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ORIGINAL RESEARCH

Under-recording of hospital bleeding events in UK primary care: a linked Clinical Practice Research Datalink and Hospital Episode Statistics study

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Background: Primary care databases represent a rich source of data for health care research; however, the quality of recording of secondary care events in these databases is uncertain. This study sought to investigate the completeness of recording of hospital admissions for bleeds in primary care records and explore the impact of incomplete recording on estimates of bleeding risk associated with antithrombotic treatment.

Methods: The study population consisted of adults with non-valvular atrial fibrillation who had at least one bleed recorded in either the Clinical Practice Research Datalink (CPRD) or Hospital Episode Statistics (HES) while receiving prescriptions for an oral anticoagulant. The proportion of bleeds recorded in HES that had a corresponding bleed recorded in the subsequent 12 weeks in CPRD was calculated, and factors associated with having a corresponding record were identified. Cox proportional hazards analyses investigating the hazard of subsequent bleeding associated with antithrombotic treatment were carried out using linked CPRD-HES data and using CPRD only data, and the results were compared.

Results: Less than 20% of the 14,361 bleeds recorded in the HES data had a corresponding bleed coded in the CPRD in the subsequent 12 weeks. This proportion varied by bleed characteristics, calendar time, day of week of admission (weekday vs weekend) and oral anticoagulant treatment at the time of the bleed. The hazard of subsequent bleeding associated with vitamin K antagonists (VKAs) and antiplatelet agents (APAs) relative to no antithrombotic treatment were similar using the linked primary and secondary care dataset (VKA HR_{adj} 1.06 CI_{95} 0.96–1.16; APA HR_{adj} 1.08 CI_{95} 0.96–1.21) and the unlinked primary care data (VKA HR_{adj} 1.12 CI_{95} 1.01–1.24; APA HR_{adj} 1.06 CI_{95} 0.95–1.20).

Conclusion: Secondary care bleeding events are not completely recorded in primary care records and under-recording may be differential with respect to a variety of factors, including antithrombotic treatment. While the impact of under-recording on estimates of the comparative safety of antithrombotic drugs was limited, the extent of the under-recording suggests its potential impact should be considered, and ideally evaluated in future studies utilizing standalone primary care data.

Keywords: real-world data, data linkage, comparative effectiveness, secondary care, atrial fibrillation

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Background

Within the UK National Health Service (NHS), services which typically act as the first point of contact with the health care system are referred to as "primary care" and include general practitioners (GPs), dentists, pharmacists and optometrists. Within

the NHS, the GP also plays the role of gatekeeper, managing referral to most non-emergency secondary (hospital and community) and tertiary (highly specialized) health care services. As a result, the majority of the UK population are registered with a GP and the GP record is the patient's primary medical record.[1] In line with this, guidelines indicate that the details of secondary care encounters should be routinely communicated to an individual's GP practice in order to allow for these details to be recorded and ensure continuity of care.[2] Databases containing data collected in UK primary care have therefore been widely used as a stand-alone resource for research into medical conditions and the drugs used to treat them.[3]

More recently, the linkage of English secondary and primary care datasets has facilitated the conduct of studies exploring the extent to which secondary care events are coded in primary care records. A number of these studies have found coding to be suboptimal, with 17% of cancers, 34% of GI bleeds, 21% of myocardial infarctions, 22% of poisoning events and 9% of fractures recorded in the linked dataset not appearing in the primary care record.[4–7] These results suggest the use of primary care records as a stand-alone source for research into these conditions is unsuitable and may generate bias.

In order to explore the potential for UK primary care databases to generate real world evidence (RWE) on the safety and effectiveness of antithrombotic treatment, this study investigated the extent to which secondary care bleeds are coded in primary care records among a cohort of individuals with non-valvular atrial fibrillation (NVAF). The study also sought to understand the impact of incomplete recording on estimates of bleeding risk associated with antithrombotic treatment.

Methods

Data source

The study was carried out using a linked Clinical Practice Research Datalink (CPRD) – Hospital Episode Statistics (HES) dataset. This dataset combines anonymized medical-record data for patients registered with participating GPs in England (the CPRD dataset) with details of their admissions to NHS hospitals (the HES dataset). The linked dataset therefore includes longitudinal information on diagnoses, symptoms, laboratory tests and prescriptions issued by the GP in addition to information on referrals to specialists, hospital admission diagnoses, hospital procedures and deaths.[8] Clinical events in the CPRD are recorded using the "Read code" clinical coding system. Hospital discharge diagnoses in HES are recorded using the international classification of disease (ICD)–10 clinical coding system. Greater than 98% of the UK population are registered with a GP and individuals registered with a GP must opt out of data collection in order to be excluded from the CPRD dataset. Despite over-representing certain geographical areas of the UK, the CPRD has been found to be representative of the UK population with regard to sex, age and ethnicity.[8] HES captures information on all NHS hospital admissions occurring in England and on admissions to independent sector providers if funded by the NHS (est. 98–99% of hospital activity).[9]

Recording of secondary care bleeds in primary care data

The study population consisted of all adults with a diagnosis of atrial fibrillation recorded in the CPRD or HES who had at least one clinically relevant bleed recorded in either data source between first January 2003 and 31 January 2016 while receiving prescriptions for oral anticoagulant (OAC) treatment. Individuals with codes indicating their atrial fibrillation was valvular were excluded as despite sharing the same electrophysiological abnormality, the differing etiology of this valvular atrial fibrillation warrants the separate consideration of such individuals. Code lists defining atrial fibrillation, valvular conditions and clinically relevant bleeds are provided in the data supplement (Tables 1–6).

Within this population, all clinically relevant bleeding events recorded in the HES and the CPRD were identified using relevant diagnostic codes and classified according to the location in the body in which they occurred (Tables 5 and 6). We refer to "clinically relevant bleeds" to distinguish these from minor bleeds which are non-clinically consequential; such bleeds are not captured by our data source. The proportion of bleeds recorded in HES that had a corresponding record in the CPRD in the subsequent 12 weeks was calculated, overall and stratified by bleed location.

To identify factors associated with a HES bleed having a corresponding bleeding record coded in the CPRD in the

Table 1 ICD codes used to identify individuals with atrial fibrillation

ICD10_code	Diagnosis
I48	Atrial fibrillation and flutter
I48.0	Paroxysmal atrial fibrillation
I48.1	Persistent atrial fibrillation
I48.2	Chronic atrial fibrillation
I48.3	Typical atrial flutter
I48.4	Atypical atrial flutter
I48.9	Atrial fibrillation and atrial flutter, unspecified

Table 2 ICD codes used to identify and exclude individuals whose atrial fibrillation was valvular in nature

ICD10_code	Diagnosis
I05	Rheumatic mitral valve diseases
I05.0	Rheumatic mitral stenosis
I05.2	Rheumatic mitral stenosis with insufficiency
I05.8	Other rheumatic mitral valve diseases
I05.9	Rheumatic mitral valve disease, unspecified
I08	Multiple valve diseases
I08.0	Disorders of both mitral and aortic valves
I08.1	Disorders of both mitral and tricuspid valves
I08.3	Combined disorders of mitral, aortic and tricuspid valves
I08.8	Other multiple valve diseases
I08.9	Multiple valve disease, unspecified
T82.0	Mechanical complication of heart valve prosthesis
T82.6	Infection and inflammatory reaction due to cardiac valve prosthesis
T82.8	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts
T82.9	Unspecified complication of cardiac and vascular prosthetic device, implant and graft
Z95.2	Presence of prosthetic heart valve
Z95.4	Presence of other heart-valve replacement

Table 3 Read codes used to identify individuals with atrial fibrillation

Read code	Read term
14AN.00	H/O: atrial fibrillation
14AR.00	History of atrial flutter
3272.00	ECG: atrial fibrillation
3273.00	ECG: atrial flutter
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
7,936A00	Implant intravenous pacemaker for atrial fibrillation
793M100	Percutaneous transluminal ablation of atrial wall for atrial flutter
793M200	Percutaneous transluminal internal cardioversion NEC
793M300	Percutaneous transluminal ablation of conducting system of heart for atrial flutter NEC
8CMW200	Atrial fibrillation care pathway
8HTy.00	Referral to atrial fibrillation clinic
8OAD.00	Provision of written information about atrial fibrillation
9hF..00	Exception reporting: atrial fibrillation quality indicators
9hF1.00	Excepted from atrial fibrillation quality indicators: informed dissent
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
G573.00	Atrial fibrillation and flutter
G573000	Atrial fibrillation
G573100	Atrial flutter
G573200	Paroxysmal atrial fibrillation
G573300	Non-rheumatic atrial fibrillation
G573400	Permanent atrial fibrillation
G573500	Persistent atrial fibrillation
G573600	Paroxysmal atrial flutter
G573z00	Atrial fibrillation and flutter NOS

Abbreviations: ECG, electrocardiogram; NEC, not elsewhere classified; H/O, history of; NOS, not otherwise specified.

subsequent 12 weeks, generalized estimating equations (GEE) binary regression analysis was performed. The GEE analysis used a binomial distribution, a logit-link and an exchangeable correlation structure to account for the inclusion of repeat bleeds per individual. Bleed characteristics considered in the analysis included OAC treatment at the time of the bleed, bleed type, calendar period, period of week of bleed occurrence (weekday vs weekend). A range of patient characteristics were also considered for inclusion in the model, including age, sex, deprivation (English Index of Multiple Deprivation),[10] body mass index (BMI), stroke risk factors (history of stroke/TIA, systemic thromboembolism, congestive heart failure, vascular disease, hypertension, diabetes, CHA2DS2-VASc score), bleeding risk factors (bleeding history, liver disease, renal disease, modified HAS-BLED score) and concomitant medical treatment.

Impact of recording completeness on comparative safety of antithrombotic treatment

In order to further explore the impact under-recording of HES bleeds in primary care data can have on comparative safety and effectiveness analyses, a comparative safety analysis was carried out using two different data sources: a linked CPRD-HES data (linked analysis) and a CPRD only dataset (unlinked analysis). The analysis investigated the impact of using the different data sources on the relative hazard of subsequent bleeding across antithrombotic treatment strategies, within a population of individuals who had suffered a first bleed while using OACs.

For this analysis, the study population consisted of adults with a diagnosis of atrial fibrillation recorded in the CPRD or HES who had a clinically relevant bleed (index bleed) recorded in either data source between 1 January 2003 and 15 March 2012 which occurred while receiving prescriptions for an OAC. Patients were followed from index bleed until the earliest of either 15 March 2012, the date of leaving the database, or the date of death. Prescriptions for vitamin K antagonists (VKAs) or antiplatelet agents (APAs) issued following the first bleed were identified and used to stratify

Table 4 Read codes used to identify and exclude individuals whose atrial fibrillation was valvular in nature

Read code	Read term
7910200	Prosthetic replacement of mitral valve
7910211	Bjork–Shiley prosthetic replacement of mitral valve
7910212	Bjork–Shiley prosthetic replacement of mitral valve
7910213	Carpentier prosthetic replacement of mitral valve
7910214	Edwards prosthetic replacement of mitral valve
7910300	Replacement of mitral valve NEC
7910400	Mitral valvuloplasty NEC
7911200	Prosthetic replacement of aortic valve
7911300	Replacement of aortic valve NEC
7911500	Transapical aortic valve implantation
7911600	Transluminal aortic valve implantation
7914200	Prosthetic replacement of valve of heart NEC
7914211	Edwards prosthetic replacement of valve of heart
7914212	Starr prosthetic replacement of valve of heart
7914300	Replacement of valve of heart NEC
7914600	Replacement of truncal valve
7915000	Revision of plastic repair of mitral valve
7916000	Open mitral valvotomy
7917000	Closed mitral valvotomy
7919000	Percutaneous transluminal mitral valvotomy
7910.00	Plastic repair of mitral valve
7910.11	Mitral valvuloplasty
7910.12	Replacement of mitral valve
7910y00	Other specified plastic repair of mitral valve
7910z00	Plastic repair of mitral valve NOS
7911.12	Replacement of aortic valve
7914.11	Replacement of unspecified valve of heart
G11..00	Mitral valve diseases
G110.00	Mitral stenosis
G112.00	Mitral stenosis with insufficiency
G112.12	Mitral stenosis with incompetence
G112.13	Mitral stenosis with regurgitation
G113.00	Nonrheumatic mitral valve stenosis
G11z.00	Mitral valve disease NOS
G13..00	Diseases of mitral and aortic valves
G130.00	Mitral and aortic stenosis
G131.00	Mitral stenosis and aortic insufficiency
G131.13	Mitral stenosis and aortic incompetence
G131.14	Mitral stenosis and aortic regurgitation
G13y.00	Multiple mitral and aortic valve involvement
G13z.00	Mitral and aortic valve disease NOS
G540z00	Mitral valve disorders NOS
G544.00	Multiple valve diseases
G544100	Disorders of both mitral and tricuspid valves
G544200	Combined disorders of mitral, aortic and tricuspid valves
G544X00	Multiple valve disease, unspecified
Gyu1000	[X]Other mitral valve diseases
Gyu5500	[X]Other nonrheumatic mitral valve disorders
Gyu5D00	[X]Multiple valve disorders/diseases CE
P65..00	Congenital mitral stenosis
P650.00	Congenital mitral stenosis, unspecified
P65z.00	Congenital mitral stenosis NOS
SP00200	Mechanical complication of heart valve prosthesis
SyuK611	[X]Embolism from prosthetic heart valve
TB01200	Implant of heart valve prosthesis + complication, no blame
ZV43300	[V]Has artificial heart valve
ZV45H00	[V]Presence of prosthetic heart valve
ZVu6e00	[X]Presence of other heart valve replacement

Notes: [V] Supplementary factors influencing health status or contact with health services other than for illness (ICD). [X] Terms which have been added to the Read Codes in order to ensure that every ICD-10 code is cross-mapped to from a Read Code.

Abbreviations: NEC, not elsewhere classified; NOS, not otherwise specified.

each individuals' follow-up time into one of three antithrombotic treatment groups: VKA treatment, APA treatment, no antithrombotic treatment. Gaps in treatment of up to 60 days between two prescriptions from the same treatment group were considered to constitute continuous treatment. Cox proportional hazard regression models were used to compare the hazard of subsequent bleeding events across treatment groups in each population, including treatment group as a time varying covariate and controlling for the same patient and bleed characteristics outlined for the GEE analysis above. Hazard ratios are reported along with Wald 95% confidence intervals.

All analyses were carried out in [SAS/STAT] software (SAS Institute Inc., Cary, NC, USA).

Results

A total of 14,361 bleeds recorded in HES were identified among patients with NVAF receiving OAC treatment between 2003 and 2016. The proportion of HES bleeds with a corresponding bleed recorded in the CPRD increased from 12.5% in the first week following the HES bleed to 19.6% after 12 weeks (Table 7). Similar results, stratified by the location of the bleed, are provided in Table 8. A greater proportion of respiratory, intraarticular and intracranial bleeds had a consistent bleed code recorded in the CPRD within 12 weeks (30.1%, 40.7% and 39.2%, respectively) compared to bleeds in other locations, including GI bleeds (13.5%) and intraspinal bleeds (11.6%).

Patient characteristics in the linked and unlinked datasets are shown in Table 9. The results of the GEE regression model are provided in Table 10. Of the 14,361 bleeds recorded in HES, intracranial bleeds, bleeds resulting in weekend hospital admission, bleeds occurring longer ago, bleeds occurring during OAC treatment and bleeds occurring in individuals without a history of bleeding risk factors were more likely to have a corresponding bleed recorded in the CPRD in the 12 weeks after hospital admission.

After applying inclusion and exclusion criteria, 5,197 individuals were identified for inclusion in the Cox regression analyses using CPRD data only (Figure S1) and 7,063 individuals were identified for inclusion in the analysis using CPRD-HES linked data (Figure S2). On average, the population identified using linked CPRD-HES data was slightly older than the population identified using unlinked data only, and contained a greater proportion of females, individuals more recently diagnosed with NVAF, individuals with a history of stroke and bleeding risk factors and individuals with evidence of active cancer (Table 9). The index bleeds identified in the linked population occurred more recently and were more severe than those in the unlinked population,

Table 5 ICD codes defining clinically relevant hospital bleeds and their locations

ICD code	Description	Location
I85.0	Esophageal varices with bleeding	GI
K25.0	Gastric ulcer, acute with hemorrhage	GI
K25.2	Gastric ulcer, acute with both hemorrhage and perforation	GI
K25.4	Gastric ulcer, chronic or unspecified with hemorrhage	GI
K25.6	Chronic or unspecified with both hemorrhage and perforation	GI
K26.0	Duodenal ulcer, acute with hemorrhage	GI
K26.2	Duodenal ulcer, acute with both hemorrhage and perforation	GI
K26.4	Duodenal ulcer, chronic or unspecified with hemorrhage	GI
K26.6	Chronic or unspecified with both hemorrhage and perforation	GI
K27.0	Peptic ulcer, acute with hemorrhage	GI
K27.2	Peptic ulcer, acute with both hemorrhage and perforation	GI
K27.4	Peptic ulcer, chronic or unspecified with hemorrhage	GI
K27.6	Chronic or unspecified with both hemorrhage and perforation	GI
K28.0	Gastrojejunal ulcer, acute with hemorrhage	GI
K28.2	Acute with both hemorrhage and perforation	GI
K28.4	Gastrojejunal ulcer, chronic or unspecified with hemorrhage	GI
K28.6	Chronic or unspecified with both hemorrhage and perforation	GI
K29.0	Acute hemorrhagic gastritis	GI
K62.5	Hemorrhage of anus and rectum	GI
K92.0	Hematemesis	GI
K92.1	Melena	GI
K92.2	Gastrointestinal hemorrhage, unspecified	GI
I84.1	Internal hemorrhoids with other complications	GI
I84.3	External thrombosed hemorrhoids	GI
I84.4	External hemorrhoids with other complications	GI
I84.8	Unspecified hemorrhoids with other complications	GI
I98.3	Esophageal varices with bleeding in diseases classified elsewhere	GI
K22.6	Gastro-esophageal laceration-hemorrhage syndrome	GI
K31.8	Angiodysplasia of stomach and duodenum with hemorrhage	GI
K55.2	Angiodysplasia of the colon with bleeding	GI
K55.8	Angiodysplasia of the small intestine with hemorrhage	GI
K57.0	Diverticulosis of the small intestine with perforation, abscess and bleeding	GI
K57.1	Diverticulosis of the small intestine without perforation and abscess, with bleeding	GI
K57.2	Diverticulosis of the colon with perforation, abscess and bleeding	GI
K57.3	Diverticulosis of the colon without perforation or abscess, with bleeding	GI
K57.4	Diverticular disease of both the small intestine and the large intestine with perforation, abscess and bleeding	GI
K57.5	Diverticular disease of both the small intestine and the large intestine without perforation or abscess, with bleeding	GI
K57.8	Diverticular disease of intestine, part unspecified, with perforation, abscess and bleeding	GI
K57.9	Diverticular disease of intestine, part unspecified, without perforation or abscess, with bleeding	GI
I60	Subarachnoid hemorrhage	IC
I60.0	Subarachnoid hemorrhage from carotid siphon and bifurcation	IC
I60.1	Subarachnoid hemorrhage from middle cerebral artery	IC
I60.2	Subarachnoid hemorrhage from anterior communicating artery	IC
I60.3	Subarachnoid hemorrhage from posterior communicating artery	IC
I60.4	Subarachnoid hemorrhage from basilar artery	IC
I60.5	Subarachnoid hemorrhage from vertebral artery	IC
I60.6	Subarachnoid hemorrhage from other intracranial arteries	IC
I60.7	Subarachnoid hemorrhage from intracranial artery, unspecified	IC
I60.8	Other subarachnoid hemorrhage	IC
I60.9	Subarachnoid hemorrhage, unspecified	IC
I61	Intracerebral hemorrhage	IC
I61.0	Intracerebral hemorrhage in hemisphere, subcortical	IC
I61.1	Intracerebral hemorrhage in hemisphere, cortical	IC
I61.2	Intracerebral hemorrhage in hemisphere, unspecified	IC
I61.3	Intracerebral hemorrhage in brain stem	IC

(*Continued*)

Table 5 (*Continued*)

ICD code	Description	Location
I61.4	Intracerebral hemorrhage in cerebellum	IC
I61.5	Intracerebral hemorrhage, intraventricular	IC
I61.6	Intracerebral hemorrhage, multiple localized	IC
I61.8	Other intracerebral hemorrhage	IC
I61.9	Intracerebral hemorrhage, unspecified	IC
I62	Other nontraumatic intracranial hemorrhage	IC
I62.0	Subdural hemorrhage (acute) (nontraumatic)	IC
I62.1	Nontraumatic extradural hemorrhage	IC
I62.9	Intracranial hemorrhage (nontraumatic), unspecified	IC
I69.0	Sequelae of subarachnoid hemorrhage	IC
I69.1	Sequelae of intracerebral hemorrhage	IC
I69.2	Sequelae of other nontraumatic intracranial hemorrhage	IC
S06.5	Traumatic subdural hemorrhage	IC
S06.6	Traumatic subarachnoid hemorrhage	IC
S06.4	Epidural hemorrhage	IS
G95.1	Vascular myelopathies (including hematomyelia)	IS
H21.0	Hyphema	IO
H31.41	Hemorrhagic choroidal detachment	IO
H35.73	Hemorrhagic detachment of retinal pigment epithelium	IO
H44.81	Hemophthalmos	IO
H47.02	Hemorrhage in optic nerve sheath	IO
H31.3	Choroidal hemorrhage and rupture	IO
H35.6	Retinal hemorrhage	IO
H43.1	Vitreous hemorrhage	IO
H45.0	Vitreous hemorrhage in diseases classified elsewhere	IO
N42.1	Congestion and hemorrhage of prostate	U
N02	Recurrent and persistent hematuria	U
N02.6	Recurrent and persistent hematuria, dense deposit disease	U
N02.8	Recurrent and persistent hematuria, other	U
N02.9	Recurrent and persistent hematuria, unspecified	U
R31	Unspecified hematuria	U
R31.0	Gross hematuria	U
R31.9	Hematuria, unspecified	U
M25.0	Hemarthrosis	IA
R04	Hemorrhage from respiratory passages	R
R04.1	Hemorrhage from throat	R
J94.2	Hemothorax	R
R04.0	Epistaxis	R
R04.2	Hemoptysis	R
R04.8	Hemorrhage from other sites in respiratory passages	R
R04.9	Hemorrhage from respiratory passages, unspecified	R
I23.0	Hemopericardium as current complication following acute myocardial infarction	PC
I31.2	Hemopericardium, not elsewhere classified	PC
S26.0	Injury of heart with hemopericardium	PC
N83.6	Hematosalpinx	GYN
N85.7	Hematometra	GYN
N89.7	Hematocolpos	GYN
N92.1	Excessive and frequent menstruation with irregular cycle	GYN
N93	Other abnormal uterine and vaginal bleeding	GYN
N93.8	Other specified abnormal uterine and vaginal bleeding	GYN
N93.9	Abnormal uterine and vaginal bleeding, unspecified	GYN
N95.0	Postmenopausal bleeding	GYN
D69	Purpura and other hemorrhagic conditions	CUT
I71.3	Abdominal aortic aneurysm, ruptured	RP
I71.5	Thoracoabdominal aortic aneurysm, ruptured	RP
K66.1	Hemoperitoneum	RP

(*Continued*)

Table 5 (*Continued*)

ICD code	Description	Location
H11.3	Conjunctival hemorrhage	OTH
R31.1	Benign essential microscopic hematuria	OTH
H92.2	Otorrhagia	OTH
I71.1	Thoracic aortic aneurysm, ruptured	OTH
I71.8	Aortic aneurysm of unspecified site, ruptured	OTH
E07.8	Other specified disorders of thyroid (including hemorrhage of thyroid)	OTH
E27.4	Other and unspecified adrenocortical insufficiency (including adrenal hemorrhage)	OTH
M62.2	Ischemic infarction of muscle (compartment syndrome, non-traumatic)	COMP
T79.6	Traumatic ischemia of muscle (compartment syndrome)	COMP

Abbreviations: IC, intracranial bleed; GI, gastrointestinal bleed; IS, intraspinal bleed; IO, intraocular bleed; PC, pericardial bleed; U, urinary bleed; IA, intraarticular bleed; R, respiratory; GYN, gynecological bleed; COMP, compartment syndrome; CUT, cutaneous/subcutaneous hemorrhage; RP, retroperitoneal bleed; OTH, other bleed.

Table 6 Read codes identifying bleeds in the CPRD

Readcode	Description	Location
158..12	Vaginal bleeding	GYN
16R..00	Bleeding symptom	OTH
1928.00	Bleeding gums	GUM
196B.00	Painful rectal bleeding	GI
196C.00	Painless rectal bleeding	GI
1C6..00	Nose bleed symptom	R
1C62.00	Has nose bleeds - epistaxis	R
1C6Z.00	Nose bleed symptom NOS	R
2BB5.00	O/E - retinal haemorrhages	IO
2BB8.00	O/E - vitreous haemorrhages	IO
7017000.00	Evacuation of subdural haematoma	IC
7404.00	Surgical arrest of bleeding from internal nose	R
F42y.11	Haemorrhage - retinal	IO
F42y400	Subretinal haemorrhage	IO
F42y500	Retinal haemorrhage NOS	IO
F444000	Hyphaema	IO
F4K2800	Vitreous haemorrhage	IO
G60..00	Subarachnoid haemorrhage	IC
G61..00	Intracerebral haemorrhage	IC
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage	IC
G61..12	Stroke due to intracerebral haemorrhage	IC
G610.00	Cortical haemorrhage	IC
G612.00	Basal nucleus haemorrhage	IC
G613.00	Cerebellar haemorrhage	IC
G617.00	Intracerebral haemorrhage, intraventricular	IC
G61X000	Left sided intracerebral haemorrhage, unspecified	IC
G61X100	Right sided intracerebral haemorrhage, unspecified	IC
G61z.00	Intracerebral haemorrhage NOS	IC
G62..00	Other and unspecified intracranial haemorrhage	IC
G620.00	Extradural haemorrhage - nontraumatic	IC
G621.00	Subdural haemorrhage - nontraumatic	IC
G622.00	Subdural haematoma - nontraumatic	IC
G623.00	Subdural haemorrhage NOS	IC
G62z.00	Intracranial haemorrhage NOS	IC
G850.00	Oesophageal varices with bleeding	GI
G8y0.00	Haemorrhage NOS	OTH
Gyu6200	[X]Other intracerebral haemorrhage	IC
J110100	Acute gastric ulcer with haemorrhage	GI
J110111	Bleeding acute gastric ulcer	GI
J121100	Chronic duodenal ulcer with haemorrhage	GI
J121111	Bleeding chronic duodenal ulcer	GI
J130100	Acute peptic ulcer with haemorrhage	GI
J150000	Acute haemorrhagic gastritis	GI
J510900	Bleeding diverticulosis	GI
J573.00	Haemorrhage of rectum and anus	GI
J573.11	Bleeding PR	GI
J573000	Rectal haemorrhage	GI
J573011	Rectal bleeding	GI
J573012	PRB - Rectal bleeding	GI
J68..00	Gastrointestinal haemorrhage	GI
J681.00	Melaena	GI
J68z.00	Gastrointestinal haemorrhage unspecified	GI
J68z.11	GIB - Gastrointestinal bleeding	GI
J68z000	Gastric haemorrhage NOS	GI
J68z100	Intestinal haemorrhage NOS	GI
J68z200	Upper gastrointestinal haemorrhage	GI
J68zz00	Gastrointestinal tract haemorrhage NOS	GI
K0A2.00	Recurrent and persistent haematuria	U
K197.00	Haematuria	U
K197000	Painless haematuria	U
K197100	Painful haematuria	U
K197300	Frank haematuria	U
K19y400	Bleeding from urethra	U
K19y411	Urethral bleeding	U
K31y000	Breast haematoma due to nontraumatic cause	OTH
K56y111	Bleeding - vaginal NOS	GYN
K56y112	BPV - Vaginal bleeding	GYN
K5E..00	Other abnormal uterine and vaginal bleeding	GYN
K5E2.00	Abnormal vaginal bleeding, unspecified	GYN
N091.00	Haemarthrosis	IA
N091611	Haemarthrosis of the knee	IA
N091M00	Haemarthrosis of knee	IA
N091z00	Haemarthrosis NOS	IA
R047.00	[D]Epistaxis	R
R047.11	[D]Nosebleed	R
R063.00	[D]Haemoptysis	R

(*Continued*)

Table 6 (*Continued*)

Readcode	Description	Location
R063100	[D]Pulmonary haemorrhage NOS	R
R063z00	[D]Haemoptysis NOS	R
S62..00	Cerebral haemorrhage following injury	IC
S62..11	Extradural haemorrhage following injury	IC
S62..13	Subdural haemorrhage following injury	IC
S622.00	Closed traumatic subdural haemorrhage	IC
S629.00	Traumatic subdural haematoma	IC
S62A.00	Traumatic extradural haematoma	IC
S63..00	Other cerebral haemorrhage following injury	IC
S780500	Retroperitoneal haematoma	RP
SE...11	Haematoma with intact skin	CUT
SE46.00	Traumatic haematoma	OTH
SE4z.11	Haematoma NOS	OTH
SK02.00	Secondary and recurrent haemorrhage	OTH
SK0y.11	Anterior compartment syndrome	COMP
SK0y.12	Compartment syndrome	COMP
SK0y700	Compartment syndrome	COMP
SP21.00	Peri-operative haemorrhage or haematoma	OTH
SP21.12	Haemorrhage - postoperative	OTH

Notes: [D] diagnosis. [X] Terms which have been added to the Read Codes in order to ensure that every ICD-10 code is cross-mapped to from a Read Code.
Abbreviations: O/E, on examination; PRB, per-rectal bleeding; PR, per-rectum; NOS, not otherwise specified; BPV, bleeding per vagina; IC, intracranial bleed; GI, gastrointestinal bleed; IS, intraspinal bleed; IO, intraocular bleed; PC, pericardial bleed; U, urinary bleed; IA, intraarticular bleed; R, respiratory; GYN, gynecological bleed; COMP, compartment syndrome; CUT, cutaneous/subcutaneous hemorrhage; RP, retroperitoneal bleed; GUM, gum bleed; OTH, other bleed.

Table 7 HES bleeds with a corresponding bleed recorded in the CPRD in the subsequent 12 weeks

Bleeds in HES (n=14,361)	Corresponding bleed recorded in CPRD N (%)	
Weeks after bleed		
+1 (0–7 days)	1,799	(12.5)
+2 (0–14 days)	2,110	(14.7)
+4 (0–28 days)	2,372	(16.5)
+6 (0–42 days)	2,543	(17.7)
+8 (0–56 days)	2,653	(18.5)
+10 (0–70 days)	2,748	(19.1)
+12 (0–84 days)	2,822	(19.6)

Abbreviations: HES, hospital episode statistics; CPRD, Clinical Practice Research Datalink.

Table 8 HES bleeds with direct, plausible or possible supporting evidence in the CPRD within 12 weeks, by location of HES bleed

Bleeds in HES	Corresponding bleed recorded in CPRD N (%)	
Location		
Total (n=14,361)	2,822	(19.6)
Intracranial bleed (n=1,713)	620	(39.2)
GI bleed (n=7,797)	1,051	(13.5)
Intraspinal bleed (n=43)	5	(11.6)
Intraocular bleed, major (n=7)	<5	(NR)
Intraocular bleed, not major (n=82)	13	(15.8)
Pericardial bleed (n<5)	<5	(NR)
Urinary bleed (n=2,296)	449	(19.6)
Intraarticular bleed (n=162)	66	(40.7)
Respiratory bleed, major (n<5)	<5	(NR)
Respiratory bleed, not major (n=1,984)	597	(30.1)
Gynecological bleed (n<5)	<5	(NR)
Compartment syndrome (n=39)	7	(17.9)
Cutaneous/subcutaneous hemorrhage (n<5)	<5	(NR)
Retroperitoneal bleed (n=84)	<5	(NR)
Intraabdominal retroperitoneal bleed (n=41)	11	(26.8)
Gum bleed (n<5)	<5	(NR)
Other bleed (n=107)	<5	(NR)

Abbreviations: HES, hospital episode statistics; CPRD, Clinical Practice Research Datalink; GI, gastrointestinal; NR, not reported.

with a greater proportion of gastrointestinal and intracranial bleeds identified (Table 9).

Figure 1 shows the cumulative incidence of bleeding in the unlinked primary care data and the linked primary and secondary care dataset. Adjusting for statistically significant differences in the above characteristics across treatment groups within each population, we found that the hazard of subsequent bleeding associated with VKAs and APAs relative to no antithrombotic treatment were 12% and 6% higher, respectively, when using the unlinked primary care data (VKA $HR_{adj\ 1.12}$ CI_{95} 1.01–1.24; APA $HR_{adj\ 1.06}$ CI_{95} 0.95–1.20) and were 6% and 8% higher, respectively, when using the linked primary and secondary care dataset (VKA $HR_{adj\ 1.06}$ CI_{95} 0.96–1.16; APA $HR_{adj\ 1.08}$ CI_{95} 0.96–1.21).

Discussion

This study found that the coding of hospital bleeds in the primary care record was incomplete, with less than 20% of individuals with an inpatient diagnosis for a bleed having a bleed coded in their primary care record in the subsequent 12 weeks. Moreover, differences with respect to key clinical and demographic characteristics were observed between patients identified from primary care vs linked data. While under-recording was found to be differential with regard to a number of factors, including OAC treatment, the incomplete recording of bleeds in primary care was not found to considerably bias estimates of the risk of bleeding associated with antithrombotic treatment.

The low proportion of secondary care bleeds having a corresponding bleed recorded in primary care indicates that as much as 80% of such bleeds could be excluded from a study which utilized primary care data only to identify bleeds. Using primary care data alone will therefore result in false-negative misclassification of exposure, outcome and/or covariate status. The impact of such misclassification is

Table 9 Patient characteristics in the linked and unlinked datasets used in the Cox regression analyses

	Linked CPRD-HES n=7,063	Unlinked CPRD n=5,197
Age, mean (SD)	76.7 (9.5)	76.0 (9.4)
Female, %	45.9	42.2
NVAF characteristics		
NVAF duration (from first AF diagnosis to index bleed)	24.9 (24.2)	29.1 (24.1)
NVAF duration (categorized), %		
<3 months, %	19.0	8.4
3–6 months, %	8.4	8.0
6–9 months, %	7.1	7.7
9–12 months, %	5.6	6.6
≥12 months, %	59.8	69.3
Newly diagnosed NVAF (past 12 months), %	40.2	30.7
Duration of available baseline period (months), mean (SD)	465 (213)	476 (208)
Duration of follow-up period in months, mean (SD)	59.7 (40.7)	56.0 (35.9)
Index bleed characteristics		
Calendar year of index bleed, %		
2003–2007	52.3	59.0
2008–2012	47.7	41.0
Site of initial bleed, %		
Gastrointestinal	39.5	29.6
Respiratory	20.2	23.6
Urinary	20.0	23.9
Intracranial	7.4	5.0
Intraocular	1.7	2.3
Gynecological	1.7	2.7
Intraarticular	1.4	1.5
Gum	0.7	1.2
Retroperitoneal	0.5	0
All other bleeds	7.0	10.2
Major bleed, %	17.2	8.3
History of bleeding risk factors		
Bleeding history/predisposition, %	55.1	42.2
Liver disease, %	1.7	0.5
Renal disease, %	23.5	25.6
Drugs predisposing to bleeding[a], %	13.2	18.1
Modified HAS-BLED score (0–8), mean (SD)	3.0 (1.1)	2.6 (1.2)
Serum creatinine, mean (SD)	103.7 (52.1)	104.9 (51.3)
Glomerular filtration rate, mean (SD)	0.34 (0.4)	0.34 (0.3)
History of stroke risk factors		
Stroke/TIA, %	24.6	20.4
Systemic thromboembolism, %	1.4	0.7
Congestive heart failure, %	28.2	21.8
Vascular diseases, %	25.2	38.2
Hypertension, %	90.0	60.9
Diabetes, %	16.4	15.7
CHAD2 score (0 to 6), mean (SD)	2.5 (1.3)	2.0 (1.3)
CHA2DS2-VASc score (0–10), mean (SD)	4.1 (1.6)	3.7 (1.7)
Other medical histories		
Smoking status, %		
Current	14.3	15.2
Past or never[b]	2.5	2.9
Unknown	84.2	83.0
BMI, mean (SD)	27.4 (5.7)	28.1 (5.8)
Underweight, %	2.2	1.6
Normal, %	30.5	20.0
Obese, %	23.5	21.6
Overweight, %	35.3	25.0
Unknown, %	8.5	31.8
Weight, mean (SD)	78.7 (18.4)	81.0 (19.4)
Active cancer (current/prior 12 months), %	9.6	4.9
Falls, %	0.1	0.2

Notes: [a]Prescriptions within 90 days prior to index bleed. [b]May overlap with current smoker.

Abbreviations: HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; HES, hospital episode statistics; CPRD, Clinical Practice Research Datalink; AF, atrial fibrillation; NVAF, non-valvular atrial fibrillation; BMI, body mass index; TIA, transient ischemic attack.

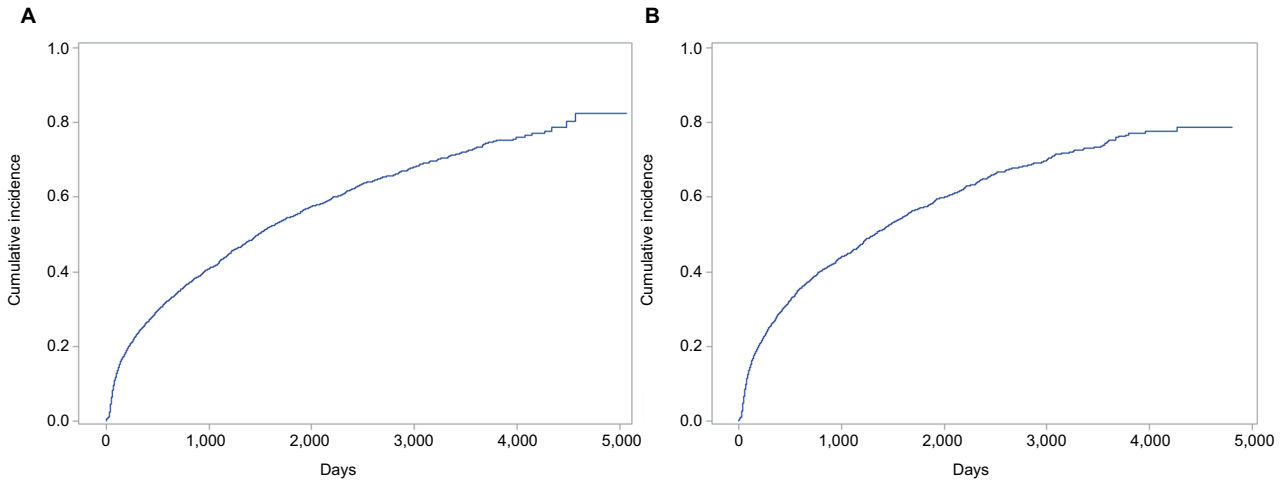

Figure 1 Cumulative incidence of bleeding in the unlinked primary care data (**A**) and the linked primary and secondary care dataset (**B**).

unpredictable and dependent on the study question. While our stratified and GEE analyses suggest that incompleteness varies by a range of factors including OAC treatment, calendar time and bleed location/type, our comparative safety analyses investigating the risk of subsequent bleeding associated with antithrombotic treatment illustrates that for certain study questions the impact on estimates of comparative safety or effectiveness may be small. Despite this, given the extent of under-recording and observed differences in patient characteristics, potential bias introduced through differential misclassification by these and other factors should be taken into consideration in interpreting the results of studies which have used primary care data only to identify bleeds[11,12] and in the planning of future studies.

Of GP practices contributing to the CPRD, 57% are eligible for linkage with HES, and no individuals registered with Scottish, Welsh or Northern Irish practices are eligible.[13] As a result, the use of a HES linked CPRD dataset can have a considerable impact on the generalizability and sample size available for a given study. Given our observation that the impact of under-recording on relative measures of safety or effectiveness can be limited, the decision to use unlinked CPRD vs HES-linked CPRD data must be made on a study specific basis, based on a comparison of the anticipated value that the HES data can add against the reduction in sample size and generalizability it enforces. Based on the extent of under-recording of secondary care bleeding events in primary care data reported here, and the finding that the HR of subsequent bleeding for VKAs compared to no antithrombotic treatment was slightly higher when using unlinked CPRD data, we suggest that for studies in which bleeding is a key variable, HES linked data is used; at a minimum, to illustrate that findings in the HES-linked data are similar to those in the unlinked data.

Our finding that the odds of a HES bleed having a corresponding CPRD bleed has decreased over time (Table 10) is notable as it suggests that the quality of recording in primary care datasets has decreased over time. This is an interesting finding as it suggests recent efforts to improve and standardize the communication of discharge details between secondary and primary care (eDischarge summaries,[2] have yet to make an impact. There is a possibility that the decrease in recording over time may represent a change in recording practices rather than a decrease in the quality of recording, as we used specific Read codes related to a bleed in the CPRD to assess consistency with HES data; however, there may have been other Read codes recorded that suggest a bleed occurred (eg, a code for a medical condition for which bleeding is a common symptom). A previous study investigating recording of upper gastrointestinal bleeds in the CPRD and HES included a range of "probable" and "possible" bleed Read codes and found supporting evidence for a much higher percentage of HES bleeds in the CPRD (66%).[5] Further, in clinical practice, some Read codes may have "free text" information recorded against them confirming a bleed occurred. These "free text" data consist of unstandardized text which can be used to elaborate on the information contained in the Read code. Free text data are not currently made available for research purposes; however, they are available to individuals involved in the clinical care of patients. While the information contained in related Read codes and the free text may therefore confirm bleeds in some of the cases we have identified, given the magnitude of uncoded secondary care events it is likely that a clinically relevant proportion of individuals did not have their bleed recorded anywhere in their primary care record. These findings are in line with those of a number of studies that have identified shortcomings in communication

Table 10 Generalized estimating equations (GEE) binary regression analysis investigating factors associated with a HES bleed being recorded in the CPRD

Variables		OR	95% CI
Day of week	Weekday (reference)	1	–
	Weekend	1.25	(1.12–1.39)
Calendar period	2003–2005	1.43	(1.19–1.71)
	2006–2008	1.31	(1.12–1.52)
	2009–2011	1.09	(0.93–1.26)
	2012–2016 (reference)	1	–
OAC treatment at time of index bleed	No (reference)	1	–
	Yes	2.26	(1.58–3.23)
Bleed type	Intracranial major (reference)	1	–
	Extracranial major	0.39	(0.32–0.48)
	GI CRNMB leading to hospitalization	0.29	(0.24–0.35)
	GI CRNMB not leading to hospitalization	0.32	(0.24–0.43)
	Other CRNMB leading to hospitalization	0.44	(0.34–0.56)
	Other CRNMB not leading to hospitalization	0.48	(0.37–0.63)
History of GI ulceration, GI bleeding or intracranial hemorrhage	No (reference)	1	–
	Yes	0.75	(0.62–0.91)

Notes: Time since NVAF diagnosis also adjusted for in the analysis.
Abbreviations: HES, hospital episode statistics; CPRD, Clinical Practice Research Datalink; OAC, oral anticoagulant; GI, gastrointestinal; CRNMB, clinically relevant non-major bleed; NVAF, non-valvular atrial fibrillation.

during transition of care between secondary and primary care and which have highlighted the safety issues that may result from them.[14–21] From a research perspective, the unavailability of free text and non-specificity of the "possible" and "probable" codes included by Crooks et al[5] mean that neither represent feasible approaches to identifying bleeding events in stand-alone primary care data and the high proportions of unreported data we report remain relevant.

The observation that the odds of a HES bleed having a corresponding CPRD bleed is higher for bleeds admitted at the weekend is of interest given the publicity surrounding so-called "weekend effects" in the UK, whereby individuals admitted to hospital at the weekend are more likely to have poor outcomes. It may be possible that admission for bleeds at weekends are more likely to be recorded in the CPRD due to their association with poorer outcomes and therefore being more clinically relevant. Previous methodological work exploring the accuracy of HES data for exploring weekend effects has found that events recorded in HES data on weekdays are more likely to be prevalent events inappropriately recorded as incident events and that this may partly explain the better outcomes observed following these events.[22] Our finding that HES bleeds admitted on weekdays are less likely to have a corresponding bleed record in the CPRD may therefore reflect the fact that a greater proportion of the weekday admissions are not being recorded by GPs as they are not truly incident bleeds.

Beyond the weekend effect, the potential for inaccurate recording of incident events in HES is an important consideration in interpreting our findings, as thus far we have considered HES to represent a "gold standard" for recording of secondary care events and any events not recorded in the CPRD to represent under-recording in primary care. Inaccuracy in HES coding has been reported previously for a number of event types; however, since the Payment by Results system was introduced in 2004 the average accuracy of coding has been reported to be 96.0% (interquartile range: 89.3–96.2%), P=0.020).[23] Notably, this figure has been derived across a range of types of event and most of the studies contributing to this figure focused on the accuracy of ICD coding at the four digit ICD code level. This latter point is important as most of the bleeding ICD codes we have investigated would still have been captured as bleeds had they been miscoded at the four digit level but not at the three digit level. While some of the 80% of secondary care events not coded in the CPRD may therefore not have been true incident bleeds, we believe it is unlikely that a substantial proportion were. An additional limitation of our study is that it explores only the sensitivity of recording in primary care, but does not explore the specificity. In utilizing the CPRD to investigate bleeding events it is important that the potential for false positive classification of bleeds is given consideration.

A further limitation is that our descriptive analyses do not account for extended hospital stays and deaths. That is,

9% of individuals were not discharged from hospital within the 12 weeks following their index bleed. Such individuals may therefore have supporting evidence recorded later, upon discharge from hospital. Removing undischarged individuals from the denominator has a minimal impact on results, increasing the proportion with supporting evidence recorded to 21.5%. Among the 14,361 individuals with an index bleed, 16% died during the 12 week follow-up. While individuals who died during the 12 week follow-up do not have the same opportunity to have supporting evidence recorded, this is still notable from a methodological point of view as a study using primary care data may not capture bleeds presenting in secondary care and resulting in deaths within 12 weeks.

Conclusion

Our results add to the evidence base suggesting secondary care events are not completely recorded in primary care records, and further that under-recording of bleeding events is differential with respect to a variety of factors, including treatment. While the impacts of under-recording on estimates of the comparative safety of antithrombotic drugs obtained from stand-alone primary care data were small, the extent of the under-recording suggests its potential impact should be considered, and ideally evaluated in future studies utilizing stand-alone primary care data.

Disclosure

SR and LM are full-time employees of Bristol-Myers Squibb, and SR is a shareholder of Bristol-Myers Squibb. CJS and MS are full-time employees of PHMR, PHMR received financial support for the work described in this manuscript from Bristol-Myers Squibb. The authors report no other conflicts of interest in this work.

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Supplementary material

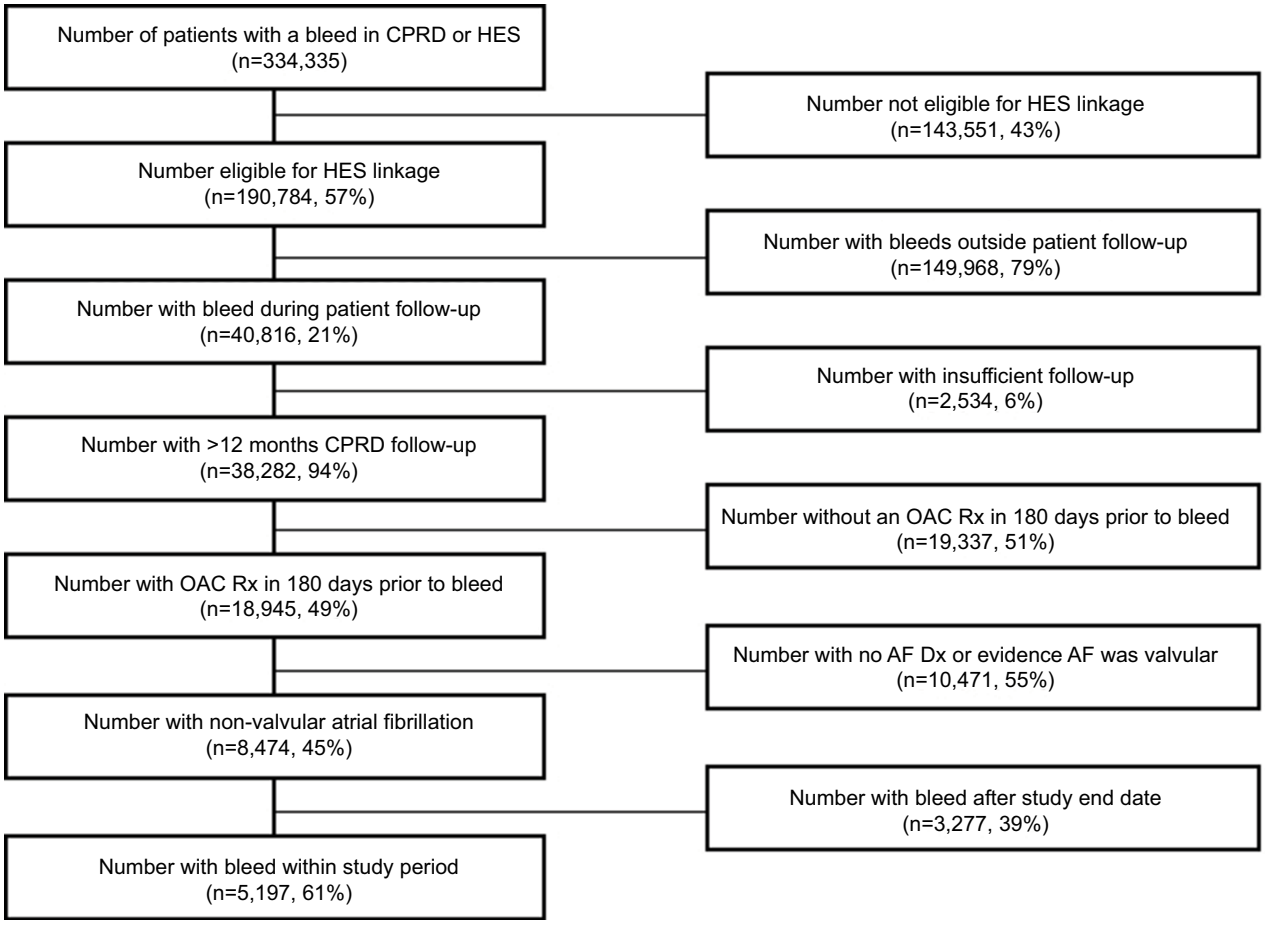

Figure S1 Derivation of the study population for the Cox proportional hazards regression analysis using CPRD data only. Percentages shown use the total number of individuals at the next highest level in the flow as their denominator.

Abbreviations: CPRD, Clinical Practice Research Database; HES, hospital episode statistics; OAC, oral anticoagulant; Rx, prescription; Dx, diagnosis.

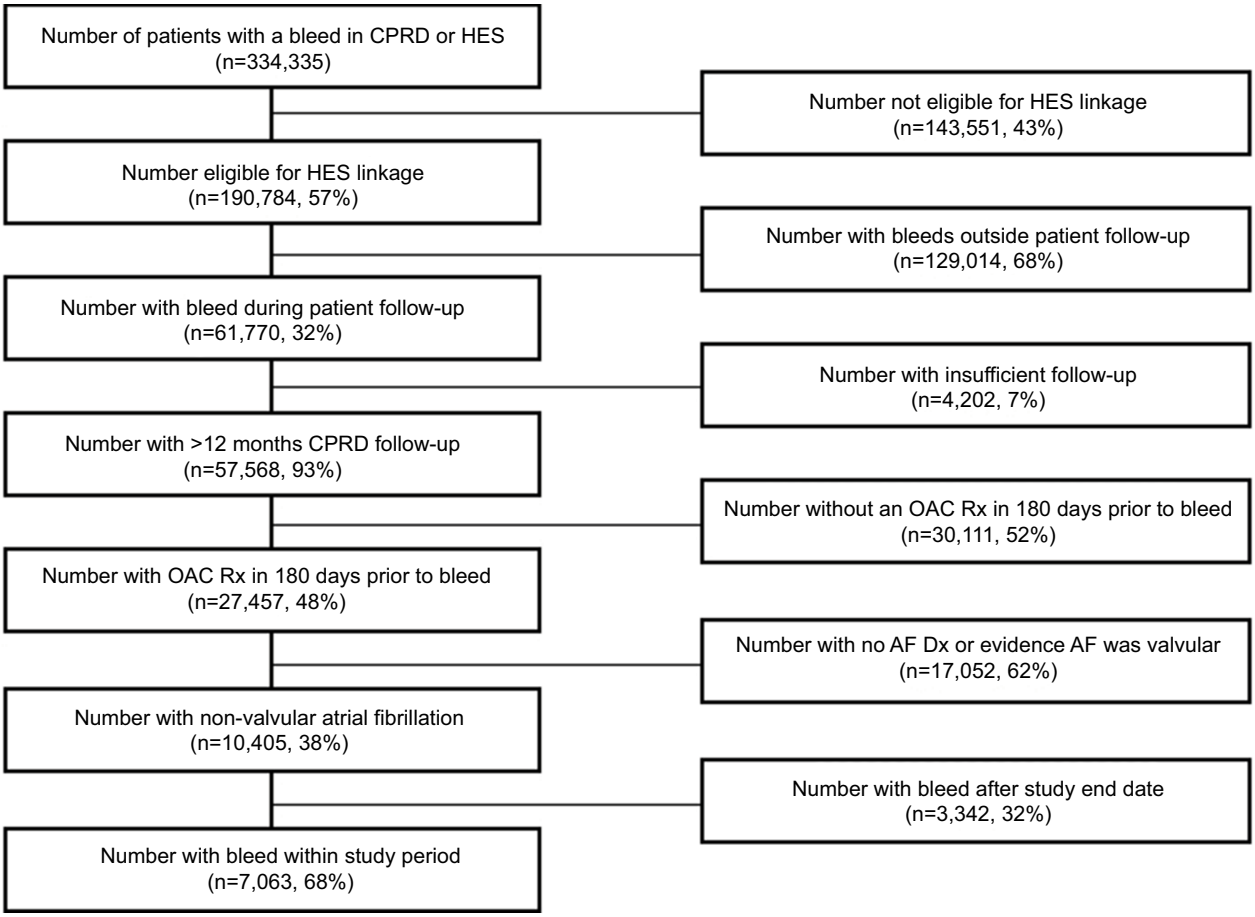

Figure S2 Derivation of the study population for the Cox proportional hazards regression analysis using linked CPRD-HES data. Percentages shown use the total number of individuals at the next highest level in the flow as their denominator.

Abbreviations: CPRD, Clinical Practice Research Database; HES, hospital episode statistics; OAC, oral anticoagulant; Rx, prescription; Dx, diagnosis.