into cavity
38180	F4H4100	Optic nerve sheath haemorrhage
38184	7404	Surgical arrest of bleeding from internal nose
3822	2BB8.00	O/E - vitreous haemorrhages
38304	S620.00	Closed traumatic subarachnoid haemorrhage
3872	J573.11	Bleeding PR
38792	66UH.00	Hormone replacement therapy bleed pattern - normal
38851	R048.00	[D]Throat haemorrhage
39108	S750100	Spleen haematoma without mention of open wound into cavity
39274	K138300	Intrarenal haematoma
39328	8513	Pack non-obst.uterine bleeding
39516	ZA13800	Drainage of subungual haematoma with drill

39575	C063000	Thyroid haemorrhage
39775	SE05.12	Bruise of auricle
4028	SE4z.11	Haematoma NOS
40338	G611.00	Internal capsule haemorrhage
4107	7032000	Evacuation of extradural haematoma
41122	L10zz00	Early pregnancy haemorrhage NOS
41783	L041100	Incomp spontaneous abortion + delayed/excessive haemorrhage
41910	G605.00	Subarachnoid haemorrhage from basilar artery
42283	S63z.00	Other cerebral haemorrhage following injury NOS
42331	G603.00	Subarachnoid haemorrhage from anterior communicating artery
42421	D3y..00	Other specified disorders of clotting or bleeding
42581	25T0.00	Bleeding stoma
4273	G621.00	Subdural haemorrhage - nontraumatic
42967	L443.11	Haematoma - perineal wound
43418	S624.11	Epidural haematoma following injury
43451	G682.00	Sequelae of other nontraumatic intracranial haemorrhage
4354	J68z200	Upper gastrointestinal haemorrhage
4367	L362.00	Secondary and delayed postpartum haemorrhage
43682	7004200	Evacuation of haematoma from cerebellum
4398	SE45.11	Haematoma of leg
44258	J062100	Haemorrhagic cyst of jaw
44637	J130100	Acute peptic ulcer with haemorrhage
44740	G680.00	Sequelae of subarachnoid haemorrhage

45002	Q412.00	Perinatal subarachnoid haemorrhage
45304	J130300	Acute peptic ulcer with haemorrhage and perforation
45340	L040111	Spontaneous abortion with heavy bleeding
45372	7G2H400	Liposuction removal of haematoma
45421	S624.00	Closed traumatic extradural haemorrhage
45489	ZA13600	Drainage of subungual haematoma
45670	K275100	Corpus cavernosum haematoma
45844	L336.11	Bruising of cord
45929	D211.11	Normocytic anaemia following acute bleed
4594	1C62.00	Has nose bleeds - epistaxis
46097	L111100	Placenta praevia with haemorrhage - delivered
46152	7J01300	Reopen cranium reexploration op site arrest post op bleeding
46179	7008200	Aspiration of haematoma of brain tissue
46267	S740100	Liver haematoma and contusion without open wound into cavity
46316	G612.00	Basal nucleus haemorrhage
4636	J68zz00	Gastrointestinal tract haemorrhage NOS
46446	Q200200	Local subdural haematoma due to birth trauma
46479	J573z00	Haemorrhage of rectum and anus NOS
46545	S62z.00	Cerebral haemorrhage following injury NOS
46591	SE11.12	Bruise of periocular tissue
46938	F42y100	Superficial retinal haemorrhage
4702	K286000	Scrotal haematoma due to nontraumatic cause
47026	K59A.00	Premenopausal postcoital bleeding

47195	D31yz00	Other specified haemorrhagic condition NOS
47203	D31y.00	Other specified haemorrhagic conditions
47231	7F22700	Pack to control postnatal vaginal bleeding
4729	158..11	C/O p.v. bleeding
47542	L362200	Secondary postpartum haemorrhage with postnatal problem
48086	K138100	Renal artery haemorrhage
48149	G681.00	Sequelae of intracerebral haemorrhage
48181	K221100	Prostatic haemorrhage
48304	L10z200	Early pregnancy haemorrhage NOS - not delivered
48730	J120300	Acute duodenal ulcer with haemorrhage and perforation
48731	Q200700	Cerebral haemorrhage due to birth injury
48883	L113.00	Antepartum haemorrhage with coagulation defect
48951	J121100	Chronic duodenal ulcer with haemorrhage
49111	66UI.00	Hormone replacement therapy bleed pattern - abnormal
49162	K286400	Testicular haemorrhage
4917	7017000	Evacuation of subdural haematoma
49363	Q200100	Subdural haemorrhage unspecified, due to birth trauma
49374	SK02.11	Secondary and recurrent haemorrhage
49487	K537.00	Haematoma of the broad ligament
49516	Q414300	Neonatal vaginal haemorrhage
49824	K531100	Corpus luteum cyst haemorrhage
50097	K167.00	Haemorrhage into bladder wall
501	R047.00	[D]Epistaxis

5018	K286v00	Male genital haematoma NOS
5051	G61..00	Intracerebral haemorrhage
5130	SE4..11	Leg bruise
51504	S626.00	Epidural haemorrhage
51571	7405300	Insertion of Brighton epistaxis balloon
51717	H5y0000	Tracheostomy haemorrhage
52186	K275200	Corpus cavernosum haemorrhage
52215	S761100	Kidney haematoma with open wound into cavity
52717	7517511	Surgical arrest of bleeding post dental extraction
52896	Kyu9D00	[X]Other specified abnormal uterine and vaginal bleeding
52968	S63..00	Other cerebral haemorrhage following injury
53054	D305.00	Haemorrhagic disorder due to circulating anticoagulants
53126	J131100	Chronic peptic ulcer with haemorrhage
5320	SE33200	Contusion, fingernail (includes subungual haematoma)
53707	Q416100	Perinatal cutaneous bruising
53810	Gyu6200	[X]Other intracerebral haemorrhage
53980	S629000	Traumatic subdural haematoma without open intracranial wound
54099	7F22711	Pack to control postnatal vaginal bleeding
54107	L10z000	Early pregnancy haemorrhage NOS unspecified
5422	SK02.12	Secondary and recurrent haemorrhage
54248	Q415.00	Perinatal adrenal haemorrhage
54652	L362z00	Secondary and delayed postpartum haemorrhage NOS
55153	C154200	Adrenal haemorrhage

55166	J017200	Teeth staining due to pulpal bleeding
56007	G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
5682	S62..00	Cerebral haemorrhage following injury
57142	L371z00	Retained products with no haemorrhage NOS
57249	L11z000	Antepartum haemorrhage NOS, unspecified
57315	G618.00	Intracerebral haemorrhage, multiple localized
57783	Q417000	Intracerebral (nontraumatic) haemorrhage of fet and newborn
5779	K596.11	Intermenstrual bleeding - irregular
5785	1C6..11	Epistaxis symptom
5793	1C6..00	Nose bleed symptom
57958	J11y100	Unspecified gastric ulcer with haemorrhage
5808	K5E..00	Other abnormal uterine and vaginal bleeding
58545	S627.00	Traumatic subarachnoid haemorrhage
58691	Dyu3300	[X]Other specified haemorrhagic conditions
5981	D30..11	Bleeding disorders
59812	F436z00	Choroidal haemorrhage or rupture NOS
60346	J14y100	Unspecified gastrojejunal ulcer with haemorrhage
60436	Q413z00	Umbilical haemorrhage after birth NOS
60692	G606.00	Subarachnoid haemorrhage from vertebral artery
6070	16B..00	Bruising symptom
60741	L115.12	Antepartum haemorrhage with uterine fibroid
60744	L115.11	Antepartum haemorrhage with fibroid
61301	L10y000	Other haemorrhage in early pregnancy unspecified

61552	L360000	Third-stage postpartum haemorrhage unspecified
61686	L37..11	Retained membrane without haemorrhage
61761	Q414200	Perinatal rectal haemorrhage
62038	7609y11	Tanner devascularisation for bleeding varices
621	J573011	Rectal bleeding
62121	L3A..00	Intrapartum haemorrhage with coagulation defect
62292	66UJ.00	Hormone replacement therapy bleed pattern - not relevant
62342	G615.00	Bulbar haemorrhage
62560	Q41y000	Perinatal epistaxis
62734	L11y000	Other antepartum haemorrhage unspecified
62741	7404z00	Surgical arrest of bleeding from internal nose NOS
63006	L370000	Retained placenta with no haemorrhage unspecified
6309	K56y111	Bleeding - vaginal NOS
63360	Q412000	Subarachnoid haemorrhage due to birth injury
63582	J111100	Chronic gastric ulcer with haemorrhage
63620	D305000	Haemorrhagic disorder due to antithrombinaemia
63656	L113.13	Antepartum haemorrhage with hypofibrinogenaemia
63806	Q200y00	Subdural or cerebral haemorrhage due to birth trauma OS
63966	Q20y300	Vulval haematoma due to birth trauma
63974	Q313200	Perinatal massive pulmonary haemorrhage
64451	J636.00	Central haemorrhagic necrosis of liver
64523	L091z00	Delayed/excess haemorrhage NOS following abortive pregnancy
64687	D305100	Haemorrhagic disorder due to hyperheparinaemia

64748	L370z00	Retained placenta with no haemorrhage NOS
64752	L111200	Placenta praevia with haemorrhage - not delivered
64982	S751100	Spleen haematoma with open wound into cavity
6554	J573012	PRB - Rectal bleeding
6569	S62..13	Subdural haemorrhage following injury
6574	J573000	Rectal haemorrhage
65745	Gyu6100	[X]Other subarachnoid haemorrhage
65976	C12y100	Haemorrhage of parathyroid
6622	K595.11	Intermenstrual bleeding - regular
66335	L260.00	Fetal-maternal haemorrhage
66836	L361z00	Other immediate postpartum haemorrhage NOS
66837	L360z00	Third-stage postpartum haemorrhage NOS
6711	R027.11	[D]Spontaneous bruising
67184	Q200z00	Subdural or cerebral haemorrhage due to birth trauma NOS
67197	A786.00	Haemorrhagic nephrosonephritis
68029	L111z00	Placenta praevia with haemorrhage NOS
68511	L040100	Unspec spontaneous abortion + delayed/excessive haemorrhage
68624	7404y00	Surgical arrest of bleeding from internal nose OS
68903	Q313400	Tracheobronchial haemorrhage origin in the perinatal period
68936	L051100	Incomplete legal abortion + delayed or excessive haemorrhage
69002	L11y200	Other antepartum haemorrhage - not delivered
69183	L052100	Complete legal abortion with delayed/excessive haemorrhage
6931	7D1C000	Evacuation of haematoma from vagina

69327	L10yz00	Other haemorrhage in early pregnancy NOS
69344	L11z200	Antepartum haemorrhage NOS - not deliv
69500	L114100	Antepartum haemorrhage with trauma - delivered
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
69788	L260200	Fetal-maternal haemorrhage with antenatal problem
69892	F424300	Retinal pigment epithelium haemorrhagic detachment
70132	L11yz00	Other antepartum haemorrhage NOS
7017	7004300	Evacuation of intracerebral haematoma NEC
70456	J13y100	Unspecified peptic ulcer with haemorrhage
70557	L110000	Placenta praevia without haemorrhage unspecified
70615	L345z00	Vulval and perineal haematoma during delivery NOS
70912	L110z00	Placenta praevia without haemorrhage NOS
7096	G844.11	Perianal haematoma
71057	L345100	Vulval and perineal haematoma during delivery - delivered
71155	L115.00	Antepartum haemorrhage with uterine leiomyoma
71197	F437200	Haemorrhagic choroidal detachment
712	F4C7100	Subconjunctival haemorrhage
71251	L361.00	Other immediate postpartum haemorrhage
71253	F42y300	Deep retinal haemorrhage
71403	J110300	Acute gastric ulcer with haemorrhage and perforation
7144	SE43.11	Toenail bruise
71590	Q414.00	Perinatal gastrointestinal haemorrhage
71783	K221z00	Prostatic congestion or haemorrhage NOS

71829	2DE7.00	O/E - throat haemorrhage
7183	R09z000	[D]Umbilical bleeding
71881	J121300	Chronic duodenal ulcer with haemorrhage and perforation
71897	J111300	Chronic gastric ulcer with haemorrhage and perforation
7285	R063100	[D]Pulmonary haemorrhage NOS
7290	7M0G000	Aspiration of haematoma of organ NOC
73028	L357100	Obstetric pelvic haematoma - delivered
73471	S625.00	Open traumatic extradural haemorrhage
73917	L10y200	Other haemorrhage in early pregnancy - not delivered
7472	SE46.00	Traumatic haematoma
7733	K19y411	Urethral bleeding
7862	S629.00	Traumatic subdural haematoma
7912	G614.00	Pontine haemorrhage
8181	S628.00	Traumatic subdural haemorrhage
8189	Q41y111	Perinatal transient vaginal bleeding
8197	SE2..11	Bruise, trunk
8239	R063000	[D]Cough with haemorrhage
85182	L113000	Antepartum haemorrhage with coagulation defect unspecified
85204	L115100	Antepartum haemorrhage with uterine leiomyoma - delivered
8544	K593.11	Pubertal bleeding and menorrhagia
8742	2BB5.00	O/E - retinal haemorrhages
8775	SP21.11	Haematoma - postoperative
87841	7303200	Drainage haematoma ext ear control cavity c bolster suture

8845	SE3..11	Arm bruise
90580	Q416.00	Perinatal cutaneous haemorrhage
90773	7421300	Surgical arrest of postoperative bleeding of adenoid
9106	1584	Heavy episode of vaginal bleeding
91278	L357000	Obstetric pelvic haematoma unspecified
9143	D3...00	Clotting and bleeding disorders
93190	7F22712	Pack to control postnatal haemorrhage
93436	J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
9395	1928	Bleeding gums
9408	L10y.11	Bleeding in early pregnancy
94146	Ryu7300	[X]Haemorrhage, not elsewhere classified
94351	S623.00	Open traumatic subdural haemorrhage
94397	J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
9503	D31..00	Purpura and other haemorrhagic conditions
9571	SP21100	Post-operative haemorrhage
96415	L111000	Placenta praevia with haemorrhage unspecified
96622	J13y300	Unspecified peptic ulcer with haemorrhage and perforation
96628	J140100	Acute gastrojejunal ulcer with haemorrhage
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
96677	S629100	Traumatic subdural haematoma with open intracranial wound
96717	S621.00	Open traumatic subarachnoid haemorrhage
96747	L360100	Third-stage postpartum haemorrhage - deliv with p/n problem
96756	G852000	Oesophageal varices with bleeding in diseases EC

9696	G604.00	Subarachnoid haemorrhage from posterior communicating artery
97046	7G31400	Drainage of subungual haematoma
9740	SE0..12	Bruise of head
9761	G842000	Internal bleeding haemorrhoids
97719	L360200	Third-stage postpartum haemorrhage with postnatal problem
98663	Qyu3500	[X]Oth pulmonary haemorrhages originating/perinatal period
98945	98BR.00	GMS3 claim - arrest dental haemorrhage (Rate B) paid
98964	L114.00	Antepartum haemorrhage with trauma
99261	98BN.00	GMS3 claim - arrest dental haemorrhage (Rate A) sent to HA
99262	98BO.00	GMS3 claim - arrest dental haemorrhage (Rate A) paid
99263	98BP.00	GMS3 claim - arrest dental haemorrhage (Rate B) signed
99264	98BQ.00	GMS3 claim - arrest dental haemorrhage (Rate B) sent to HA
99361	L345200	Vulval and perineal haematoma during delivery + p/n problem
99362	Dyu3400	[X]Haemorrhagic condition, unspecified
99904	S741100	Liver haematoma and contusion with open wound into cavity
99935	Lyu4D00	[X]Other immediate postpartum haemorrhage

ICD10 CODES FOR MI, STROKE, CVD MORTALITY, BLEED AND DYSPNEA

Diagnosis	ICD 10 Codes	
MI	I21 xx	Acute MI
	I22 xx	Subsequent MI

Stroke	I63 (I631-I639)	Cerebral infarction
	I64	Stroke, not specified as haemorrhage or infarction
	I60 (I600-I609)	Subarachnoid haemorrhage
	I61 (I610-I619)	Intracerebral haemorrhage
	I62 (I620, I621, I 629)	Other nontraumatic intracranial haemorrhage
CVD mortality	I00–I99	
Bleeding	I60	Subarachnoid haemorrhage
	I61	Intracerebral haemorrhage
	I62	Other nontraumatic intracranial haemorrhage
	K250	Gastric ulcer ; Acute with haemorrhage
	K252	Gastric ulcer ; Acute with both haemorrhage and perforation
	K254	Gastric ulcer ; Chronic or unspecified with haemorrhage
	K256	Gastric ulcer ; Chronic or unspecified with both haemorrhage and perforation
	K260	Duodenal ulcer ; Acute with haemorrhage
	K262	Duodenal ulcer ; Acute with both haemorrhage and perforation
	K264	Duodenal ulcer ; Chronic or unspecified with haemorrhage
	K266	Duodenal ulcer ; Chronic or unspecified with both haemorrhage and perforation
	K270	Peptic ulcer, site unspecified ; Acute with haemorrhage
	K272	Peptic ulcer, site unspecified ; Acute with both haemorrhage and perforation
	K274	Peptic ulcer, site unspecified ; Chronic or unspecified with haemorrhage
	K276	Peptic ulcer, site unspecified ; Chronic or unspecified with both haemorrhage and perforation
	K280	Gastrojejunal ulcer ; Acute with haemorrhage
	K282	Gastrojejunal ulcer ; Acute with both haemorrhage and perforation
	K284	Gastrojejunal ulcer ; Chronic or unspecified with haemorrhage
	K286	Gastrojejunal ulcer ; Chronic or unspecified with both haemorrhage and perforation
	K290	Acute haemorrhagic gastritis

	K625	Haemorrhage of anus and rectum
	K920	Haematemesis
	K921	Melaena
	K922	Gastrointestinal haemorrhage, unspecified
	R041	Haemorrhage from throat
	R048	Haemorrhage from other sites in respiratory passages
	R049	Haemorrhage from respiratory passages, unspecified
	H356	Retinal haemorrhage
	H431	Vitreous haemorrhage
	H450	Vitreous haemorrhage in diseases classified elsewhere
Dyspnoea	R060	Dyspnoea

READ CODES OBSERVED FOR BLEEDS AND MAPPED TO BARC CLASS

Read code description	**BARC class**
Spontaneous bruising	1
Bleeding PR	2
Bruising symptom	1
[D]Epistaxis	1
Rectal bleeding	2
GIB - Gastrointestinal bleeding	3a
Epistaxis symptom	1
Painless rectal bleeding	2
[D]Spontaneous bruising	1
Contusion (bruise) with intact skin	1
Bleeding symptom	1
Haematoma NOS	1
Nose bleed symptom	1
CVA - cerebrovascular accid due to intracerebral haemorrhage	3c
Subconjunctival haemorrhage	2
Painful rectal bleeding	2
Vaginal bleeding	1
Bleeding gums	1
Evacuation of haematoma NEC	2
Gastrointestinal haemorrhage	3a
Heavy menstrual bleeding	2

O/E - vitreous haemorrhages	3c
Rectal haemorrhage	2
Traumatic haematoma	2
Upper gastrointestinal haemorrhage	2

Office of Population Censuses and Surveys (OPCS) classification of interventions and procedures for blood transfusion

X33 Other blood transfusion

X331 Intra-arterial blood transfusion

X332 Intravenous blood transfusion of packed cells

X333 Intravenous blood transfusion of platelets

X338 Other specified other blood transfusion

X339 Unspecified other blood transfusion