ORIGINAL RESEARCH

Bleeding After Hospital Discharge Following Acute Coronary Syndrome: Incidence, Types, Timing, and Predictors

Nafiu Ismail, MPH; Kelvin P. Jordan, PhD; Umesh T. Kadam, PhD; John J. Edwards, PhD; Tim Kinnaird, MD; Mamas A. Mamas, PhD

***Background*—**The incidence and predictors of bleeding after acute coronary syndrome are unclear within the real-world setting. Our objective was to determine the incidence, types, timing, and predictors of bleeding complications following hospital discharge after acute coronary syndrome.

***Methods and Results*—**We used the Clinical Practice Research Datalink, with linkage to Hospital Episode Statistics, to determine the incidence, timing, and types of bleeding events within 12 months after hospital discharge for acute coronary syndrome. We assessed independent associations between postdischarge bleeding and baseline patient characteristics using a competing risk regression model, accounting for death as a competing event. Among 27 660 patients surviving to hospital discharge, 3620 (13%) experienced bleeding complications at a median time of 123 days (interquartile range, 45–223 days) after discharge. The incidence of bleeding was 162/1000 person-years (95% CI, 157–167/1000 person-years) within the first 12 months after hospital discharge. Bruising (949 bleeds [26%]) was the most common type of first bleeding event, followed by gastrointestinal bleed (705 bleeds [20%]), whereas intracranial bleed was relatively rare (81 bleeds [2%]). Significant predictors of postdischarge bleeding included history of bleeding complication, oral anticoagulant prescription, history of peripheral vascular disease, chronic obstructive pulmonary disease, and advanced age (>80 years). Predictors for postdischarge bleeding varied, depending on the anatomic site of the bleeding event.

***Conclusions*—**Bleeding complications after hospital discharge for acute coronary syndrome are common. Patients who experience these bleeding events have distinct baseline characteristics, which vary by anatomic site of the bleed. These characteristics can inform risk-benefit considerations in deciding on favorable combination and duration of secondary antithrombotic therapy. **(*J Am Heart Assoc*. 2019;8:e013679. DOI: 10.1161/JAHA.119.013679.)**

Key Words: hemorrhage • incidence • postdischarge • real world • risk factors • sites

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The management of acute coronary syndrome (ACS) with antithrombotic medications achieves the desired goal of reducing the risk of future ischemic events. But these reductions are accompanied by bleeding complications.[1]

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Accompanying Data S1 and Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013679

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In clinical trials, the incidence of major bleeding complications is reported to be between 1% and 10%, depending on the bleeding definition used,[2–4] with observational studies reporting incidences of between 2.8%[5] and 11%.[6] However, the emphasis in most of these studies has been on major in-hospital or 30-day bleeding events (a composite of in-hospital and postdischarge events), with little consideration for events in the longer term after hospital discharge. After hospital discharge, patients with ACS often remain on dual antiplatelet therapy for up to a year, and aspirin indefinitely, so their risk of bleeding complications persists in the longer term.[7]

Major in-hospital bleeding has been associated with sociodemographic characteristics, cardiovascular and noncardiovascular comorbidities, and pharmacological and procedural characteristics,[8–10] leading to the development of risk scoring algorithms that stratify patients into risk profiles for these bleeding events.[8–10] However, it is unclear whether these characteristics are also predictive of bleeding events after hospital discharge. For example, procedural characteristics may become less relevant in predicting the risk of postdischarge bleeding events, whereas patient

Clinical Perspective

What Is New?

- Bleeds after hospital discharge for acute coronary syndrome are common, with bruising and gastrointestinal bleeds the most common.
- History of bleeding complications, chronic obstructive pulmonary disease, peripheral vascular disease, management with oral anticoagulants after hospital discharge, and aged >80 years were the most significant determinants of postdischarge bleeding.
- Predictors for postdischarge bleeding varied, depending on the anatomic site of the bleeding event.

What Are the Clinical Implications?

- These baseline predictors can assist clinicians in identifying patients at risk of bleeding complications after hospital discharge so that longer-term antithrombotic therapy can be tailored to fit an individual patient's risk profile.

characteristics and pharmacological choice may become more important after discharge. The few studies that have reported on characteristics associated with postdischarge bleeding events have mostly been randomized controlled trials,[11–13] where minor bleeding events, high-risk multimorbid "real-world" patients, and those receiving long-term oral anticoagulation (a potential risk factor for bleeding) have been excluded. Therefore, the generalizability of these studies to the wider population with ACS in the real-world setting is unclear.

While the nature of in-hospital bleeds and their predictors have been well described,[8–10,14] the incidence, types, and predictors of bleeding events that occur after hospital discharge are unclear. The first objective of this study was to determine the incidence, timing, and types of bleeding events within 12 months after hospital discharge. The second objective was to determine the predictors of bleeding events and site-specific bleeds after hospital discharge.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Setting

This was a cohort study set within the Clinical Practice Research Datalink (CPRD),[15] with linkage to Hospital Episode Statistics (HES) and Office for National Statistics mortality data. CPRD is a primary care electronic healthcare record database containing anonymized routinely collected consultation records from >670 general practices in the United Kingdom. The CPRD population is representative of the UK population on age, sex, and ethnicity.[15] Practices included in our analysis (n=377, all from England) had to have linked HES and Office for National Statistics mortality data. Practices with and without such linkage are similar in respect of demographic data, years of follow-up, and prescribing.[16] The CPRD data set is described further in Data S1. HES is a secondary care database containing detailed information on diagnosis, procedures, admissions, and discharge dates from National Health Service hospitals or hospitals where the cost of care is reimbursed by the National Health Service. The National Health Service is the main healthcare provider in the United Kingdom that is free at the point of care. The Office for National Statistics mortality data contain records of date of death and the underlying cause of death of all deceased individuals in the United Kingdom. The validity of diagnoses for conditions such as ACS is high in both CPRD and HES.[17,18] The study was approved by the CPRD Independent Scientific Advisory Committee (protocol No. 17_181). The requirement for informed consent was waived because these databases are anonymized following strict confidentiality guidelines before being distributed for research purposes.

Study Population

Patients were included in the study if they were aged ≥18 years, with a primary care record for ACS in CPRD between 2006 and 2016 and a matching ACS record in HES within 1 month of the primary care ACS event, but without a primary care record of ACS in the preceding 2 years. The period of 2 years was selected to identify only incident ACS cases. The index date for each patient was the date of hospital discharge after the matched ACS event in HES. Read codes and *International Classification of Diseases, Tenth Revision* (*ICD-10*) code lists used in defining ACS in CPRD and HES are available at http://www.keele.ac.uk/mrr. Patients were excluded if they did not survive to discharge, they had no discharge date recorded in HES, or their first ACS event preceded the date their registered practice was deemed to have up to standard data in CPRD.

Predictors

We identified potential predictors of bleeding by reviewing previously published risk scores for in-hospital and postdischarge bleeding events,[8–14,19–21] as well as studies that had reported on characteristics associated with bleeding after ACS.[22–26] Nineteen potential predictors were selected for inclusion in the study on the basis of clinical judgement.

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These predictors included sociodemographic characteristics, cardiovascular and noncardiovascular comorbidities (recorded in the previous 2 years before the index date, except body mass index, which was defined as last measurement until 30 days after index date to capture the most recent body mass index for a patient), in-hospital procedures, and pharmacological characteristics (recorded in the previous 6 months before the index date in the case of NSAIDs and selective serotonin reuptake inhibitors, or within 90 days after hospital discharge in the case of antithrombotic drugs). See Table S1 for the full list of potential predictors and their baseline definitions.

Bleeding End Point

The outcome of bleeding was defined as having a diagnostic record for bleeding in a patient primary care record or a death record in Office for National Statistics mortality data, with bleeding as the underlying cause within 12 months after the index date. Bleeding events included gastrointestinal bleeding, hematemesis, melena, gastrointestinal ulcers with bleeding, intracranial bleeding, hemoptysis, epistaxis, hemarthrosis, hemopericardium, hematuria, vaginal bleeding, retinal bleeding, anemia caused by blood loss, spontaneous bruising, petechiae, spontaneous ecchymoses, and bleeding not elsewhere classified. Bleeding events were further classified based on site into bruising; respiratory/ears, nose, and throat; gastrointestinal; genitourinary; intraocular; and intracranial. Read codes used to define and classify bleeding events are available at http://www.keele.ac.uk/mrr. Where the date of the bleeding event was the same as the index date, these bleeding events were regarded as in-hospital bleeds and, therefore, excluded.

Follow-Up

For all analyses, patients who were discharged alive were longitudinally followed up for a maximum of 12 months for records of bleeding consultations after hospital discharge for ACS. Follow-up started from the index date (date of hospital discharge) until earliest of first bleeding event or date patient ceased contributing to CPRD because of death or transfer out of practice or practice leaving CPRD or the end of 12 months from the index date of hospital discharge or the date of last data collection at the time of data request.

Statistical Analysis

All analyses were based on a first bleeding event for a patient after hospital discharge for ACS. Baseline sociodemographic characteristics, comorbidities, in-hospital procedures, and pharmacological characteristics were descriptively compared between those who did and those who did not experience bleeding events within the first 12 months after hospital discharge. Continuous variables are presented as mean and SD or median and interquartile range, and they were compared using Student *t* test or Mann-Whitney test, as appropriate. Categorical variables are presented as frequencies and percentages, and they were compared using χ^2 test.

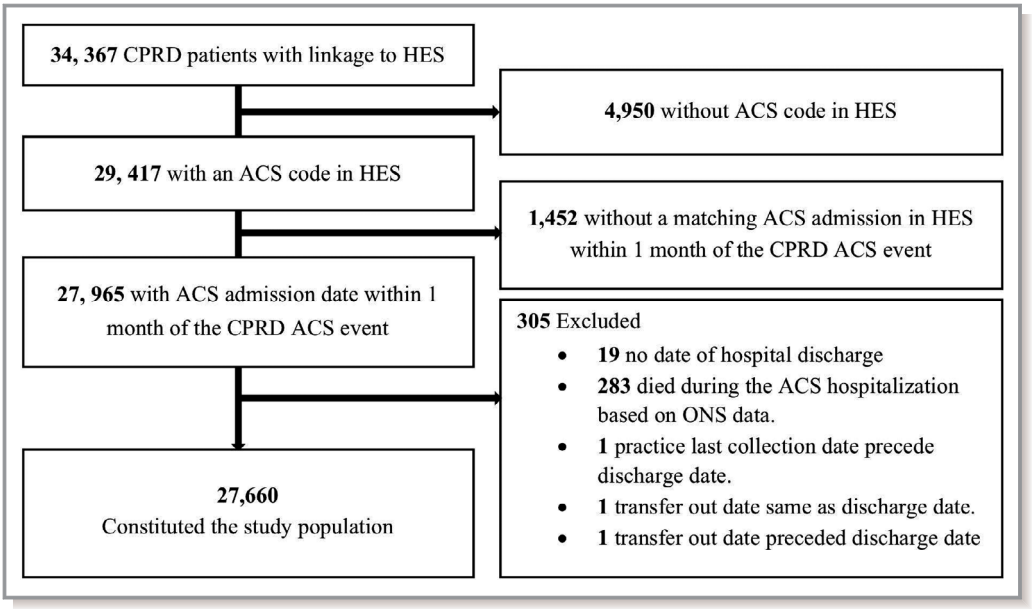


Figure 1. Flow diagram describing the steps involved in identifying the study population. ACS indicates acute coronary syndrome; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data.

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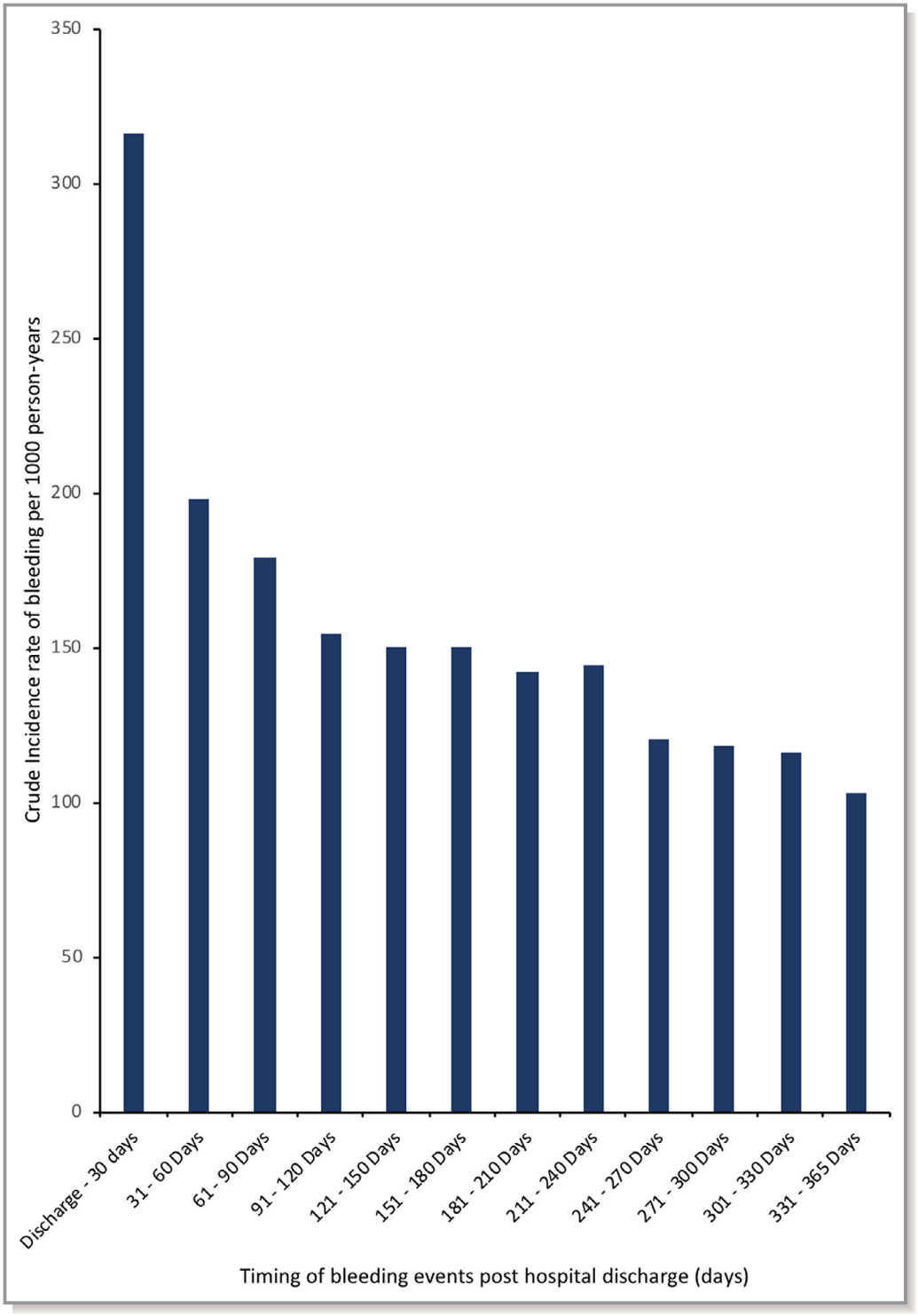


Figure 2. Crude incidence rates (per 1000 person-years) of bleeding within 12 months after hospital discharge by time from the date of hospital discharge.

Fine and Gray competing risk regression model[27] was used to determine univariable and multivariable associations between the outcomes of bleeding (and of each type of bleeding event) with potential predictors, accounting for death as a competing event, and reported using sub–hazard ratios (sHRs) with their corresponding 95% CIs. Death from a non-bleeding cause was selected as a competing event because of the older age of the cohort and will prevent a bleeding event occurring. All multivariable associations were adjusted for year of index hospital discharge, geographic region, and all

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other potential predictors. Robust variance estimators were used to account for clustering within general practices. Fractional polynomials were used to determine the functional form of age, and a plot of age against rates of bleeding (per 1000 person-years) was then used to create cut points in categorizing age when the linear form was not appropriate. The proportional hazard assumption was examined by inclusion of time-by-covariate interactions in the final models.

To address missing data in smoking status and body mass index, multiple imputation (10 imputations) was performed.[28] To assess the impact of missing data, a sensitivity analysis was performed (for the outcome of all bleeds) in which only patients with complete data on all variables were included (complete case analysis). Results of the complete case analysis were compared with those from the imputed data analysis. Only results of analyses on the imputed data sets are presented here. Results of the complete case analysis are reported in Data S1. As a subgroup analysis, the predictors for bleeding in patients managed with percutaneous coronary intervention (PCI) during the ACS hospitalization were determined. All comparisons were 2 tailed, and $P<0.05$ was considered statistically significant. All analyses were performed using Stata, version 14.2.

Results

Incidence, Timing, and Types of Postdischarge Bleeding Events

Figure 1 shows the number of patients included in the study, with exclusions. A total of 27 660 patients constituted the study population, of which 3620 (13%) experienced 5041 bleeding events over a median follow-up of 365 days (interquartile range, 246–365 days) after hospital discharge. Of the 3620 patients with bleeding events, 947 (26%) had multiple bleeding events within the first 12 months of hospital discharge. Of those with multiple bleeding events, 69% (n=654) had 2 bleeding events, 21% (n=197) had 3 bleeding events, and 10% (n=96) had ≥4 bleeding events after hospital discharge. The median time to a first bleeding event within the first 12 months was 123 days (interquartile range, 45–223 days). The incidence of bleeding was 162/1000 person-years (95% CI, 157–167/1000 person-years), and bleeding events occurred more frequently in the first 30 days after hospital discharge (Figure 2).

Table 1 shows the incidence, timing, and types of bleeding events (based on first bleed). Bruising was the most common (26% of all first bleeds), followed by gastrointestinal bleeds (20%). The incidence was highest for bruising (42/1000 person-years) and lowest for intracranial bleeding events (3/1000 person-years).

Baseline Characteristics

Table 2 summarizes the baseline characteristics of those who experienced bleeding complications and those who did not within the first 12 months after hospital discharge for ACS. Patients who experienced bleeding complications after hospital discharge were, on average, older (mean, 72 versus 70 years) and more commonly ex-smokers with higher prevalence of baseline hypertension, chronic obstructive pulmonary disease (COPD), anemia, hyperlipidemia, chronic kidney disease, history of bleeding complications (in 2 years before the index date), and a lower level of hemoglobin. Those who experienced bleeding events were also more commonly treated with oral anticoagulants after discharge. The baseline characteristics of the study population, stratified by site-specific bleeding events, are summarized in Table S2. Patients who experienced bruising were, on average, younger (age, 70 years) and more commonly women, whereas those who experienced intracranial bleeds were mostly older (age, 76 years) with a higher prevalence of chronic kidney disease.

Predictors of Bleeding Events

Age violated the linearity assumption of the competing risk model and was, therefore, categorized. Predictors that violated the proportional hazard assumption were included in the relevant models as time-dependent coefficients. The change in risk of bleeding for each predictor that interacted with time, and was significantly associated with bleeding, is reported in Table S3 at 2 time points (at 30 and at 365 days) after hospital discharge.

The crude and adjusted associations of each predictor with bleeding are presented in Table S4. Figure 3 presents the

Table 1. Incidence and Timing of Each (First) Bleeding Event Within 12 Months After Hospital Discharge

Site of Bleed	Bleeding Events, No. (% of All First Bleeds)	Incidence Rate (per 1000 Person-Years) (95% CI)	Timing of Bleed Within 12 Months, Median (IQR), d
All bleeds	3620 (100)	162 (157–167)	123 (45–223)
Bruising	949 (26)	42 (39–44)	126 (49–212)
Gastrointestinal	705 (20)	32 (30–35)	116 (41–230)
Other unclassified	700 (19)	32 (30–35)	118 (41–231)
Respiratory/ENT	582 (16)	27 (25–29)	128 (47–222)
Genitourinary	468 (13)	22 (20–24)	119 (41–226)
Intraocular	135 (4)	6 (5–7)	162 (52–239)
Intracranial	81 (2)	3 (3–4)	117 (42–222)

ENT indicates ears, nose, and throat; IQR, interquartile range.

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Table 2. Baseline Characteristics of the Study Population by Bleeding Events Within 12 Months After Hospital Discharge

Demographic Characteristics	Bleeding After Discharge		
	Bleed (n=3620)	No Bleed (n=24 040)	*P* Value
Age, mean±SD, y	72.1±12.9	69.6±13.7	
Age, n (%)			
≤65	1079 (29.8)	9309 (38.7)	<0.001
66–80	1433 (39.6)	8614 (35.8)	
>80	1108 (30.6)	6117 (25.4)	
Sex, n (%)			
Men	2126 (58.7)	15 729 (65.4)	<0.001
Women	1494 (41.3)	8311 (34.6)	
BMI, n (%)			
Underweight (BMI <18.50 kg/m^2)	62 (2.3)	325 (1.9)	0.262
Normal weight (BMI 18.50–<25 kg/m^2)	828 (31.4)	5096 (30.2)	
Overweight (BMI 25–<30 kg/m^2)	1031 (39.0)	6798 (40.3)	
Obese (BMI ≥30 kg/m^2)	720 (27.3)	4647 (27.6)	
Smoking status, n (%)			
Nonsmoker	1032 (34.0)	6428 (33.1)	<0.001
Ex-smoker	1269 (41.8)	7432 (38.2)	
Current smoker	735 (24.2)	5576 (28.7)	
Comorbidities			
Diabetes mellitus, n (%)	814 (22.5)	5002 (20.8)	0.021
Hypertension, n (%)	1075 (29.7)	6028 (25.1)	<0.001
Heart failure, n (%)	337 (9.3)	2184 (9.1)	0.662
Cancer, n (%)	431 (11.9)	2526 (10.5)	0.011
PVD, n (%)	174 (4.8)	776 (3.2)	<0.001
Stroke/TIA, n (%)	249 (6.9)	1326 (5.5)	0.001
COPD, n (%)	944 (26.1)	4616 (19.2)	<0.001
Anemia, n (%)	1123 (31.0)	5535 (23.0)	<0.001
Atrial fibrillation, n (%)	284 (7.8)	1450 (6.0)	<0.001
Hyperlipidemia, n (%)	2499 (69.0)	15 309 (63.7)	<0.001
History of bleeding, n (%)	759 (21.0)	2563 (10.7)	<0.001
CKD (eGFR <60 mL/min per 1.73 m^2), n (%)	1314 (36.3)	7093 (29.5)	<0.001
ACS presentation, n (%)			
STEMI	439 (12.1)	3193 (13.3)	0.003
NSTEMI	1452 (40.1)	8963 (37.3)	
ACS not otherwise specified	1729 (47.8)	11 884 (49.4)	
Hemoglobin, mean±SD, g/L	132±19.8	136±18.7	<0.001
Diastolic blood pressure, mean±SD, mm Hg	76.2±12.1	77.2±12.0	<0.001
Systolic blood pressure, mean±SD, mm Hg	137±19.8	137±19.4	0.872
White cell count (×10^9/L), median (IQR)	7.4 (6.2–8.9)	7.4 (6.2–9.1)	0.305
In-hospital procedures, n (%)			
Coronary angiography (only)	567 (15.7)	3693 (15.4)	0.641

Continued

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Table 2. Continued

Demographic Characteristics	Bleeding After Discharge		
	Bleed (n=3620)	No Bleed (n=24 040)	*P* Value
PCI	1201 (33.2)	8484 (35.3)	0.013
Drug therapy, n (%)			
Baseline NSAIDs	500 (13.8)	2983 (12.4)	0.018
Baseline SSRIs	320 (8.8)	1771 (7.4)	0.002
Discharge antithrombotic			
Single antiplatelet	908 (25.1)	6046 (25.1)	<0.001
Dual antiplatelet	2151 (59.4)	14 319 (59.6)	
Oral anticoagulant	276 (7.6)	1283 (5.3)	
No record	285 (7.9)	2392 (10.0)	

Number of patients with missing data: smoking (n=5188), BMI (n=8153), hemoglobin (n=8702), diastolic and systolic blood pressure (n=9592), white cell count (n=8914). ACS indicates acute coronary syndrome; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSTEMI, non ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SSRI, selective serotonin reuptake inhibitor; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack.

independent predictors for bleeding within the first 12 months after hospital discharge. After multivariable adjustment, age >65 years, female sex, history of hypertension, peripheral vascular disease (PVD), COPD, not having a history of heart failure, history of bleeding complications, management with PCI during the ACS hospitalization stay, use of NSAIDs, and treatment with oral anticoagulants or single antiplatelet after hospital discharge were independently associated with 12-month postdischarge bleeding events. The most significant predictors of bleeding were baseline history of bleeding complications (sHR, 1.88; 95% CI, 1.73–2.04), management with oral anticoagulants versus single antiplatelet after hospital discharge (sHR, 1.35; 95% CI, 1.17–1.55), aged >80 years versus aged ≤65 years (sHR, 1.42; 95% CI, 1.22–1.66), COPD (sHR, 1.29; 95% CI, 1.20–1.39), and PVD (sHR, 1.28; 95% CI, 1.09–1.50). The increased risk of bleeding in those managed with PCI or those aged >80 years (compared with those aged ≤65 years) was highest immediately after hospital discharge, but then decreased with time (Table S3).

Results of the sensitivity analysis did not reveal any disparities in findings between the imputed data analysis and the complete case analysis (Table S5). In the subgroup analysis, advanced age (>80 versus age ≤65 years), female sex, history of cancer, PVD, COPD, bleeding complications, and use of NSAIDs were the main predictors of bleeding events within the first 12 months after hospital discharge in patients managed with PCI (Figure 4). Treatment with oral anticoagulant was also associated with an increased risk of bleeding in patients managed with PCI, but this association did not reach statistical significance.

Predictors of Site-Specific Bleeding Events

Characteristics independently associated with each site-specific bleeding event are reported in Table 3. After multivariable adjustment, history of bleeding complications (sHR, 2.22; 95% CI, 1.87–2.64), advanced age (>80 versus ≤65 years) (sHR, 1.29; 95% CI, 1.01–1.65), and COPD (sHR, 1.29; 95% CI, 1.08–1.55) were the independent predictors of gastrointestinal bleeding events. Treatment with single antiplatelet after hospital discharge was also associated with an increased risk of gastrointestinal bleed. History of diabetes mellitus (sHR, 1.77; 95% CI, 1.08–2.89) and bleeding complications (sHR, 1.91; 95% CI, 1.05–3.45) were the main predictors of intracranial bleeds after hospital discharge. Treatment with oral anticoagulants, use of NSAIDs, history of PVD, aged 66 to 80 years, and advanced age (>80 years) were also associated with increased risk of intracranial bleed, but these associations did not reach statistical significance. Risk factors independently associated with each site-specific bleeding event are reported in Table 3.

Discussion

This is the first electronic health record–based study to examine the incidence, timing, and types of postdischarge bleeding events and their predictors from a primary care perspective. Our study reports that bleeding complications after hospital discharge are common and occur in ≈1 in 10 patients within the first 12 months after hospital discharge, with bruising and gastrointestinal bleeds the most common. We report that the median time to a first bleeding event was

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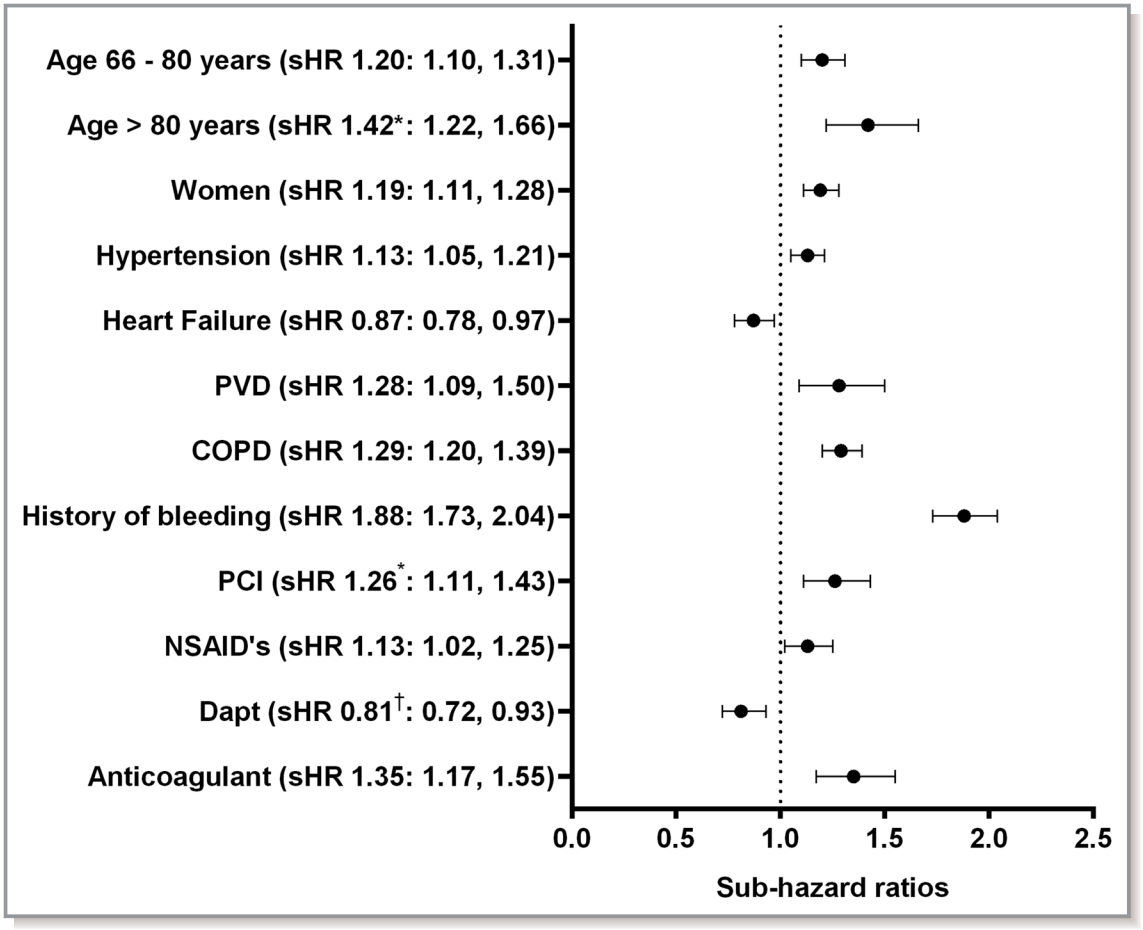


Figure 3. Characteristics associated with bleeding events within 12 months after hospital discharge for acute coronary syndrome. *Included as time-dependent coefficient: estimated sub–hazard ratio (sHR) at day of hospital discharge but decreases with time after discharge. †Included as time-dependent coefficient: estimated sHR at day of hospital discharge but increases with time after discharge. COPD indicates chronic obstructive pulmonary disease; Dapt, dual antiplatelet; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

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123 days, with bleeding events more commonly occurring in the first 30 days after hospital discharge. Our analysis found that history of bleeding complications in 2 years before hospital discharge, management with oral anticoagulants after hospital discharge, COPD, PVD, and advanced age (>80 years) were the major predictors of bleeding complications in the first 12 months after hospital discharge. Predictors for postdischarge bleeding varied, depending on the anatomic site of the bleeding event. We report that characteristics, such as COPD, use of NSAIDs, and history of cancer, which have not been previously examined in a population with ACS, may carry greater risk for bleeding complications after hospital discharge.

The results of our study add granularity to the growing body of literature evaluating the risk of bleeding complications after hospital discharge. The finding that 13% of patients had experienced bleeding complications in the year after discharge was higher than those reported in the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study[29] and other previous studies in the postdischarge setting (range, 2.5%–7.9%).[30,31] This higher incidence likely reflects differences in the definition of bleeding used, as the emphasis in previous studies has been on major bleeding events. The higher incidence may also be because of the primary care population with elderly multimorbid patients, which were mostly excluded from randomized controlled trials. Our study did not capture bleeding events that are not actionable and did not cause patients to seek medical advice. This highlights that the actual incidence of postdischarge bleeding events may be higher than what we have reported. Our study and previous studies[25,26] have identified the first 30 days of hospital discharge as the period for greater vulnerability for these bleeding complications and highlight the time when resources can be better used to improve longer-term patient prognosis, such as by personalization of antithrombotic drugs at the time of hospital discharge. We

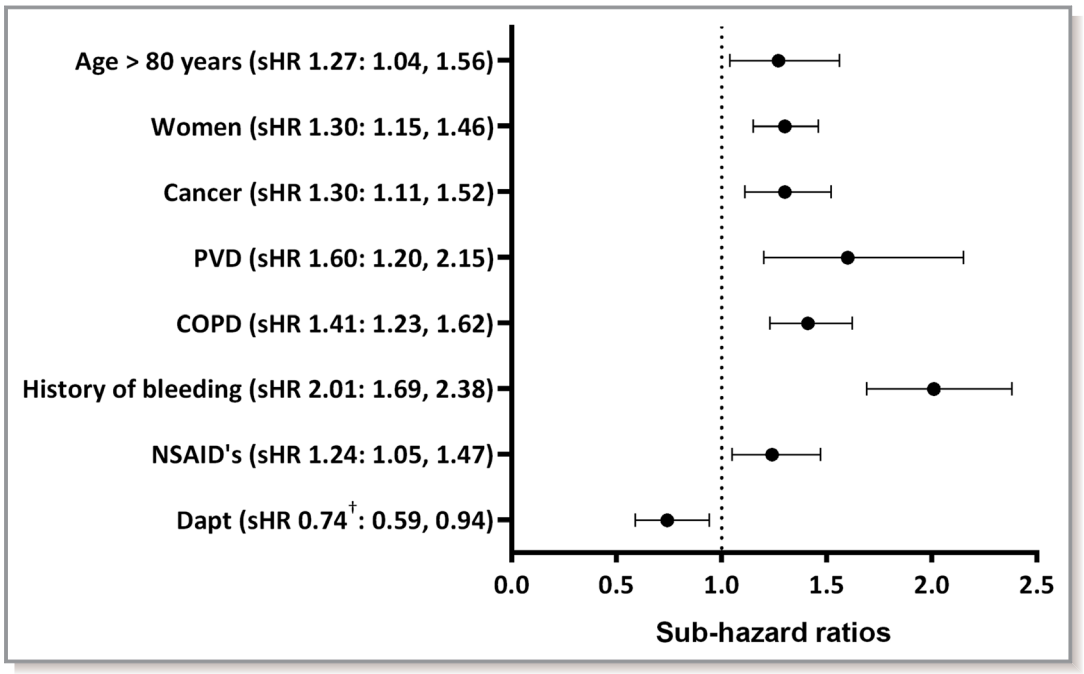


Figure 4. Characteristics associated with bleeding events within 12 months after hospital discharge for acute coronary syndrome in patients managed with percutaneous coronary intervention. †Included as time-dependent coefficient: estimated sub–hazard ratio (sHR) at day of hospital discharge but increases with time after discharge. COPD indicates chronic obstructive pulmonary disease; Dapt, dual antiplatelet; PVD, peripheral vascular disease.

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report that bruising was the most common type of bleeding complication after hospital discharge. These types of bleeding events, which have mostly been neglected in previous studies, can be detrimental. Bruising may impact on patient quality of life, leading to discontinuation of antithrombotic therapy, which can have indirect adverse consequences.[32,33]

We found that the predictors (eg, age, hypertension, PVD, history of bleeding, management with PCI during ACS hospitalization, and use of oral anticoagulants)[8–10,14] for in-hospital bleeding have some overlap with those for postdischarge bleeding events. But characteristics, such as those related to ACS presentation, may carry less impact on risk of postdischarge bleeding. Although there was some overlap between the predictors for in-hospital and postdischarge bleeding events, the predictors for site-specific bleeds vary, depending on the anatomic site of the bleeding event.

A novel finding of this study in reviewing the predictors of site-specific bleeding complications was that, although characteristics such as advanced age (>80 years) and prior history of bleeding complications were predictive of all types of bleeding events (except bruising), some predictors were more associated with certain types of bleeds. We found that the female sex was only predictive of nuisance bruising, and not major bleeds (eg, gastrointestinal or intracranial bleeds), contrary to that reported by in-hospital studies.[8,9,14] This finding is consistent with most studies of bleeding in the postdischarge setting, which showed a lack of association between female sex and major bleeding events.[21,34]

Another novel finding from our analysis was that COPD is a strong predictor of bruising, respiratory, gastrointestinal, and genitourinary bleeding events. Most contemporary studies in the ACS setting have either not included COPD as a potential predictor or not recorded its diagnosis. Our finding on the effect of COPD on the occurrence of bleeding suggests that COPD should be taken into account when evaluating future risk of bleeding complications. COPD is characterized by local and systemic inflammation.[35] Patients with COPD are exposed to oxidative stress via chronic hypoxia and increased release of reactive oxygen species by leukocytes.[36] This damages gastric mucosa[37] and may predispose to peptic ulcer bleeds.[38] Patients with COPD are often treated with steroids to control lung inflammation. Steroids may delay peptic ulcer healing,[39] thus increasing the risk of perforation and bleeding complications.[40] The association of COPD with bleeding events should be explored further to confirm the result of our study.

Our study found cancer to be a strong predictor of respiratory bleeding events and a modest nonsignificant increased risk of gastrointestinal bleeds. Malignancy has been an exclusion criterion in previous studies, such as the CRUSADE (Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early

Table 3. Characteristics Independently Associated With Site-Specific Bleeding Events Within 12 Months After Hospital Discharge for ACS

Risk Factors	Bruising (n=949)*	Respiratory/ ENT Bleeds (n=582)*	Gastrointestinal Bleeds (n=705)*	Genitourinary Bleeds (n=468)*	Intraocular Bleeds (n=135)*	Intracranial Bleeds (n=81)*
Demographics						
Age, y						
≤65	1.00	1.00	1.00	1.00	1.00	1.00
66–80	0.98 (0.84–1.14)	1.27 (1.01–1.60)†	1.05 (0.86–1.29)	1.37 (1.05–1.79)†	2.02 (1.26–3.25)†	1.81 (0.86–3.83)
>80	0.81 (0.65–1.03)	1.60 (1.21–2.12)†	1.29 (1.01–1.65)†	1.65 (1.21–2.24)†	1.49 (0.81–2.75)	2.31 (0.92–5.79)
Women	2.11 (1.85–2.41)†	0.94 (0.79–1.12)	0.97 (0.82–1.13)	0.84 (0.67–1.06)	0.78 (0.55–1.11)	1.13 (0.74–1.73)
BMI, kg/m^2						
Normal weight (18.50–<25)	1.00	1.00	1.00	1.00	1.00	1.00
Underweight (<18.50)	1.16 (0.73–1.87)	2.02 (0.89–4.58)‡	0.94 (0.49–1.79)	0.73 (0.26–2.04)	0.93 (0.23–3.70)	1.14 (0.34–3.80)
Overweight (25–<30)	1.10 (0.93–1.31)	0.93 (0.75–1.16)	1.23 (0.84–1.81)‡	0.95 (0.74–1.22)	0.74 (0.45–1.21)	0.59 (0.34–1.02)
Obese (≥30)	0.99 (0.81–1.21)	0.91 (0.71–1.17)	1.03 (0.82–1.31)	1.12 (0.82–1.51)	0.81 (0.49–1.33)	0.42 (0.20–0.88)†
Smoking status						
Nonsmoker	1.00	1.00	1.00	1.00	1.00	1.00
Ex-smoker	0.97 (0.80–1.17)	1.13 (0.90–1.43)	0.95 (0.77–1.17)	1.10 (0.88–1.38)	1.07 (0.71–1.61)	1.15 (0.69–1.92)
Current smoker	0.87 (0.71–1.07)	0.96 (0.74–1.24)	0.99 (0.79–1.25)	0.97 (0.72–1.30)	0.94 (0.52–1.68)	0.79 (0.37–1.68)
Comorbidities						
Diabetes mellitus	0.73 (0.61–0.88)†	0.91 (0.73–1.13)	0.92 (0.77–1.10)	0.96 (0.76–1.19)	1.10 (0.73–1.65)	1.77 (1.08–2.89)†
Hypertension	1.02 (0.88–1.18)	1.43 (1.20–1.72)†	1.11 (0.94–1.31)	0.98 (0.79–1.22)	1.43 (1.02–2.02)†	1.01 (0.62–1.66)
Heart failure	0.75 (0.59–0.96)†	1.09 (0.82–1.43)	0.87 (0.67–1.13)	0.80 (0.57–1.11)	1.10 (0.42–2.91)‡	0.36 (0.13–0.97)†
Cancer	0.97 (0.79–1.19)	1.86 (1.26–2.74)†,‡	1.17 (0.94–1.46)	1.10 (0.84–1.45)	0.77 (0.43–1.37)	0.78 (0.38–1.63)
PVD	1.20 (0.82–1.76)	1.30 (0.90–1.87)	1.06 (0.72–1.54)	1.33 (0.85–2.08)	1.03 (0.46–2.30)	1.31 (0.49–3.55)
COPD	1.21 (1.04–1.40)†	1.66 (1.36–2.01)†	1.29 (1.08–1.55)†	1.26 (1.01–1.58)†	1.02 (0.64–1.63)	1.11 (0.64–1.93)
CKD (eGFR <60 mL/ min per 1.73 m^2)	1.10 (0.93–1.31)	0.81 (0.66–1.00)	1.12 (0.95–1.33)	0.93 (0.73–1.18)	1.71 (1.11–2.65)†	1.06 (0.61–1.84)
Hyperlipidemia	1.09 (0.93–1.26)	1.15 (0.94–1.40)	0.94 (0.73–1.22)§	1.00 (0.83–1.20)	1.32 (0.88–1.95)	0.74 (0.45–1.23)
History of bleeding	1.11 (0.79–1.56)§	2.06 (1.70–2.49)†	2.22 (1.87–2.64)†	2.79 (2.26–3.44)†	2.11 (1.34–3.34)†	1.91 (1.05–3.45)†
ACS presentation						
STEMI	1.00	1.00	1.00	1.00	1.00	1.00
NSTEMI	1.13 (0.92–1.39)	0.89 (0.69–1.15)	0.82 (0.65–1.04)	1.18 (0.85–1.64)	1.07 (0.59–1.93)	0.75 (0.40–1.42)
Not otherwise specified	1.01 (0.83–1.22)	0.85 (0.65–1.11)	0.83 (0.65–1.05)	1.21 (0.89–1.63)	1.09 (0.62–1.94)	0.69 (0.37–1.30)
In-hospital procedure						
PCI	1.24 (1.06–1.44)†	1.87 (1.37–2.54)†,‡	1.04 (0.87–1.26)	1.03 (0.81–1.30)	1.20 (0.77–1.86)	1.01 (0.58–1.77)
Drug therapy						
Baseline NSAIDs	1.06 (0.89–1.27)	1.29 (1.04–1.59)†	1.12 (0.89–1.42)	1.26 (0.95–1.66)	0.96 (0.58–1.59)	1.95 (0.71–5.32)‡
Baseline SSRIs	1.23 (1.00–1.50)†	0.93 (0.68–1.28)	1.12 (0.88–1.42)	1.23 (0.90–1.68)	1.64 (0.97–2.77)	1.03 (0.48–2.19)
Single antiplatelet	1.00	1.00	1.00	1.00	1.00	1.00
Dual antiplatelet	1.34 (1.14–1.57)†	0.75 (0.54–1.04)§	0.67 (0.49–0.91)†,§	1.17 (0.93–1.48)	2.10 (1.27–3.45)†	1.03 (0.62–1.72)

Continued

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Table 3. Continued

Risk Factors	Bruising (n=949)*	Respiratory/ ENT Bleeds (n=582)*	Gastrointestinal Bleeds (n=705)*	Genitourinary Bleeds (n=468)*	Intraocular Bleeds (n=135)*	Intracranial Bleeds (n=81)*
Oral anticoagulant	1.18 (0.90–1.56)	1.61 (1.15–2.25)†	1.15 (0.83–1.59)	1.61 (1.11–2.34)†	3.64 (1.90–6.98)†	1.45 (0.25–8.46)‡
No record	0.49 (0.34–0.68)†	0.60 (0.43–0.85)†	1.26 (0.98–1.60)	0.96 (0.66–1.39)	1.33 (0.63–2.82)	6.53† (2.35–18.12)

Data are given as sub–hazard ratio (95% CI). ACS indicates acute coronary syndrome; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ENT, ears, nose, and throat; NSTEMI, non ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SSRI, selective serotonin reuptake inhibitor; STEMI, ST-segment–elevation myocardial infarction.

*Adjusted for year of hospital discharge, geographic region, general practice, and all listed characteristics in the table.

†Statistically significant predictors of bleeding at the 5% threshold.

‡Included as time-dependent coefficient: estimated sub–hazard ratio at day of hospital discharge but decreases with time after discharge (1.00=reference category).

§Included as time-dependent coefficient: estimated sub–hazard ratio at day of hospital discharge but increases with time after discharge.

implementation of the ACC/AHA guidelines), DAPT (Dual antiplatelet therapy study), and Trilogy-ACS (Targeted platelet inhibition to clarify the optimal strategy to medically manage acute coronary syndromes).[8,12,13] Cancers that are systemic, such as those emanating from the gastroesophageal tract, are more likely to increase bleeding complications. Therefore, thoughtful consideration should be given to this group of patients when deciding on secondary management strategy after ACS. We found dual antiplatelet therapy to be associated with a decreased risk of gastrointestinal bleed in the immediate period after hospital discharge. The decreased risk of gastrointestinal bleed with dual antiplatelet may be caused by an element of confounding by indication, with patients deemed to be at highest risk for this type of bleed only prescribed single antiplatelet at the time of hospital discharge.

We found treatment with oral anticoagulants to be associated with higher risk of respiratory, genitourinary, and intraocular bleeding events after hospital discharge. Of patients in our study, 6% were prescribed oral anticoagulants, with most (92%) given warfarin at discharge. Replacing warfarin with the newer oral anticoagulants that have a more favorable safety profile may mitigate the bleeding complications in this group of patients.[41,42] In patients managed with PCI, who have an indication for oral anticoagulants, such as those with atrial fibrillation who are at increased risk of stroke, secondary management involving an antiplatelet (eg, clopidogrel) and a newer oral anticoagulant, as stipulated in the updated American Heart Association guideline for the management of patients with atrial fibrillation, will reduce the risk of late bleeding events.[43] For patients prescribed triple therapy (aspirin plus P2Y12 inhibitor plus an oral anticoagulant), the duration of this therapy should be minimized to a period of 4 to 6 weeks and dual therapy (a P2Y12 inhibitor plus an oral anticoagulant) should be considered thereafter,[43] to minimize the risk of bleeding.

The findings of this study should be interpreted in light of some limitations. First, bleeding events were not independently adjudicated. The observational design of the study does not preclude residual confounding. The definition for bleeding did not include laboratory parameters, such as decrease in hemoglobin measurements and/or receipt of blood transfusion. Classifying bleeding on the basis of severity (major and minor) was, therefore, not possible. The study was not adequately powered to examine the independent predictors of some types of bleeding events, such as intracranial and intraocular bleeds that occurred relatively rarely. Thus, findings in relation to these bleeding events should be viewed as exploratory. Reporting bias may be a cause for concern in our study because not all patients who experience minor and nuisance bleeding events (eg, nose bleeds and bruising) will seek medical advice. Therefore, the incidence of bleeding is likely to have been underreported, although more significant bleeds may have been likely recorded. Prasugrel, ticagrelor, and the newer oral anticoagulants became available during the study period, but most patients (90%) were mostly treated with aspirin, clopidogrel, or warfarin after discharge. We restricted our study to people in England. Thus, the generalizability of our results outside of England is unclear. Finally, we were unable to examine the impact of dosing and duration of discharge antithrombotic drugs and those of emerging risk factors, such as frailty and genetic factors, on risk of future bleeding events.

In summary, bleeding complications after hospital discharge are common and occur more frequently in the first 30 days after hospital discharge. Patients who experience these bleeding events have distinct baseline characteristics. These characteristics differ, depending on the anatomic site of the bleeding event. Identification of these characteristics is an important step toward developing a real-world risk stratification tool that can facilitate a more patient-centered approach in deciding on favorable combination and duration of secondary antithrombotic therapy after ACS.

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Disclosures

None.

References

1. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, Cutlip DE, Cohen DJ, Tanguay J-F, Jacobs A, Wiviott SD, Massaro JM, Iancu AC, Mauri L; DAPT Study Investigators. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. *J Am Coll Cardiol*. 2015;65:2211–2221.
2. Rao S, Eikelboom J, Granger C, Harrington R, Califf R, Bassand J. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1193–1204.
3. Mehta SR, Granger CB, Eikelboom JW, Bassand J-P, Wallentin L, Faxon DP, Peters RJG, Budaj A, Afzal R, Chrolavicius S, Fox KAA, Yusuf S. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol*. 2007;50:1742–1751.
4. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. *J Am Coll Cardiol*. 2009;53:2019–2027.
5. Spencer FA, Moscucci M, Granger CB, Gore JM, Goldberg RJ, Steg PG, Goodman SG, Budaj A, FitzGerald G, Fox KAA; GRACE Investigators. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? *Circulation*. 2007;116:2793–2801.
6. Amlani S, Nadarajah T, Afzal R, Pal-Sayal R, Eikelboom JW, Natarajan MK. Mortality and morbidity following a major bleed in a registry population with acute ST elevation myocardial infarction. *J Thromb Thrombolysis*. 2010;30:434–440.
7. Ismail N, Jordan KP, Rao S, Kinnaird T, Potts J, Kadam UT, Mamas MA. Incidence and prognostic impact of post discharge bleeding post acute coronary syndrome within an outpatient setting: a systematic review. *BMJ Open*. 2019;9:e023337.
8. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV, Peterson ED, Alexander KP. Baseline risk of major bleeding in non–ST-segment–elevation myocardial infarction. *Circulation*. 2009;119:1873–1882.
9. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian S V., Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010;55:2556–2566.
10. Mathews R, Peterson ED, Chen AY, Wang TY, Chin CT, Fonarow GC, Cannon CP, Rumsfeld JS, Roe MT, Alexander KP. In-hospital major bleeding during ST-elevation and non–ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry®-GWTG™. *Am J Cardiol*. 2011;107:1136–1143.
11. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong M-K, Kim H-S, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034.
12. Alfredsson J, Neely B, Neely ML, Bhatt DL, Goodman SG, Tricoci P, Mahaffey KW, Cornel JH, White HD, Fox KA, Prabhakaran D, Winters KJ, Armstrong PW, Ohman EM, Roe MT; TRILOGY ACS Investigators. Predicting the risk of bleeding during dual antiplatelet therapy after acute coronary syndromes. *Heart*. 2017;103:1168–1176.
13. Yeh RW, Secemsky EA, Kereiakes DJ, Normand S-LT, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315:1735.
14. Moscucci M, Fox KAAAA, Cannon CP, Klein W, López-Sendón J, Montalescot G, White K, Goldberg RJJ, Moscucci M. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE) for the GRACE Investigators 1. *Eur Heart J*. 2003;24:1815–1823.
15. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol*. 2015;44:827–836.
16. Gallagher A, Puri S, van Staa T. Linkage of the General Practice Research Database (GPRD) with other data sources. *Pharmacoepidemiol Drug Saf*. 2011;20:S230.
17. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69:4–14.
18. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, Timmis A, Hemingway H. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *BMJ*. 2013;346:f2350.
19. Barra S, Providência R, Caetano F, Almeida I, Paiva L, Dinis P, Leitão Marques A. BLEED-Myocardial Infarction Score: predicting mid-term post-discharge bleeding events. *World J Cardiol*. 2013;5:196–206.
20. Baber U, Mehran R, Giustino G, Cohen DJ, Henry TD, Sartori S, Ariti C, Litherland C, Dangas G, Gibson CM, Krucoff MW, Moliterno DJ, Kirtane AJ, Stone GW, Colombo A, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S. Coronary thrombosis and major bleeding after PCI with drug-eluting stents. *J Am Coll Cardiol*. 2016;67:2224–2234.
21. Raposeiras-Roubín S, Faxén J, Íñiguez-Romo A, Henriques JPS, D'Ascenzo F, Saucedo J, Szummer K, Jernberg T, James SK, Juanatey JRG, Wilton SB, Kikkert WJ, Nuñez-Gil I, Ariza-Sole A, Song X, Alexopoulos D, Liebetrau C, Kawaji T, Moretti C, Huczek Z, Nie S-P, Fujii T, Correia L, Kawashiri M, Caneiro-Queija B, Cobas-Paz R, Acuña JMG, Southern D, Alfonso E, Terol B, Garay A, Zhang D, Chen Y, Xanthopoulou I, Osman N, Möllmann H, Shiomi H, Giordana F, Gaita F, Kowara M, Filipiak K, Wang X, Yan Y, Fan J-Y, Ikari Y, Nakahayshi T, Sakata K, Yamagishi M, Kalpak O, Kedev S, Rivera-Asenjo D, Abu-Assi E. Development and external validation of a post-discharge bleeding risk score in patients with acute coronary syndrome: the BleeMACS score. *Int J Cardiol*. 2018;254:10–15.
22. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med*. 2005;165:784.
23. Khan R, Lopes RD, Neely ML, Stevens SR, Harrington RA, Diaz R, Cools F, Jansky P, Montalescot G, Atar D, Lopez-Sendon J, Flather M, Liaw D, Wallentin L, Alexander JH, Goodman SG. Characterising and predicting bleeding in high-risk patients with an acute coronary syndrome. *Heart*. 2015;101:1475–1484.
24. Lattuca B, Fabbro-Peray P, Leclercq F, Schmutz L, Ledermann B, Cornillet L, Benezet J-F, Macia J-C, de La Coussaye J-E, Messner-Pellenc P, Cayla G. One-year incidence and clinical impact of bleeding events in patients treated with

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prasugrel or clopidogrel after ST-segment elevation myocardial infarction. *Arch Cardiovasc Dis*. 2016;109:337–347.

25. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. *J Am Coll Cardiol*. 2015;66:1036–1045.
26. Valle JA, Shetterly S, Maddox TM, Ho PM, Bradley SM, Sandhu A, Magid D, Tsai TT. Postdischarge bleeding after percutaneous coronary intervention and subsequent mortality and myocardial infarction. *Circ Cardiovasc Interv*. 2016;9:e003519.
27. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
29. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD; ADAPT-DES Investigators. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet*. 2013;382:614–623.
30. Bacquelin R, Oger E, Filippi E, Hacot J-P, Auffret V, Le Guellec M, Coudert I, Castellant P, Moquet B, Druelles P, Rialan A, Rouault G, Boulanger B, Treuil J, Leurent G, Bedossa M, Boulmier D, Avez B, Gilard M, Le Breton H. Safety of prasugrel in real-world patients with ST-segment elevation myocardial infarction: 1-year results from a prospective observational study (Bleeding and Myocardial Infarction Study). *Arch Cardiovasc Dis*. 2016;109:31–38.
31. Ko DT, Yun L, Wijeysundera HC, Jackevicius CA, Rao SV, Austin PC, Marquis J-FF, Tu JV. Incidence, predictors, and prognostic implications of hospitalization for late bleeding after percutaneous coronary intervention for patients older than 65 years. *Circ Cardiovasc Interv*. 2010;3:140–147.
32. Amin AP, Bachuwar A, Reid KJ, Chhatriwalla AK, Salisbury AC, Yeh RW, Kosiborod M, Wang TY, Alexander KP, Gosch K, Cohen DJ, Spertus JA, Bach RG. Nuisance bleeding with prolonged dual antiplatelet therapy after acute myocardial infarction and its impact on health status. *J Am Coll Cardiol*. 2013;61:2130–2138.
33. Amin AP, Wang TY, McCoy L, Bach RG, Effron MB, Peterson ED, Cohen DJ. Impact of bleeding on quality of life in patients on DAPT: insights from TRANSLATE-ACS. *J Am Coll Cardiol*. 2016;67:59–65.
34. Grodecki K, Huczek Z, Scisło P, Kowara M, Raposeiras-Roubín S, D'Ascenzo F, Abu-Assi E, Henriques JPS, Saucedo J, González-Juanatey JR, Wilton SB, Kikkert WJ, Nuñez-Gil I, Ariza-Sole A, Song X, Alexopoulos D, Liebetrau C, Kawaji T, Moretti C, Nie S-P, Fujii T, Correia L, Kawashiri M, García-Acuña JM, Southern D, Alfonso E, Terol B, Garay A, Zhang D, Chen Y, Xanthopoulou I, Osman N, Möllmann H, Shiomi H, Giordana F, Scarano S, Gaita F, Wang X, Yan Y, Fan J-Y, Ikari Y, Nakahashi T, Sakata K, Yamagishi M, Kalpak O, Kedev S, Opolski G, Filipiak KJ. Gender-related differences in post-discharge bleeding among patients with acute coronary syndrome on dual antiplatelet therapy: a BleeMACS sub-study. *Thromb Res*. 2018;168:156–163.
35. Moermans C, Heinen V, Nguyen M, Henket M, Sele J, Manise M, Corhay JL, Louis R. Local and systemic cellular inflammation and cytokine release in chronic obstructive pulmonary disease. *Cytokine*. 2011;56:298–304.
36. MacNee W. Pulmonary and systemic oxidant/antioxidant imbalance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2:50–60.
37. Kang JM, Kim N, Kim J-H, Oh E, Lee B-Y, Lee BH, Shin CM, Park JH, Lee MK, Nam RH, Lee HE, Lee HS, Kim JS, Jung HC, Song IS. Effect of aging on gastric mucosal defense mechanisms: ROS, apoptosis, angiogenesis, and sensory neurons. *Am J Physiol Liver Physiol*. 2010;299:G1147–G1153.
38. Huang K-W, Luo J-C, Leu H-B, Lin H-C, Lee F-Y, Chan W-L, Lin S-J, Chen J-W, Chang F-Y. Chronic obstructive pulmonary disease: an independent risk factor for peptic ulcer bleeding: a nationwide population-based study. *Aliment Pharmacol Ther*. 2012;35:796–802.
39. Luo JC, Shin VY, Liu ESL, Ye YN, Wu WKK, So WHL, Chang FY, Cho CH. Dexamethasone delays ulcer healing by inhibition of angiogenesis in rat stomachs. *Eur J Pharmacol*. 2004;485:275–281.
40. Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. *BMJ Open*. 2014;4:e004587.
41. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
42. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
43. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151.

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Data S1.

Clinical Practice Research Datalink (CPRD)

The CPRD is a primary care database containing individual patient's demographic information, tests, clinical events (such as diagnosis), referrals, prescriptions, and immunisations from a subset of UK general practices that had consented to periodically provide patient data for research purposes (1). In the UK, general practices are the first point of contact for non-emergency health related issues, and diagnoses during these encounters are electronically recorded using the Read coding system. A subset of practices in England (75% of English practices, 55% of all UK practices) contributing to CPRD have consented to their primary care records being linked to HES and ONS (1). CPRD is generally representative of the UK population on age, gender and ethnicity (1, 2).

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Table S1. Candidate predictors of bleeding for model development.

Socio-demographic characteristics (recorded in the 2 years prior to index date except BMI which was recorded until 30 days after index date)
Advanced age
Female sex
Body mass index* (BMI)
History of smoking†
Comorbidities (recorded in the 2 years prior to index date)
History of diabetes
History of hypertension
History of heart failure
History of cancer
History of peripheral vascular disease
History of chronic obstructive pulmonary disease (COPD)
History of renal insufficiency‡
Hyperlipidemia
History of bleeding
STEMI at presentation
NSTEMI at presentation
In-hospital procedure
Percutaneous coronary intervention (PCI) at index ACS hospitalisation
Pharmacological characteristics
NSAID prescription within 6 months prior to hospital discharge
SSRI prescription within 6 months prior to hospital discharge
Discharge antithrombotic therapy§ (whether single antiplatelet (SAPT), dual antiplatelet (DAPT) or receipt of oral anticoagulant)

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*BMI was classified into underweight, normal weight, overweight, and obese following the WHO classification.

†Smoking was defined as non-smoker, ex-smoker and current smoker.

‡Renal insufficiency was defined by Estimated Glomerular Filtration Rate (eGFR), calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) as eGFR < 60 mL/min per 1.73 m^2 (3).

§Discharge antithrombotic therapy was classified into **single antiplatelet therapy** (a prescription record for one of aspirin, clopidogrel, prasugrel or ticagrelor), **dual antiplatelet therapy** (a prescription record for aspirin and one of clopidogrel, prasugrel or ticagrelor) and **receipt of oral anticoagulation** (a prescription record for one of warfarin, apixaban, rivaroxaban or dabigatran, with or without concomitant antiplatelets) all measured within 90 days post index date in the patient's primary care record.

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Table S2. Baseline characteristics of the study population by site of bleeding events within the first 12 months after hospital discharge.

Demographic characteristics	No Bleeds (n = 24040)	Bruising (n = 949)	Respiratory/ent bleeds (n = 582)	Gastrointestinal bleeds (n = 705)	Genitourinary bleeds (n = 468)	Intraocular bleeds (n = 135)	Intracranial bleeds (n = 81)
Age (Mean ± SD)	69.6 ± 13.7	69.6 ± 13.0	72.6 ± 12.7	71.9 ± 13.6	72.1 ± 13.5	72.4 ± 10.9	76.3 ± 11.8
Age (n, %)							
≤ 65	9309 (38.7)	348 (36.7)	167 (28.8)	225 (31.9)	134 (28.6)	29 (21.5)	15 (18.1)
66 - 80	8614 (35.8)	367 (38.8)	228 (39.3)	256 (36.3)	185 (39.5)	68 (50.4)	31 (37.3)
> 80	6117 (25.4)	232 (24.5)	185 (31.9)	224 (31.8)	149 (31.8)	38 (28.1)	37 (44.6)
Sex (n, %)							
Male	15729 (65.4)	455 (48.0)	373 (64.3)	445 (63.1)	313 (66.9)	89 (65.9)	46 (55.4)
Female	8311 (34.6)	492 (52.0)	207 (35.7)	260 (36.9)	155 (33.1)	46 (34.1)	37 (44.6)
BMI (kg/m^2) (n, %)							
Underweight (BMI < 18.50)	325 (1.9)	20 (2.9)	12 (2.9)	9 (1.8)	5 (1.5)	*	*
Normal weight (BMI 18.50 to < 25)	5096 (30.2)	201 (29.4)	133 (31.7)	154 (30.0)	101 (30.4)	36 (35.3)	30 (49.2)
Overweight (BMI 25 to < 30)	6798 (40.3)	286 (41.8)	163 (38.9)	202 (39.4)	123 (37.0)	36 (35.3)	20 (32.8)
Obese (BMI ≥ 30)	4647 (27.6)	177 (25.9)	111 (26.5)	148 (28.8)	103 (31.0)	28 (27.5)	8 (13.1)
Smoking Status (n, %)							
Non smoker	6428 (33.1)	288 (36.5)	152 (31.4)	201 (34.0)	126 (32.4)	39 (34.8)	24 (37.5)

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Ex-smoker	7432 (38.2)	288 (36.5)	220 (45.5)	235 (39.7)	175 (45.0)	51 (45.5)	29 (45.3)
Current smoker	5576 (28.7)	212 (26.9)	112 (23.1)	156 (26.4)	88 (22.6)	22 (19.6)	11 (17.2)
Comorbidities							
Diabetes (n, %)	5002 (20.8)	157 (16.6)	121 (20.9)	155 (22.0)	104 (22.2)	35 (25.9)	24 (28.9)
Hypertension (n, %)	6028 (25.1)	253 (26.7)	199 (34.3)	206 (29.2)	123 (26.3)	48 (35.6)	23 (27.7)
Heart failure (n, %)	2184 (9.1)	65 (6.9)	66 (11.4)	67 (9.5)	41 (8.8)	8 (5.9)	*
Cancer (n, %)	2526 (10.5)	94 (9.9)	78 (13.4)	95 (13.5)	61 (13.0)	13 (9.6)	8 (9.6)
PVD (n, %)	776 (3.2)	35 (3.7)	29 (5.0)	28 (4.0)	23 (4.9)	6 (4.4)	*
Stroke/TIA (n, %)	1326 (5.5)	47 (5.0)	43 (7.4)	46 (6.5)	37 (7.9)	7 (5.2)	12 (14.5)
COPD (n, %)	4616 (19.2)	216 (22.8)	177 (30.5)	182 (25.8)	121 (25.9)	30 (22.2)	20 (24.1)
Anemia (n, %)	5535 (23.0)	187 (19.7)	168 (29.0)	220 (31.2)	136 (29.1)	40 (29.6)	23 (27.7)
Atrial fibrillation (n, %)	1450 (6.0)	60 (6.3)	51 (8.8)	49 (7.0)	45 (9.6)	9 (6.7)	15 (18.1)
Hyperlipidemia (n, %)	15309 (63.7)	624 (65.9)	403 (69.5)	497 (70.5)	313 (66.9)	101 (74.8)	51 (61.4)
History of bleeding (n, %)	2563 (10.7)	137 (14.5)	126 (21.7)	162 (23.0)	126 (26.9)	30 (22.2)	19 (22.9)
CKD (eGFR < 60 mL/min/1.73 m^2 (n, %))	7093 (29.5)	304 (32.1)	187 (32.2)	258 (36.6)	158 (33.8)	63 (46.7)	35 (42.2)
ACS presentation (n, %)							
STEMI	3193 (13.3)	122 (12.9)	81 (14.0)	103 (14.6)	50 (10.7)	16 (11.9)	12 (14.5)
NSTEMI	8963 (37.3)	368 (38.9)	224 (38.6)	271 (38.4)	184 (39.3)	53 (39.3)	34 (41.0)

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ACS Not otherwise specified	11884 (49.4)	457 (48.3)	275 (47.4)	331 (47.0)	234 (50.0)	66 (48.9)	37 (44.6)
Hemoglobin (g/L (Mean ± SD))	136 ± 18.7	136 ± 17.6	133 ± 21.2	133 ± 20.5	133 ± 19.0	134 ± 19.0	130 ± 23.5
Diastolic (mm Hg (Mean ± SD))	77.2 ± 12.0	77.4 ± 11.7	75.9 ± 11.6	76.9 ± 12.2	75.4 ± 12.0	75.3 ± 10.9	78.6 ± 14.2
Systolic (mm Hg (Mean ± SD))	137 ± 19.4	137 ± 18.1	136 ± 19.1	137 ± 20.4	136 ± 20.0	136 ± 18.2	142 ± 22.7
White cell count ($x10^9$/L (Median ± IQR))	7.4 (6.2, 9.1)	7.2 (6.1, 8.7)	7.5 (6.2, 9.1)	7.6 (6.3, 9.0)	7.5 (6.2, 9.2)	7.3 (6.0, 8.6)	7.4 (6.1, 9.8)
In-hospital procedures							
Coronary angiography (only) (n, %)	3693 (15.4)	154 (16.3)	78 (13.4)	105 (14.9)	80 (17.1)	19 (14.1)	7 (8.4)
PCI (n, %)	8484 (35.3)	366 (38.6)	198 (34.1)	232 (32.9)	154 (32.9)	48 (35.6)	22 (26.5)
Drug Therapy (n, %)							
Baseline NSAIDs	2983 (12.4)	131 (13.8)	88 (15.2)	95 (13.5)	70 (15.0)	16 (11.9)	6 (7.2)
Baseline SSRIs	1771 (7.4)	95 (10.0)	43 (7.4)	64 (9.1)	44 (9.4)	15 (11.1)	7 (8.4)
Discharge antithrombotic							
Single antiplatelet	6046 (25.1)	211 (22.3)	153 (26.4)	181 (25.7)	113 (24.1)	21 (15.6)	19 (22.9)
Dual antiplatelet	14319 (59.6)	649 (68.5)	339 (58.4)	394 (55.9)	275 (58.8)	87 (64.4)	40 (48.2)
Oral anticoagulant	1283 (5.3)	51 (5.4)	54 (9.3)	46 (6.5)	40 (8.5)	17 (12.6)	*
No record	2392 (10.0)	36 (3.8)	34 (5.9)	84 (11.9)	40 (8.5)	10 (7.4)	22 26.5)

***** = *frequency count is < 5,* ***ACS*** *= acute coronary syndrome,* ***BMI*** *= body mass index,* ***CKD*** *= chronic kidney disease,* ***COPD*** *= chronic obstructive pulmonary disease,* ***eGFR*** *= estimated glomerular filtration rate,* ***ENT*** *= ear, nose, throat,* ***IQR*** *= interquartile range,* ***MI*** *= myocardial infarction,* ***n*** *= number of patients in each category,* ***NSAID*** *=*

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non-steroidal anti-inflammatory drugs, ***NSTEMI =*** *Non ST-elevation myocardial infarction,* ***PCI =*** *percutaneous coronary intervention,* ***PVD =*** *peripheral vascular disease,* ***SD =*** *standard deviation,* ***SSRI =*** *selective serotonin re-uptake inhibitors,* ***STEMI =*** *ST-elevation myocardial infarction.*

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Table S3. The change in hazard of bleeding for each (statistically significant) predictor that was included as a time dependent coefficient in the competing risk model.

Outcome	Predictors	Baseline Hazard* *(sHR (95% CI)*	Change in baseline hazard for each day post hospital discharge *(sHR (95% CI)*	Risk of bleeding at 30 days after hospital discharge† *(sHR (95% CI)*	Risk of bleeding at 365 days after hospital discharge† *(sHR (95% CI)*
All bleed	Age > 80 years	1.42 (1.22 to 1.66)	0.99921 (0.99839, 1.00003)	1.39 (1.16 to 1.67)	1.06 (0.67, 1.68)
	PCI	1.26 (1.11 to 1.43)	0.99907 (0.99840, 0.99974)	1.22 (1.05 to 1.41)	0.89 (0.62, 1.30)
	Dual antiplatelet	0.81 (0.72 to 0.93)	1.00211 (1.00134, 1.00289)	0.87 (0.74 to 1.01)	1.76 (1.16, 2.44)
Respiratory/ent bleeds	Cancer	1.86 (1.26 to 2.74)	0.99659 (0.99383, 0.99934)	1.68 (1.05 to 2.69)	0.53 (0.13, 2.20)
	PCI	1.87 (1.37 to 2.54)	0.99674 (0.99494, 0.99853)	1.69 (1.18 to 2.43)	0.57 (0.22, 1.55)
Gastrointestinal bleeds	Dual antiplatelet	0.67 (0.49 to 0.91)	1.00281 (1.00103, 1.00460)	0.73 (0.50 to 1.05)	1.86 (0.71, 4.25)

** = Immediate hazard from day of hospital discharge,* † *= estimated as exponentiated* $^{((Ln\ (change\ in\ baseline\ hazard)*time\ post\text{-}discharge\ (i.e.\ 30\ or\ 365\ days\ post\text{-}discharge))\ +\ Ln\ (baseline\ hazard))}$*,* ***ENT*** *= ear, nose, throat,* ***PCI =*** *percutaneous coronary intervention.*

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Table S4. Characteristics associated with bleeding events within 12 months post-hospital discharge for ACS.

Characteristics		Unadjusted		Adjusted*	
Demographics		*sHR (95% CI)*	*P-value*	*sHR (95% CI)*	*P-value*
Age (years)					
	≤ 65	1.00		1.00	
	66 - 80	**1.39 (1.28 to 1.51)**	P<0.001	**1.20 (1.10 to 1.31)**	P<0.001
	> 80	**1.55 (1.43 to 1.69)**	P<0.001	**1.42‡ (1.22 to 1.66)**	P<0.001
Female		**1.32 (1.23 to 1.40)**	P<0.001	**1.19 (1.11 to 1.28)**	P<0.001
BMI (kg/m^2)					
	Normal weight *(18.50 to < 25)*	1.00		1.00	
	Underweight *(< 18.50)*	1.09 (0.81 to 1.45)	0.571	1.01 (0.76 to 1.34)	0.963
	Overweight *(25 to < 30)*	0.92 (0.84 to 1.02)	0.104	0.96 (0.87 to 1.06)	0.410
	Obese *(≥ 30)*	0.93 (0.84 to 1.03)	0.182	0.95 (0.85 to 1.06)	0.354
Smoking Status					
	Non smoker	1.00		1.00	
	Ex-smoker	1.02 (0.94 to 1.12)	0.584	1.05 (0.96 to 1.14)	0.329
	Current smoker	**0.82 (0.75 to 0.91)**	P<0.001	0.96 (0.87 to 1.07)	0.486
Comorbidities					
Diabetes		**1.10**	0.013	0.99	0.812

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	(1.02 to 1.18)		(0.91 to 1.07)	
Hypertension	**1.24 (1.15 to 1.34)**	P<0.001	**1.13 (1.05 to 1.21)**	0.001
Heart failure	1.02 (0.91 to 1.14)	0.703	**0.87 (0.78 to 0.97)**	0.016
Cancer	**1.14 (1.04 to 1.26)**	0.006	1.06 (0.96 to 1.17)	0.232
PVD	**1.46 (1.25 to 1.71)**	P<0.001	**1.28 (1.09 to 1.50)**	0.003
COPD	**1.44 (1.34 to 1.55)**	P<0.001	**1.29 (1.20 to 1.39)**	P<0.001
CKD (eGFR < 60 mL/min/1.73 m^2)	**1.34 (1.25 to 1.43)**	P<0.001	1.07 (0.99 to 1.16)	0.107
Hyperlipidemia	**1.24 (1.16 to 1.33)**	P<0.001	0.97† (0.86 to 1.09)	0.641
History of bleeding	**2.08 (1.92 to 2.25)**	P<0.001	**1.88 (1.73 to 2.04)**	P<0.001
ACS presentation				
STEMI	1.00		1.00	
NSTEMI	**1.17 (1.06 to 1.30)**	0.002	1.06 (0.95 to 1.18)	0.292
ACS not otherwise specified	1.04 (0.94 to 1.16)	0.466	1.00 (0.89 to 1.12)	0.978
In-hospital procedure				
PCI	**0.92 (0.86 to 0.99)**	0.019	**1.26‡ (1.11 to 1.43)**	P<0.001
Drug Therapy				
Baseline NSAIDs	**1.11 (1.00 to 1.22)**	0.042	**1.13 (1.02 to 1.25)**	0.017
Baseline SSRIs	**1.22 (1.09 to 1.37)**	P<0.001	1.09 (0.97 to 1.22)	0.142
Discharge antithrombotic				
Single antiplatelet	1.00		1.00	

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Dual antiplatelet	1.00 (0.92 to 1.08)	0.962	**0.81**† **(0.72 to 0.93)**	0.002
Oral anticoagulant	**1.39 (1.21 to 1.60)**	P<0.001	**1.35 (1.17 to 1.55)**	P<0.001
No record	0.90 (0.80 to 1.03)	0.117	1.07‡ (0.88 to 1.30)	0.469

** = adjusted for year of hospital discharge, geographic region, general practice, and all listed characteristics in the table,* † *= included as time dependent coefficient – estimated sHR at day of hospital discharge but increases with time post-discharge,* ‡ *= included as time dependent coefficient – estimated sHR at day of hospital discharge but decreases with time post-discharge,* ***1.00*** *= reference category,* ***ACS*** *= acute coronary syndrome,* ***BMI*** *= body mass index,* ***Bold text*** *= indicates statistically significant predictors of bleeding at the 5% threshold,* ***CI*** *= confidence interval,* ***CKD*** *= chronic kidney disease,* ***COPD*** *= chronic obstructive pulmonary disease,* ***eGFR*** *= estimated glomerular filtration rate,* ***IQR*** *= interquartile range,* ***MI*** *= myocardial infarction,* ***n*** *= number of patients in each category,* ***NSAID*** *= non-steroidal anti-inflammatory drugs,* ***NSTEMI*** *= Non ST-elevation myocardial infarction,* ***PCI*** *= percutaneous coronary intervention,* ***PVD*** *= peripheral vascular disease,* ***sHR*** *= subhazard ratio,* ***SSRI*** *= selective serotonin re-uptake inhibitors,* ***STEMI*** *= ST-elevation myocardial infarction.*

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Table S5. Characteristics independently associated with bleeding events in the imputed and complete case analysis.

Characteristics	Imputed data analysis* (n = 27660) Bleeding events (n = 3620)		Complete case analysis* (n = 16273) Bleeding events (n = 2259)	
Demographics	sHR (95% CI)	P-value	sHR (95% CI)	P-value
Age (years)				
≤ 65	1.00		1.00	
66 - 80	**1.20 (1.10 to 1.31)**	P<0.001	**1.14 (1.02 to 1.27)**	0.019
> 80	**1.42‡ (1.22 to 1.66)**	P<0.001	**1.50‡ (1.22 to 1.84)**	P<0.001
Female	**1.19 (1.11 to 1.28)**	P<0.001	**1.14 (1.05 to 1.25)**	0.003
BMI (kg/m^2)				
Normal weight (BMI 18.50 to < 25)	1.00		1.00	
Underweight (BMI < 18.50)	1.01 (0.76 to 1.34)	0.963	1.09 (0.81 to 1.47)	0.579
Overweight (BMI 25 to < 30)	0.96 (0.87 to 1.06)	0.410	0.99 (0.90 to 1.10)	0.907
Obese (BMI ≥ 30)	0.95 (0.85 to 1.06)	0.354	0.98 (0.88 to 1.09)	0.674
Smoking Status				
Non smoker	1.00		1.00	
Ex-smoker	1.05 (0.96 to 1.14)	0.329	1.03 (0.92 to 1.15)	0.609
Current smoker	0.96 (0.87 to 1.07)	0.486	0.92 (0.80 to 1.05)	0.194
Comorbidities				
Diabetes	0.99 (0.91 to 1.07)	0.812	1.04 (0.96 to 1.14)	0.341

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Hypertension	**1.13 (1.05 to 1.21)**	0.001	**1.11 (1.02 to 1.22)**	0.020
Heart failure	**0.87 (0.78 to 0.97)**	0.016	**0.85 (0.75 to 0.98)**	0.024
Cancer	1.06 (0.96 to 1.17)	0.232	1.10 (0.97 to 1.24)	0.126
PVD	**1.28 (1.09 to 1.50)**	0.003	**1.33 (1.10 to 1.61)**	0.003
COPD	**1.29 (1.20 to 1.39)**	P<0.001	**1.24 (1.14 to 1.36)**	P<0.001
CKD (eGFR < 60 mL/min/1.73 m^2)	1.07 (0.99 to 1.16)	0.107	1.06 (0.96 to 1.18)	0.231
Hyperlipidemia	0.97† (0.86 to 1.09)	0.641	0.98† (0.84 to 1.15)	0.843
History of bleeding	**1.88 (1.73 to 2.04)**	P<0.001	**1.85 (1.67 to 2.06)**	P<0.001
ACS presentation				
STEMI	1.00		1.00	
NSTEMI	1.06 (0.95 to 1.18)	0.292	1.14 (0.99 to 1.31)	0.063
Not otherwise specified	1.00 (0.89 to 1.12)	0.978	1.03 (0.90 to 1.18)	0.640
In-hospital procedure				
PCI	**1.26‡ (1.11 to 1.43)**	P<0.001	**1.30‡ (1.10 to 1.53)**	0.002
Drug Therapy				
Baseline NSAIDs	**1.13 (1.02 to 1.25)**	0.017	1.13 (1.00 to 1.28)	0.057
Baseline SSRIs	1.09 (0.97 to 1.22)	0.142	1.11 (0.96 to 1.29)	0.146
Discharge antithrombotic				
Single antiplatelet	1.00		1.00	
Dual antiplatelet	**0.81**†	0.002	0.85†	0.056

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	(0.72 to 0.93)		(0.71 to 1.00)	
Oral anticoagulant	**1.35 (1.17 to 1.55)**	P<0.001	**1.38 (1.16 to 1.65)**	P<0.001
No record	1.07‡ (0.88 to 1.30)	0.469	1.12‡ (0.88 to 1.42)	0.366

** = adjusted for year of hospital discharge, geographic region, general practice, and all listed characteristics in the table,* † *= included as time dependent coefficient – estimated sHR at day of hospital discharge but increases with time post discharge,* ‡ *= included as time dependent coefficient – estimated sHR at day of hospital discharge but decreases with time post discharge,* ***1.00*** *= reference category,* ***ACS*** *= acute coronary syndrome,* ***BMI*** *= body mass index,* ***Bold text*** *= indicates statistically significant predictors of bleeding at the 5% threshold,* ***CI*** *= confidence interval,* ***CKD*** *= chronic kidney disease,* ***COPD*** *= chronic obstructive pulmonary disease,* ***eGFR*** *= estimated glomerular filtration rate,* ***IQR*** *= interquartile range,* ***MI*** *= myocardial infarction,* ***n*** *= number of patients in each category,* ***NSAID*** *= non-steroidal anti-inflammatory drugs,* ***NSTEMI*** *= Non ST-elevation myocardial infarction,* ***PCI*** *= percutaneous coronary intervention,* ***PVD*** *= peripheral vascular disease,* ***sHR*** *= subhazard ratio,* ***SSRI*** *= selective serotonin re-uptake inhibitors,* ***STEMI*** *= ST-elevation myocardial infarction.*

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Supplemental References:

(1) Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, Smeeth L. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; 44: 827–836.

(2) Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, Smeeth L. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. *J Public Health (Oxf)* 2014; 36: 684–92.

(3) KDIGO. *Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*. 2013. Epub ahead of print 2013. DOI: doi:10.1038/kisup.2012.72.