Bayer HealthCare

Cover Page

Report No.: PH-39786 **2017-05-17**
Version No.: 1.0

Title:
A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK

Test Compound Number(s): BAYE004465

INN/Generic Name:
Acetylsalicylic acid

Trade Name: ASPIRIN

Study Number: 18116

PASS information Study Information

Title	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK
Version identifier of the final study report	Version 1.0 IMPACT 18116
Date of last version of the final study report	NA
EU PAS register number	EUPAS 10837
Active substance	Acetylsalicylic acid
Product	ASPIRIN
Product reference	
Procedure number	
Marketing authorisation holder(s)	Bayer AG (Bayer Pharma AG at the time the study was initiated) (Note: Bayer AG's low-dose Aspirin is not registered in the UK. This study examined use of low-dose aspirin in the UK, irrespective of the marketing authorization holder)
Joint PASS	No

Research question and objectives	To evaluate the risk of intracranial bleeding (ICB) upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB) associated with new use of low-dose ASA in clinical practice. The primary objectives were to i) estimate the incidence of ICB, LGIB and LGIB in new users of low-dose ASA, and ii) to estimate the risk of ICB, UGIB and LGIB associated with new user of low-dose ASA, including by sex and age, and to establish any duration or dose–response associations. The secondary objective was to estimate the relative risk of ICB, UGIB, and LGIB associated with use of other medications including clopidogrel, oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs), both independently from use of low-dose ASA and concomitantly.
Country(-ies) of study	The study was carried out using The Health Improvement Network (THIN) primary care electronic medical record database in the United Kingdom.
Authors	

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Bayer AG, 51368 Leverkusen, Germany
MAH contact person	

Study Description	
Study Sponsor:	Bayer AG
Study Number:	IMPACT 18116
Study Phase:	Post-authorization
Official Study Title:	New use of low-dose acetylsalicylic acid and risk of major bleeding: a cohort study with nested case–control analyses in the United Kingdom.
Therapeutic Area:	Established products
Product	
Name of observed Product:	Aspirin, BAY e 4465
Name of Active Ingredient:	Acetylsalicylic acid (ASA)
Dose and Mode of Administration:	oral administration; dose 75–300mg/day
Reference Therapy	
Reference Therapy:	Never use of low-dose ASA
Dose and Mode of Administration:	NA
Duration of Treatment:	NA
Studied period:	Date of first patient observation: 01/01/2000 Date of last patient observation: 31/12/2013
Study Center(s):	This was an observational study carried out using pre-collected anonymized electronic medical record patient data from UK primary care pratices. The analysis of these data was carried out at the Spanish Centre for Pharmacoepidemiologic Research, Madrid, Spain.

Methodology:	Among a study population with no prior use of low-dose ASA, two population-based cohorts from The Health Improvement Network (THIN) primary care database in the UK were identified – new users of low-dose ASA at the start of follow-up (N=199,079) and a matched comparison cohort of individuals free of low-dose ASA at the start of follow-up (N=199,079). To address the research objectives, the research program involved three separate follow-ups of the two study cohorts, with subsequent nested case–control analysis at the end of each follow-up. The two study cohorts were followed-up for up to 13 years to ascertain incident cases of the major bleeding outcomes of interest (intracranial bleeding [ICB], upper gastrointestinal bleedin [UGIB] and lower gastrointestinal bleeding [LGIB]). Incidence rates of the bleeding outcomes with 95% confidence intervals (CIs) were calculated. Three separate nested case–control analyses were performed (one for each bleeding outcome) to estimate the association between new use of low-dose ASA (versus never use) and each of the bleeding outcomes. Individuals from both cohorts who experienced a bleeding event (index date) were used as cases. Frequency-Controls (frequency-matched) were selected from both cohorts using incidence density sampling; the index date for controls was a random date within their eligible follow-up time.
Indication/ Main Inclusion Criteria:	Individuals were required to meet the following inclusion criteria before being eligible to enter the study: • at least 2 years' registration with the primary care practitioner (PCP) • at least 1 year previous computerized prescription history • at least one encounter/visit recorded in the previous 3 years. The date an individual met all these criteria was considered the study entry date. Individuals were excluded if they had a prescription for low-dose ASA (75 or 300 mg; tablets available in the UK) for the prevention of cardiovascular disease or a diagnosis of cancer, alcohol abuse, coagulopathies, oesophageal varices or chronic liver disease any time before study entry. Individuals aged ≥60 years with a follow-up longer than 1 year and with fewer than two recorded consultations with a PCP during their entire follow-up (a proxy for incomplete and/or invalid data recording) were also excluded. Individuals eligible to enter one of the two study cohorts were followed up until study entry date until one of the following endpoints, whichever came first: a first prescription for low-dose ASA, diagnosis of cancer, alcohol abuse, coagulopathies, oesophageal varices, chronic liver disease, age 85 years, death, 31 December 2012 (end of enrolment follow-up).

	Individuals whose first endpoint was a prescription for low-dose ASA entered the new users of low-dose ASA cohort, and each member of this cohort was matched 1:1 to a person free of low-dose ASA on this day (a membr of the non-user cohort) by age, sex, time since study entry and number of primary care practitioner visits in the previous year. The two cohorts were then followed up to 31 December 2013 to identify bleeding outcomes.
Study Objectives:	Primary objectives were: • to estimate the incidence and time to event of ICB, UGIB and lower gastrointestinal bleeding (LGIB) among new users of low-dose ASA in the UK general population. • to estimate the relative risk of ICB, UGIB and LGIB associated with use of low-dose ASA overall, and in age- and sex-specific strata, compared with never-use of low-dose ASA. • to analyze the duration and dose–response of low-dose ASA use on the risk of ICB, UGIB and LGIB. The secondary objective was to estimate the relative risk of ICB, UGIB, and LGIB associated with use of other medications including clopidogrel, oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs), both independently from use of low-dose ASA and concomitantly.
Evaluation Criteria:	Primary objective: the occurrence of ICB, UGIB and LGIB association with new users of low-dose ASA (compared with never use of low-dose ASA) including by recency of use, duration of use and dose. Secondary objective: the occurrence of ICB, UGIB, and LGIB associated with use of other medications including clopidogrel, oral anticoagulants, non-steroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors, both independently from use of low-dose ASA and concomitantly.
Statistical Methods:	In the cohort analyses, incidence rate ratios (RRs) were calculated comparing the incidence rate of each bleeding outcome in the low-dose ASA cohort versus the non-user (at start of follow-up) cohort. In the nested case–control analyses (for the primary and secondary objectives), multivariate adjusted unconditional logistic regression adjusting for potential confounding variables was used to estimate odds ratios (with 95% CIs) for the association between new use of low-dose ASA and each bleeding outcome. Controls for the nested case–control analyses were frequency-matched and selected by incidence density

	sampling – under this design, the odds ratio is an unbiased estimate of the incidence RR.
Number of Participants:	There was a total of 2,354,840 individuals in the source population before exclusion criteria were applied. From the eligible source population, and following application of exclusion criteria, a total of 199,079 individuals entered the low-dose ASA cohort and, owing to the 1:1 matching in the study design, 199,079 individuals (free of low-dose ASA use at the start of follow-up) entered the non-user cohort.
Early Termination:	NA, this was an observational study.
Substantial Protocol Changes:	There were no substantial protocol changes.

Study Results

A total of 1611 individuals suffered an ICB during follow-up, 881 (54.7%) in the low-dose ASA cohort and 730 (45.3%) in the comparison cohort. The distribution of ICB cases by site of bleed was as follows: 46.1% (743/1611) for intracerebral haemorrhage (ICH), 30.0% (483/1611) for subdural haematoma (SDH) and 23.7% (385/1611) for subarachnoid haemorrhage (SAH). A quarter of all ICB cases (25.0%, n=402) were fatal cases, and approximately a quarter of all ICB cases (27.0%; n=435) were recorded as trauma-related; almost two-thirds of trauma-related cases of ICB (63.9%; n=278) were cases of SDH. A total of 1843 suffered an episode of UGIB during follow-up, 1115 (60.5%) in the low-dose ASA cohort and 728 (39.5%) in the comparison cohort. Sixty per cent of UGIB cases (n=1106) were hospitalized. Under 7% (6.9%, n=128) UGIB cases were fatal.

Incidence rates (95% CIs) of bleeding outcomes over the whole follow-up period in the low-dose ASA and comparison cohort, respectively, were 7.61 vs. 6.78 cases per 10,000 person-years for ICB (3.52 vs. 3.12 per 10,000 person-years for ICH, 2.45 vs. 1.86 per 10,000 person-years for SDH and 1.65 vs. 1.80 per 10,000 person-years for SAH), 0.97 vs. 0.67 per 1000 person-years for UGIB and 1.68 vs. 0.76 per 1000 person-years for LGIB. Incidence rate ratios (low-dose ASA vs. comparison cohort) over the whole duration of the follow-up were 1.11 (95% CI: 1.01–1.22) for all ICB, 1.12 (95% CI: 0.97–1.29) for ICH, 1.28 (95% CI: 1.07–1.53) for SDH, 0.92 (95% CI: 0.75–1.13) for SAH, 1.42 (95% CI: 1.29–1.56) for UGIB and 2.17 (95% CI: 2.00–2.35) for LGIB. The IRR in the first year of follow-up was 1.02 (95% CI: 0.81–1.29) for all cases of ICB, 1.80 (95% CI: 1.46–2.22) for UGIB and 2.30 (95% CI: 1.91–2.77) for LGIB.

Compared with individuals who had never used low-dose ASA, no significant change in risk of ICB was seen among current users of low-dose ASA (RR 0.98, 95% CI: 0.84–1.13); this lack of association was observed for both sexes for ICH and SDH, whereas a significant 43% decreased risk of SAH was seen among women (RR 0.57, 95% CI: 0.39–0.82; no association apparent in men). For GIB, current users of low-dose ASA had an increased risk of UGIB (RR 1.62, 95%

CI:1.40–1.87) and LGIB (1.97, 95% CI: 1.75–2.22) compared with never users.

Analyses stratified by case-fatality status showed that, compared with never users of low-dose ASA, current use was not associated with a significant change in risk of fatal UGIB or LGIB, and was associated with a significant 37% decreased risk of fatal ICB (RR 0.63, 95% CI: 0.48–0.82). No significant change in the risk of non-fatal ICB was seen with current use of low-dose ASA (compared with never use) while the risk of non-fatal UGIB and non-fatal LGIB was significantly raised, approaching a two-fold increased risk: RR 1.73 (95% CI: 1.49–2.01) for non-fatal UGIB and RR 1.98 (95% CI: 1.76–2.23) for non-fatal LGIB.

Among current users of low-dose ASA, short-, medium- or long-term use was not associated with a significant change in risk of ICB, when considering all cases types of ICB as a single group, and compared with never users. Some duration of use associations were seen when evaluating current use of low-dose ASA and risk of individual ICB subtypes or after stratification by trauma/non-trauma-related status. For example, a significant 33% decrease in risk of SAH was seen with long-term use (1–<5 years; RR 0.67, 95% CI: 0.47–0.94), while a two-fold significant increase in risk was seen for traumatic SDH with short-term use (<3 months; RR 1.96, 95% CI: 1.10–3.48), and a borderline significant increased risk of all traumatic cases of ICB was seen with medium-term use (RR 1.83, 95% CI: 1.07–3.13 for 3–<6 months and RR 1.68, 95% CI: 1.06–2.64 for 6 months–<1 year). Current use of low-dose ASA was associated with significantly increased risks of UGIB and LGIB when used either in the short- medium- or long-term, and no clear relationships between duration of low-dose ASA and risk of UGIB or LGIB were apparent. No significant dose–response relationship between current use of low-dose ASA and risk of ICB or LGIB for the doses of ASA evaluated in this study (75 mg–300 mg per day), however, the results were suggestive of a dose–response relationship between low-dose ASA and UGIB (RR 1.30, 95% CI: 0.93–1.83) for current user of low-dose ASA at a dose or 75 mg/day compared with current use of low-dose ASA at a dose of more than 75 mg/day).

For all bleeding outcomes, use of DAT always carried a greater risk than the sum of each antiplatelet used in monotherapy. Current use of DAT was associated with a two-fold risk of traumatic ICB (RR 2.09, 95% CI: 1.13–3.89); the effect being restricted to cases of traumatic SDH (RR 2.29, 95% CI: 1.09–4.80), and a three-to-four-fold risk of GIB; RR 3.87 (95% CI: 2.73–5.50) for UGIB and 3.33 (95% CI: 2.47–4.48) for LGIB, when compared with never use of either medication. Compared with never use of either medication, concomitant current use of low-dose ASA and warfarin was associated with a two-fold significantly increased risk of ICB (RR 2.31, 95% CI: 1.36–3.91); the effect being restricted to cases of SDH (RR 4.43, 95% CI: 2.16–9.09) with an eight-fold increased risk seen among non-traumatic cases of SDH (RR 8.63, 95% CI: 3.57–20.86), when compared with never users of either low-dose ASA or warfarin. Similar to the findings for DAT, current use of low-dose ASA and warfarin was associated with a three to four-fold increased risk of UGIB (RR 3.35, 95% CI: 2.01–5.60) and LGIB (RR 3.76, 95% CI: 2.43–5.82).

Conclusion New use of low-dose ASA is not associated with a significant increase in the risk of ICB overall compared with never use, and may be associated with a significantly decreased risk of fatal ICB, and of SAH in women or when used for a long duration. The risk of non-fatal UGIB and LGIB events is significantly higher among new users of low-dose ASA compared with never users, but not significantly different for fatal cases of UGIB or LGIB when compared with never users. These estimates should be weighed against the cardiovascular and CRC benefits of low-dose ASA to make an informed risk–benefit evaluation of low-dose ASA use in the general population.	
Publication:	Lucía Cea Soriano, David Gaist, Montse Soriano-Gabarró, Luis A. García Rodríguez. Incidence of intracranial bleeds in new users of low-dose aspirin: a cohort study using The Health Improvement Network. Accepted for publication by Journal of Thrombosis and Haemostasis on 11 March 2017
Date Created or Date Last Updated:	31 March 2017

Table of Contents

1. Abstract

Title

New use of low-dose acetylsalicylic acid and risk of major bleeding: a cohort study with nested case–control analyses in the United Kingdom.

Keywords

low-dose acetylsalicylic acid; intracranial bleeds; upper gastrointestinal bleeds; lower gastrointestinal bleeds; nested case–control

Rationale and background

Use of low-dose acetylsalicylic acid (ASA) reduces the risk of ischaemic cardiovascular events and colorectal cancer (CRC) but may increase the risk of major bleeding events. Evaluations on the safety profile of low-dose ASA are warranted for incorporation into risk–benefit evaluations regarding long-term use in the general population.

Research question and objectives

To evaluate the risk of intracranial bleeding (ICB), upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB) associated with new use of low-dose ASA in clinical practice. The primary objectives were to i) estimate the incidence of ICB, LGIB and LGIB in new users of low-dose ASA, and ii) estimate the risk of ICB, UGIB and LGIB associated with new use of low-dose ASA, including by sex and age, and to establish any duration or dose–response associations.

Study design

Cohort study with nested case–control analyses.

Setting

UK general practice between 01 January 2000 and 31 December 2013.

Subjects and Study Size, including dropouts

199,079 individuals in the low-dose ASA cohort and 199,079 individuals in the comparison cohort followed for up to 13 years.

Variables and Data sources

The Health Improvement Network UK (THIN) primary care database of anonymized patient electronic medical records. Demographics, lifestyle factors, comorbidities and medication use were assessed for potential confounding effects and included in the analyses where required.

Results

There were 1611 incident cases of ICB, 1843 cases of UGIB and 2763 cases of LGIB (median follow-up of 5.4 years for each outcome). Among the low-dose ASA cohort and comparison cohort, respectively, incidence rates per 10,000 person-years were 3.52 vs. 3.12 for intracerebral haemorrhage (ICH), 2.45 vs. 1.86 for subdural haematoma (SDH) and 1.65 vs. 1.80 for subarachnoid haemorrhage (SAH). Comparable rates per 1000 person-years were 0.97 vs. 0.67 for UGIB and 1.68 vs .0.76 for LGIB.

Rate ratios (RRs; 95% CIs) for ICB with current use of low-dose ASA vs. never use were 0.98 (0.84–1.13) for ICB, 0.88 (0.74–1.03) for non-traumatic ICB, 1.30 (1.00–1.68) for traumatic ICB, 0.63 (0.48–0.82) for fatal ICB, 1.14 (0.97–1.35) for non-fatal ICB, 0.98 (0.80–1.20) for ICH, 1.23 (0.95–1.59) for SDH and 0.77 (0.58–1.01) for SAH. A significant 43% decreased risk of SAH was seen among women (RR 0.57, 95% CI: 0.39–0.82) but no corresponding association in men. Corresponding RRs (95% CIs) for gastrointestinal bleeding were 1.62 (1.40–1.87) for UGIB, 0.75 (0.49–1.15) for fatal UGIB, 1.73 (1.49–2.01) for non-fatal UGIB, 1.97 (1.75–2.22) for LGIB, 1.06 (0.40–2.81) for fatal LGIB and 1.98 (1.76–2.23) for non-fatal LGIB.

Discussion

Compared with never use, new use of low-dose ASA is not associated with a significant increase in the risk of ICB overall and may be associated with a significantly decreased risk of fatal ICB, and of SAH in women, or when used for a long duration. An approximate two-fold significant increased risk of non-fatal UGIB and LGIB was seen with new use of low-dose ASA but no association was seen with risk of fatal UGIB or LGIB, when compared with never use. These estimates should be weighed against the cardiovascular and CRC benefits of low-dose ASA to make an informed risk–benefit evaluation of low-dose ASA use in the general population.

Marketing Authorisation Holder(s)

Bayer AG

Names and affiliations of principal investigators

2. List of abbreviations

AHI	additional health information
ASA	acetylsalicylic acid
BMI	body mass index
CEIFE	Centro Español de Investigación Farmacoepidemiológica
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COXIB	cyclooxygenase-2 (COX-2) inhibitor
CRC	colorectal cancer
CVD	cardiovascular disease
DAT	dual antiplatelet therapy
DVT	deep vein thrombosis
EMRs	electronic medical records
GERD	gastroesophageal reflux disease
GI	gastroinestinal
GIB	gastrointestinal bleed
HES	Hospital Episode Statistics
HR	hazard ratio
H_2RA	H_2–receptor antagonist
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICB	intracranial bleeding / intracranial bleed
ICD	International Classification of Diseases
ICH	intracerebral haemorrhage
IHD	ischaemic heart disease
INR	international normalized ratio
IRR	incidence rate ratio
ITT	Intention-to-treat
LGIB	lower gastroinestinal bleeding
MAH	Marketing Authorization Holder
MI	myocardial infarction
NA	not applicable
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PAD	peripheral artery disease
PASS	Post-Authorization Safety Study
PCP	primary care practitioner
PPI	proton pump inhibitor
PPV	positive predictive value
PU	peptic ulcer
RCT	randomized controlled trials
RR	rate ratio

SAH	subarachonid haemorrhage
SD	standard deviation
SDH	subdural haemorrhage
RR	relative risk
SSRI	selective serotonin reuptake inhibitor
TIA	transient ischaemic attack
THIN	The Health Improvement Network
UGIB	upper gastrointestinal bleeding
UK	United Kingdom
USPST	United States Preventive Services Task Force
u/w	units per week

4. Other responsible parties

5. Milestones

Table 1. Study milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	01 January 2002	02 January 2002	
End of data collection	31 December 2012	31 December 2012	NA
Registration in the EU PAS register	02 September 2015	02 September 2015	EUPAS number 10837
Draft report 1	–	29 February 2016	Initial results from cohort analyses for ICB
Draft report 2	–	18 May 2016	Initial results from case–control analyses for ICB
Draft report 3	–	29 November 2016	ICB results
Draft report 4	31 October 2016	09 December 2016	GI results
Final report of study results	31 January 2017	15 February 2017	

6. Rationale and background

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for approximately 30% of all deaths.(1) Low-dose acetylsalicylic acid (ASA) is effective in the prevention of ischaemic cardiovascular events owing to its antiplatelet properties; (2) guidelines recommend the long-term use of low-dose ASA for the secondary prevention of cardiovascular events. (3, 4) Historically, there has been some uncertainty regarding the role of low-dose ASA in the primary prevention of ischaemic CVD. The accumulation of evidence regarding the chemoprotective effects of ASA, however, especially in reducing colorectal cancer (CRC) incidence and mortality, has influenced expert opinion in favour of use of low-dose ASA for primary CVD prevention in certain patient populations, owing to a favourable risk–benefit profile. (5-7) While U.S. guidelines now recommend use of low-dose ASA in individuals without symptomatic CVD aged ≥50 years, (5) a Position Paper of the European Society of Cardiology Working Group of Thrombosis recommends use of low-dose ASA in patients at high cardiovascular risk who are not at increased risk of bleeding.(6) The United States Preventive Services Task Force (USPST) also includes an assessment of bleeding risk in their recommendations for use of low-dose ASA for primary CVD prevention. The USPST specifically recommends long-term use of low-dose ASA for the primary prevention of both CRC and CVD among middle-aged men and women who have a 10% or greater 10-year CVD risk and are not at elevated risk of bleeding. (7) In a recent meta–analysis by Xie et al,(8) of 14 randomized controlled trials (RCTs) providing data on ASA in primary prevention, the authors reported a 10% reduction in major cardiovascular events (relative risk: 0.90, 95% confidence interval [CI]: 0.85–0.95) and a 6% decrease in all-cause mortality (relative risk: 0.94, 95% CI: 0.89–0.99), but also a 34% increase in the risk of intracranial bleeds (ICBs; RR 1.34, 95% CI: 1.01–1.79) and a 55% increase in all major bleeding events (RR 1.55, 95% CI: 1.35–1.78).

For any drug therapy, it is important that an accurate overall risk–benefit assessment is made. Although relative risks are useful in estimating the relative effects of drug therapies, attributable risks are considered to have greater public health relevance as they take into account the baseline incidence of the event of interest. Thus, a rare adverse outcome with a high relative risk may be of less clinical importance than a frequent event with a low relative risk. The Spanish Centre for Pharmacoepidemiologic Research (CEIFE) have previously independently carried out a series of studies involving approximately 40,000 patients with either ischaemic heart disease (IHD) or cerebrovascular disease who were newly prescribed low-dose ASA for secondary CVD prevention. This previous programme of research has found that approximately 30% of new users of low-dose ASA ended up having at least one episode of discontinuing their low-dose ASA therapy. (9) Moreover, it showed that for every 1000 patients, discontinuation of low-dose ASA in the first year of therapy accounts for an increase of eight ischaemic events (five events of non-fatal myocardial infarction [MI] and three events of ischaemic stroke/transient ischaemic attack [TIA]) and a reduction of 0.4 cases of upper gastrointestinal bleeding (UGIB). (10) Risk management decisions should not only include an evaluation of risk and benefits of a medication but also the consequences of both harms and benefits on quality of life. For example, prevention strategies can be used that

minimize gastrointestinal (GI) problems associated with ASA use, and these have an acceptable safety profile in the general population. Further evaluations on the safety profile (including GI and other major bleeding events) of low-dose ASA in the target population are warranted to establish its role for long-term use in general population.

7. Research Question and objective

This report describes a pharmacoepidemiology safety research programme, initiated and funded by Bayer AG in collaboration with CEIFE, which was designed to investigate the risk of major bleeding events (ICB and GI bleeding) among new users of low-dose ASA in clinical practice. The study was based on two population-based cohorts using data from a primary care database in the United Kingdom (UK) – The Health Improvement Network (THIN; see **Section 9.5**). It is expected that findings from this study will help inform risk–benefit evaluations of low-dose ASA in clinical practice.

7.1 Primary objectives

The primary objectives were:

- to estimate the incidence and time to event of ICB, UGIB and lower gastrointestinal bleeding (LGIB) among new users of low-dose ASA in the UK general population.
- to estimate the relative risk of ICB, UGIB and LGIB associated with use of low-dose ASA overall, and in age- and sex-specific strata, compared with never-use of low-dose ASA.
- to analyze the duration and dose–response of low-dose ASA use on the risk of ICB, UGIB and LGIB.

7.2 Secondary objectives

The secondary objective was to estimate the relative risk of ICB, UGIB, and LGIB associated with use of other medications including clopidogrel, oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs), both independently from use of low-dose ASA and concomitantly.

8. Amendments and updates

None.

9. Research methods

9.1 Study design

9.1.1 Overall research design

Among a study population with no prior use of low-dose ASA, two population-based cohorts from THIN database in the UK (see **Section 9.5**) were identified – new users of low-dose ASA at the start of follow-up and a matched comparison cohort of individuals still free of low-dose ASA at the start of follow-up. To address the research objectives, the research program involved three separate follow-ups of the two study cohorts, with subsequent nested case–control analysis at the end of each follow-up, which were carried out in UK primary care. The two study cohorts were followed-up to ascertain incident cases of the major bleeding outcomes of interest (ICB, UGIB and LGIB). Nested case–control analyses were performed to estimate the association between new use of low-dose ASA and each of the bleeding outcomes.

The two study cohorts were followed-up from the start date (date of first low-dose ASA prescription for each member of the low-dose ASA cohort; this date was also the start date for their matched partner in the comparison cohort) until the occurrence of a major bleeding outcome or censoring, whichever came first. Three separate follow-ups and nested case–control analyses were performed, one for each bleeding outcome (ICB, UGIB and LGIB). In the case–control analyses, individuals from both cohorts who experienced a bleeding event were used as cases. Controls were selected using incidence density sampling in both cohorts.

The overall study design in depicted in **Figure 1**.

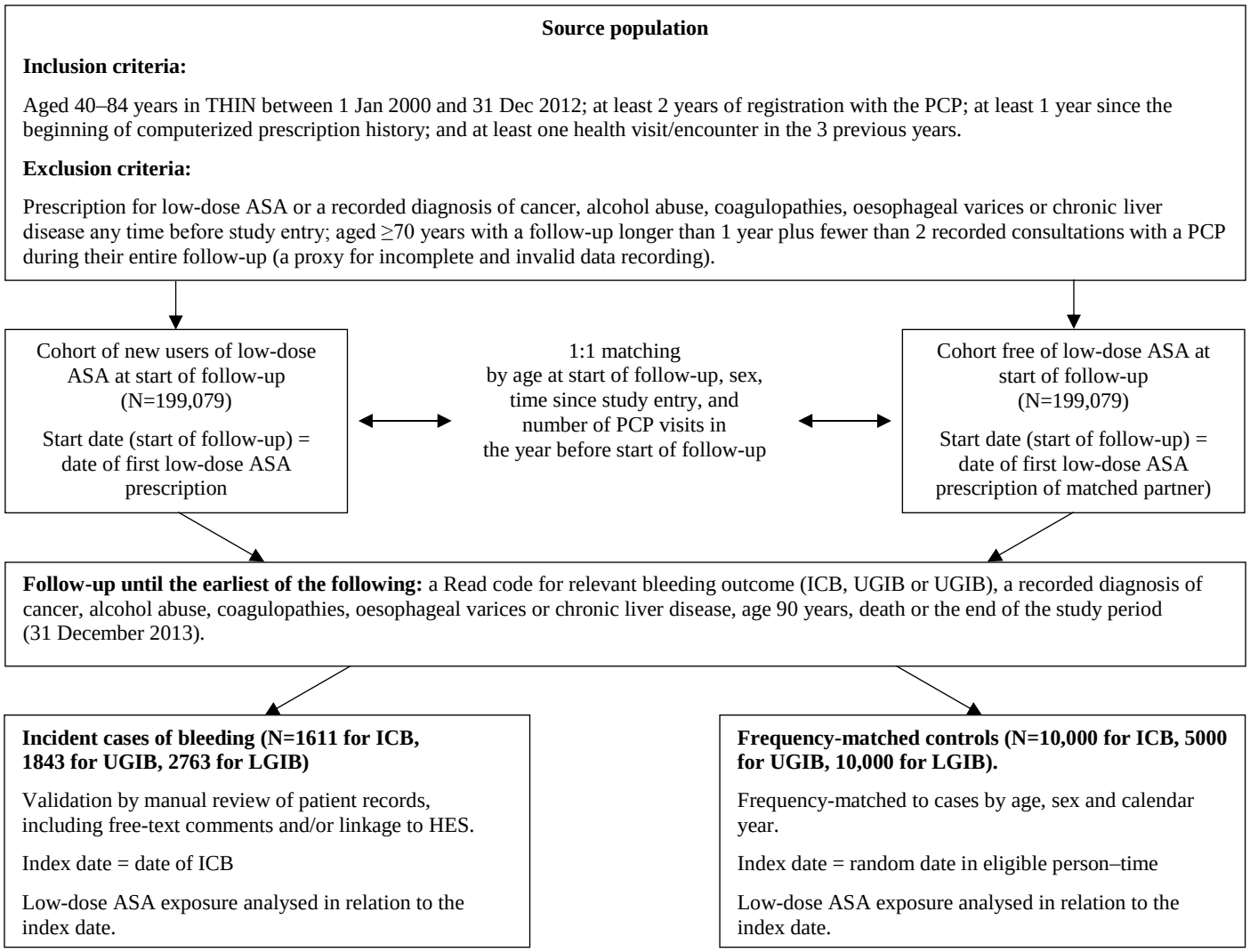

Figure 1. Flowchart depicting the cohort study with nested case–control analysis study design.

9.1.2 Rationale and strengths of the study design

- The rationale for using a cohort study design was the ability to estimate incidence rates of ICB, UGIB and LGIB. Nelson–Aalen cumulative incidence estimates (of the hazard rate function) were produced for all cases of ICB; Kaplan–Meier survival curves were produced for cases of UGIB and LGIB to describe the time to occurrence of both bleeding outcomes.
- The inclusion of only new-users of low-dose ASA in the study cohorts (members of the comparison cohort could have started low-dose ASA during follow-up) enhanced the internal validity of the identified low-dose ASA users, removing the possibility of survivor bias that can occur with the inclusion of prevalent users of a medication.
- Ascertaining all information available on new users of low-dose ASA and for a random sample of the comparison cohort maximized the efficiency of the sample size.
- Matching the comparison cohort to the low-dose ASA cohort for time since date of entry into the study controlled for potential temporal trends in both low-dose ASA use and outcome incidence, thereby reducing confounding. This matching also allowed the same reference period before start of follow-up for baseline information in both cohorts to be collected, thereby increasing the internal validity of the measurement of associations and reducing differential information bias.
- Nested case–control analyses are efficient and may also enhance the internal validity of the study because these analyses permit information to be ascertained on potential confounders for all cases and only a sample of controls. This is particularly efficient when manual review is needed to obtain information for some variables, e.g. ascertaining dosage instructions for medications. It also permits a direct analysis of time-dependent use of medications. In addition, incidence density sampling used in the selection of controls in the nested case–control analyses minimizes bias analyses by competing risks.(11)

9.1.3 Primary endpoints

The primary endpoints in the study were ICB, UGIB and LGIB.

9.1.4 Secondary endpoints

Not applicable. There were no secondary endpoints.

9.1.5 Main measures of effect

The odds ratio (OR) was the main measure of effect in the nested case–control analyses to quantify the association between new use of low-dose ASA and the risk of the study outcomes. Odds ratios are unbiased estimates of the incidence rate ratio (IRR) when incidence density sampling is used.(12)

9.2 Setting

9.2.1 Study time frame

9.2.1.1 Time windows

The study was set in UK general practice between 01 January 2000 and 31 December 2013. Individuals were eligible to enter one of the two study cohorts between 01 January 2000 and 31 December 2012. Data were collected for each study participant at the start of follow-up to assess bleeding outcomes and at time intervals relative to their index date (date of the bleeding episode; see **Section 9.3.4.1** and **Section 9.3.4.2**).The end of follow-up to assess bleeding outcomes was 31 December 2013. **Figure 1** illustrates the time windows in the study design.

9.2.1.2 Index date

Start of follow-up of the two study cohorts was not termed ‘index date’ in this study. The index date instead referred to the date of the bleeding outcomes of interest (see **Section 9.3.4.1** and **Section 9.3.4.2**)

9.2.2 Selection criteria

9.2.2.1 Inclusion criteria

Individuals were required to meet the following inclusion criteria before being eligible to enter the study:

- at least 2 years’ registration with the primary care practitioner (PCP)
- at least 1 year previous computerized prescription history
- at least one encounter/visit recorded in the previous 3 years.

The date an individual met all these criteria was considered the study entry date.

9.2.2.2 Exclusion criteria

Individuals were excluded if they had a prescription for low-dose ASA (75 or 300 mg; tablets available in the UK) or a diagnosis of cancer, alcohol abuse, coagulopathies, oesophageal varices or chronic liver disease any time before study entry. Individuals aged ≥60 years with a follow-up longer than 1 year and with fewer than two recorded consultations with a PCP during their entire follow-up (a proxy for incomplete and/or invalid data recording) were also excluded.

9.2.3 Study population

9.2.3.1 Source

The two study cohorts were drawn from in THIN (see **Section 9.5**) aged 40–84 years between 01 January 2000 and 31 December 2012 (see **Section 9.3.1** and **Figure 2**).

9.2.3.2 Sampling strategy

The sampling strategy for the selection of the two study cohort is described in Section 9.3.2. and **Figure 3**.

9.2.3.3 Representativeness

Individuals in THIN are representative of the UK population with regards to age, sex and geographic distribution, and has been validated for use in pharmacoepidemiologic research (see **Section 9.5.1** for further details).

9.3 Subjects

9.3.1 Source population

The source population for identification of the two cohorts in the study comprised individuals in THIN (see **Section 9.5**) aged 40–84 years between 01 January 2000 and 31 December 2012 (the enrolment period for the two study cohorts) who met the inclusion criteria described in **Section 9.2.2.1** before being eligible to enter the study and who did not have any exclusion criterion described in **Section 9.2.2.2**.

9.3.2 Identification of the two study cohorts

Identification of the two study cohorts is depicted in **Figure 2**. To identify individuals in the low-dose ASA cohort, all members of the source population were followed up from their study entry date until one of the following, whichever came first:

- a first prescription for low-dose ASA
- diagnosis of cancer
- alcohol abuse
- coagulopathies
- oesophageal varices
- chronic liver disease
- age 85 years
- death
- 31 December 2012 (end of enrolment follow-up).

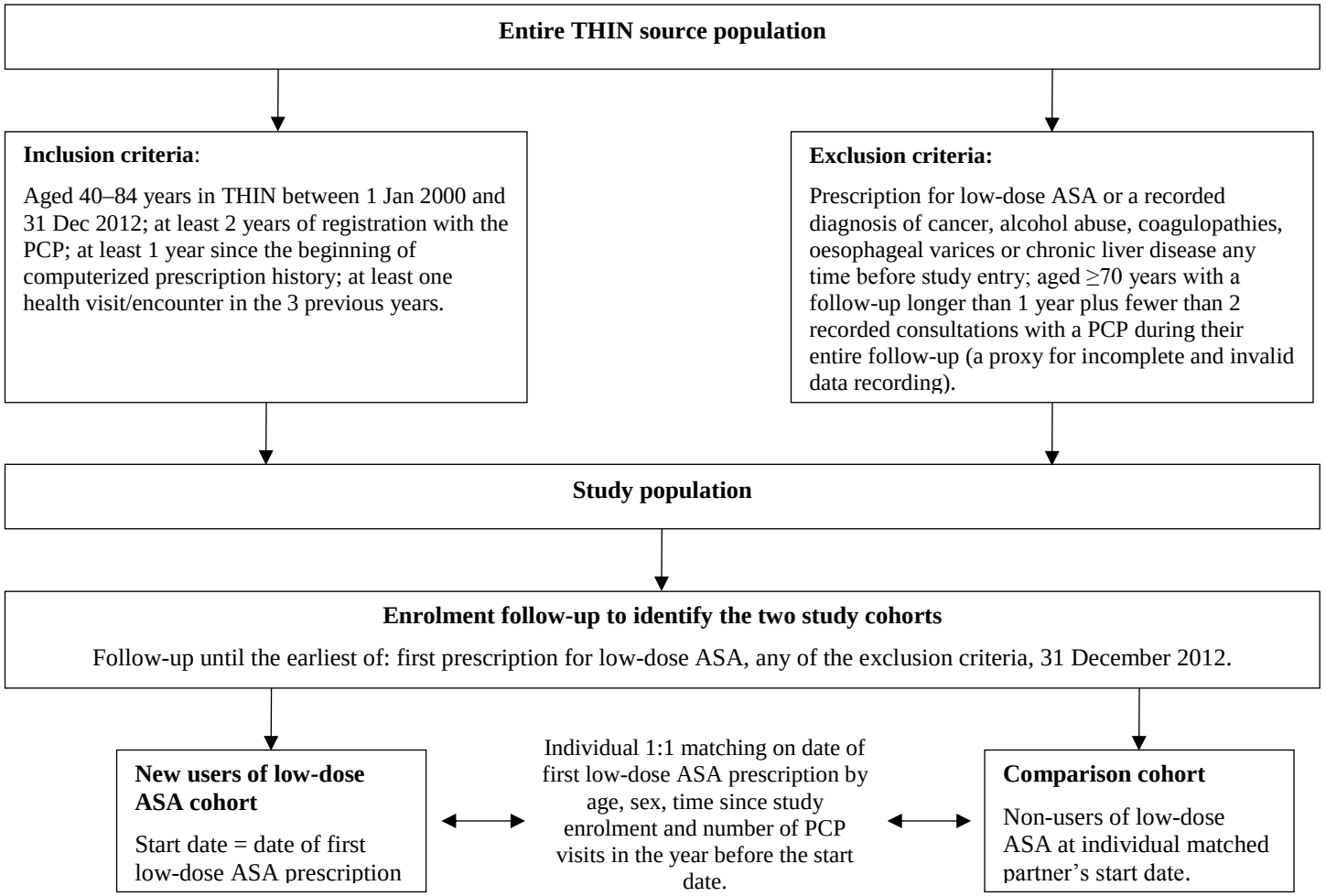

Figure 2. Identification of the two study cohorts from the THIN source population. Note that individuals were assigned only once to the first cohort for which they became eligible.

Each day an individual became newly exposed to low-dose ASA (their start date for the outcomes follow-up), a member of the study population not yet censored and of the same age, sex, time since study entry and number of PCP visits in the year before the start date (cohort matching factors) was identified and designated as the low-dose ASA cohort member's matched 'non-exposed at start of follow-up' partner (**Figure 3**). All non-exposed partners comprised the comparison cohort. This method of concurrent ascertainment of the low-dose ASA cohort and comparison cohort is an emulation of the RCT design. As with RCTs, once an individual became a member of one of the two cohorts, they were not eligible to be selected again as a member of the other cohort any time afterwards, even if their low-dose ASA exposure status changed during follow-up (e.g. a member of the low-dose ASA cohort could have discontinued low-dose ASA during follow-up, while a member of the comparison cohort could have started low-dose ASA during follow-up). This is in line with an intention-to-treat (ITT) philosophy used in RCTs – subjects do not switch from the group they are randomized to into another treatment group, even if they change treatment over time. Unlike RCTs, however, in which baseline characteristics of the two study groups are generally comparable as a consequence of the randomization process, the two study cohorts in our non-experimental observational study design would most likely be unbalanced in their baseline characteristics. The matching process as described above aimed to minimize any selection bias resulting from differences between the study cohorts, and additional adjustments in the analysis stage were performed to also meet this end. (see **Section 9.9.2.2**).

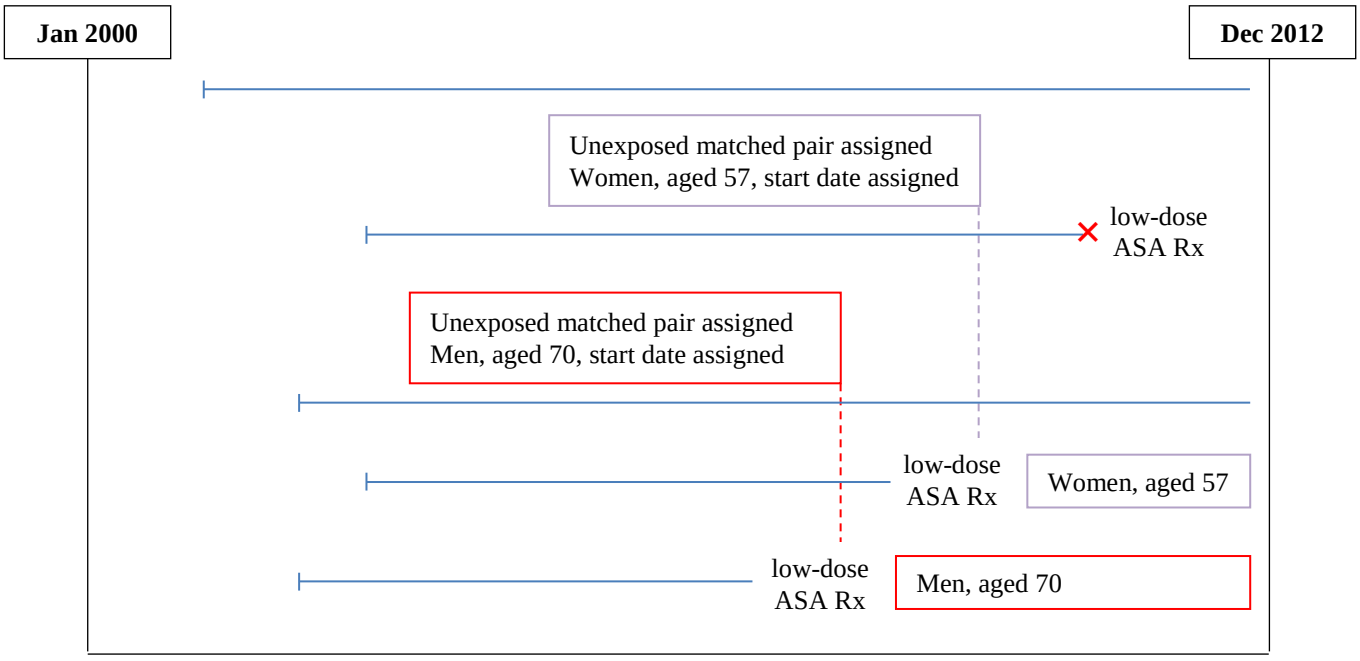

Figure 3. Example of the identification of the individuals in the matched comparison cohort.

9.3.3 Follow-up of the study cohorts to identify bleeding outcomes

Both cohorts (199,079 matched pairs) were followed from the start date for up to 14 years until the earliest of the following:

- a Read code for the outcome of interest (either ICB, UGIB or LGIB; see **Appendix Tables 1–3** for specific Read codes)
- cancer
- alcohol abuse
- coagulopathies
- oesophageal varices
- chronic liver disease
- age 90 years
- death
- end of the study period (31 December 2013).

Individuals with a Read code for ICB, UGIB or LGIB during the respective follow-up were identified as potential incident cases of the respective bleeding event. It should be noted that owing to eligibility criteria not being met during the follow-up to identify the study outcomes (i.e. gaps of information in patients' electronic medical records (EMRs) and thereby not meeting data quality control requirements), a total of 30 patients in the low-dose ASA cohort and 159 individuals in the comparison cohort were excluded. Therefore, the final number of individuals in the two study cohorts included in the analysis was 199,049 individuals in the low-dose ASA cohort and 198,920 individuals in the comparison cohort.

9.3.4 Case ascertainment and validation

9.3.4.1 Intracranial bleeds

All individuals with a Read code for ICB in THIN during follow-up had their recorded diagnosis validated. A three-step process was undertaken (**Figure 4** and **Appendix Figure 1**).

Step 1: All individuals with a Read code for ICB in THIN during follow-up who had been confirmed as either an incident case of ICB (N=440) or a non-case (N=151) during previous research projects (13, 14) were identified.

Step 2: Among the remaining individuals who could not be cross-linked to previous projects (N=1501) those belonging to general practices linked to Hospital Episode Statistics (HES) data (see **Section 9.5.3**) were identified (N=529). HES was searched to identify individuals with an International Classification of Diseases-10 (ICD–10) code, recorded at the time of hospital discharge, suggestive of ICB (**Appendix Table 4**) with subsequent review of these individuals' HES records to confirm the diagnosis. Following this process, 229 potential cases were confirmed as incident cases, 15 were deemed non-cases by virtue of meeting study exclusion criteria, and 285 remained unconfirmed.

Step 3: For all potential cases not cross-linked to previous projects and either not linked to HES (N=972) or linked to HES but not confirmed by review of HES data (N=285), free-text comments were obtained from their EMRs in THIN in order to manually review these patients' records, while masked to all medication exposure. The free-text comments that were obtained included:

- all comments in THIN within the 30 days before and after the index date (date of ICB)
- all comments assigned to unspecific Read codes related to referrals and discharge summaries that were related to cerebrovascular diseases (**Appendix Table 5** recorded any time in the 180 days before the date of recorded ICB and up to one year after
- all comments recorded in relation to the recording of additional health information (**Appendix Table 6**) (e.g. computed tomography scan) specific to cerebrovascular episodes within the 90 days before this record and up to 180 days after.

Patients were considered to be incident cases of ICB unless there was evidence from the patient record to indicate otherwise, e.g. a prevalent case or no definite diagnosis. Cases of ICB were classified as intracerebral haemorrhage (ICH), subdural haematoma (SDH) or subarachnoid haemorrhage (SAH), in addition to whether the event was trauma-related (traumatic event) or non-trauma related (non-traumatic event). The index date was the date of the recorded ICB diagnosis. Cases who died on the index date or within 30 days following the index date were deemed to be fatal cases.

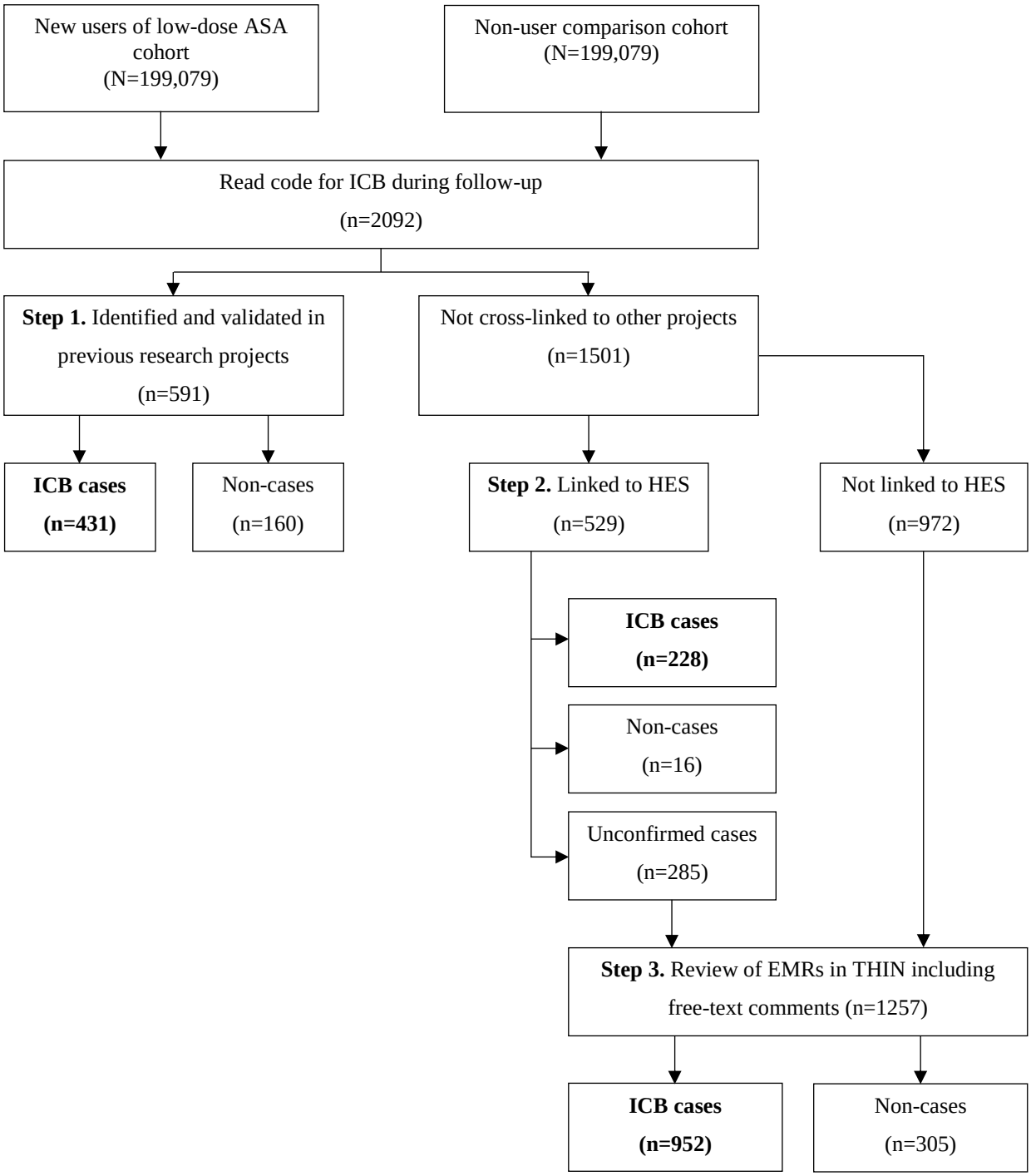

Figure 4. Flowchart depicting the identification and validation of incident cases of ICB.

9.3.4.2 Upper and lower gastrointestinal bleeds

CEIFE have previous experience studying UGIB using THIN, as shown in a number of publications that have included case validation exercises. In previous studies by CEIFE, a positive predictive value (PPV) for UGIB in THIN of nearly 95% following validation using questionnaires to PCPs as the gold standard has been found.(15, 16) In the case validation steps for this study where manual review of patient profiles was undertaken, all personal identifiers and information on drug use among the patients' EMRs were masked to the reviewer. Confirmed cases of UGIB were those who had been referred to a consultant or admitted to hospital and for whom the site of bleeding or perforation was the stomach or duodenum. Patients whose site of bleeding or perforation was the oesophagus were excluded.

CEIFE have also previously undertaken research on LGIB in THIN, in which the recorded diagnosis of LGIB was validated. In a cohort of patients followed-up after an episode of acute coronary syndrome,(17) a confirmation rate of 82% was found after comparing the case ascertainment status based on review of patients' EMRs (including free-text comments) with the information obtained from questionnaires to PCPs.(14) In this present study, confirmed cases of LGIB were those who had been referred to a consultant or admitted to hospital, and where the site of bleeding was in the jejunum, ileum, colon or rectum. Cases were classified according to the clinical diagnosis of the bleed into diverticulosis/diverticulitis, polyposis, inflammatory bowel disease (IBD), ischaemic colitis, angiodysplasia and other causes of bleeding. Cases of bleeding due to haemorrhoids or cancer were excluded.

In this present study, all individuals with a Read code for UGIB, LGIB or non-specific gastrointestinal bleed (GIB) in THIN during follow-up had their recorded diagnosis validated. This was achieved through a multi-step process (**Figures 5–11** and **Appendix Figures 2–8**).

9.3.4.2.1 Preliminary case-ascertainment step: cross-linking with cases ascertained in previous studies

Step 1 involved the identification of all individuals with a first Read code for UGIB or LGIB (as appropriate) during follow-up (N=4651 for UGIB and N=18,557 for LGIB) who had been confirmed as either an incident case of UGIB (N=978) or a non-case of UGIB (N=304) during previous UGIB research projects (15, 16) (**Figure 5** and **Appendix Figure 2**), or for LGIB as the outcome, who had been confirmed as either an incident case of LGIB (N=195) or a non-case of LGIB (N=137) during previous LGIB research projects (14, 17) (**Figure 6** and **Appendix Figure 3**).

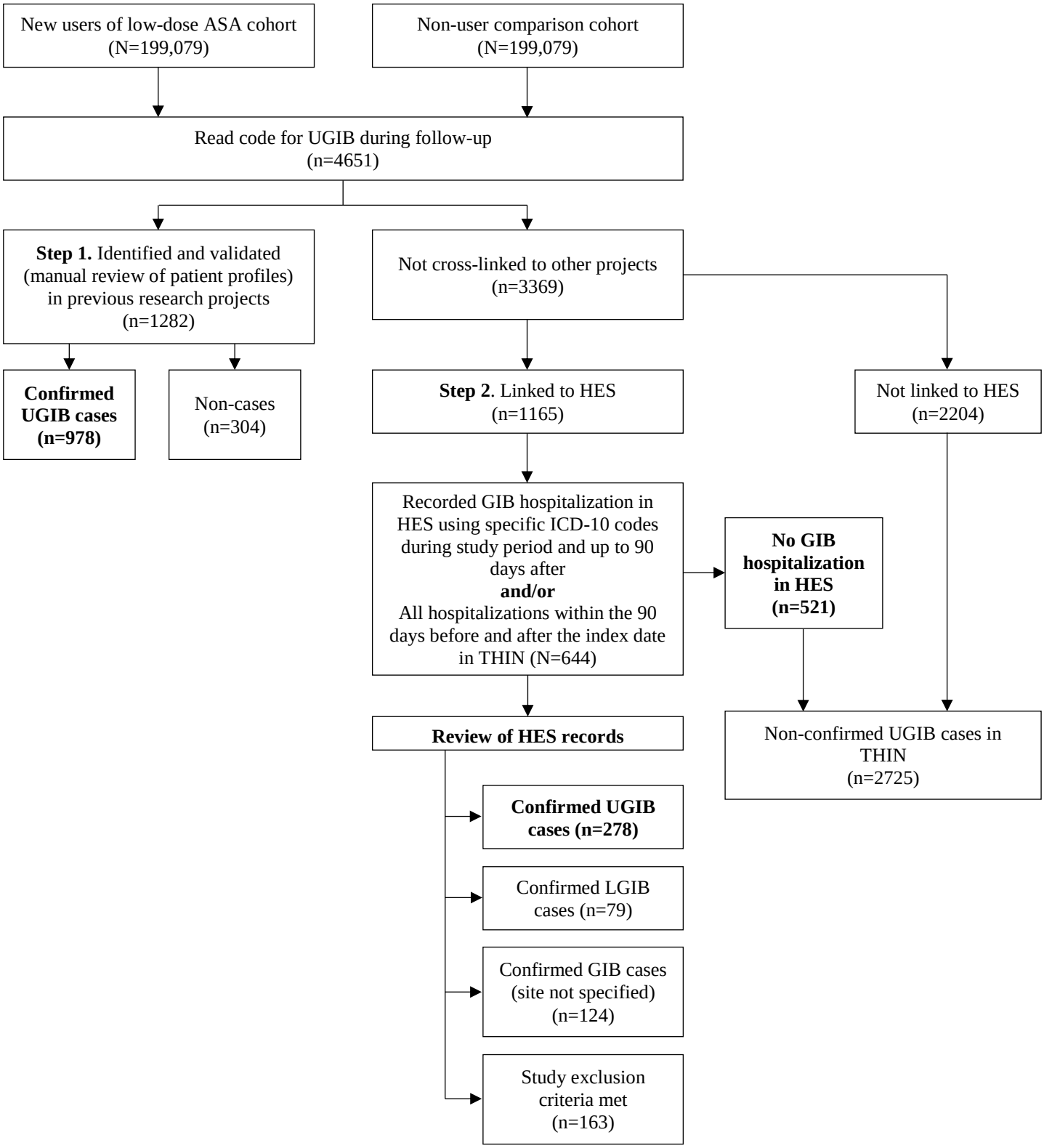

Figure 5. Flowchart depicting preliminary UGIB case ascertainment phase (cross-linking with previous studies) and case ascertainment Phase 1 (cross-linking with HES) for UGIB.

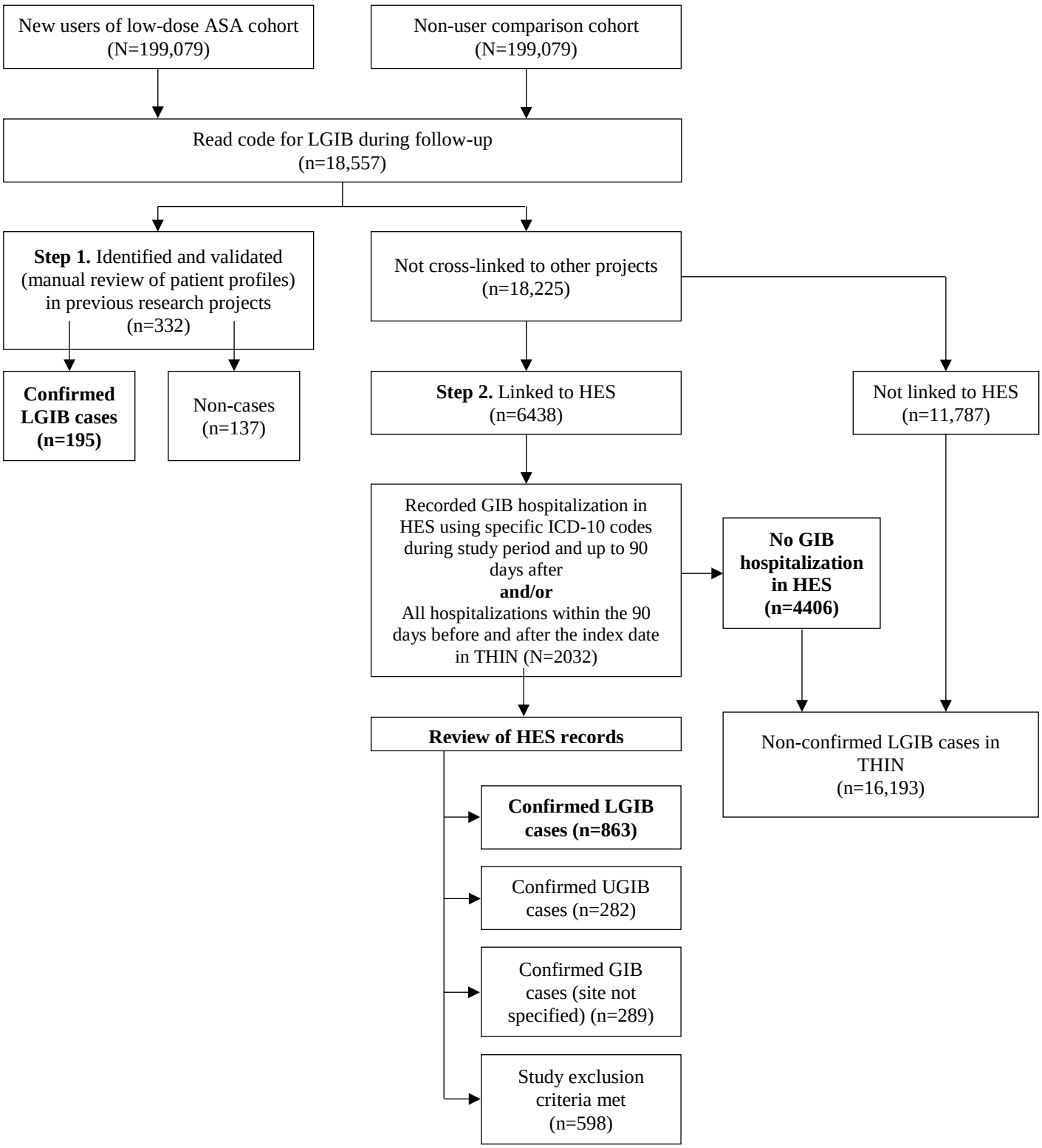

Figure 6. Flowchart depicting preliminary LGIB case ascertainment phase (cross-linking with previous studies) and case ascertainment Phase 1 (cross-linking with HES) for LGIB.

9.3.4.2.2 Case ascertainment phase I: cross-linking to HES

The number of potential UGIB and LGIB cases identified and categorized at each step of case ascertainment phase I is shown in **Figure 5** (for UGIB case ascertainment) and **Figure 6** (for LGIB case ascertainment). Among the remaining individuals who had a first Read code for UGIB (or a non-specific GIB code) and who were not cross-linked to previous UGIB projects (N=3369), those belonging to general practices linked to HES were identified (N=1165). Similarly, among the remaining individuals who had a first Read code for LGIB (or a non-specific GIB code) and who were not cross-linked to previous LGIB projects (N=18,225), those belonging to general practices linked to HES (n=6438) were identified. These patients' HES records were searched for relevant ICD-10 codes (i.e. those indicating a hospitalization for a GIB; **Appendix Table 7**) from the date follow-up started in THIN until the end of observation of THIN. Searches for relevant ICD-10 codes were also undertaken within 90 days after the end of observation in THIN to ensure hospitalizations recorded in HES towards the end date of follow-up in THIN were not missed. These searches aimed to identify patients who had a hospital episode for which the hospital did not record the main bleeding code but another code suggestive of bleeding (e.g. specific digestive diseases leading to bleeding) and also to identify individuals meeting any exclusion criteria (e.g. cancer or an episode not eligible to be UGIB/LGIB as appropriate). All individuals with a potential HES record suggestive of an incident UGIB/LGIB (as appropriate) had their HES records manually reviewed and were categorized into cases and non-cases. A total of 644 individuals were identified in the UGIB/non-specific GIB ICD-10 code search, and 2032 individuals were identified in the LGIB/non-specific GIB ICD-10 code search.

Following review of HES records, there were 278 confirmed cases of UGIB (164 arising from the low-dose ASA cohort and 114 arising from the comparison cohort). The total number of individuals with a Read code for UGIB during follow-up that were left non-confirmed as either a UGIB case or a non-case following this process was 2725 (1558 arising from the low-dose ASA cohort and 1167 arising from the comparison cohort). Similarly, following review of HES records, there were 863 confirmed cases of LGIB (498 arising from the low-dose ASA cohort and 365 arising from the comparison cohort). The total number of individuals with a Read code for LGIB during follow-up that were left non-confirmed as either a LGIB case or a non-case following this process was 16,193 (9091 arising from the low-dose ASA cohort and 7102 arising from the comparison cohort).

9.3.4.2.3 Case ascertainment phase II: removal of duplicates in both sets (UGIB and LGIB outcomes) before requesting free-text comments

Following the previous validation steps, there were 18,918 individuals with a Read code for UGIB, LGIB or GIB with non-specific site, which had not been confirmed as a case or non-case (2725 were potential cases of UGIB and 16,193 were potential cases of LGIB). Before progressing to the next stage of validation for these individuals (to establish case or non-case status), a search was undertaken for duplicate patients, i.e. members of the 18,918 individuals who had arisen following both the UGIB/non-specific GIB search in THIN and the LGIB/non-specific GIB search in THIN (**Figure 7** and **Appendix Figure 4**). Duplicates could potentially have occurred because there were some codes that were non-specific for the

site of the GI bleed that were included in both searches, and therefore some patients were identified in both the UGIB and LGIB searches. The rationale for performing two different follow-ups rather one single follow-up to identify individuals with a code for UGIB, LGIB or GIB unspecified in the same single follow-up, was to aid the reporting of certain estimates such as incidence rates of the particular outcome without having the expense of performing additional data management. Each of the 2725 non-confirmed but potential UGIB cases arising from the UGIB search and each of the 16,193 non-confirmed but potential LGIB cases arising from the LGIB search, were classified according to the type of search from which they had arisen, i.e. UGIB only, LGIB only or both.

As shown in **Figure 7**, there were 920 individuals identified from the UGIB search only, and there were 14,388 individuals identified from the LGIB search only. There were 1805 individuals who arose in both searches and were therefore duplicates. Of these, 1551 individuals (3102 entries, 2 per patient) had an end of follow-up date that was the same in both entries and was for the same Read code (i.e. indicating it was the same event). Of the remaining 254 individuals (508 entries, 2 per patient), the end of follow-up for that patient was different in the two follow-ups (i.e. the Read code was on a different date, and the Read code on this date was also different).

Therefore, after this process, there were 17,367 potential UGIB/LGIB cases that entered the next steps of case ascertainment (920 + 14,388 + 1551 + 508 (254 pairs).

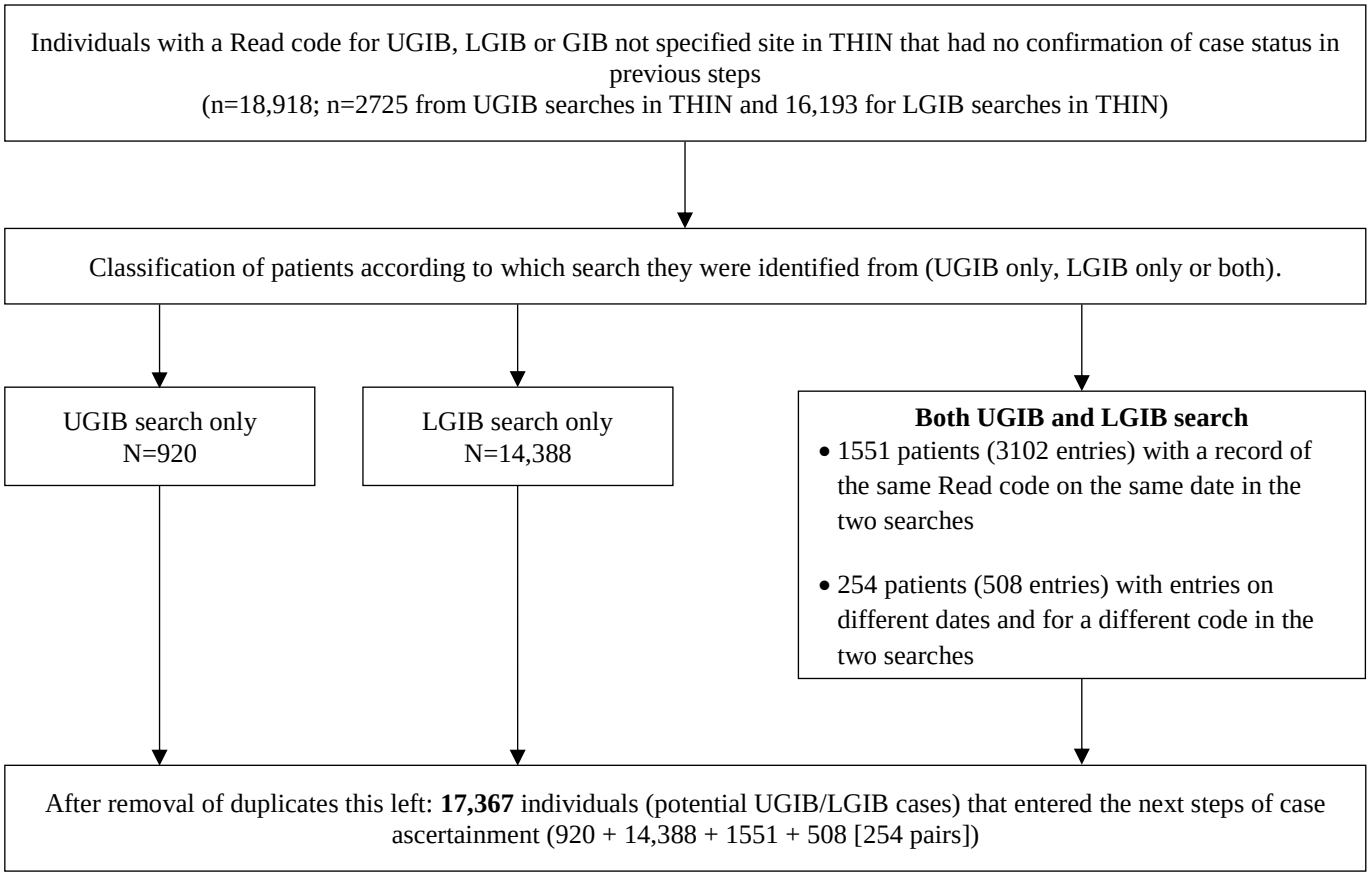

Figure 7. Flowchart depicting case ascertainment phase II: identifying duplicate patients occurring from the two separate GIB follow-ups (UGIB and LGIB).

9.3.4.2.4 Case ascertainment phase III: looking for indicators of case status in THIN and manual review of free-text comments

The classification of individuals in case ascertainment phase III is depicted in **Figure 8** and **Appendix Figure 5**. For all 17,367 individuals without an assigned case status following the previous validation steps, their medical records in THIN were searched, firstly, for Read codes indicative of a probable case (i.e. bleeding site, aetiology such as diverticulosis) or suggestive of a non-probable case (e.g. exclusion criteria such as digestive malignancies, haemorrhoids and anal fissure) recorded within 90 days before or 30 days after the computer-detected date of bleeding in THIN. Based on this search, individuals were classified into three mutually exclusive groups: *probable cases*, *non-probable cases* and *remaining* (i.e. no information was available to assign the individual into one of the two former groups). Secondly, among the 17,367 individuals, those that could be cross-linked to a set of patients (with free-text comments) that were already available in CEIFE were identified, and from these, those where the available free-text comments covered the same date of the recorded GIB codes (UGIB, LGIB or GIB unspecified) were identified. For this subset of patients (those who could be cross-linked to previous datasets in CEIFE), their THIN medical records were manually reviewed and case status ascertained (case or non-case).

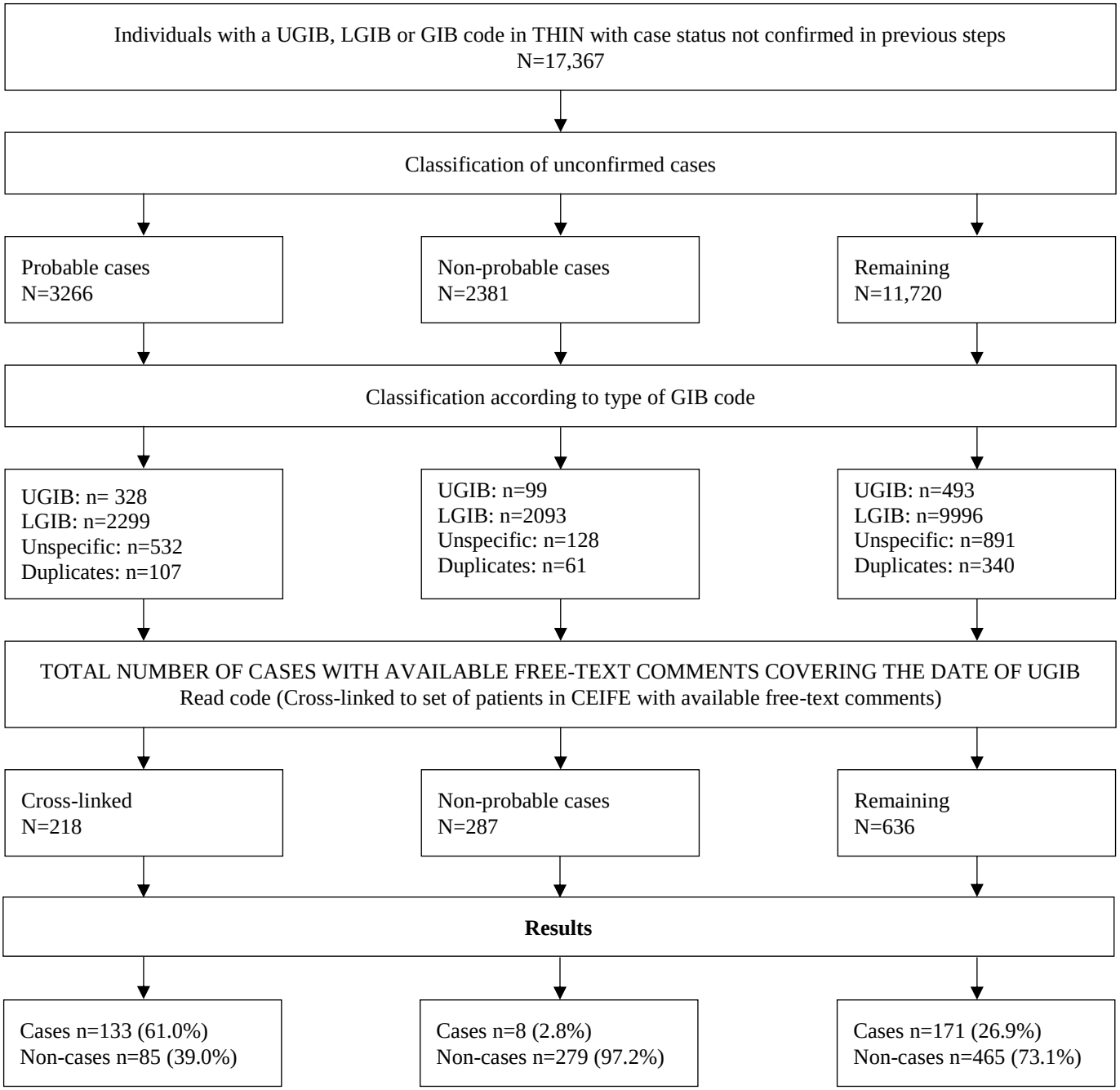

Figure 8. Flowchart depicting UGIB/LGIB case ascertainment phase III: looking for indicators in THIN and manual review.

9.3.4.2.5 Case ascertainment phase IV: extrapolation of results from the manual review process in case ascertainment phase III to all remaining unclassified potential cases

9.3.4.2.5.1 Probable cases

Case ascertainment phase IV is illustrated in **Figure 9** and **Appendix Figure 6**. For all probable cases (N=3266), two strategies were followed:

Step 1: For individuals with an unspecified site of bleeding, their medical records were searched for a subsequent Read code entry of UBIB and/or LGIB, separately. This process was intended to see if the patient had a subsequent Read code with more specific information (i.e. a Read code suggestive of the bleeding site). To do this, two different time frames were used: from the day after the original censored/index date [date of recorded bleeding diagnosis) up to 90 days after, and also from 91–180 days after the original censored/index date. The number of patients who had a subsequent entry of UGIB/LGIB within the 90 days after the original GIB entry date was then determined. Moreover, among those without any entry within these first 90 days, searches were performed further on (91–180 days). There were very few numbers of cases with a subsequent entry (<20 cases arising from each study cohort; **Table 2**). Therefore, it was assumed that none of these were cases, and subsequently free-text comments were requested for these individuals in order to better assign the source and site of bleeding episode.

Step 2: For all probable cases classified as UGIB probable (N=3288) or LGIB probable (N=2299), the PPV was calculated according to the Read code entry of UGIB or LGIB (following the manual review with free-comments undertaken in case ascertainment phase III). Among those with an entry of UGIB, the PPV was 85% in the low-dose ASA cohort and 57% in the comparison cohort, while the PPV for LGIB was 53.2% in the low-dose ASA cohort and 85.7% in the comparison cohort. Therefore, the EMRs of a small sample of patients were manually reviewed to ensure their confirmed case status. While it seemed that the vast majority of these individuals might be confirmed cases, there was a lack of information for the site (for UGIB) or reason of bleeding (for LGIB). It should therefore be kept in mind that to create this group of potential cases, individuals were required to meet one of the following criteria:

- defined site of bleeding (UGIB; specific diseases of LGIB [colitis, diverticulosis])
- hospital entry or referral to hospital
- not having an exclusion criterion (i.e. other upper GI disease such as oesophageal varices, other lower GI disease such as haemorrhoids, fissures or digestive malignancies).

However, assuming that all potential cases were confirmed without applying an extra validation step would mean that specific and valuable information on the site of bleed or reason for LGIB would be missed, which could potentially limit further analysis on causation of the research question. Therefore, from the pool of potential cases (N=3048; 2400 probable cases from the low-dose ASA cohort and 348 probable cases from the comparison cohort), free-text comments from their EMRs were obtained in order to manually review their records and better characterize the bleeding episode.

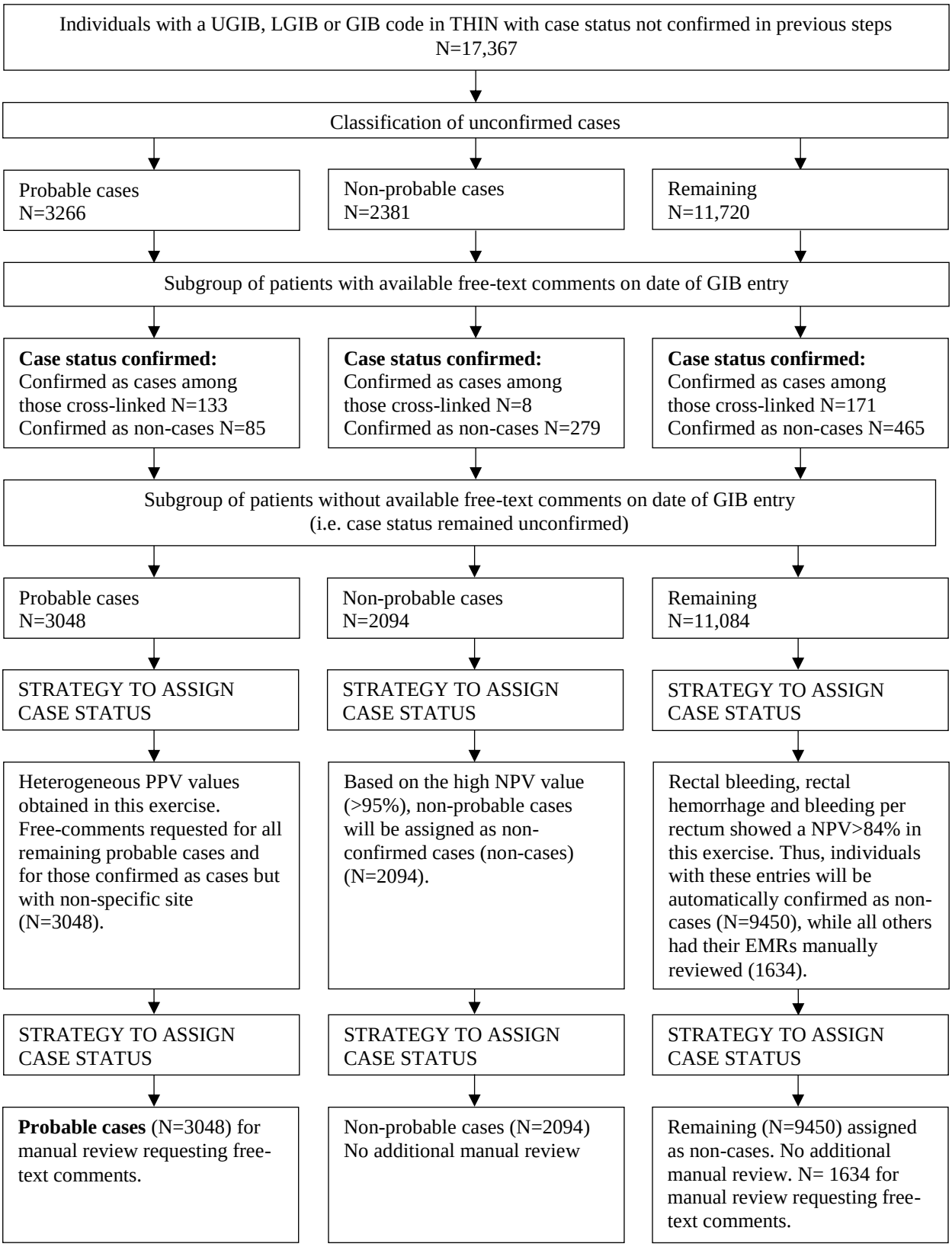

Figure 9. Flowchart depicting case ascertainment phase IV.

Table 2. Number of cases with a subsequent entry of GIB after the original entry (either in the first 90 days after the original GIB date, or 91–180 days after the original GIB date) during case ascertainment phase IV.

	Low-dose ASA cohort N=14 (unspecified potential cases N=444)			**Comparison cohort N=9 (unspecified potential cases N=176)**		
Entries of UGIB in the first 90 days after the original GIB code						
Acute duodenal ulcer with haemorrhage	2	14.29	14.29	1	11.11	11.11
Bleeding acute gastric ulcer	1	7.14	21.43	1	11.11	22.22
Bleeding chronic gastric ulcer	1	7.14	28.57	-	-	-
Coffee ground vomit	1	7.14	35.71	1	11.11	33.33
H/O: haematemesis	1	7.14	42.86	1	11.11	44.44
Gastric haemorrhage NOS	-	-	-	1	11.11	55.56
Haematemesis	5	35.71	78.57	3	33.33	88.89
Unspecified duodenal ulcer with haemorrhage	-	-	-	1	11.11	100.00
Upper gastrointestingal haemorrhage	1	7.14	85.71	-	-	-
Vagotomy & pyloroplasty	1	7.14	92.86	-	-	-
Vomiting of blood	1	7.14	100.00	-	-	-
Total	**14**	**100.00**		**9**	**100.00**	
Entries of LGIB in the first 90 days after the original GIB code						
Angiodysplasia of colon	1	5.88	5.88	-	-	-
Bleeding PR	12	70.59	76.47	3	42.86	42.86
PRB – rectal bleeding	-	-	-	1	14.29	57.14
Rectal bleeding	4	23.53	100.00	1	14.29	71.43
Rectal haemorrhage	-	-	-	2	28.57	100.00
Total	**17**	**100.00**		**100.00**		

9.3.4.2.5.2 Remaining non-probable cases

Among remaining non-probable cases not reviewed in the previous exercise (review of free-text comments) and based on the high negative predictive value (NPV; greater than 80% in both samples), all non-probable cases were deemed non-cases. A total of 2094 non-probable cases were classed as non-cases (1062 from the low-dose ASA cohort and 1032 from the comparison cohort).

9.3.4.2.5.3 Remaining group of cases

Among the group classed as ‘Remaining’ (neither probable nor non-probable) and not reviewed in the previous free-text comments review exercise (N=11,084; 5524 from the low-dose ASA cohort and 5560 from the comparison cohort), the distribution of Read codes in both cohorts was evaluated and the PPV and NPV were calculated according to the findings of the manual review. There were three codes showing a very high NPV (>80%):

- rectal bleeding (NPV of 89.6% for individuals in the low-dose ASA cohort and 88.9% for individuals in the comparison cohort)

- bleeding per rectum (NPV of 93.1% for individuals in the low-dose ASA cohort and 85.7% for individuals in the comparison cohort)
- rectal haemorrhage (NPV of 90.9% for individuals in the low-dose ASA cohort and 70.0% for individuals in the comparison cohort; the combined NPV for this code was 84.5%).

Thus all remaining cases with these Read code entries were confirmed as non-cases. This corresponded to a total of 9450 non-cases; 4670 in the low-dose ASA cohort and 4780 in the comparison cohort. Following this process, there was still a total of 1634 individuals (854 in the low-dose ASA cohort and 780 in the comparison cohort) that were unclassified.

9.3.4.2.6 Summary of case ascertainment phases I–IV

The previous case ascertainment phases served to identify a set of confirmed cases and confirmed non-cases, as well as to discard some potential cases owing to a high NPV and thereby suggestive of another kind of bleeding episode not meeting our inclusion criteria and case definition (e.g. bleeding per rectum due to haemorrhoids, bleeding due to digestive malignancies or bleeding due to oesophageal problems). Following these previous phases of case ascertainment, there were still individuals whose case status was not yet confirmed (as a case or non-case) or could not be characterized properly. **Figure 10** (and **Appendix Figure 7**) summarizes the case ascertainment phases described thus far. There were a total of 864 confirmed UGIB cases (549 from the low-dose ASA cohort and 315 from the comparison cohort) and a total of 1107 confirmed LGIB cases (677 from the low-dose ASA cohort and 430 from the comparison cohort). Of note is that these final numbers of confirmed and non-confirmed cases do not sum the numbers shown in previous case ascertainment phases (specifically case ascertainment phase I) owing to the existence of some duplicate patients included in both the UGIB and LGIB searches (which were counted, for example, as LGIB in the HES exercise for UGIB cases, and vice versa). The refining strategy to erase duplicated patients was performed during case ascertainment phase II.

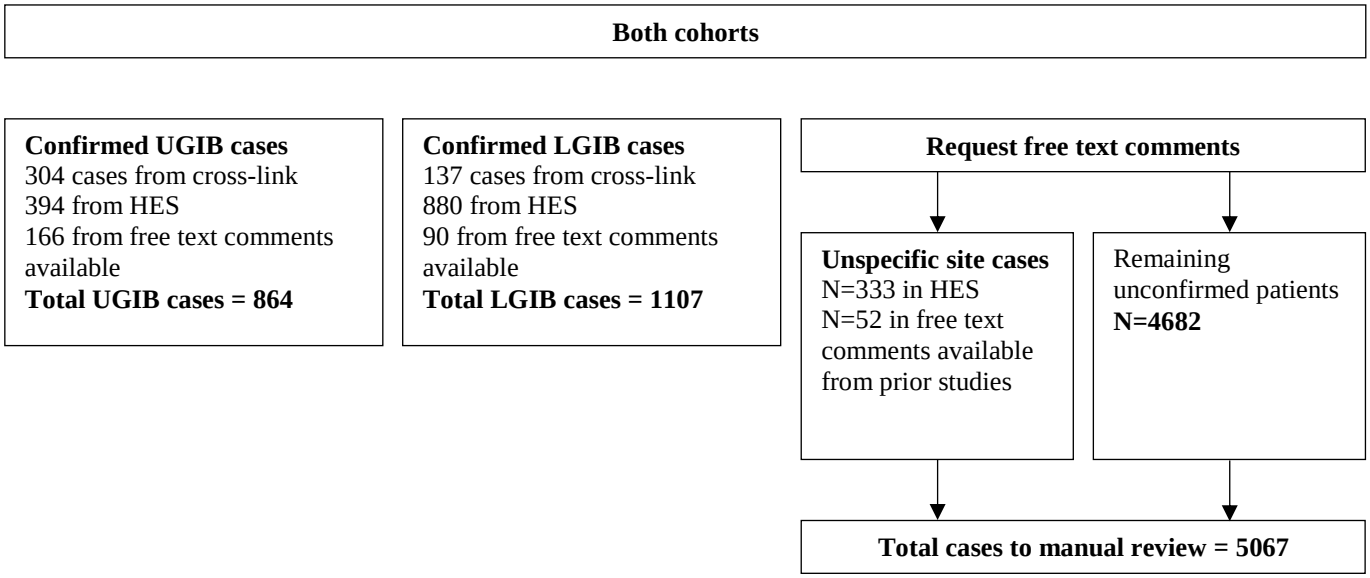

Figure 10. Summary of case ascertainment phases I to IV.

Thus, following case ascertainment phases I to IV, there were 5067 potential cases still unconfirmed as either a case or a non-case. A total of 3456 of these individuals were in the low-dose ASA cohort and 1611 were in the comparison cohort. Among the 3456 individuals in the low-dose ASA cohort, 168 cases still had an unspecified site following HES review, 34 had unspecified site from case ascertainment phase IV, and 3254 had not had their medical records reviewed/confirmed in any of the previous case ascertainment phases. Among the 1611 individuals in the comparison cohort, 165 had unspecified site following HES review, the site was unspecified in 18 individuals from case ascertainment phase IV, and 1428 individuals had not had their medical records reviewed/confirmed in any of the previous case ascertainment phases.

9.3.4.2.7 Case ascertainment phase V

For these 5067 remaining potential cases, free-text comments from their EMRs in THIN were obtained and the records were manually reviewed to confirm the individuals as a case or a non-case as well as to characterize the bleeding episode (including establishing the site of bleed). The following free-text comments were obtained for this process:

- all comments available in the database from 7 days before the GIB entry date
- all comments available from specific Read codes suggestive of GI disorders and referrals, hospitalization and test procedures from 15 days before the recorded GIB episodes and up to 180 days afterwards.

9.3.4.2.8 Case ascertainment phase VI

The research group at CEIFE has experience in terms of understanding PCP recording patterns; for example, the most frequent Read codes used, Read codes suggestive of a confirmed case or a non-confirmed case, the most common text notes included for GI outcomes (e.g. when bleed comes from anus [haemorrhoids]). Primary care practitioners typically record the type of blood (e.g. fresh) and indicate the location of haemorrhoids (e.g. 3 o'clock). Thus, for all individuals for whom free-text comments were requested, and for whom were available, a novel method was performed to assign the case status (confirmed case or confirmed non-case). This was a combination of recording patterns in the database as previously studied and observed by the researchers at CEIFE while reviewing this GIB outcomes in THIN, together with an automatic search algorithms based on Read codes and key strings included in the PCP notes. Definitions, algorithms and subgroups were created in an attempt to optimize and identify confirmed and non-confirmed GIB cases. The 5067 potential cases who remained unconfirmed cases after requesting free-text comments were subdivided according to the Read code entry into the following subgroups and looked for specific strings and/or Read codes within a time frame of 365 days before and after to help the decision.

9.3.4.2.8.1 Individuals with a Read code for 'Haematemesis'

Because the Read code for haematemesis is specific to an upper GI site (with a very low grade of misclassification), *a priori*, all cases with this entry were classified as GI bleed of the upper GI site, and therefore were considered to be UGIB cases.

To classify the aetiology (i.e. specific reason to bleed) for these patients, the following text strings were searched for: *peptic ulcer*, *duodenal ulcer*, *stomach ulcer*, *duodenal*, *gastritis*, *dyspepsia*, *gastric polyp*, *duodenitis*, *gastro-jejunal*, *helicobacter pylori*, *du*, *stomach bleed*, *secondary to aspirin*,*secondary to NSAID*, *hiatus hernia*, *clo positive*, *antrum*. In the absence of these text strings, the string *oesophag* was searched for and identified patients were marked for further review. This was because an entry of 'oesophagus' might indicate a site other than the stomach, and would therefore meet the study exclusion criteria.

9.3.4.2.8.2 Individuals with a Read code for 'Bleeding per rectum'

This group included individuals with at least one of the following Read codes:

'Bleeding PR', 'Rectal bleeding', 'Rectal haemorrhage' or 'Haemorrhage of rectum and anus'. After review of a random sample of medical records, it was apparent that there were no differences in the pattern of recording based on each code, thus all individuals were assigned to a single group. Although these codes refer to the lower GI tract, sometimes they could indicate an upper GI site (although very few cases of UGIB were expected in this recording pattern). Therefore, among this group of individuals the following three steps were undertaken:

Step 1: The following indicators (all suggestive of lower GI tract) were searched for: *divert*, *colitis*, *ibs*, *uc*, *polyp*, *crohn*, *angiodysplasia*. To help find these indicators, codes for sigmoidoscopy and colonoscopy were particularly scrutinized.

Step 2: In the absence of any of the strings in step 1, the following text strings were searched for: *carcinoma*, *colorectal cancer*, *tumour*, *piles*, *fissure*, *oncology*, *haemorrhoids*, *motions*, *pain*.

Step 3: Thirdly, in the absence of any of the strings indicated in step 1 and step 2, the remaining group was marked and patients with the following text strings were identified: *endoscopy*, *duodenitis* or *helicobacter pylori*.

9.3.4.2.8.3 Individuals with a Read code for 'Gastrointestinal bleeding'

This group included individuals with a Read code for 'GIB – Gastrointestinal bleeding' or 'Gastrointestinal haemorrhage'. Although these codes are unspecific, they usually indicate an upper GI site rather than a lower GI site of bleeding, thus the same strategy as used for the haematemesis group was undertaken. To classify aetiology of the bleed in this group of individuals, the following text strings were searched for: *upper* (this string was the most important because usually the PCP records this string close to the entry of GIB), *peptic ulcer*, *duodenal ulcer*, *duodenal*, *gastritis*, *dyspepsia*, *gastric polyp*, *duodenitis*, *gastro-jejunal*, *helicobacter pylori*, *du*, *stomach bleed*, * vomited blood*, *haematemesis*, *coffee ground*, *secondary to aspirin*, *secondary to NSAIDs*, *hiatus hernia*, *clo positive*, *antrum*. These entries would indicate an upper GI site, so among them the aetiology was classified based on the type of string found (e.g. if 'du', then duodenal ulcer was assumed). To ensure that none of these patients had their bleed in the oesophagus, patients with the string *oesophag* were identified and marked for further review. If no strings from above were found, two possible scenarios could have occurred: a bleed in the lower GI site or a bleed in an unknown site. Thus, among remaining patients, those with the following text strings were identified: *divert*, *colitis*, *ibs *, * uc*, *polyp*, *crohn, and *angiodysplasia*. Searches for these strings were undertaken particularly looking among the free-text entered alongside codes for sigmoidoscopy and colonoscopy. Identified patients were classed as having a LGIB.

All remaining patients were subject to further review. This group contained the most unspecific GIB entries, and the GIB episode could have been either UGIB or LGIB. It was thought that these patients were more likely to have had a UGIB: one of the main characteristics of this group was that the bleeding episode was not severe and it was not subject to substantial investigation. These patients underwent the following review steps:

Step 1: Patients with the following text strings, indicative of a UGIB, were identified: *upper*, *peptic ulcer*, *duodenal ulcer*, *stomach ulcer*, *duodenal*, *gastritis*, *dyspepsia*, *gastric polyp*, *duodenitis*, *gastro-jejunal*, *helicobacter pylori*, *du*, *stomach bleed*, *secondary to aspirin*, *secondary to NSAIDs*, *haematemesis*, *coffee ground*, *secondary to aspirin*, *secondary to NSAIDs*, *heartburn*, *hiatus hernia*, *clo positive*, *antrum*. In patients without any of these text strings, those with the following text strings, indicative of a LGIB were identified: *lower*, *divert*, *colitis*, *ibs*, * uc*,

*polyp *, *crohn*, * angiodysplasia*, looking particularly among free-text entered with codes for sigmoidoscopy and colonoscopy.

Step 2: Among patients without any of the text strings in step 1, those with the following strings were identified: *oesophag*, *carcinoma *, *colorectal cancer *, *tumour*, *piles*, *fissure*, *oncology*, *haemorrhoids*, *motions*, *pain*.

Step 3: All remaining patients not classified in any of the above strategies were subject to further review.

9.3.4.2.8.4 Other scenarios

9.3.4.2.8.4.1 Specific site included in Read code (n=114)

Read codes that specified the site and aetiology of the GIB included the following: 'Acute duodenal ulcer with haemorrhage', 'Acute haemorrhagic gastritis', 'Bleeding acute gastric ulcer', 'Bleeding chronic duodenal ulcer', 'Bleeding diverticulosis', 'Perforated chronic duodenal ulcer', 'Unspecified duodenal ulcer with haemorrhage', 'Intestinal hemorrhage', 'Upper gastrointestinal haemorrhage'. A complete manual review of EMRs was undertaken for this small group of patients in order to classify their case status.

9.3.4.2.8.4.2 Codes difficult to assign with algorithms

Some individuals had Read codes that made case status difficult to determine. These Read codes included 'Coffee ground vomit' (individuals with this code may have shown different patterns of medical entries, i.e. not related to GI disorders but related to pancreatic diseases or due to diet), 'vomiting blood' and 'blood in stool'. Patients where the bleed was not acute, not referred, nor associated with another comorbidity different to the digestive tract were reviewed further.

With the information obtained from the free-text comments together with an algorithm that searched for specific text strings suggestive of upper or lower site of GI bleeding, patients were classified as confirmed cases of UGIB or LGIB and the site of bleeding was specified. For UGIB, the site was classified as follows: duodenal ulcer, gastric ulcer, peptic ulcer, hiatus hernia, gastritis/dyspepsia, *Helicobacter pylori*, duodenitis and 'other' (jejunum problems, duodenal bulb, angiodysplasia or contraindications of gastrotoxic drugs such as NSAIDs, warfarin or antiplatelets). In the absence of a specific site recorded in the patient's medical records, the site was classed as 'unknown'. For LGIB, the site was classified as follows: diverticular diseases, polyps, colitis (including ischaemic colitis), Crohn's disease, irritable bowel syndrome (IBS), angiodysplasia, coeliac disease and 'other' (proctitis, IBD unspecified and obstruction). In the absence of a specific site displayed in the medical records, the site of the bleed was classed as 'unknown'. The resulting classification is shown in **Table 3** and **Appendix Table 8**.

Table 3. Classification of UGIB and LGIB cases following GIB case ascertainment phase VI.

	Both cohorts (N=5067) Confirmed cases, N=2822, 55.7%)	
	UGIB* N=1077	**LGIB* N=1745**
Site	Duodenal ulcer=192 Gastric ulcer=163 Duodenal/gastric ulcer=2 Peptic ulcer=6 Hiatus hernia=79 Gastritis/dyspepsia=275 Helicobacter pylori=19 Duodenitis=16 Gastritis/duodenitis=21 Other=46 Unknown=258	Diverticular diseases=865 Polyps=198 Diverticular/polyps=117 Colitis=167 Colitis/polyps=2 Diverticular/colitis=1 Crohn's disease=15 IBS=72 Angiodysplasia=9 Coeliac disease=2 Other=32 Unknown=265

*There were three patients who fell in both episodes of both UGIB and LGIB on different dates.

9.3.4.2.9 Case ascertainment phase VII: assigning site to confirmed cases in case ascertainment phase V

In order to ascertain the site and aetiology of the bleed among individuals confirmed as cases in phase V, the algorithm described in phase VI was applied. This extra information led to some patients having their case status changed, e.g. from a confirmed case to a non-case. There were a total of 864 confirmed UGIB cases (549 in the low-dose ASA cohort and 315 in the comparison cohort) and a total of 1107 confirmed LGIB cases (677 in the low-dose ASA cohort and 430 in the comparison cohort). After reviewing patients' EMRs to identify the site of the bleed, the final classification yielded a total of 762 confirmed UGIB cases (501 [91.8%] in the low-dose ASA cohort and 261 [82.8%] in the comparison cohort and a total of 990 cases of LGIB (604 [82.8%] in the low-dose ASA cohort and 386 [89.8%] in the comparison cohort). Confirmed cases were classed as shown in **Figure 11** (and **Appendix Figure 8**).

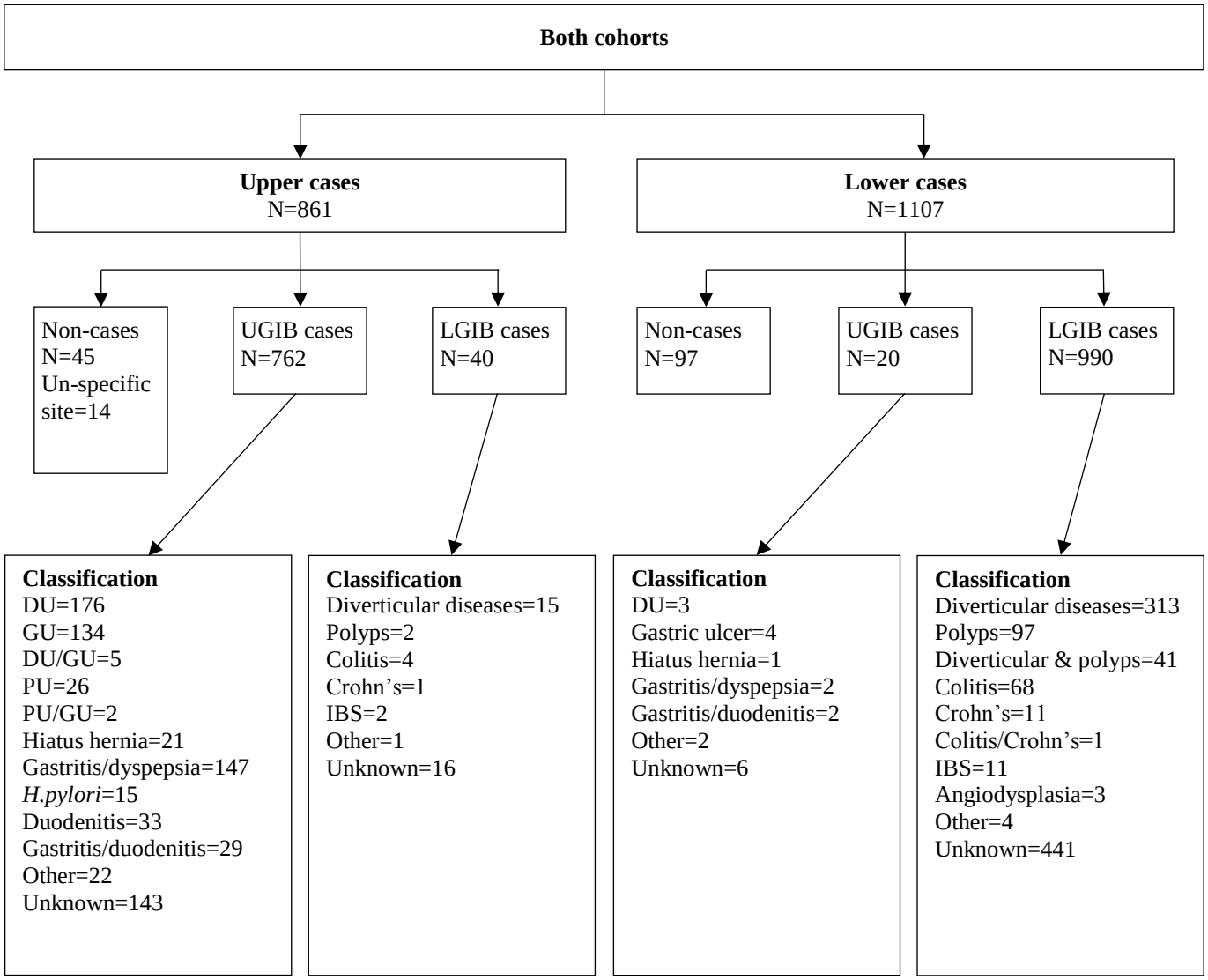

Figure 11. Flowchart depicting case ascertainment phase VII.

9.3.4.2.10 Case ascertainment phases VIII: last case ascertainment before assignment of healthcare assistance

Pooling together all final cases ascertained in case ascertainment phases V–VII, there was a total 4634 confirmed GIB cases, 1859 confirmed UGIB cases (1125 in the low-dose ASA cohort and 734 in the comparison cohort) and 2775 confirmed LGIB cases (1943 in the low-dose ASA cohort and 832 in the comparison cohort). This resulting classification is shown in **Table 4** and **Appendix Table 9** by site (UGIB or LGIB) and aetiology of the cases. Of note is that, as mentioned in previous steps of the case status ascertainment process, all cases for whom there was not enough information regarding the site were excluded as cases and were deemed non-cases.

Table 4. Classification of UGIB and LGIB cases following GIB case ascertainment phase VIII.

	Both cohorts	
	UGIB* N=1859	**LGIB* N=2775**
Site	Duodenal ulcer=371 Gastric ulcer=302 Duodenal/gastric ulcer=16 Peptic ulcer=32 Duodenal/peptic ulcer=2 Hiatus hernia=101 Gastritis/dyspepsia=424 *Helicobacter pylori*=34 Duodenitis=49 Gastritis/duodenitis=52 Other=70 Unknown=407	Diverticular diseases=1193 Polyps=297 Diverticular/polyps=159 Colitis=237 Colitis/diverticular =2 Colitis/polyps=2 Colitis/Crohn's =1 Crohn's=26 IBS=85 Angiodysplasia=12 Coeliac diseases=2 Other=37 Unknown=722

*There were three patients who fell in both episodes of both UGIB and LGIB on different dates.

9.3.4.2.11 Case ascertainment phase IX: final case ascertainment

Confirmed cases (N=4634) were subdivided into fatal cases (defined as cases who died within the 30 days following the event) and non-fatal cases. There were a total of 153 fatal cases and 4453 non-fatal cases. Both subgroups were classified according to the type of health assistance they received:

- An episode that required hospitalization or referral to a specialist. To ascertain this, the medical records within the 15 days before and 30 days after the computerized entry of the GIB were searched. Individuals requiring a hospitalization were automatically assigned to the 'hospitalization' group, while remaining patients were classed into the 'referral' group
- No hospitalization or referral to a specialist. Among individuals not assigned to either the 'hospitalization' or 'referral' group, their EMRs were manually reviewed to identify any strings in the medical records suggestive of hospitalization/referral.

As summarized in **Table 5** (**Appendix Table 10**), after carrying out this search, for non-fatal GIB cases (N=4481), there were a total of 1770 cases with hospitalization, 2683 cases with referrals and 28 cases for which no further investigation of the GIB, apart from being seen by the PCP, and therefore these 28 individuals were excluded as cases, resulting in a total number of cases of 4453. Among those whose bleed was fatal, the same strategy was followed: there were a total of 107 (70%) cases with hospitalization (died in the hospital), 35 (22.9%) cases who had been referred and 11 (7.2%) cases whose death occurred at home.

Table 5. Classification of UGIB and LGIB cases following GIB case ascertainment phase IX.

	Both cohorts, confirmed cases N=4609	
	UGIB*	**LGIB***
Non-fatal case	**1715**	**2758**
Hospitalization	1016	754
Referral	699	1984
Fatal-case	**128**	**25**
Hospitalization	90	17
Referral	30	5
Home	8	3

*Three patients experienced an episode of UGIB and LGIB on different dates.

9.3.5 Sampling of controls for the nested case–control analyses

In each of the three separate follow-ups (i.e. to identify incident cases of ICB, UGIB or LGIB), for each member of both study cohorts, a random date within the study period was generated for all study members of the two study cohorts. If the random date for a study member was included in her/his follow-up period, that person was marked as an eligible control and the random date was used as their index date in the respective nested case–control analysis. This method of selection of controls in nested case–control studies is known as incidence density sampling, where the likelihood of being selected as a control is proportional to the person-time at risk. Controls were subject to the same eligibility criteria applied to cases. For each outcome, the final size of the control sample was determined by being at least four times the size of the set of cases and rounded to the closest 1000 unit.

9.3.6 Matching criteria for cases and controls in nested case–control analyses

For the ICB outcome, 10,000 controls were randomly sampled from both cohorts and frequency matched to ICB cases by age, sex and calendar year of the index date. For the UGIB outcome, 5000 controls were frequency-matched to the set of cases by calendar year. For the LGIB outcome, 10,000 controls were frequency-matched to the set of cases by calendar year. The index date for controls in each nested case–control analysis was the random date within her/his follow-up period.

9.4 Variables

9.4.1 Patient characteristics

9.4.1.1 Demographic variables

For each member of both study cohorts, information on demographic variables was collected at the start of follow-up (start date) on sex, age (categorized into 40–59 years, 60–69 years, 70–79 years and 80–84 years), Townsend deprivation index (five quintiles) and urban/rural location (grouped into three categories: urban, town and village).

9.4.1.2 Lifestyle variables

Lifestyle variables for each member of the two study cohorts were ascertained any time before the start date (date of the first low-dose ASA prescription for members of the low-dose ASA cohort and the same date for the individual's matched partner in the comparison cohort). Lifestyle variables included smoking status, alcohol consumption and body mass index (BMI). These variables were ascertained any time before the start date for the cohort analyses, and any time before the index date for cases and controls in the case–control analyses, using the most recent value/status as appropriate. BMI was calculated as weight in kg divided by height in metres squared. Standard cut-offs were used to classify subjects as underweight (BMI <20 kg/m^2), normal weight (BMI 20–24.99 kg/m^2), overweight (BMI 25–29.99 kg/m^2), obese (BMI ≥30 kg/m^2) or unknown. Smoking status was categorized into current smoker, past smoker, never smoker or unknown. Alcohol consumption was categorized into units per week (u/w): 1–9, 10–20, 21–41, ≥42 and unknown. Units per week are defined as 10 ml (1 cl) by volume, or 8 g by weight, of pure ethanol.

9.4.1.3 Healthcare use

For each member of both study cohorts, the number of PCP visits, referrals and hospitalizations in the year before the start date was ascertained, as well as the number of different medications (polypharmacy) in the month before the start date (0–1, 2–4 or ≥5). These variables were also ascertained for cases and controls in each case–control analysis within the year before the index date (for PCP visits, referrals and hospitalizations) and in the month before the index date (for polypharmacy).

9.4.1.4 CVD prevention population

All members of both study cohorts were assigned a primary or secondary CVD prevention population. A computer algorithm was used that searched each individual's EMRs in THIN for Read codes suggestive of CVD (**Appendix Tables 11a–11h**) from any time before the start date and up to 30 days after. The information closest to the start of follow-up (date of first low-dose ASA prescription for members of the low-dose ASA cohort) was prioritized. Patients with a Read code suggestive of CVD were assigned to the secondary CVD prevention population, and using both a hierarchy of the Read codes and the date the Read code was recorded. All individuals without CVD codes in the specified time interval were assigned to the primary CVD prevention population.

9.4.1.5 Comorbidities

For all individuals in both study cohorts, comorbidities were ascertained any time before the start date (for the cohort analyses) and any time before the index date (for cases and controls in the nested case–control analyses). Comorbidities evaluated included the following: cerebrovascular diseases (i.e. ischaemic stroke and TIA, separately), ICB, CVD, hypertension, diabetes (type I and II, separately), hyperlipidaemia, IHD, atrial fibrillation, haemodialysis, estimated glomerular filtration rate (eGFR), chronic obstructive pulmonary diseases (COPD), asthma, anaemia, depression, osteoarthritis, pancreatic disease, gastroesophageal reflux disease (GERD) and peptic ulcer antecendents. In addition, information on the following variables related to upper GI disorders were collected: dyspepsia, uncomplicated peptic ulcer peptic ulcer and complicated peptic ulcer, previous UGIB, previous LGIB or previous unspecified GIB, as well as colorectal polyps, IBD, IBS and constipation.

9.4.1.6 Medication use: cohort analysis

Medication use for the cohort analysis was classed as *current use*, when supply of the most recent prescription lasted until the start date or ended 0–90 days before the start date, and *past use*, when supply of the most recent prescription ended at least 91 days before the start date.

9.4.1.7 Medication use: nested case–control analysis

9.4.1.7.1 Recency of medication use (including low-dose ASA)

Medication use, including low-dose ASA, was ascertained any time before the index date, and was classified into five categories:

- *current use*, when supply of the most recent prescription lasted until the index date or ended 0–7 days before the index date (for the ICB analysis) or ended 0–30 days before the index date (for the GIB outcomes)
- *recent use*, when supply of the most recent prescription ended 8–90 days before the index date (for the ICB analyses) or ended 31–90 days before the index date (for the GIB outcomes)

- *past use*, when supply of the most recent prescription ended 91–365 days before the index date
- *distant use*, when supply of the most recent prescription ended ≥365 days before the index date
- *never-use*, when there was no recorded use at any time before the index date.

9.4.1.7.2 Duration of medication use (including low-dose ASA)

Duration of treatment was calculated by summing the individual duration of all consecutive prescriptions: gaps in treatment of >30 days were considered to be genuine breaks in treatment, and duration was computed using the consecutive period of uninterrupted treatment closest to the index date (i.e. gaps in treatment ≤30 days were included in the computation of duration). The following cut-offs for duration were applied among current users and recent users, separately: <3 months, 3–<6 months, 6 months– <1 year, 1–<5 years and ≥5 years.

9.4.1.7.3 Daily dose of low-dose ASA

The following doses for daily dose were used: 75 mg, 150 mg and 300 mg. The dose at the index date was evaluated using the information recorded in the database and classified current users into one of these three dose categories.

9.4.1.7.4 Low-dose ASA reason for use

Among users of low-dose ASA, the reason for use – primary or secondary CVD prevention – was assigned as described in **Section 9.4.1.4.**

9.4.1.7.5 Concomitant use of low-dose ASA and other medications

To evaluate the interaction between the medications of interest, designated A + B (e.g., low-dose ASA & clopidogrel; low-dose ASA and warfarin), one variable was created with five mutually exclusive levels of exposure: *non-use of either agent (No A, No B)* within the year before index date; current *use of both agents (A+B)*; *current use of only A (non-use* of *B within the year before the index date)*; *current use of only B (non-use of A within the year prior)*; and *remaining* (other combinations of recency of both agents). Another variable was created using non-use of either agent any time before the index date (to be used as an alternative reference category in the analyses) instead of in the year before the index date (as the main reference category in the analyses).

Among current users of warfarin, information on their INR values recorded in the 60 days before the index date was collected from THIN. Current users of warfarin were categorized according to the levels of international normalized ratio **(**INR) as follows: current users with INR <3, current users with INR ≥3, and unknown. The INR value in the 60 days before the index date that was closest to the index date was used.

9.5 Data sources and measurement

9.5.1 The Health Improvement Network (THIN)

The Health Improvement Network (THIN) is a computerized medical research database that contains over 80 million patient-years of anonymized patient data, and which covers approximately 6% of the UK population. (18) The database is representative of the UK population with regards to age, sex and geographic distribution, and has been validated for use in pharmacoepidemiologic research. (19, 20) Participating PCPs record data prospectively as part of their routine patient care, and regularly send their data to THIN for anonymization and use in research projects.

9.5.2 THIN data recording

The computerized information in THIN is entered by PCPs using Read codes or as free-text. Read codes are the standard clinical terminology used in UK general practice, supporting detailed clinical encoding of diagnoses, symptoms, laboratory tests and results, therapeutics, surgical procedures and demographics.(21) Other information recorded in THIN includes lifestyle factors (e.g. alcohol use and smoking), height and weight (enabling the calculation of BMI), referrals to specialists in secondary care and hospital admissions. Information from secondary care is communicated back to the PCP and entered in the database retrospectively. All prescriptions issued by the PCP are automatically recorded using Gemscript codes based on the National Health Service's (NHS) dictionary of medicines and devices.(22)

9.5.3 Linkage to Hospital Episode Statistics

For a subset of THIN practices, data can be linked at the patient level to HES data.(23) Hospital Episode Statistics contain clinical and administrative data on hospital episodes (admissions and visits), which are collected from UK NHS hospitals and linked to ICD-10 codes.

9.5.3.1 Hospital Episode Statistics: data recording

Hospital Episode Statistics are data collected from NHS hospitals in England by the Secondary Uses Services, a programme that supports secondary care in the NHS. The data include details of all hospital care funded by the NHS in England. It contains information on patient admissions from 1997 onwards, outpatient attendance data from 2003 onwards, and accident and emergency data from 2007 onwards. It should be noted that HES files were available up to March 2012 and included 158 practices (approximately one third of all THIN practices). The full HES dataset contains more than 400 fields, although in most cases many of these are not completed by the hospital, either because they are not applicable or because recording is not mandatory. Each HES record may contain a wide range of information about an individual patient admitted to an NHS hospital, including:

- clinical information about diagnoses, procedures and operations
- information about the patient, such as age, sex and ethnicity

- administrative information, such as dates of admission and discharge dates.

Outpatient records in HES are complete as far as the recording of visits, yet rarely have diagnoses listed. In addition to the date of the outpatient visit, the service where the outpatient visit was booked is also recorded.

9.6 Bias

Efforts to address potential sources of bias were as follows:

- The design of the study attempted to minimize bias between low-dose ASA users and non-users at the start of follow-up that are hard to control for. By obtaining incident cases of ICB/UGIB/LGIB for our case–control analyses from two cohorts of patients –new users of low-dose ASA and non-users of low-dose ASA at the start of follow-up – matched by factors including a proxy for general health status (number of PCP visits in the year before start of follow-up), this possible selection bias was minimized.
- In the cohort analyses, by calculating incidence rates and IRRs, which ensured that individuals remained in the study cohort they were assigned to at the start of follow-up (akin to an ITT analysis in a RCT), the study attempted to control for differences in adherence to drug therapy and similar factors that are difficult to control for. In addition, in the cohort analyses, incidence rates and IRRs were calculated not only for the whole duration of follow-up but also restricted to the first year of follow-up. This was to minimize the misclassification that would inevitably occur during a longer follow-up period.
- Use of a new-user design minimized the potential survivor bias that can occur by the inclusion of prevalent low-dose ASA users.
- The use of incidence density sampling to select controls in the nested case–control analyses ensured these analyses were not biased by competing risks.
- The information used in the study, which was originally collected by PCPs as part of routine patient care, was recorded prospectively thereby minimizing information bias.
- In the case validation parts of the study, the review of patients' EMRs was performed while masked to medication exposure. Thus the reviewer was unaware of whether individuals in the study were exposed to low-dose ASA at the time of case ascertainment, thus minimizing information bias.

9.7 Study Size

All individuals in THIN database meeting the study inclusion criteria and not meeting any study exclusion criteria were included in the study.

9.8 Data transformation

Quantitative data were managed as described in **Section 9.4.1**.

9.9 Statistical Methods

9.9.1 Main Summary Measures

9.9.1.1 Descriptive statistics

Characteristics of the two study cohorts at the start of follow-up (start date) were described and compared; frequency counts, percentages and Chi^2 tests were used for categorical variables, and means with standard deviation (SD) and t-tests were used for continuous variables. For each nested case–control analysis (with ICB, UGIB and LGIB cases), characteristics of cases and controls were described using frequency counts and percentages. Also, in each nested case–control analyses, the follow-up duration (time between the start date and index date) was described for cases and controls and categorized into <6 months, 6 months–<1 year, 1–<2 years, 2–<3 years, 3–<5 years and ≥5 years.

9.9.1.2 Incidence rates

Incidence rates with 95% CIs were calculated and expressed as the number of cases per 10,000 person-years (for ICB) or per 1000 person-years (for UGIB and LGIB). For ICB, incidence rates were calculated for all cases of ICB and for each type of bleed (ICH, SDH and SAH), for both cohorts combined and for each cohort separately. This was undertaken for the whole of follow-up as well as for the first year of follow-up (the latter aimed to minimize the misclassification of low-dose ASA exposure that would inevitably occur during a longer follow-up period).

Incidence rates of all ICB and each subtype were also calculated following stratification by trauma/non trauma-related status, as well as by age (40–64 years, 65–74 years and 75–84 years), sex, case-fatality status (fatal case = death within 30 days following the event) and by CVD prevention population (primary or secondary) assigned at the start of follow-up. For UGIB and LGIB, incidence rates were calculated for the whole duration of follow-up, as well as for the first year of follow-up. Incidence rates of UGIB and LGIB were also calculated stratified by healthcare assistance at the time of the bleed (whether the episode led to the patient being hospitalized or referred), and by age (40–64 years, 65–74 years and 75–84 years), sex and case-fatality status (fatal case = death within 30 days following the event).

9.9.1.3 Relative measure of effect: cohort analyses

For each of the three bleeding outcomes (ICB, UGIB and LGIB), IRRs with 95% CIs comparing the incidence rate in the low-dose ASA cohort with the incidence rate in the comparison cohort were calculated using Poisson regression with adjustment made for age, sex and number of PCP visits in the year before the start date. The relative risk (hazard ratio,

HR) and 95% CI of the study outcomes (incident ICH/UGIB/LGIB) associated with new use of low-dose ASA was calculated.

9.9.1.4 Relative measure of effect: case–control analyses

Odds ratios (ORs) were used as the relative measure of effect in quantifying the association between new use of low-dose ASA and risk of bleeding outcomes. Under the study design of incidence density sampling, the OR is an unbiased estimator of the IRR.(12)

9.9.2 Main Statistical Methods

9.9.2.1 Cohort analysis

In each of the three separate follow-ups, follow-up time was calculated for each individual in the study, from their start date to the end of follow-up (either the date of the outcome of interest or censoring, as described in **Section 9.3.3**).The two study cohorts were followed-up from the start date (first low-dose ASA prescription for each member of the low-dose ASA cohort; this date was also the start date for their matched partner in the comparison cohort) until the occurrence of one of the major bleeding outcomes of interest or censoring, whichever came first.

Kaplan–Meier survival curves for the two study cohorts were produced for UGIB and LGIB. For the ICB outcome, Nelson–Aalen cumulative incidence estimates were produced for all cases of ICB and for each subtype (ICH, SDH and SAH). Also for the ICB outcome, an adjusted Cox proportional hazard model was used to estimate hazard ratios (HRs) adjusted for the matching variables and potential risk factors (**Section 9.4**; ascertained before the start date). Cox regression models take time to event into account; these analyses were performed based on the rationale of emulating the ITT analysis of RCTs, i.e. based on the initial treatment randomly assigned and not taking into account any changes in treatment occurring over the period of the study. The rationale for performing an ITT analysis in RCTs is based on the possibility that factors affecting adherence or treatment discontinuation may be hard to identify and adjust for.

9.9.2.2 Nested case–control analysis (as-treated analysis)

Three separate nested case–control analyses were performed using unconditional logistic regression adjusting for potential confounding variables. All patients confirmed as incident cases in the cohort analyses were used as cases in nested case–control analyses. In the ICB nested case–control analyses, the final model included adjustment for age, sex, calendar year, number of PCP visits in the year before the index date, smoking, BMI, alcohol consumption, hypertension and history of ischemic stroke, atrial fibrillation, TIA, prior ICB, clopidogrel and warfarin. In the UGIB nested case–control analyses, the final model included adjustment for age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, prior UGIB, prior LGIB, prior unspecified GIB, pancreatic disease, uncomplicated peptic ulcer problems, and use of NSAIDs, PPIs, clopidogrel and warfarin. In the LGIB nested case–control analyses, the final model included adjustment for age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol

consumption, BMI, polyps, prior LGIB, prior unspecified GIB, peptic ulcer diseases (complicated and uncomplicated), GERD, IBD, IBS and use of NSAIDs, PPIs , clopidogrel and warfarin. To select the variables to be included in the final models, in each case–control analysis a univariate analysis was first undertaken adjusting for the matched factors (age, sex, calendar year and PCP visits in the the year before the index date). All variables independently associated with an increased risk of the study outcome were then added into a comprehensive and stepwise logistic regression model, retaining those that remained associated with the outcome. In addition, traditional risk factors associated with the bleeding outcome of interest were retained in the final model to avoid residual confounding.

9.9.3 Missing Values

Individuals with missing values for a specific variable were assigned to a category 'Unknown' for that variable.

9.9.4 Sensitivity Analyses

In the case–control analyses for UGIB and LGIB, sensitivity analyses were performed on the data to evaluate the association between low-dose ASA and risk of UGIB and LGIB (as appropriate), and to evaluate the association between PPIs with risk of UGIB/LGIB (as appropriate). These sensitivity analyses involved the removal of any user of anticoagulants or other antiplatelets (other than low-dose ASA) from the dataset. This was undertaken to implement another approach of controlling for potential confounders by restriction.

9.9.5 Amendments to Statistical Analysis Plan

Not applicable.

9.10 Quality Control

The study exclusion criteria required individuals' records in THIN to meet data completion standards (**Section 9.3.1**).

10. Results

All tables and figures that are part of the main results of the study are situated at the end of this section. All additional results and figures are situated in the **Appendix Tables** and **Appendix Figures** sections as an **Annex** at the end of the report.

10.1 Participants

There was a total of 2,354,840 individuals in the source population before exclusion criteria were applied. From the eligible source population, and following application of exclusion criteria (**Figure 1)**, a total of 199,079 individuals entered the low-dose ASA cohort and, owing to the 1:1 matching in the study design, 199,079 individuals (free of low-dose ASA use at the start of follow-up) entered the comparison cohort.

10.2 Descriptive Data

10.2.1 Characteristics of the two study cohorts

Table 6 presents the frequency of demographics, lifestyle characteristics, healthcare use and polypharmacy levels for both study cohorts at the start of follow-up. Just over half (51.5%) of each cohort were male. The mean (SD) and median age at start of follow-up for both cohorts was 63.9 (10.8) years and 64.0 years, respectively. Among the low-dose ASA cohort, the mean (SD) and median BMI at start of follow-up was 28.18 (5.48) kg/m^2 and 27.4 kg/m^2, respectively, while among the comparison cohort, the mean (SD) and median BMI at start of follow-up was 27.11 (5.06) kg/m^2 and 26.4 kg/m^2, respectively. There was a higher prevalence of smokers, obese individuals (BMI ≥30 kg/m^2) and highly deprived individuals (5th quartile of the Townsend index) among the low-dose ASA cohort than the comparison cohort. A high level of referrals, hospitalization and PCP visits in the previous year were more frequent among individuals in the low-dose ASA cohort. Alcohol consumption was similar between the two cohorts, although there were fewer non-drinkers among the comparison cohort. Levels of polypharmacy were also similar between the two cohorts, with slightly higher levels of different medication use seen among the low-dose ASA cohort. Sixty three per cent (n=126,072) of the low-dose ASA cohort were using low-dose ASA for primary CVD prevention, while 36.7% (n=72,977) were using low-dose ASA for secondary CVD prevention.

Table 7 presents the frequency of comorbidities at the start of follow-up for the two study cohorts. Cardiovascular and metabolic conditions were much more prevalent in the low-dose ASA cohort than in the comparison cohort, e.g. 8.6% of the low-dose ASA cohort had previously experienced an MI compared to 1.1% in the comparison cohort. Corresponding percentages for hypertension and diabetes were 48.2% vs. 34.8% and 18.4% vs 8.0%, respectively. A previous ICB had occurred in 0.7% of the low-dose ASA cohort compared with 0.4% in the comparison cohort.

The frequency of medication use among the two study cohorts at the start of follow-up is shown in **Table 8**. Medications that were higher in the low-dose ASA cohort compared with

the comparison cohort included antihypertensive medications, statins, clopidogrel, antidiabetic medications, PPIs and diuretics. Warfarin use was higher among the comparison cohort than the low-dose ASA cohort, and other medications showed similar levels of use between the two cohorts.

10.3 Outcome Data

10.3.1 Intracranial bleeding

A total of 1611 individuals suffered an ICB during follow-up, 881 (54.7%) in the low-dose ASA cohort and 730 (45.3%) in the comparison cohort (**Table 9**). The distribution of ICB cases by site of bleed was as follows: 46.1% (743/1611) for ICH, 30.0% (483/1611) for SDH and 23.7% (385/1611) for SAH. Fifty one per cent of ICB cases were men and the mean age of ICB cases was 72.7 years (SD: 10.1). A quarter of all ICB cases (25.0%, n=402) were fatal cases, with most fatalities being cases of ICH (60.2%). Case-fatality rates were 32.4% (241/743) for ICH, 9.1% (44/483) for SDH and 30.4% (117/385) for SAH. Approximately a quarter of all ICB cases (27.0%; n=435) were recorded as trauma-related; almost two-thirds of trauma-related cases of ICB (63.9%; n=278) were cases of SDH.

10.3.2 Upper gastrointestinal bleeding

A total of 1843 suffered an episode of UGIB during follow-up, 1115 (60.5%) in the low-dose ASA cohort and 728 (39.5%) in the comparison cohort (**Table 10**). Sixty per cent of UGIB cases (n=1106) were hospitalized. Under 7% (6.9%, n=128) UGIB cases were fatal.

10.3.3 Lower gastrointestinal bleeding

A total of 2763 suffered an episode of LGIB during follow-up, 1936 (70.1%) in the low-dose ASA cohort and 827 (29.9%) in the comparison cohort (**Table 11**). Twenty eight percent of LGIB cases (n= 771) were hospitalized. Less than 1% of LGIB cases were fatal (n=24).

10.4 Main Results

10.4.1 Cohort analyses: ICB

10.4.1.1 Incidence rates of ICB

The incidence rate of ICB among both cohorts combined and for each cohort separately is shown in **Table 12** for all cases of ICB and for each subtype (ICH, SDH and SAH). The overall incidence rate of ICB was 7.21 cases per 10,000 person-years (95% CI: 6.87–7.57) over the whole study period: 7.61 cases per 10,000 person-years (95% CI: 7.13–8.13) in the low-dose ASA cohort and 6.78 cases per 10,000 person-years (95% CI: 6.30–7.29) in the comparison cohort. The highest incidence rate was for ICH, with an overall incidence of 3.33 cases per 10,000 person-years (95% CI: 3.10–3.57): 3.52 per 10,000 person-years (95% CI: 3.19–3.88) in the low-dose ASA cohort and 3.12 per 10,000 person-years (95% CI: 2.80–3.47) in the comparison cohort. The second most frequent type of ICB was SDH, with an

overall incidence rate of 2.16 cases per 10,000 person-years (95% CI: 1.98–2.36): 2.45 per 10,000 person-years (95% CI: 2.18–2.75) in the low-dose ASA cohort and 1.86 per 10,000 person-years (95% CI: 1.62–2.13) in the comparison cohort. For SAH, the overall incidence was 1.72 per 10,000 person-years (95% CI: 1.56–1.90), with incidence rates lower in the low-dose ASA cohort than the comparison cohort: 1.65 (95% CI: 1.43–1.90) vs. 1.80 (95% CI: 1.56–2.07) per 10,000 person-years. The IRR (low-dose ASA vs. comparison cohort) over the whole duration of follow-up was 1.11 (95% CI: 1.01–1.22) for all ICB, 1.12 (95% CI: 0.97–1.29) for ICH, 1.28 (95% CI: 1.07–1.53) for SDH and 0.92 (95% CI: 0.75–1.13) for SAH.

As shown in **Table 13**, the overall incidence of ICB in the first year of follow-up was slightly higher than among the whole duration of follow-up, at 7.57 per 10,000 person-years (95% CI: 6.74–8.50): 7.66 per 10,000 person-years (95% CI: 6.51–9.00) in the low-dose ASA cohort and 7.49 per 10,000 person-years (95% CI: 6.34–8.82) in the comparison cohort. The IRR (low-dose ASA vs. comparison cohort) in the first year of follow-up for all cases of ICB was 1.02 (95% CI: 0.81–1.29). Incidence rates in the first year of follow-up were higher in the low-dose ASA cohort than the comparison cohort for ICH (3.54 vs. 3.45 per 10,000 per person-years) and for SDH (2.24 vs. 1.33 per 10,000 person-years), whereas the incidence of SAH was lower in the low-dose ASA cohort compared with the comparison cohort (1.88 vs. 2.71 per 10,000 person-years).

Incidence rates stratified by trauma/non-trauma related status are shown in **Table 14** for all cases of ICB and for each subtype separately. The overall incidence rate of non-traumatic ICB was 5.26 cases per 10,000 person-years (95% CI: 4.97–5.57) and the overall incidence rate of trauma-related ICB was 1.95 per 10,000 person-years (95% CI: 1.78–2.14). By site, incidence rates of non-traumatic ICB per 10,000 person-years were 2.95 (95% CI: 2.74–3.19) for ICH, 0.92 (95% CI: 0.80–0.11) for SDH and 1.39 (95% CI: 1.25–1.56) for SAH. Incidence rates of traumatic ICB per 10,000 person-years were 0.37 (95% CI: 0.30–0.46) for ICH, 1.24 (95% CI: 1.11–1.40) for SDH and 0.33 (95% CI: 0.26–0.42) for SAH.

Incidence rates of ICB according to case-fatality status are shown in **Table 15** for all cases of ICB and for each subtype separately. The incidence of fatal ICB was 1.80 per 10,000 person-years (95% CI: 1.63–1.98): 1.08 per 10,000 person-years (95% CI: 0.95–1.22) for ICH, 0.20 per 10,000 person-years (95% CI: 0.15–0.27) for SDH and 0.52 per 10,000 person-years (0.44–0.63) for SAH. The incidence of non-fatal ICB was 5.41 per 10,000 person-years (95% CI: 5.11–5.73): 2.25 per 10,000 person-years (95% CI: 2.06–2.45) for ICH, 1.97 per 10,000 person-years (95% CI: 1.79–2.16) for SDH and 1.20 per 10,000 person-years (95% CI: 1.06–1.35) for SAH. Incidence rates of ICB stratified by case-fatality and trauma-related status are shown in **Table 16** for all cases of ICB and for each subtype of ICB, separately for the two study cohorts. Incidence rates of ICB among the low-dose ASA cohort and comparison cohort, respectively, were 0.24 vs. 0.25 per 10,000 person-years for fatal trauma-related ICB, 1.36 vs. 1.76 per 10,000 person-years for fatal non-trauma-related ICB, 1.92 vs. 1.47 per 10,000 person-years for non-fatal trauma-related ICB and 4.10 vs. 3.30 per 10,000 person-years for non-fatal non-trauma-related ICB. For SDH, incidence rates among the low-dose

ASA cohort and comparison cohort, respectively, were 0.15 vs. 0.08 per 10,000 person-years for fatal trauma-related cases, 0.09 vs. 0.07 per 10,000 person-years for fatal non-trauma-related cases, 1.31 vs. 0.93 per 10,000 person-years for non-fatal trauma-related cases and 0.89 vs. 0.78 per 10,000 person-years for non-fatal non-trauma-related cases.

The overall incidence rate of ICB was similar between the sexes (**Table 17**): 7.28 per 10,000 person-years (95% CI: 6.81–7.80) in men and 7.13 per 10,000 person-years (95% CI: 6.65–7.65) in women. Similar sex ratios were observed in the low-dose ASA cohort and comparison cohort. There was a marked increase in the incidence of ICB with age. Younger patients (40–64 years) presented an overall incidence rate of 3.97 per 10,000 person-years (95% CI: 3.63–4.33) compared with 15.34 per 10,000 person-years (95% CI 14.07–16.72) in those aged 75–89 years. Incidence rates according to sex and age for each type of ICB are shown in **Tables 18–20**.

For ICH (**Table 18**), the overall incidence rate was similar between men (3.30 per 10,000 person-years, 95% CI: 2.98–3.65) and women (3.35 per 10,000 person-years, 95% CI: 3.03–3.71). Sex differences in the incidence rate of ICH were also small (<0.85 per 10,000 person-years) in both the low-dose ASA cohort and comparison cohort. There was a marked increase in the incidence of ICH with age: younger patients (40–64 years) presented an overall incidence rate of 1.49 cases per 10,000 person-years (95% CI: 1.28–1.72) compared with 8.14 per 10,000 person-years (95% CI 7.23–9.16) in those aged 75–89 years. Similar age differences for ICH incidence were found in both the low-dose ASA and comparison cohort.

The overall incidence rate of SDH in men (2.62 cases per 10,000 person-years, 95% CI: 2.34– 2.94) was markedly higher than in women (1.69 per 10,000 person-years, 95% CI: 1.46–1.95) (**Table 19**). Analyses by cohort revealed comparable sex differences, although for both sexes, the incidence rate of SDH was slightly higher in the low-dose ASA cohort compared with the comparison cohort. Similarly to ICH, there was a marked increase in the incidence of SDH with age. Younger patients (40–64 years) presented an overall incidence of 0.89 cases per 10,000 person-years (95% CI: 0.74–1.07) compared with 5.12 per 10,000 person-years (95% CI: 4.41–5.95) in those aged 75–89 years. Similar age-related trends were seen in each study cohort, although individuals in the low-dose ASA cohort had slightly higher incidence rates of SDH than the corresponding age group in the comparison cohort, e.g. 5.74 per 10,000 person-years (95% CI: 4.72–6.99) vs. 4.46 per 10,000 person-years (95% CI: 3.55–5.61) in the age stratum 75–89 years.

The incidence rate of SAH was higher for women compared with men, overall and in each separate study cohort (**Table 20**). Overall, women had an incidence rate of 2.10 cases per 10,000 person-years (95% CI: 1.84–2.38) and men had an incidence rate of 1.36 per 10,000 person-years (95% CI: 1.17–1.60). Contrary to other types of bleeding, SAH did not present any marked increase with age. The overall incidence rate estimates for SAH were 1.59 cases per 10,000 person-years (95% CI: 1.38–1.83) for ages 40–64 years, 1.79 per 10,000 person-years (95% CI: 1.50–2.14) for ages 65–74 years and 2.07 cases per 10,000 person-years (95% CI: 1.64–2.62) for ages 75–89 years.

The incidence of ICB among the primary and secondary CVD prevention populations is shown in **Table 21** for all cases of ICB and separately for each subtype, stratified by study cohort. In the primary CVD prevention population, the incidence of ICB in the low-dose ASA cohort and in the comparison cohort was 6.81 per 10,000 person-years (95% CI: 6.24–7.43) and 5.94 per 10,000 person-years (95% CI: 5.48–6.45), respectively. In the secondary CVD prevention population, the overall incidence of ICB in the low-dose ASA cohort and comparison cohort was 9.07 per 10,000 person-years (95% CI: 8.19–10.04) and 14.81 per 10,000 person-years (95% CI: 12.62–17.38), respectively.

The incidence of ICB among the primary and secondary CVD prevention populations stratified by sex and age group is shown in **Table 22** for each study cohort. In the primary CVD prevention population, the overall incidence of ICB in the low-dose ASA cohort and comparison cohort in men was 7.12 per 10,000 person-years (95% CI: 6.29–8.05) and 6.04 per 10,000 person-years (95% CI: 5.39–6.77), respectively; corresponding rates in women were 6.53 (95% CI: 5.78–7.39) and 5.85 (95% CI 5.21–6.57). In the secondary CVD prevention population, the overall incidence of ICB in the low-dose ASA cohort and comparison cohort, respectively, in men, was 8.52 per 10,000 person-years (95% CI: 7.42–9.79) and 14.05 per 10,000 person-years (95% CI: 11.27–17.51); corresponding rates in women were 5.85 (95% CI: 5.21–6.57) and 15.77 (95% CI: 12.49–19.89). Among both study cohorts, the incidence of ICB was higher among individuals in the secondary CVD prevention population than among individuals in the primary CVD prevention population of the same age group. For example, in the low-dose ASA cohort, the incidence of ICB among individuals aged 75–89 years in the primary CVD prevention population was 14.62 per 10,000 person-years (95% CI: 12.43–17.19), while for comparable individuals in the CVD prevention population the incidence of ICB was 16.96 per 10,000 person-years (95% CI: 14.24–20.20).

10.4.1.2 Nelson-Aelen cumulative estimates of ICB

Nelson–Aalen cumulative incidence estimates of ICB (all cases) and for each subtype (ICH, SDH and SAH) are shown in **Figures 12–15**.

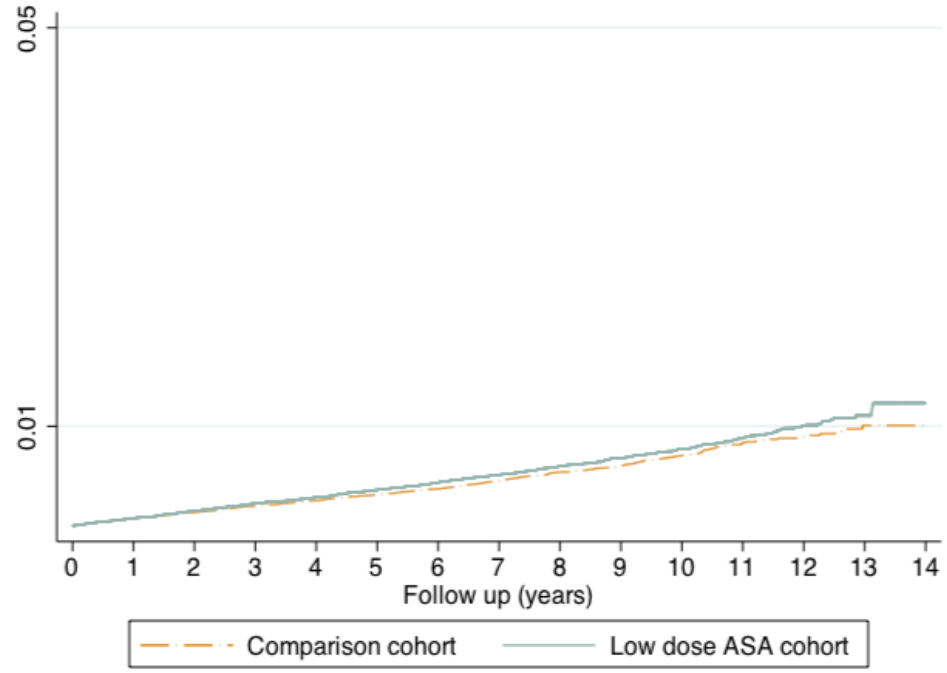

Figure 12. Nelson–Aalen cumulative incidence of ICB according to type of cohort.

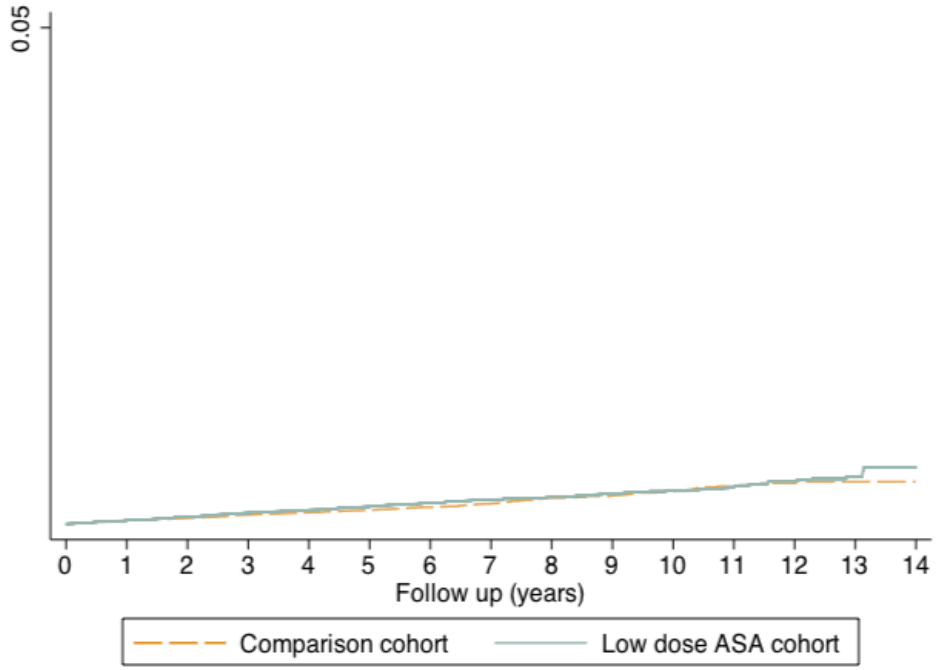

Figure 13. Nelson–Aalen cumulative incidence estimates of ICH according to type of cohort.

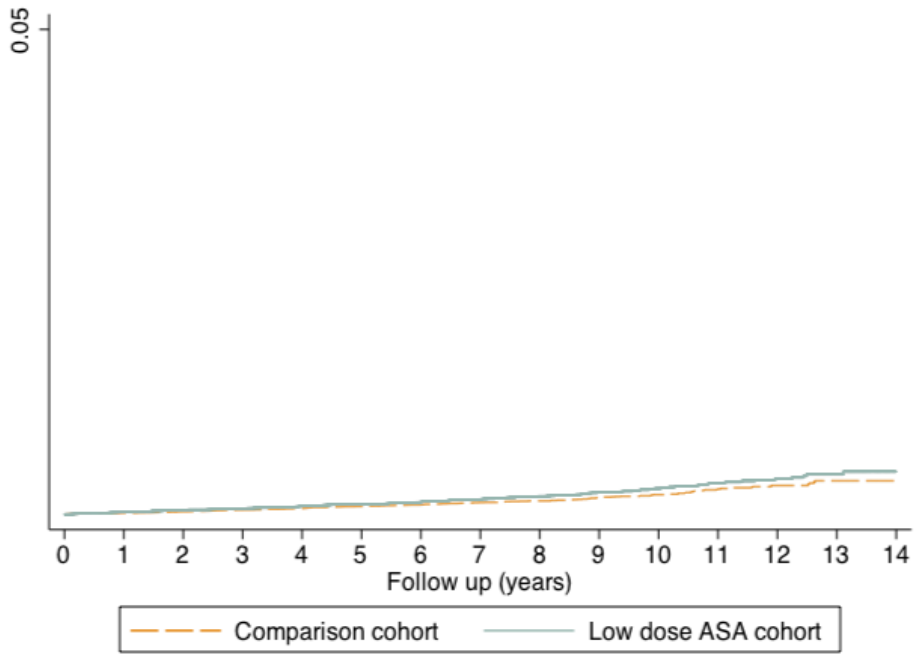

Figure 14. Nelson–Aalen cumulative incidence estimates of SDH according to type of cohort.

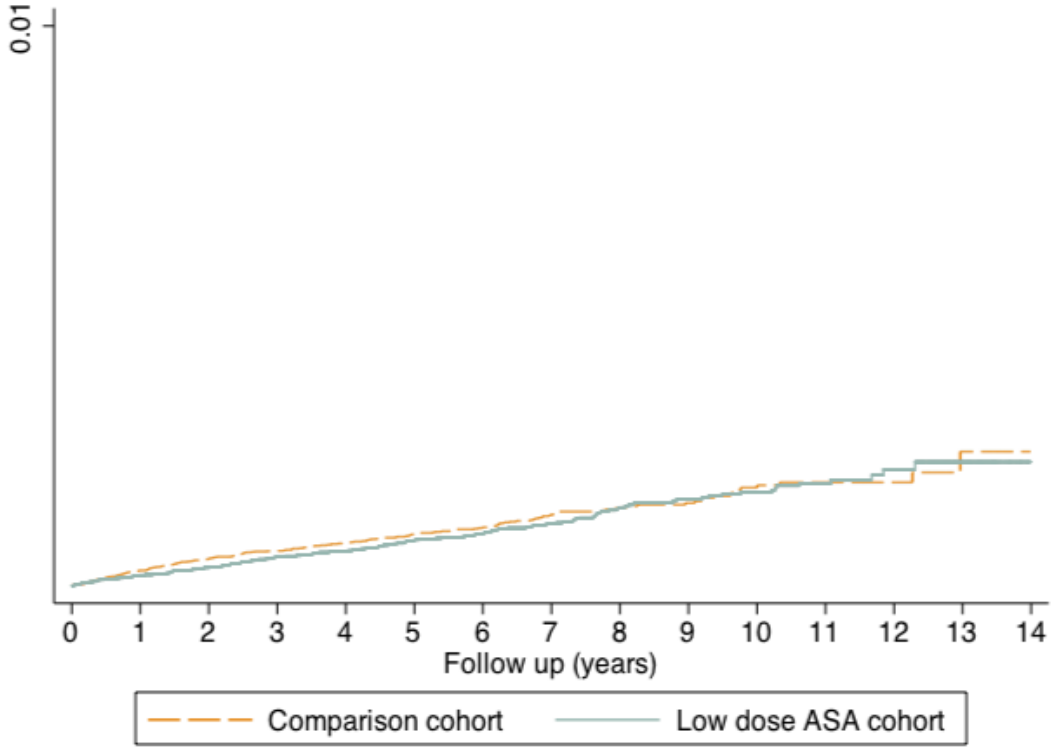

Figure 15. Nelson–Aalen cumulative incidence estimates of SAH according to type of cohort.

10.4.1.3 Cox regression analyses

As shown in **Table 23**, individuals in the low-dose ASA cohort showed a HR for ICB of 1.11 (95% CI: 1.01–1.22) compared with the comparison cohort, and individuals in the secondary CVD prevention population (i.e. with CVD antecedents) showed a HR of 1.41 (95% CI: 1.26–1.58) compared with those in the primary CVD prevention population (i.e. without CVD antecedents). Risk factors for ICB were age (HR 4.10, 95% CI: 3.62–4.65) for ages 75–89 years), current smoking (HR 1.38, 95% CI: 1.21–1.58), underweight (BMI <20 kg/m^2; HR 1.60, 95% CI: 1.26–2.03), a previous episode of ICB (HR 6.27, 95% CI: 4.68–8.41), history of ischaemic stroke (HR of 1.72, 95% CI: 1.38–2.15) and current use of warfarin at the start date (HR: 2.60, 95% CI: 2.09–3.22). **Tables 24–26** present the HRs separately for each subtype of bleeding.

For ICH (**Table 24**), the low-dose ASA cohort showed a HR of 1.12 (95% CI: 0.97–1.29) compared with the comparison cohort. Individuals in the secondary CVD prevention population showed a HR of 1.49 (95% CI: 1.27–1.75) compared with individuals in the primary CVD prevention population. Risk factors for ICH were older age (HR 5.79, 95% CI: 4.79–7.00) for ages 75–89 years, underweight (<20 kg/m^2; HR 1.99, 95% CI: 1.42–2.79), a previous episode of ICB (HR 6.50, 95% CI: 4.25–9.94), history of ischaemic stroke (HR 2.14, 95% CI: 1.60–2.86) and current use of warfarin at the start date (HR 2.77, 95% CI: 2.02–3.79).

For SDH (**Table 25**), the low-dose ASA cohort showed a HR of 1.28 (95% CI: 1.07–1.53) compared with the comparison cohort. Individuals in the secondary CVD prevention population showed a HR of 1.23 (95% CI: 1.01–1.51) compared with individuals in the primary CVD prevention population. Women presented a lower risk than men (HR 0.49, 95% CI: 0.41–0.60) and the risk of SDH increased with age. Current users of warfarin at the start date presented with a HR of 3.14 (95% CI: 2.22–4.43).

For SAH (**Table 26**), the low-dose ASA cohort showed a HR of 0.92 (95% CI: 0.75–1.12) compared with the comparison cohort. Individuals in the secondary CVD prevention population showed a HR of 1.53 (95% CI: 1.21–1.93) compared with individuals in the primary CVD prevention population. Women had a greater risk of SAH compared with men (RR 1.50, 95% CI: 1.22–1.85). Other identified risk factors for SAH were current smoking (HR 2.38, 95% CI: 1.85–3.05) and previous ICB (HR 11.29, 95% CI: 7.11–17.93).

10.4.2 Case–control analyses: all cases of ICB

The distribution of follow-up time (time between the start date and index date) among ICB cases and controls in the nested case–control analysis is shown in **Appendix Table 12**.

10.4.2.1 Demographics, lifestyle factors, healthcare use and polypharmacy among ICB cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among ICB cases and controls, and their association with ICB, is shown in **Table 27**. Among these variables, identified risk factors for ICB were current smoking (RR 1.38, 95% CI: 1.16–1.63), underweight (BMI <20 kg/m^2, RR 1.48, 95% CI: 1.15–1.92), a high level of deprivation (fifth quintile of Townsend score; RR 1.45, 95% CI: 1.20–1.74) and greater healthcare use (e.g. RR for ≥20 PCP visits in the year before the index date was 2.23, 95% CI: 1.79–2.77 when compared with 0–4 visits). Overweight and obesity were associated with a protective effect against ICB: RR 0.86 (95% CI: 0.75–0.99) for BMI 25–29 kg/m^2 and RR 0.69 (95% CI: 0.58–0.81) for BMI ≥30 kg/m^2.

10.4.2.2 Comorbidities among ICB cases and controls

The frequency of comorbidities among ICB cases and controls and their association with ICB is shown in **Table 28**. Previous ICB was the main predictor of ICB conferring an eight-fold increased risk (RR 8.42, 95% CI: 5.66–12.51). Haemodialysis was another strong predictor of ICB, conferring a nearly three-fold increased risk of ICB when evaluating all haemodialysis (RR 2.88, 95% CI: 1.08–7.70) and a four-fold increased risk of ICB when evaluating extracorporeal haemodialysis (RR 4.17, 95% CI: 1.42–12.19). Prior ischemic stroke, TIA, and eGFR less than 30 mL/min/1.73 m^2, depression, epilepsy, falls in the previous year and dementia were also identified as risk factors for ICB. Ischaemic heart disease (excluding MI) was associated with a reduced risk of ICB (RR 0.73, 95% CI: 0.61–0.87).

10.4.2.3 Medication use (including low-dose ASA) among ICB cases and controls

The frequency of medication use, including low-dose ASA, among ICB cases and controls and their association with ICB is shown in **Table 29**.

10.4.2.3.1 Low-dose ASA

Compared with never use of low-dose ASA, current use of low-dose ASA was not associated with a significant change in the risk of ICB (RR 0.98, 95% CI: 0.84–1.13); recent, past and distant use were similarly not associated with a change in the risk of ICB. Neither short-term use (<3 months) nor longer durations of use were associated with a significant change in risk of ICB, compared with never use. No dose–response relationship was observed between current use of low-dose ASA and risk of ICB, although it should be noted that a dose of 75 mg was used by the majority of current low-dose ASA users (94% of cases and 95% of controls). The RR for current use of low-dose ASA among the secondary CVD prevention population was 0.87 (95% CI: 0.63–1.19) when compared with current use of low-dose ASA among the primary CVD prevention population.

The frequency of low-dose ASA use among ICB cases and controls and the association with ICH, stratified by sex is shown in **Table 30**. No associations between current use of low-dose ASA and risk of ICB were seen among either men or women. The RR of ICB for current use of low-dose ASA compared with never use was 1.00 (95% CI: 0.81–1.22) among men and 0.95 (95% CI: 0.77–1.17) among women. For current/recent use of low-dose ASA vs. never use, the RR was 0.99 (95% CI: 0.82–1.21) among men and 1.00 (95% CI: 0.82–1.22) among women.

The frequency of low-dose ASA use among ICB cases and controls, and association with ICB, stratified by case-fatality status, is shown in **Table 31**. Compared with never use, no association was seen between current use or current/recent use of low-dose ASA and risk of non-fatal ICB (RR 1.14, 95% CI: 0.97–1.35 for current use and RR 1.16, 95% CI: 0.98–1.36 for current/recent use). In contrast, a significant decrease in the risk of fatal ICB was seen associated with current use and current/recent use of low-dose ASA (RR 0.63, 95% CI: 0.48–0.82 for current use and RR 0.67, 95% CI: 0.52–0.86 for current/recent use).

10.4.2.3.2 Other medications

As shown in **Table 29**, an increased risk of ICB was seen in individuals currently taking warfarin at the index date (RR 2.04, 95% CI: 1.60–2.61) or SSRIs (RR 1.50, 95% CI: 1.20–1.88) compared with never users of the respective drug. Current users of warfarin with high INR levels (≥3) had close to a four-fold increased risk of ICB (RR 3.64, 95% CI: 2.36–5.60), while a small yet still significant increase in ICB risk was observed for warfarin users with INR levels <3 (RR 1.55, 95% CI: 1.13–2.12). Current users of acetaminophen had a borderline increased risk of ICB (RR 1.21, 95% CI: 1.01–1.43) compared with never users. No significant change in ICB risk was seen associated with current use of clopidogrel (RR 1.13, 95% CI: 0.86–1.49), NSAIDs (RR 1.17, 95% CI: 0.93–1.48), oral steroids (RR 0.88, 95% CI: 0.63–1.21), PPIs (RR 1.00, 95% CI: 0.86–1.16) or H_2RAs (RR 1.14, 95% CI: 0.80–1.62), when compared with never use of the respective medication. There were too few patients with a prescription for other anticoagulants to provide any meaningful results; only two cases of ICB and ten controls were current users of these medications.

10.4.2.3.3 Other medications (combined therapy)

As shown in **Table 29**, current users of dual antiplatelet therapy (DAT) with low-dose ASA and clopidogrel did not have a significantly different risk of ICB compared with never users of both low-dose ASA and clopidogrel (RR 1.10, 95% CI: 0.71–1.69). In contrast, current users of low-dose ASA with concomitant warfarin use was associated with a significantly increased risk of ICB (RR 2.31, 95% CI: 1.36–3.91) compared with never users of both low-dose ASA and warfarin.

10.4.3 Case–control analyses: non-traumatic ICB

10.4.3.1 Demographics, lifestyle factors, healthcare use and polypharmacy among non-traumatic ICB cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic ICB cases and controls, and their association with non-traumatic ICB are shown in **Appendix Table 13**.

10.4.3.2 Comorbidities among non-traumatic ICB cases and controls

The frequency of comorbidities among non-traumatic ICB cases and controls, and their association with non-traumatic ICB is shown in **Appendix Table 14**.

10.4.3.3 Medication use (including low-dose ASA) among non-traumatic ICB cases and controls

The frequency of medication use, including low-dose ASA, among non-traumatic ICB cases, and controls, and their association with non-traumatic ICB, is shown in **Table 32**.

10.4.3.3.1 Low-dose ASA

The RR for non-traumatic ICB among current users of low-dose ASA compared with never users was 0.88 (95% CI: 0.74–1.03). Neither short-term use (<3 months) nor longer durations of use were associated with a significant change in risk of non-traumatic ICB, compared with never use. No dose–response relationship was observed between current use of low-dose ASA and risk of non-traumatic ICB.

10.4.3.3.2 Other medications

As shown in **Table 32**, an increased risk of non-traumatic ICB was seen in individuals currently taking warfarin at the index date (RR 1.96, 95% CI: 1.48–2.60) compared with never users, while individuals taking SSRIs (RR 1.33, 95% CI: 1.02–1.75) or NSAIDs (RR 1.33, 95% CI: 1.02–1.75) had a borderline increased risk of non-traumatic ICB compared with never users of the respective drug. Current users of warfarin with high INR levels (≥3) had close to a four-fold increased risk of non-traumatic ICB (RR 3.92, 95% CI: 2.45–6.59), while a smaller yet still significant increase in non-traumatic ICB risk was observed for warfarin users with INR levels <3 (RR 1.53, 95% CI: 1.07–2.19). Current use of inhaled steroids (RR 0.54, 95% CI: 0.39–0.73), antihypertensives (RR 0.55, 95% CI: 0.40–0.75) and statins (RR 0.73, 95% CI: 0.62–0.86) were associated with a decreased risk of non-traumatic ICB compared with never use of the respective drug. No significant change in non-traumatic ICB risk was seen associated with current use of clopidogrel (RR 0.94, 95% CI: 0.67–1.32) or any of the other medications evaluated, compared with never use of the respective drug.

10.4.3.3.3 Other medications (combined therapy)

As shown in **Table 32**, current users of DAT with low-dose ASA and clopidogrel did not have a significantly different risk of non-traumatic ICB compared with never users of both low-dose ASA and clopidogrel (RR 0.80, 95% CI: 0.46–1.39). In contrast, current users of low-dose ASA with concomitant warfarin use was associated with a significantly increased risk of non-traumatic ICB (RR 2.38, 95% CI: 1.33–4.25) compared with never users of both low-dose ASA and warfarin.

10.4.4 Case–control analyses: traumatic ICB

10.4.4.1 Demographics, lifestyle factors, healthcare use and polypharmacy among traumatic ICB cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among traumatic ICB cases and controls, and their association with traumatic ICB, is shown in **Appendix Table 15**.

10.4.4.2 Comorbidities among traumatic ICB cases and controls

The frequency of comorbidities among traumatic ICB cases and controls, and their association with traumatic ICB, are shown in **Appendix Table 16**.

10.4.4.3 Medication use (including low-dose ASA) among traumatic ICB cases and controls

The frequency of medication use, including low-dose ASA, among traumatic ICB cases and controls, and their association with traumatic ICB, is shown in **Table 33**.

10.4.4.3.1 Low-dose ASA

The RR for traumatic ICB among current users of low-dose ASA compared with never users was 1.30 (95% CI: 1.00–1.68). Short-term use (<3 months) was not associated with a significant change in the risk of traumatic ICB compared with never-use (RR 1.34, 95% CI: 0.79–2.27). Current use of low-dose ASA of 3 months–1 year was associated with an increase in risk of borderline statistical significance: RR 1.83 (95% CI: 1.07–3.13) for 3–<6 months duration, and RR 1.68 (95% CI: 1.06–2.64) for durations of 6 months–1 year. Among current users of low-dose ASA, a daily dose of 150–300 mg was associated with an RR of 2.24 (95% CI: 1.25–4.00) compared with never use, while the RR for a daily dose of 75 mg was 1.25 (95% CI: 0.96–1.63).

10.4.4.3.2 Other medications

As shown in **Table 33**, an increased risk of traumatic ICB was seen in individuals currently taking warfarin at the index date (RR 2.23, 95% CI: 1.45–3.42), clopidogrel (RR 1.67, 95% CI: 1.10–2.54), SSRIs (RR 2.02, 95% CI: 1.41–2.90) and acetaminophen (borderline

increased risk; RR 1.39, 95% CI: 1.03–1.90) compared with never users of the respective drug. Current users of warfarin with high INR levels (≥3) had close to a three-fold increased risk of traumatic ICB (RR 2.84, 95% CI: 1.35–5.97), while a small non-significant increase in ICB risk was observed for warfarin users with INR levels <3 (RR 1.56, 95% CI: 0.91–2.69). Current users of inhaled steroids and antihypertensives had a decreased risk of traumatic ICB, RR 0.56 (95% CI: 0.28–1.11) for inhaled steroids and 0.65 (95% CI: 0.45–0.94) for antihypertensives. No significant changes in traumatic ICB risk were seen with use of the other medications evaluated.

10.4.4.3.3 Other medications (combined therapy)

As shown in **Table 33**, current users of DAT with low-dose ASA and clopidogrel had a significantly increased risk of traumatic ICB compared with never users of both low-dose ASA and clopidogrel (RR 2.09, 95% CI: 1.13–3.89). In contrast, no association was seen between current users of low-dose ASA with concomitant warfarin and risk of traumatic ICB (RR 1.92, 95% CI: 0.70–5.25) compared with never users of both low-dose ASA and warfarin.

10.4.5 Case–control analyses: ICH

10.4.5.1 Demographics, lifestyle factors, healthcare use and polypharmacy among ICH cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among ICH cases and controls, and their association with ICH are shown in **Appendix Table 17**.

10.4.5.2 Comorbidities among ICH cases and controls

The frequency of comorbidities of ICH cases and controls, and their association with ICH are shown in **Appendix Table 18**.

10.4.5.3 Medication use (including low-dose ASA) among ICH cases and controls

The frequency of medication use, including low-dose ASA, among ICH cases and controls, and their association with ICH, is shown in **Table 34**.

10.4.5.3.1 Low-dose ASA

The RR for ICH among current users of low-dose ASA compared with never users was 0.98 (95% CI: 0.80–1.20). Among current users of low-dose ASA, neither short-term use (<3 months) nor longer durations of use were associated with a significant change in the risk of ICH risk when compared with never use. No dose–response relationship was observed between current use of low-dose ASA and risk of ICH.

The frequency of low-dose ASA use among ICH cases and controls, and their association with ICH, stratified by sex, is shown in **Table 35**. No associations between current use of low-dose ASA and risk of ICH were seen among either men or women. The RR of ICH with current low-dose ASA use compared with never use was 0.84 (95% CI: 0.63–1.12) among men and 1.16 (95% CI: 0.86–1.56) among women. For current/recent use of low-dose ASA compared with never use, the RR of ICH was 0.87 (95% CI: 0.67–1.15) among men and 1.20 (95% CI: 0.90–1.60) among women.

The frequency of low-dose ASA use among ICH cases and controls and association with ICH, stratified by case-fatality status, is shown in **Table 36**. Compared with never use, no association was seen between current use or current/recent use of low-dose ASA and risk of non-fatal ICH (RR 1.22, 95% CI: 0.95–1.58 for current use and RR 1.30, 95% CI: 1.02–1.66 for current/recent use). In contrast, a significant decrease in the risk of fatal ICB was seen associated with current use and current/recent use of low-dose ASA (RR 0.66, 95% CI: 0.48–0.92 for current use and RR 0.66, 95% CI: 0.48–0.91 for current/recent use).

10.4.5.3.2 Other medications

As shown in **Table 34**, among the medications evaluated, an increased risk of ICH was seen among individuals currently taking warfarin at the index date (RR 1.87, 95% CI: 1.35–2.61) compared with never users. Current users of warfarin with high INR levels (≥3) had a four-fold increased risk of ICH (RR 4.31, 95% CI: 2.54–7.30), while a non-significant increase in traumatic ICH risk was observed for warfarin users with INR levels <3 (RR 1.38, 95% CI: 0.90–2.10). Decreased risks of ICH were seen among current users of statins (RR 0.73, 95% CI: 0.59–0.89), inhaled steroids (RR 0.54, 95% CI: 0.37–0.80) and antihypertensives (RR 0.63, 95% CI: 0.47–0.83) compared with never users of the respective drug. No other significant associations between current use of a medication and risk of ICH were observed for any of the other medications evaluated.

10.4.5.3.3 Other medications (combined therapy)

As shown in **Table 34**, current users of DAT with low-dose ASA and clopidogrel did not have a significantly different risk of ICH compared with never users of both low-dose ASA and clopidogrel (RR 0.85, 95% CI: 0.42–1.71). Similarly, current users of low-dose ASA with concomitant warfarin did not have a significantly different risk of ICH (RR 2.01, 95% CI: 1.00–4.07) compared with never users of both low-dose ASA and warfarin.

10.4.6 Case–control analyses: non-traumatic ICH

10.4.6.1 Demographics, lifestyle factors, healthcare use and polypharmacy among non-traumatic ICH cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic ICH cases and controls, and their association with non-traumatic ICH is shown in **Appendix Table 19**.

10.4.6.2 Comorbidities among non-traumatic ICH cases and controls

The frequency of comorbidities among non-traumatic ICH cases and controls, and their association with non-traumatic ICH is shown in **Appendix Table 20**.

10.4.6.3 Medication use (including low-dose ASA) among non-traumatic ICH cases and controls

The frequency of medication use, including low-dose ASA, among non-traumatic ICH cases and controls, and their association with non-traumatic ICH, is shown in **Table 37**.

10.4.6.3.1 Low-dose ASA

The RR for non-traumatic ICH among current users of low-dose ASA compared with never users was 0.97 (95% CI: 0.78–1.20). Neither short-term use (<3 months) nor longer durations of use were associated with a significant change in risk of non-traumatic ICH, compared to never-use. No dose–response relationship was observed between current use of low-dose ASA and risk of non-traumatic ICH.

10.4.6.3.2 Other medications

As shown in **Table 37**, among the medications evaluated, an increased risk of non-traumatic ICH was seen in individuals currently taking warfarin at the index date (RR 1.51, 95% CI: 1.06–2.17) compared with never users. Current users of warfarin with high INR levels (≥3) had close to a four-fold increased risk of non-traumatic ICH (RR 3.64, 95% CI: 2.07–6.42), while a small, non-significant increase in non-traumatic ICH risk was observed for warfarin users with INR levels <3 (RR 1.19, 95% CI: 0.76–1.87). Current use of statins (RR 0.71, 95% CI: 0.57–0.88), antihypertensives (RR 0.60, 95% CI: 0.45–0.81) and inhaled steroids (RR 0.53, 95% CI: 0.35–0.78) were all associated with a decreased risk of non-traumatic ICH compared with never users of the respective drug. No significant changes in non-traumatic ICH risk were seen with use of clopidogrel (RR 0.92, 95% CI: 0.60–1.42) or any of the other medications evaluated.

10.4.6.3.3 Other medications (combined therapy)

As shown in **Table 37**, current users of DAT with both low-dose ASA and clopidogrel did not have a significantly different risk of non-traumatic ICH compared with never users of both low-dose ASA and clopidogrel (RR 1.13, 95% CI: 0.74–1.71). Similarly, current users of low-dose ASA with concomitant warfarin use did not have a significantly different risk of non-traumatic ICH (RR 1.76, 95% CI: 0.82–3.77) compared with never users of both low-dose ASA and warfarin.

10.4.7 Case–control analyses: SDH

10.4.7.1 Demographics, lifestyle factors, healthcare use and polypharmacy among SDH cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among SDH cases and controls, and their association with SDH, is shown in **Appendix Table 21**.

10.4.7.2 Comorbidities among SDH cases and controls

The frequency of comorbidities among SDH cases and controls, and their association with SDH, is shown in **Appendix Table 22**.

10.4.7.3 Medication use (including low-dose ASA) among SDH cases and controls

The frequency of medication use, including low-dose ASA, among SDH cases and controls, and their association with SDH, is shown in **Table 38**.

10.4.7.3.1 Low-dose ASA

The RR for SDH among current users of low-dose ASA compared with never users was 1.23 (95% CI: 0.95–1.59). Neither short-term use (<3 months) nor longer durations of use were associated with a significant change in risk of SDH, compared with never-use. No dose–response relationship was observed between current use of low-dose ASA and SDH.

The frequency of low-dose ASA use among SDH cases and control and association with SDH, stratified by sex, is shown in **Table 39**. No associations between current use of low-dose ASA and risk of SDH were seen among either men or women. The RR of SDH for current low-dose ASA use compared with never use was 1.18 (95% CI: 0.86–1.64) among men and 1.29 (95% CI: 0.85–1.95) among women. For current/recent use of low-dose ASA compared with never use, the RR was 1.12 (95% CI: 0.81–1.53) among men and 1.30 (95% CI: 0.87–1.94) among women.

The frequency of low-dose ASA use among SDH cases and control and association with SDH, stratified by case-fatality status, is shown in **Table 40**. Compared with never use, no associations were seen between use of low-dose ASA and risk of SDH. The RR of fatal SDH was 1.08 (95% CI: 0.48–2.40) for current low-dose ASA use versus never use, and 1.10 (95% CI: 0.51–2.37) for current/recent use versus never use. The RR of non-fatal SDH was 1.25 (95% CI: 0.95–1.63) for current low-dose ASA use compared with never use, and 1.19 (95% CI: 0.92–1.55) for current/recent use compared with never use.

10.4.7.3.2 Other medications

As shown in **Table 38**, an increased risk of SDH was seen in individuals currently taking warfarin at the index date (RR 2.47, 95% CI: 1.67–3.63), SSRIs (RR 1.57, 95% CI: 1.08–2.29) or acetaminophen (RR 1.54, 95% CI: 1.15–2.07) compared with never users of the respective drug. Current users of warfarin with high INR levels (≥3) had a three-fold increased risk of SDH (RR 3.06, 95% CI: 1.61–5.84), while a smaller yet still significant increase in SDH risk was observed for warfarin users with INR levels <3 (RR 1.94, 95% CI: 1.21–3.10). A decreased risk of SDH was seen among current users of statins at the index date (RR 0.77, 95% CI: 0.61–0.99) compared with never users. No significant change in SDH risk was seen with current use of clopidogrel (RR 1.32, 95% CI: 0.86–2.01) or any of the other medications evaluated compared with never use of the respective drug.

10.4.7.3.3 Other medications (combined therapy)

As shown in **Table 38**, current users of DAT with low-dose ASA and clopidogrel did not have a significantly different risk of SDH compared with never users of both low-dose ASA and clopidogrel (RR 1.63, 95% CI: 0.86–3.10). In contrast, current users of low-dose ASA with concomitant warfarin use was associated with a significantly four-fold increased risk of SDH (RR 4.43, 95% CI: 2.16–9.09) compared with never user of both low-dose ASA and warfarin.

10.4.8 Case–control analyses: non-traumatic SDH

10.4.8.1 Demographics, lifestyle factors, healthcare use and polypharmacy among non-traumatic SDH cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic SDH cases and controls, and their association with non-traumatic SDH, is shown in **Appendix Table 23**.

10.4.8.2 Comorbidities among non-traumatic SDH cases and controls

The frequency of comorbidities among non-traumatic SDH cases and controls, and their association with non-traumatic SDH, is shown in **Appendix Table 24**.

10.4.8.3 Medication use (including low-dose ASA) among non-traumatic SDH cases and controls

The frequency of medication use, including low-dose ASA, among non-traumatic SDH cases and controls, and their association with non-traumatic SDH, is shown in **Table 41**.

10.4.8.3.1 Low-dose ASA

The RR for non-traumatic SDH among current users of low-dose ASA compared with never users was 1.03 (95% CI: 0.70–1.52). Neither short-term use (<3 months) nor longer durations

of use were associated with a significant change in risk of non-traumatic SDH, compared with never use. No dose–response relationship was observed between current use of low-dose ASA and risk of non-traumatic SDH.

10.4.8.3.2 Other medications

As shown in **Table 41**, an increased risk of non-traumatic SDH was seen in individuals currently taking warfarin at the index date (RR 4.15, 95% CI: 2.42–7.13), SSRIs (RR 1.57, 95% CI: 1.08–2.29) or acetaminophen (RR 1.54, 95% CI: 1.15–2.07) compared with never users of the respective drug. Current users of warfarin with high INR levels (≥3) had close to a five-fold increased risk of non-traumatic SDH (RR 4.96, 95% CI: 2.20–11.15), while the RR for warfarin users with INR levels <3 was 3.23 (95% CI: 1.71–6.09). No significant change in non-traumatic SDH risk was seen associated with current use of clopidogrel (RR 1.13, 95% CI: 0.86–1.49) or any of the other medications evaluated, compared with never use of the respective drug.

10.4.8.3.3 Other medications (combined therapy)

As shown in **Table 41**, current users of DAT with both low-dose ASA and clopidogrel did not have a significantly different risk of non-traumatic SDH compared with never users of both low-dose ASA and clopidogrel (RR 0.90, 95% CI: 0.27–2.99). In contrast, current users of low-dose ASA with concomitant warfarin use was associated with a significant eight-fold increased risk of non-traumatic SDH (RR 8.63, 95% CI: 3.57–20.86) compared with never users of both low-dose ASA and warfarin.

10.4.9 Case–control analyses: traumatic SDH

10.4.9.1 Demographics, lifestyle factors, healthcare use and polypharmacy among traumatic SDH cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among traumatic SDH cases and controls, and their association with traumatic SDH, are shown in **Appendix Table 25**.

10.4.9.2 Comorbidities among traumatic SDH cases and controls

The frequency of comorbidities among traumatic SDH cases and controls, and their association with traumatic SDH, is shown in **Appendix Table 26**.

10.4.9.3 Medication use (including low-dose ASA) among traumatic SDH cases and controls

The frequency of medication use, including low-dose ASA, among traumatic SDH cases and controls, and their association with traumatic SDH, is shown in **Table 42**.

10.4.9.3.1 Low-dose ASA

The RR for traumatic SDH among current users of low-dose ASA compared with never users was 1.39 (95% CI: 1.00–1.93). Among current users of low-dose ASA, short-term use (<3 months) was associated with a significantly increased risk of traumatic SDH compared with never use, RR 1.96 (95% CI: 1.10–3.48), while longer durations of use were not associated with a significant change in risk of traumatic SDH. No dose–response relationship was observed between current use of low-dose ASA and risk of traumatic SDH.

10.4.9.3.2 Other medications

As shown in **Table 42**, neither current use of clopidogrel nor current use of warfarin at the index date was associated with a significant change in risk of traumatic SDH compared with never use of the respective medication; RR 1.63 (95% CI: 0.99–2.70) for clopidogrel and RR 1.48 (95% CI: 0.87–2.52) for clopidogrel. The lack of association between traumatic SDH and warfarin use was seen among warfarin users with either high (≥3) or low (<3) INR levels. Of the other medications evaluated, a significant change in the risk of traumatic SDH was seen only for current use of SSRIs, where an increased risk was seen when compared with never users (RR 1.79, 95% CI: 1.13–2.83).

10.4.9.3.3 Other medications (combined therapy)

As shown in **Table 42**, current users of DAT with both low-dose ASA and clopidogrel had a significantly increased risk of traumatic SDH compared with never users of both low-dose ASA and clopidogrel (RR 2.29, 95% CI: 1.09–4.80). In contrast, current user of low-dose ASA with concomitant warfarin use was not associated with a significantly increased risk of traumatic SDH compared with never users of both low-dose ASA and warfarin (RR 1.55, 95% CI: 0.43–5.56).

10.4.10 Case–control analyses: SAH

10.4.10.1 Demographics, lifestyle factors, healthcare use and polypharmacy among SAH cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among SAH cases and controls, and their association with SAH, is shown in **Appendix Table 27**.

10.4.10.2 Comorbidities among SAH cases and controls

The frequency of comorbidities among SAH cases and controls, and their association with SAH, is shown in **Appendix Table 28**.

10.4.10.3 Medication use (including low-dose ASA) among SAH cases and controls

The frequency of medication use, including low-dose ASA, among SAH cases and controls and their association with SAH, is shown in **Table 43**.

10.4.10.3.1 Low-dose ASA

The RR for SAH among current users of low-dose ASA compared with never users was 0.77 (95% CI: 0.58–1.01). Among current users of low-dose ASA, durations of less than 1 year were not associated with a change in risk of SAH, while a duration of 1 to <5 years was associated with a significantly decreased risk of SAH, RR 0.67 (95% CI: 0.47–0.94). Among current low-dose ASA users, a daily dose of 75 mg was associated with a significantly reduced risk of SAH (RR 0.73, 95% CI: 0.56–0.97) compared with never use, while no significant change in SAH risk was seen with daily doses of 150 mg or 300 mg.

The frequency of low-dose ASA use among SAH cases and controls, and association with SAH, stratified by sex, is shown in **Table 44**. Compared with never use, no association was seen with current or current/recent use of low-dose ASA and risk of SAH among men (RR 1.13, 95% CI: 0.73–1.74 for current use and 1.14, 95% CI: 0.74–1.74 for current/recent use). In contrast, compared with never use, a significantly decreased risk of SAH was seen with current and current/recent use of low-dose ASA among women (RR 0.57, 95% CI: 0.39–0.82 for current use and RR 0.65, 95% CI: 0.46–0.91 for current/recent use).

The frequency of low-dose ASA use among SAH cases and controls and association with SAH, stratified by case-fatality status is shown in **Table 45**. While no association was seen between current use or current/recent use of low-dose ASA and risk of non-fatal SAH compared with never use (RR 0.95, 95% CI: 0.69–1.33 for current use and RR 0.95, 95% CI: 0.69–1.31 for current/recent use), a significant decrease in the risk of fatal SAH was associated with current use and current/recent use of low-dose ASA (RR 0.45, 95% CI: 0.27–0.74 for current use and RR 0.58, 95% CI: 0.37–0.92 for current/recent use).

10.4.10.3.2 Other medications

As shown in **Table 43**, individuals taking clopidogrel or warfarin did not have a significant change in risk of SAH compared with never users of the respective drug (RR 1.33, 95% CI: 0.78–2.28 for clopidogrel and RR 1.79, 95% CI: 0.97–3.29 for warfarin). Among current users of warfarin, neither those with high (≥3) of low (<3) INR levels had a significant change in risk of SAH compared with never users. An increased risk of SAH was seen in individuals currently taking SSRIs at the index date (RR 1.84 95% CI: 1.23–2.74) compared with never users of SSRIs. Current use of antihypertensives or inhaled steroids was associated with a decreased risk of SAH, RR 0.48 (95% CI: 0.33–0.70) for antihypertensives and RR 0.56 (95% CI: 0.32–0.98) for inhaled steroids. No significant change in SAH risk was seen associated with current use of any of the other medications evaluated.

10.4.10.3.3 Other medications (combined therapy)

As shown in **Table 43**, current users of DAT with both low-dose ASA and clopidogrel did not have a significantly different risk of SAH compared with never users of both low-dose ASA and clopidogrel (RR 1.35, 95% CI: 0.61–3.00). There were no cases of SAH who were current users of low-dose ASA and concomitant warfarin to be able to evaluate their use (concomitantly) with the risk of SAH.

10.4.11 Case–control analyses: non-traumatic SAH

10.4.11.1 Demographics, lifestyle factors, healthcare use and polypharmacy among non-traumatic SAH cases and controls

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic SAH cases and controls, and their association with non-traumatic SAH, is shown in **Appendix Table 29**.

10.4.11.2 Comorbidities among non-traumatic SAH cases and controls

The frequency of comorbidities among non-traumatic SAH cases and controls, and their association with non-traumatic SAH, is shown in **Appendix Table 30**.

10.4.11.3 Medication use (including low-dose ASA) among non-traumatic SAH cases and controls

The frequency of medication use, including low-dose ASA, among non-traumatic SAH cases and controls, and their association with non-traumatic SAH, is shown in **Table 46**.

10.4.11.3.1 Low-dose ASA

A significantly decreased risk of non-traumatic SAH was seen among current users of low-dose ASA compared with never users, RR 0.66 (95% CI: 0.48–0.90). Among current users of low-dose ASA, neither short-term use (<3 months) nor medium term use (3–<6 months) were not associated with a significantly decreased risk of non-traumatic SAH when compared with never users (RR 0.96, 95% CI: 0.54–1.70 for short-term use and RR 1.18, 95% CI: 0.60–2.32 for medium-term use). A significant decrease in risk was seen for between 1 and <5 years of use, RR 0.58 (95% CI: 0.39–0.86). No dose–response relationship was observed between current use of low-dose ASA and risk of non-traumatic SAH.

10.4.11.3.2 Other medications

As shown in **Table 46**, of the medications evaluated, only SSRIs when used at the index date (current use) were associated with a significantly increased risk of non-traumatic SAH compared with never use (RR 1.78, 95% CI: 1.13–2.80). Warfarin users with high INR levels (≥3) had a significantly increased risk of non-traumatic SAH (RR 3.62, 95% CI: 1.15–11.37) compared with never users, while those with lower INR levels (<3) did not have a

significantly increased risk of non-traumatic SAH compared with never users (RR 0.65, 95% CI: 0.47–0.89). Current use of antihypertensives was associated with a significantly decreased risk of non-traumatic SAH (RR 0.47, 95% CI: 0.31–0.71) compared with never users. No significant changes in non-traumatic SAH risk was seen associated with current use of any of the other medications evaluated.

10.4.11.3.3 Other medications (combined therapy)

As shown in **Table 46**, current users of DAT with both low-dose ASA and clopidogrel did not have a significantly different risk of non-traumatic SAH compared with never users of both low-dose ASA and clopidogrel (RR 0.62, 95% CI: 0.19–2.03). There were no cases of SAH who were current users of low-dose ASA and concomitant warfarin to be able to evaluate their use (concomitantly) with the risk of non-traumatic SAH.

10.4.12 Cohort analyses: UGIB and LGIB

10.4.12.1 Overall incidence rates of UGIB and LGIB

The incidence rate of UGIB and LGIB for both cohorts combined and for each cohort separately is shown in **Table 47** for all cases of UGIB and LGIB. The overall incidence rate of UGIB was 0.83 cases per 1000 person-years (95% CI: 0.79–0.86) over the whole study period, with incidence rates higher in the low-dose ASA cohort than the comparison cohort: 0.97 cases per 1000 person-years (95% CI: 0.91–1.02) in the low-dose ASA cohort and 0.67 cases per 1000 person-years (95% CI: 0.63–0.75) in the comparison cohort. The overall incidence rate of LGIB was 1.24 cases per 1000 person-years (95% CI: 1.19–1.28) over the whole study period, with incidence rates higher in the low-dose ASA cohort than the comparison cohort: 1.68 cases per 1000 person-years (95% CI: 1.60–1.75) in the low-dose ASA cohort and 0.76 cases per 1000 person-years (95% CI: 0.72–0.82) in the comparison cohort. The IRR (low-dose ASA vs. comparison cohort) over the whole duration of follow-up was 1.42 (95% CI: 1.29–1.56) for UGIB and 2.17 (95% CI: 2.00–2.35) for LGIB.

As shown in **Table 48**, the overall incidence of UGIB in the first year of follow-up was slightly higher than the incidence rate observed among the whole duration of follow-up at 1.01 per 1000 person-years (95% CI: 0.98–1.12): 1.31 per 1000 person-years (95% CI: 1.16–1.48) in the low-dose ASA cohort and 0.72 per 1000 person-years (95% CI: 0.60–0.85) in the comparison cohort. The IRR (low-dose ASA vs. comparison cohort) in the first year of follow-up was 1.80 (95% CI: 1.46–2.22) for UGIB and 2.30 (95% CI: 1.91–2.77) for LGIB.

Incidence rates of hospitalized and referred cases of UGIB and LGIB are shown in **Table 49**, overall and stratified by study cohort. The incidence of hospitalized cases of UGIB was 0.49 per 1000 person-years (95% CI: 0.47–0.53): 0.57 (95% CI: 0.53–0.61) in the low-dose ASA cohort and 0.42 (95% CI: 0.38–0.46) in the comparison cohort. The incidence of referred cases of UGIB was 0.33 per 1000 person-years (95% CI: 0.30–0.35): 0.39 (95% CI: 0.36–0.43) in the low-dose ASA cohort and 0.26 (95% CI: 0.23–0.29) in the comparison cohort. The incidence of hospitalized cases of LGIB was 0.35 per 1000 person-years (95% CI: 0.32–

0.37): 0.45 (95% CI: 0.42–0.49) in the low-dose ASA cohort and 0.23 (95% CI: 0.20–0.26) in the comparison cohort. The incidence of referred cases of LGIB was 0.89 per 1000 person-years (95% CI: 0.85–0.93): 1.22 (95% CI: 1.16–1.29) in the low-dose ASA cohort and 0.54 (95% CI: 0.49–0.58) in the comparison cohort.

Incidence rates of UGIB stratified by sex and age group are shown in **Table 50**, for both cohorts combined and by study cohort separately. The incidence of UGIB was 0.85 per 1000 person-years (95% CI: 0.80–0.91) in men and 0.80 per 1000 person-years (95% CI: 0.74–0.85) in women; rates were higher in the low-dose ASA cohort than in the comparison cohort among both sexes. Incidence rates increased with age, rising from 0.49 per 1000 person-years (95% CI: 0.46–0.54) in individuals aged 40–64 years to 1.81 per 1000 person-years (95% CI: 1.68–1.96) in individuals aged 75–89 years; incidence rates were higher in the low-dose ASA cohort than the comparison cohort in all age groups. Incidence rates of LGIB stratified by sex and age group are shown in **Table 51**, both overall and by study cohort. The incidence of LGIB was 1.18 per 1000 person-years (95% CI: 1.11–1.24) in men and 1.30 per 1000 person-years (95% CI: 1.23–1.37) in women; rates were higher in the low-dose ASA cohort than in the comparison cohort among both sexes. Incidence rates increased with age, rising from 1.02 per 1000 person-years (95% CI: 0.96–1.08) in individuals aged 40–64 years to 1.78 per 1000 person-years (95% CI: 1.65–1.93) in individuals aged 75–89 years; incidence rates were higher in the low-dose ASA cohort than in the comparison cohort in all age groups.

Incidence rates of UGIB and LGIB stratified by case-fatality status are shown in **Table 52** overall and by study cohort. The incidence rate of fatal UGIB was 0.06 per 1000 person-years (95% CI: 0.05–0.07) and the incidence of non-fatal UGIB was 0.77 per 1000 person-years (95% CI: 0.73–0.81). Incidence rates of fatal UGIB were similar in the two study cohorts, IRR 0.93 (95% CI: 0.66–1.31), while the incidence of non-fatal UGIB was significantly higher in the low-dose ASA cohort than the comparison cohort, IRR 1.47 (95% CI: 1.33–1.62). The incidence of fatal LGIB was 0.01 per 1000 person-years (95% CI: 0.008–0.02) and the incidence of non-fatal UGIB was 1.23 per 1000 person-years (95% CI: 1.18–1.27). No significant difference was seen in the incidence rate of fatal LGIB between the two study cohorts, IRR 1.41 (95% CI: 0.63–3.14, although this was based on a small number of cases). In contrast, the incidence of non-fatal LGIB was significantly higher in the low-dose ASA cohort than the comparison cohort, IRR 2.18 (95% CI: 2.01–2.37).

10.4.12.2 Kaplan-Meier survival estimates: UGIB and LGIB

Kaplan–Meier curves of cumulative incidence of UGIB and LGIB are shown in **Figure 16** and **Figure 17**, respectively.

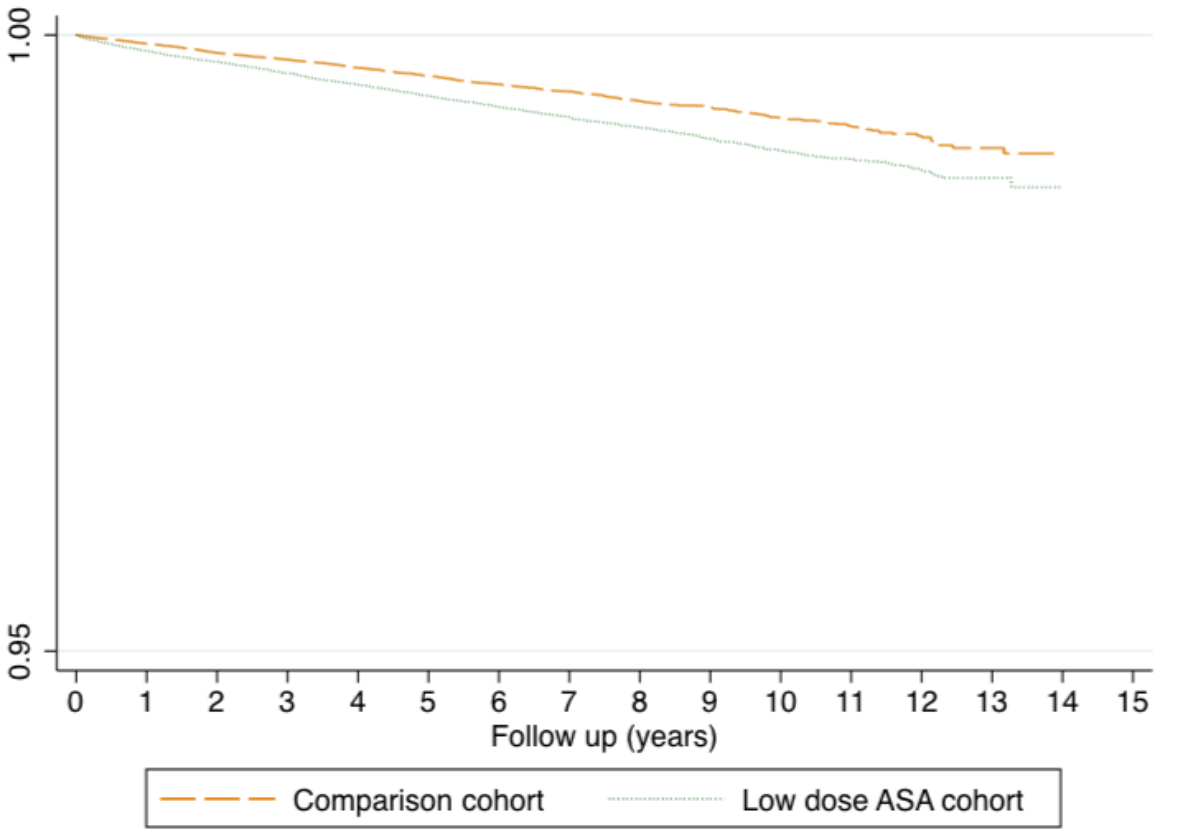

Figure 16. Kaplan–Meier survival estimates of UGIB according to type of cohort.

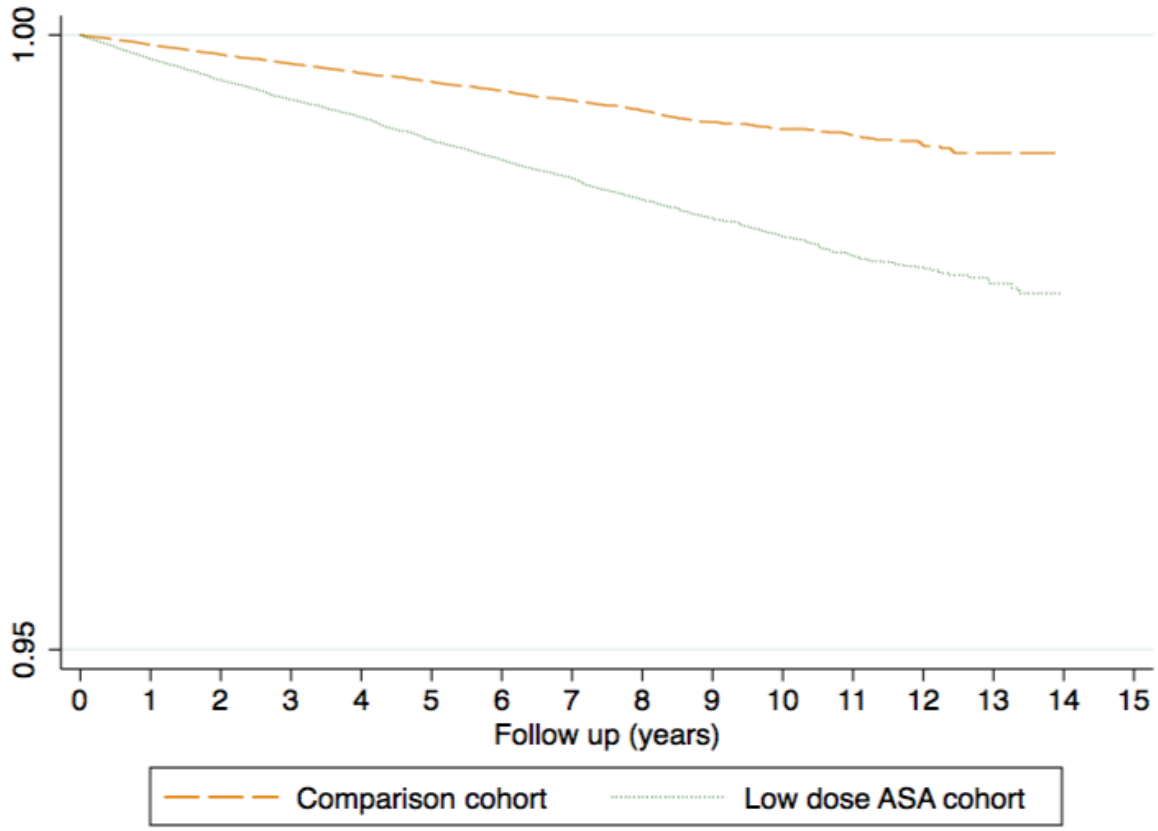

Figure 17. Kaplan–Meier survival estimates of LGIB according to type of cohort.

10.4.13 Case–control analyses: UGIB

The distribution of follow-up time (time between the start date and index date) among UGIB cases and controls in the nested case–control analysis is shown in **Appendix Table 31**.

10.4.13.1 Demographics, lifestyle factors, healthcare use and polypharmacy

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among UGIB cases and controls, and their association with UGIB, is shown in **Table 53**. Among these variables, identified risk factors for UGIB were: current smoking (RR 1.36, 95% CI: 1.14–1.63), a high level of alcohol intake (≥42 units/week; RR 1.96, 95% CI:1.18–3.26), greater healthcare use (e.g. RR for ≥20 PCP visits in the year before the index date was 3.70, 95% CI: 2.86–4.80 when compared with 0–4 visits), and a high level of polypharmacy (RR 1.20, 95% CI: 1.03–1.40 for ≥5 medications vs. 0–1 different medications in the month before the index date).

10.4.13.2 Comorbidities among UGIB cases and controls

The frequency of comorbidities among UGIB cases and controls and their association with UGIB are shown in **Table 54**. Haemodialysis extracorporeal was a strong risk factor for UGIB (RR 6.19, 95% CI: 1.88–20.45) as was having a recorded eGFR of <45 mL/min/1.73 m^2; the RR for an eGFR of <15 mL/min/1.73 m^2 was 4.30 (95% CI: 1.96–9.39). Having a previous GIB was a risk factor for experiencing UGIB, RR 1.74 (95% CI: 1.16–2.61) for previous UGIB, RR 1.44 (95% CI: 1.18–1.77) for previous LGIB and RR 2.41 (95% CI: 1.60–3.63) for previous GIB of unspecified type. Anaemia, PU, dyspepsia, constipation and heart failure were also identified as risk factors for UGIB. Pancreatic disease was identified as a borderline risk factor for UGIB.

10.4.13.3 Medication use (including low-dose ASA) among UGIB cases and controls

Frequency of medication use, including low-dose ASA, among UGIB cases and controls, and their association with UGIB, is shown in **Table 55**.

10.4.13.3.1 Low-dose ASA

Compared with never use of low-dose ASA, current use and recent use of low-dose ASA were associated with a significant change in risk of UGIB (RR 1.62, 95% CI: 1.40–1.87) for current use and RR 1.50 (95% CI: 1.11–2.03) for recent use. Among current users of low-dose ASA, all durations of use were associated with a significant increased risk of UGIB, compared with never use, although no duration–response relationship was apparent. Among current users, the increased risk of UGIB was higher when ASA was used at a daily dose of 150–300 mg/day (RR 2.12, 95% CI: 1.53–2.93) rather than a daily dose of 75 mg/day (RR 1.58, 95% CI: 1.37–1.83), compared with never use. When using current users of low-dose ASA at dose of 75 mg/day as the reference group, the RR for UGIB among current users of low-dose ASA at doses greater than 75 mg was 1.30 (95% CI: 0.93–1.83). Although not statistically significant, this finding is suggestive of a dose–response relationship between low-dose ASA and UGIB. The RR for current use of low-dose ASA among the primary CVD prevention population was 1.74 (95% CI: 1.47–2.06) when compared with never use; the corresponding RR among the secondary CVD prevention population was 1.14 (95% CI: 0.82–1.59). As shown in **Table 56**, in the sensitivity analysis, removing users of any anticoagulants or antiplatelets other than low-dose ASA from the dataset, the RR for UGIB was 1.64 (95% CI: 1.40–1.93) for current use of low-dose ASA compared with never users, which was very similar to the estimate in the main analysis.

The frequency of low-dose ASA use among UGIB cases and controls, and the association with UGIB, stratified by case-fatality status, is shown in **Table 57**. For current low-dose ASA use compared with never use, the RR for fatal UGIB was 0.75 (95% CI: 0.49–1.15) and the RR for non-fatal UGIB was 1.73 (95% CI: 1.49–2.01). The frequency of low-dose ASA use among hospitalized and referred UGIB cases and controls, and association with hospitalized UGIB and referred UGIB is shown in **Table 58**. For current low-dose ASA use compared with never use, the RR for hospitalized UGIB was 1.58 (95% CI: 1.33–1.89) and the RR for

referred UGIB was 1.69 (95% CI: 1.37–2.09). The frequency of low-dose ASA use among UGIB cases and controls, and its association with hospitalized UGIB and referred UGIB according to bleeding location, is shown in **Table 59**. For current low-dose ASA use compared with never use, the risk of UGIB was highest for cases of duodenal ulcer, RR 2.33 (95% CI: 1.69–3.21), while the RRs for cases of gastric ulcer and mucosal erosion were 1.94 (95% CI: 1.46–2.58) and 1.59 (95% CI: 1.25–2.02), respectively.

10.4.13.3.2 Other medications (monotherapy)

As shown in **Table 55**, current use of the following drugs as monotherapy was associated with a significantly increased risk of UGIB compared with never use of the respective drug: clopidogrel (RR 2.07, 95% CI: 1.62–2.65), warfarin (RR 1.74, 95% CI: 1.38–2.20), NSAIDs (RR 2.11, 1.73–2.56), COXIBS (RR 2.09, 1.34–3.25), acetaminophen (RR 1.52, 95% CI: 1.27–1.82), PPIs (RR 1.27, 95% CI: 1.09–1.47) and H_2RAs (RR 1.40, 95% CI: 1.02–1.92). Current users of warfarin with high INR levels (≥3) had a close to six-fold increased risk of UGIB (RR 5.76, 95% CI: 2.87–11.58) while a small, non-significant increase in UGIB risk observed for warfarin users with INR levels <3 (RR 1.25, 95% CI: 0.88–1.76). Current/recent use of other anticoagulants was associated with a non-significant increased risk of UGIB, RR 2.47 (95% CI: 0.92–6.61) compared with never use, although it should be noted that this estimate was based on only 10 current/recent users among cases and 9 current/recent users among controls. Current use of SSRIs was not associated with a significant change in risk of UGIB compared with never use of these medications (RR 1.22, 95% CI: 0.97–1.54). In the sensitivity analysis (**Table 56**), removing users of any anticoagulants or antiplatelets other than low-dose ASA from the dataset, the RR for current use of PPIs compared with never use remained similar to the main estimate, RR 1.25 (95% CI: 1.05–1.49).

10.4.13.3.3 Other medications (combined therapy)

As show in **Table 55**, current users of DAT with both low-dose ASA and clopidogrel had a significantly increased risk of UGIB compared with never users of either low-dose ASA or clopidogrel as the (RR 3.87, 95% CI: 2.73–5.50). Current users of low-dose ASA and concomitant warfarin also had a significantly increased risk of UGIB compared with never users of either low-dose ASA or warfarin as the reference (RR 3.35, 95% CI: 2.01–5.60).

10.4.14 Case–control analyses: LGIB

The distribution of follow-up time (time between the start date and index date) among LGIB cases and controls in the nested case–control analysis is shown in **Appendix Table 32**.

10.4.14.1 Demographics, lifestyle factors, healthcare use and polypharmacy

The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among LGIB cases and controls, and their association with ICB, is shown in **Table 60**. Among these variables, alcohol intake of 1–9 u/w (RR 1.14, 95% CI: 1.01–1.29) and living in a rural location (RR 1.20, 95% CI: 1.01–1.42) were borderline risk factors for LGIB. Greater

healthcare use was identified as a risk factor for LGIB (for example, RR for ≥20 PCP visits in the year before the index date was 2.48 (95% CI :2.03–3.03) when compared with 0–4 visits.

10.4.14.2 Comorbidities among LGIB cases and controls

The frequency of comorbidities among LGIB cases and controls, and their association with LGIB, are shown in **Table 61**. The main predictors of LGIB were haemodialysis peritoneal (RR 2.36, 95% CI: 0.63–8.86), IBD (RR 3.03, 2.35–3.89), melaena (RR 2.00, 95% CI: 1.12–3.59) and previous LGIB (RR 1.98, 95% CI: 1.73–2.26). Other comorbidities identified as risk factors for LGIB were polyps, arthritis, anaemia, previous GIB unspecified, complicated peptic ulcer, IBS, constipation, deep vein thrombosis, DVT, GERD, IHD (excluding MI) and depression.

10.4.14.3 Medication use (including low-dose ASA) among LGIB cases and controls

The frequency of medication use among LGIB cases and controls, including low-dose ASA, and the association with LGIB, is shown in **Table 62**.

10.4.14.3.1 Low-dose ASA

Compared with never use of low-dose ASA, current use of low-dose ASA was associated with a significant change in the risk of LGIB (RR 1.97, 95% CI: 1.75–2.22). Recent use, past use and distant use of low-dose ASA were also associated with a significantly increased risk of LGIB, RR 2.15 (95% CI: 1.68–2.75) for recent use, 1.93 (95% CI: 1.57–2.36) for past use and 1.79 (95% CI: 1.55–2.06) for distant use. Among current users of low-dose ASA, all durations of use were associated with significant increased risks of LGIB, compared with never use, although no significant difference between duration categories was observed. Among current users of low-dose ASA, increased risks of LGIB were seen with all daily doses of ASA evaluated; these associations were significant for a daily dose of 75 mg (RR 1.97, 95% CI: 1.74–2.22) and 150 mg (RR 2.09, 95% CI: 1.55–2.82) and not significant for 300 mg (1.31, 95% CI: 0.62–2.76), although only 9 LGIB cases and 39 controls were using ASA at this daily dose. When using current users of low-dose ASA at dose of 75 mg/day as the reference group, the RR for LGIB among current users of low-dose ASA at doses greater than 75 mg was 1.07 (95% CI: 0.80–1.42). Unlike UGIB, these data do not suggest a dose–response relationship between low-dose ASA and LGIB. The RR for current use of low-dose ASA among the primary CVD prevention population was 1.93 (95% CI: 1.68–2.21) when compared with never use; the corresponding RR among the secondary CVD prevention population was 1.90 (95% CI: 1.38–2.62). As shown in **Table 63**, in the sensitivity analysis, removing users of any anticoagulants or antiplatelets other than low-dose ASA from the dataset, the RR for LGIB was 1.94 (95% CI: 1.70–2.21) for current use of low-dose ASA compared with never users, which was very similar to the estimate in the main analysis.

The frequency of low-dose ASA use among LGIB cases and controls, and association with LGIB, stratified by case-fatality status, is shown in **Table 64**. For current low-dose ASA use

compared with never use, the RR for fatal LGIB was 1.06 (95% CI: 0.40–2.81) and the RR for non-fatal LGIB was 1.98 (95% CI: 1.76–2.23). The frequency of low-dose ASA use among hospitalized and referred LGIB cases and controls, and association with hospitalized LGIB and referred LGIB, is shown in **Table 65**. For current low-dose ASA use compared with never use, the RR for hospitalized LGIB was 1.93 (95% CI: 1.57–2.36) and the RR for referred LGIB was 1.98 (95% CI: 1.73–2.28). The frequency of low-dose ASA use among LGIB cases and controls, and its association with hospitalized LGIB and referred LGIB according to bleeding location, is shown in **Table 66**. For current low-dose ASA use compared with never use, the RR for cases of diverticular disease was 2.33 (95% CI: 1.96–2.77), and the RR for cases of polyp was 3.09 (95% CI: 2.13–4.50).

10.4.14.3.2 Other medications (monotherapy)

Current use of the following drugs as monotherapy was associated with a significantly increased risk of UGIB compared with never use of the respective drug: clopidogrel (RR 1.41, 95% CI: 1.14–1.75), warfarin (RR 1.27, 95% CI: 1.04–1.55), NSAIDs (RR 1.61, 95% CI: 1.37–1.89), COXIBS (RR 1.46, 95% CI: 1.02–2.11), PPIs (RR 1.25, 95% CI: 1.10–1.41) and antacids (RR 1.23, 95% CI: 1.01–1.49). Only one LGIB case was a current user of warfarin with high INR levels (≥3); the RR for current use of warfarin among individuals with INR levels <3 was 1.23 (95% CI: 0.96–1.58). Current use of SSRIs, H_2RAs and acetaminophen were not associated with a significant change in risk of UGIB compared with never use of these medications: RR 0.98 (95% CI: 0.82–1.18) for SSRIs, 1.03 (95% CI: 0.80–1.33) for H_2RAs, and RR 1.13 (95% CI: 0.98–1.31) for acetaminophen. In the sensitivity analysis, when removing users of any anticoagulants or antiplatelets other than low-dose ASA from the dataset, the RR for current use of PPIs compared with never use remained similar, RR 1.25 (95% CI: 1.08–1.45).

10.4.14.3.3 Other medications (combined therapy)

Current users of DAT with both low-dose ASA and clopidogrel had a significantly increased risk of LGIB compared with never users of either low-dose ASA or clopidogrel (RR 3.33, 95% CI: 2.47–4.48). Current users of low-dose ASA and concomitant warfarin also had a significantly increased risk of LGIB compared with never users of either low-dose ASA or warfarin (RR 3.76, 95% CI: 2.43–5.82).

10.5 Other Analyses

Not applicable. The results of all analyses are described in **Section 10.4**.

10.6 Adverse Events/Adverse Reactions

This study used a retrospective cohort study design with nested case–control analyses using electronic health care records. Using this study design it was not feasible to make a causality assessment at the individual case level.

10.7 Results tables

Table 6. Frequency of demographics, lifestyle factors, healthcare use and polypharmacy according to study cohort.

Characteristics	Low-dose ASA cohort N=199,049		Comparison cohort N= 198,920	
	n	%	n	%
Sex				
Male	102,432	51.5	10,2361	51.5
Female	96,617	48.5	96,559	48.5
Age (years)				
40–59	21,933	11.0	21,934	11.0
60–69	45,482	22.8	45,486	22.9
70–79	66,560	33.4	66,560	33.5
80–89	49,366	24.8	49,254	24.8
Smoking*				
Non-smoker	84,223	42.3	93,397	47.0
Current	41,137	20.7	34,275	17.2
Former	64,780	32.5	60,155	30.2
Unknown	8909	4.5	11,093	5.6
BMI (kg/m^2)*				
15–19	5449	2.7	6926	3.5
20–24	45,443	22.8	54,778	27.5
25–29	70,216	35.3	68,202	34.3
≥30	54,538	27.4	40,007	20.1
Unknown	23,403	11.8	29,007	14.6
Alcohol (u/w)*				
None	34,578	17.4	29,713	14.9
1–9	88,133	44.3	89,317	44.9
10–20	30,222	15.2	30,967	15.6
21–41	10,521	5.3	10297	5.2
≥42	2795	1.4	2593	1.3
Unknown	32,800	16.5	36,033	18.1
Polypharmacy†				
0–1	111,232	55.9	118,271	59.5
2–4	62,085	31.2	57,234	28.8
≥5	25,732	12.9	23,415	11.8
PCP visits‡				
0–4	32,534	16.3	35,345	17.8
5–9	57,102	28.7	60,574	30.5
10–19	76,021	38.2	74,276	37.3
≥20	33,392	16.8	28,725	14.4

Characteristics	Low-dose ASA cohort N=199,049		Comparison cohort N= 198,920	
	n	%	n	%
Referrals‡				
0–4	159,856	80.3	168,176	84.5
5–9	29,312	14.7	24,100	12.1
10–19	9036	4.5	6220	3.1
≥20	845	0.4	424	0.2
Hospitalizations‡				
None	154,871	77.8	176,892	88.9
1	27,058	13.6	15,202	7.6
2	10,773	5.4	4521	2.3
≥3	6347	3.2	2305	1.2
Townsend score				
Deprived 1 (least deprived)	48,980	24.6	55,361	27.8
Deprived 2	43,607	21.9	46,371	23.3
Deprived 3	40,057	20.1	39,007	19.6
Deprived 4	35,349	17.8	31,231	15.7
Deprived 5 (most deprived)	23,967	12.0	19,198	9.7
Unknown	7089	3.6	7752	3.9
Urban/rural				
Urban	124,601	62.6	126,575	63.6
Town	22,025	11.1	23,934	12.0
Rural	12,832	6.4	13,990	7.0
Unknown	39,591	19.9	34,421	17.3

*Alcohol, BMI and smoking were ascertained any time before the start date the most recent status/value as appropriate.

†Polypharmacy was taken as the number of different medications in the month before the start date.

‡PCP visits, referrals and hospitalizations were ascertained in the year before the start date.

Table 7. Comorbidities any time before the start of follow-up according to study cohort.

Comorbidity	**Low-dose ASA cohort N=199,049**		**Unexposed cohort N=198,920**	
	n	**%**	**n**	**%**
Any ICB	1189	0.7	850	0.4
Ischaemic stroke	9790	4.9	2120	1.1
MI	17,023	8.6	2092	1.1
IS	9790	4.9	2120	1.1
TIA	7025	3.5	1651	0.8
IHD*	19,768	9.9	5597	2.8
COPD	10,340	5.2	10,051	5.1
Depression	43,291	21.7	39,681	19.9
Stress	15,550	7.8	14,954	7.5
Hypertension	95,934	48.2	69,134	34.8
Hypercholesterolemia	26,833	13.5	19,297	9.7
Diabetes	36,608	18.4	15,992	8.0
DVT	10,948	5.5	9859	5.0
Anemia†	11,337	5.7	11,205	5.6
Atrial fibrillation	11,248	5.7	5629	2.8
Heart failure	5367	2.7	3113	1.6
PU, uncomplicated/complicated	10,092	5.1	10,796	5.4
PU, uncomplicated	7596	3.8	8017	4.0
PU, complicated	3508	1.8	3997	2.0
IBD	2318	1.2	2633	1.3
Dyspepsia	38,584	19.4	35,289	17.7
Gout	9771	4.9	8671	4.4
Osteoporosis	7898	4.0	8347	4.2
Anxiety	31,006	15.6	28,395	14.3
GERD	27,338	13.7	24,914	12.5
Migraine	13,563	6.8	11,346	5.7
Epilepsy	3941	2.0	3451	1.7
Dementia	33,098	16.6	27,317	13.7
Immobility	568	0.3	492	0.2
Falls†	3772	1.9	3183	1.6
Asthma	27,432	13.8	28,016	14.1

*Excluding MI.

†In the year before the index date.

Comorbidities were ascertained any time before the start date.

Table 8. Medication use at start of follow-up according to study cohort.

Medication use	**Low-dose ASA cohort N=199,049**		**Unexposed cohort N=198,920**	
	n	**%**	**n**	**%**
Warfarin				
Non-use	191,891	96.4	191,079	96.1
Current use	3794	1.9	5718	2.9
Past use	3364	1.7	2123	1.1
Clopidogrel				
Non-use	195,378	98.2	196,911	99.0
Current use	2855	1.4	1473	0.7
Past use	816	0.4	536	0.3
NSAIDs				
Non-use	66,062	33.2	73,435	36.9
Current use	30,754	15.5	28,169	14.2
Past use	102,233	51.4	97,316	48.9
Insulin				
Non-use	192,420	96.7	196,342	98.7
Current use	6270	3.1	2426	1.2
Past use	359	0.2	152	0.1
Oral antidiabetics				
Non-use	175,745	88.3	188,236	94.6
Current use	20,772	10.4	9570	4.8
Past use	2532	1.3	1114	0.6
Antihypertensive agents				
Non-use	69,150	34.7	100,309	50.4
Current use	108,529	54.5	76,567	38.5
Past use	21,370	10.7	22,044	11.1
Statins				
Non-use	142,761	71.7	165,710	83.3
Current use	48,679	24.5	28,437	14.3
Past use	7609	3.8	4773	2.4
Non statins				
Non-use	194,771	97.9	196,086	98.6
Current use	1550	0.8	1049	0.5
Past use	2728	1.4	1785	0.9
Digoxin				
Non-use	195,032	98.0	195,236	98.1
Current use	2745	1.4	2694	1.4
Past use	1272	0.6	990	0.5
Oral steroids				
Non-use	169,034	84.9	169,640	85.3
Current use	7481	3.8	7621	3.8
Past use	22,534	11.3	21,659	10.9
Inhaled steroids				
Non-use	171,038	85.9	170,572	85.7
Current use	14,655	7.4	15,767	7.9
Past use	13,356	6.7	12,581	6.3
Respiratory drugs				

Medication use	**Low-dose ASA cohort N=199,049**		**Unexposed cohort N=198,920**	
	n	**%**	**n**	**%**
Non-use	106,687	53.6	110,726	55.7
Current use	27,472	13.8	26,838	13.5
Past use	64,890	32.6	61,356	30.8
Diuretics				
Non-use	79,855	40.1	90,167	45.3
Current use	53,430	26.8	40,376	20.3
Past use	65,764	33.0	68,377	34.4
DMARDs				
Non-use	192,916	96.9	192,507	96.8
Current use	2733	1.4	3159	1.6
Past use	3400	1.7	3254	1.6
Acetaminophen				
Non-use	130,163	65.4	137,591	69.2
Current use	44,224	22.2	37,841	19.0
Past use	24,662	12.4	23,488	11.8
Antacids				
Non-use	160,009	80.4	164,847	82.9
Current use	9857	5.0	8664	4.4
Past use	29,183	14.7	25,409	12.8
PPI				
Non-use	138,700	69.7	144,620	72.7
Current use	29,689	14.9	25,701	12.9
Past use	30,660	15.4	28,599	14.4
H_2RA				
Non-use	161,845	81.3	164,914	82.9
Current use	5813	2.9	5466	2.7
Past use	31,391	15.8	28,540	14.3
Antidepressants				
Non-use	135,004	67.8	140,383	70.6
Current use	24,096	12.1	22,749	11.4
Past use	39,949	20.1	35,788	18.0

Current use = use on the start date or in the previous 90 days.

Past use = use that ended at least 91 days before the start date.

Table 9. Distribution of ICB cases for each site, overall and according to study cohort, and by trauma-related status.

		ICB cases					
		Total N= 1611		**Low-dose ASA cohort N=881**		**Comparison cohort N=730**	
		n	**%**	**n**	**%**	**n**	**%**
ICH	All	743	46.1	407	46.2	336	46.0
	Non trauma-related	660	41.0	359	88.2	301	89.6
	Trauma-related	83	5.2	48	11.8	35	10.4
SDH	All	483	30.0	283	32.1	200	27.4
	Non trauma-related	205	12.7	114	40.3	91	45.0
	Trauma-related	278	17.3	169	59.7	109	55.0
SAH	All	385	23.9	191	21.7	194	26.6
	Non trauma-related	311	19.3	158	82.7	153	78.9
	Trauma-related	74	4.6	33	17.3	41	21.1

Table 10. Distribution of UGIB cases by location, overall and according to study cohort.

	UGIB		
Location	**Both cohorts N=1843 n (%)**	**Low-dose ASA cohort N=1115 n (%)**	**Comparison cohort N=728 n (%)**
Duodenal ulcer	370 (20.1)	224 (20.1)	146 (20.1)
Gastric ulcer	299 (16.2)	191 (17.1)	108 (14.8)
Duodenal/gastric ulcer	16 (0.9)	9 (0.8)	7 (1.0)
Peptic ulcer	32 (1.7)	21 (1.9)	11 (1.5)
Duodenal/peptic ulcer	2 (0.1)	2 (0.2)	0 (0.0)
Gastroduodenal mucosal lesion*	551 (29.9)	327 (29.3)	224 (30.8)
Other	69 (3.7)	43 (3.9)	26 (3.6)
Unknown	504 (27.3)	298 (26.7)	206 (28.3)

*Gastroduodenal mucosal lesion includes gastritis, dyspepsia, duodenitis and infection from *Helicobacter pylori*.

Table 11. Distribution of LGIB by location, overall and according to study cohort.

	LGIB		
Location	**Both cohorts N=2763 n (%)**	**Low-dose ASA cohort N=1936 n (%)**	**Comparison cohort N=827 n (%)**
Diverticular diseases	1189 (43.0)	841 (43.4)	348 (42.1)
Polyps	296 (10.7)	235 (12.1)	61 (7.4)
Diverticular/polyps	159 (5.8)	107 (5.5)	52 (6.3)
Colitis	235 (8.5)	155 (8.0)	80 (9.7)
Colitis/diverticular	2 (0.1)	1 (0.1)	1 (0.1)
Colitis/polyps	2 (0.1)	2 (0.1)	
Colitis/Crohn's	1 (0.0)	1 (0.1)	
Crohn's	26 (0.9)	9 (0.5)	17 (2.1)
Angiodysplasia	12 (0.4)	7 (0.4)	5 (0.6)
Other	37 (1.3)	25 (1.3)	12 (1.5)
Unknown=804	804 (29.1)	553 (28.6)	251 (30.4)

Table 12. Crude incidence rate of ICB per 10,000 person-years (95% CI) for all ICB cases and by site of bleed (ICH, SDH and SAH), overall and by study cohort, and IRR (low-dose ASA versus comparison cohort).

	All ICB	**ICH**	**SDH**	**SAH**
Both cohorts				
No. of cases	1611	743	483	385
Median person-years	5.39	5.39	5.39	5.39
Total person-years	2,234,372	2,234,372	2,234,372	2,234,372
Incidence rate per 10,000 person-years (95% CI)	7.21 (6.87–7.57)	3.33 (3.10–3.57)	2.16 (1.98–2.36)	1.72 (1.56–1.90)
Low-dose ASA cohort				
No. of cases	881	407	283	191
Median person-years	5.58	5.58	5.58	5.58
Total person-years	1,157,112	1,157,112	1,157,112	1,157,112
Incidence rate per 10,000 person-years (95% CI)	7.61 (7.13–8.13)	3.52 (3.19–3.88)	2.45 (2.18–2.75)	1.65 (1.43–1.90)
Comparison cohort				
No. of cases	730	336	200	194
Median person-years	5.19	5.19	5.19	5.19
Total person-years	1,077,260	1,077,260	1,077,260	1,077,260
Incidence rate per 10,000 person-years (95% CI)	6.78 (6.30–7.29)	3.12 (2.80–3.47)	1.86 (1.62–2.13)	1.80 (1.56–2.07)
IRR (95% CI) low-dose ASA vs. comparison cohort*	1.11 (1.01–1.22)	1.12 (0.97–1.29)	1.28 (1.07–1.53)	0.92 (0.75–1.13)

*Adjusted by age, sex and number of PCP visits in the year before the start date.

Table 13. Crude incidence rate of ICB per 10,000 person-years (95% CI) during the first year of follow-up for all ICB cases and by site of bleed (ICH, SDH and SAH), stratified by study cohort.

	ICB	**ICH**	**SDH**	**SAH**
Both cohorts				
Number of cases	288	133	68	87
Median person-years	365	365	365	365
Total person-years	380,541	380,541	380,541	380,541
Incidence rate per 10,000 person-years (95% CI)	7.57 (6.74–8.50)	3.50 (2.95–4.14)	1.79 (1.41–2.27)	2.29 (1.85–2.82)
Low-dose ASA				
Number of cases	147	68	43	36
Median person-years	365	365	365	365
Total person-years	192,043	192,043	192,043	192,043
Incidence rate per 10,000 person-years (95% CI)	7.66 (6.51–9.00)	3.54 (2.79–4.49)	2.24 (1.66–3.02)	1.88 (1.35–2.60)
Comparison cohort				
Number of cases	141	65	25	51
Median person-years	365	365	365	365
Total person-years	192,043	188,498	188,498	188,498
Incidence rate per 10,000 person-years (95% CI)	7.49 (6.34– 8.82)	3.45 (2.70–4.40)	1.33 (0.90–1.96)	2.71 (2.06– 3.56)

Table 14. Crude incidence rate of ICB per 10,000 person-years (95% CI) for all ICB cases and by site of bleed (ICH, SDH and SAH) stratified by trauma-related stratus and by study cohort.

	Overall	**ICH**	**SDH**	**SAH**
Both cohorts				
No. of cases	1611	743	483	385
Median person-years	5.39	5.39	5.39	5.39
Total person-years	2,234,372	2,234,372	2,234,372	2,234,372
Non-trauma-related ICB				
Number of cases	1176	660	205	311
Incidence rate per 10,000 person-years (95% CI)	5.26 (4.97–5.57)	2.95 (2.74–3.19)	0.92 (0.80–0.11)	1.39 (1.25–1.56)
Trauma-related ICB				
Number of cases	435	83	278	74
Incidence rate per 10,000 person-years (95% CI)	1.95 (1.78–2.14)	0.37 (0.30–0.46)	1.24 (1.11–1.40)	0.33 (0.26–0.42)
Low-dose ASA cohort				
No. of cases	881	407	283	191
Median person-years	5.58	5.58	5.58	5.58
Total person-years	1,157,112	1,157,112	1,157,112	1,157,112
Non-trauma-related ICB				
Number of cases	631	359	114	158
Incidence rate per 10,000 person-years (95% CI)	5.45 (5.04–5.90)	3.10 (2.80–3.44)	0.99 (0.82–1.18)	1.37 (1.17–1.60)
Trauma-related ICB				
Number of cases	250	48	169	33
Incidence rate per 10,000 person-years (95% CI)	2.16 (1.91–2.45)	0.42 (0.31–0.55)	1.46 (1.26–1.70)	0.29 (0.20–0.40)

	Overall	**ICH**	**SDH**	**SAH**
Comparison cohort				
No. of cases	730	336	200	194
Median person-years	5.19	5.19	5.19	5.19
Total person-years	1,077,260	1,077,260	1,077,260	1,077,260
Non-trauma-related ICB				
Number of cases	545	301	91	153
Incidence rate per 10,000 person-years (95% CI)	5.06 (4.65–5.50)	2.79 (2.49–3.13)	0.85 (0.69–1.04)	1.42 (1.21–1.66)
Trauma-related ICB				
Number of cases	185	35	109	41
Incidence rate per 10,000 person-years (95% CI)	1.72 (1.49–1.98)	0.33 (0.23–0.45)	1.01 (0.84–1.22)	0.38 (0.28–0.52)

Table 15. Crude incidence rate of ICB per 10,000 person years (95% CI) for all ICB cases and by site of bleed (ICH, SDH and SAH) stratified by case-fatality status and by study cohort.

	ICB		**ICH**		**SDH**		**SAH**	
	Fatal case	**Non-fatal**	**Fatal case**	**Non-fatal**	**Fatal case**	**Non-fatal**	**Fatal case**	**Non-fatal**
Both cohorts								
Number of cases	402	1209	241	502	44	439	117	268
Total person-years	2,234,372	2,234,372	2,234,372	2,234,372	2,234,372	2,234,372	2,234,372	2,234,372
Incidence rate per 10,000 person-years (95% CI)	1.80 (1.63–1.98)	5.41 (5.11–5.73)	1.08 (0.95–1.22)	2.25 (2.06–2.45)	0.20 (0.15–0.27)	1.97 (1.79–2.16)	0.52 (0.44–0.63)	1.20 (1.06–1.35)
Low-dose ASA								
Number of cases	185	696	111	296	28	255	46	145
Total person-years	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112
Incidence rate per 10,000 person-years (95% CI)	1.60 (1.38–1.85)	6.02 (5.58–6.48)	0.96 (0.80–1.16)	2.56 (2.28–2.87)	0.24 (0.17–0.35)	2.20 (1.95–2.49)	0.40 (0.30–0.53)	1.25 (1.07–1.48)
Comparison cohort								
Number of cases	217	513	130	206	16	184	71	123
Total person-years	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260
Incidence rate per 10,000 person-years (95% CI)	2.01 (1.76–2.30)	4.76 (4.37–5.19)	1.21 (1.02–1.43)	1.91 (1.67–2.19)	0.15 (0.09–0.24)	1.71 (1.48–1.97)	0.66 (0.52–0.83)	1.14 (0.96–1.36)

Table 16. Crude incidence rate of ICB per 10,000 person-years (95% CI) for all ICB cases and by site of bleed (ICH, SDH and SAH), stratified by trauma-related status, case-fatality status (fatal case = death within 30 days following the event) and by study cohort.

	ICB		**ICH**		**SDH**		**SAH**	
	Fatal case	**Non-fatal**	**Fatal case**	**Non-fatal**	**Fatal case**	**Non-fatal**	**Fatal case**	**Non-fatal**
Low-dose ASA cohort								
Trauma-related cases								
Number of cases	28	222	7	41	17	152	4	29
Total person-years	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112
Incidence rate per 10,000 person-years (95% CI)	0.24 (0.17–0.35)	1.92 (1.68–2.19)	0.06 (0.03–0.13)	0.35 (0.26–0.48)	0.15 (0.09–0.24)	1.31 (1.12–1.54)	0.03 (0.01–0.09)	0.25 (0.17–0.36)
Non-trauma-related cases								
Number of cases	157	474	104	255	11	103	42	116
Total person-years	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112	1,157,112
Incidence rate per 10,000 person-years (95% CI)	1.36 (1.16–1.59)	4.10 (3.74–4.48)	0.90 (0.74–1.09)	2.20 (1.95–2.49)	0.09 (0.05–0.17)	0.89 (0.73–1.08)	0.36 (0.27–0.49)	1.00 (0.84–1.20)
Comparison cohort								
Trauma-related cases								
Number of cases	27	158	11	24	9	100	7	34
Total person-years	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260
Incidence rate per 10,000 person-years (95% CI)	0.25 (0.17–0.37)	1.47 (1.26–1.71)	0.10 (0.06–0.18)	0.22 (0.15–0.33)	0.08 (0.04–0.16)	0.93 (0.76–1.13)	0.07 (0.03–0.14)	0.32 (0.23–0.44)
Non-trauma-related cases								
Number of cases	190	355	119	182	7	84	64	89
Total person-years	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260	1,077,260
Incidence rate per 10,000 person-years (95% CI)	1.76 (1.15–2.03)	3.30 (2.97–3.66)	1.11 (0.92–1.32)	1.69 (1.46–1.95)	0.07 (0.03–0.14)	0.78 (0.63–0.97)	0.59 (0.47–0.76)	0.83 (0.67–1.02)

Table 17. Crude incidence rate of ICB per 10,000 person-years (95% CI) stratified by sex and age and by study cohort.

	Men	**Women**	**Aged 40–64 years**	**Aged 65–74 years**	**Aged 75–89 years**
Both cohorts					
Number of cases	828	783	486	607	518
Median person-years	5.31	5.47	5.76	5.44	4.22
Total person-years	1,136,706	1,097,667	1,225,559	671,052	337,761
Incidence rate per 10,000 person-years (95% CI)	7.28 (6.81–7.80)	7.13 (6.65–7.65)	3.97 (3.63–4.33)	9.05 (8.35–9.79)	15.34 (14.07–16.72)
Low-dose ASA cohort					
Number of cases	453	428	265	344	272
Median person-years	5.52	5.65	5.94	5.71	4.37
Total person-years	590,144	566,968	632,780	350,162	174,169
Incidence rate per 10,000 person-years (95% CI)	7.68 (7.00– 8.42)	7.55 (6.87–8.30)	4.19 (3.71–4.72)	9.82 (8.84–10.92)	15.62 (13.87–17.59)
Comparison cohort					
Number of cases	375	355	221	263	246
Median person-years	5.08	5.29	5.57	5.18	4.05
Total person-years	546,562	530,699	592,779	320,890	163,592
Incidence rate per 10,000 person-years (95% CI)	6.86 (6.20–7.59)	6.69 (6.03–7.42)	3.73 (3.27–4.25	8.20 (7.26–9.25)	15.04 (13.27–17.04)

Table 18. Crude incidence rate of ICH per 10,000 person-years (95% CI) stratified by sex and age and by study cohort.

	Men	Women	Aged 40–64 years	Aged 65–74 years	Aged 75–89 years
Both cohorts					
Number of cases	375	3768	182	286	275
Median person-years	5.31	5.47	5.76	5.44	4.22
Total person-years	1,136,706	1,097,667	1,225,559	671,052	337,761
Incidence rate per 10,000 person-years (95% CI)	3.30 (2.98–3.65)	3.35 (3.03–3.71)	1.49 (1.28–1.72)	4.26 (3.80–4.79)	8.14 (7.23–9.16)
Low-dose ASA					
Number of cases	194	213	107	160	140
Median person-years	5.52	5.65	5.94	5.71	4.37
Total person-years	590,144	566,968	632,780	350,165	174,169
Incidence rate per 10,000 person-years (95% CI)	3.29 (2.86–3.78)	3.76 (3.29–4.30)	1.69 (1.40–2.04)	4.57 (3.91–5.34)	8.04 (6.81–9.49)
Comparison cohort					
Number of cases	181	155	75	126	135
Median person-years	5.08	5.29	5.57	5.18	4.05
Total person-years	546,562	530,699	592,779	320,890	163,592
Incidence rate per 10,000 person-years (95% CI)	3.31 (2.86–3.83)	2.92 (2.50–3.42)	1.26 (1.01–1.59)	3.93 (7.26–9.25)	8.25 (6.97– 9.77)

Table 19. Crude incidence rate of SDH per 10,000 person-years (95% CI) stratified by sex and age group and by study cohort.

	Men	Women	Aged 40–64 years	Aged 65–74 years	Aged 75–89 years
Both cohorts					
Number of cases	298	185	109	201	173
Median person-years	5.31	5.47	5.76	5.44	4.22
Total person-years	1,136,706	1,097,667	1,225,559	671,052	337,761
Incidence rate per 10,000 person-years (95% CI)	2.62 (2.34–2.94)	1.69 (1.46–1.95)	0.89 (0.74–1.07)	3.00 (2.61–3.44)	5.12 (4.41–5.95)
Low-dose ASA					
Number of cases	174	109	59	124	100
Median person-years	5.52	5.65	5.94	5.71	4.37
Total person-years	590,144	566,968	632,780	350,162	174,169
Incidence rate per 10,000 person-years (95% CI)	2.95 (2.54–3.42)	1.92 (1.59–2.32)	0.93 (0.72–1.20)	3.54 (2.97–4.22)	5.74 (4.72–6.99)
Comparison cohort					
Number of cases	124	76	50	77	73
Median person-years	5.08	5.29	5.57	5.18	4.05
Total person-years	546,562	530,699	592,779	320,890	163,592
Incidence rate per 10,000 person-years (95% CI)	2.27 (1.90–2.71)	1.43 (1.14–1.79)	0.84 (0.64–1.11)	2.40 (1.92–3.00)	4.46 (3.55–5.61)

Table 20. Crude incidence rate of SAH per 10,000 person-years (95% CI) stratified by sex and age group and by study cohort.

	Men	**Women**	**Aged 40–64 years**	**Aged 65–74 years**	**Aged 75–89 years**
Both cohorts					
Number of cases	155	230	195	120	70
Median person-years	5.31	5.47	5.76	5.44	4.22
Total person-years	1,136,706	1,097,667	1,225,559	671,052	337,761
Incidence rate per 10,000 person-years (95% CI)	1.36 (1.17–1.60)	2.10 (1.84–2.38)	1.59 (1.38–1.83)	1.79 (1.50–2.14)	2.07 (1.64–2.62)
Low-dose ASA					
Number of cases	85	106	99	60	32
Median person-years	5.52	5.65	5.94	5.71	4.37
Total person-years	590,146	566,968	632,780	350,162	174,169
Incidence rate per 10,000 person-years (95% CI)	1.44 (1.16–1.78)	1.87 (1.55–2.62)	1.57 (1.29–1.91)	1.71 (1.33–2.21)	1.84 (1.30–2.60)
Comparison cohort					
Number of cases	70	124	96	60	38
Median person-years	5.08	5.29	5.57	5.18	4.05
Total person-years	546,563	530,700	603,977	320,891	163,592
Incidence rate per 10,000 person-years (95% CI)	1.28 (1.01–1.62)	2.34 (1.96–2.79)	1.62 (1.33–1.98)	1.87 (1.45–2.41)	2.32 (1.69–3.19)

Table 21. Crude incidence rate of ICB per 10,000 person-years (95% CI) for all ICB cases and by site (ICH, SDH and SAH) according to the CVD prevention population (primary or secondary) for each study cohort.

	All ICB	**ICH**	**SDH**	**SAH**
Primary prevention population				
Low-dose aspirin cohort				
Number of cases	508	232	163	113
Median length of follow-up (years)	5.76	5.76	5.76	5.76
Person-years	745,813	745,813	745,813	745,813
Incidence rate per 10,000 person-years (95% CI)	6.81 (6.24–7.43)	3.11 (2.74–3.54)	2.19 (1.94–2.62)	1.52 (1.26–1.82)
Comparison cohort				
Number of cases	580	259	162	159
Median length of follow-up (years)	5.21	5.21	5.21	5.21
Person-years	975,993	975,993	975,993	975,993
Incidence rate per 10,000 person-years (95% CI)	5.94 (5.48–6.45)	2.65 (2.35–3.00)	1.67 (1.42–1.94)	1.63 (1.40–1.90)
Secondary prevention population				
Low-dose aspirin cohort				
Number of cases	373	175	120	78
Person-years	5.20	5.20	5.20	5.20
Median length of follow-up (years)	411,299	411,299	411,299	411,299
Incidence rate per 10,000 person-years (95% CI)	9.07 (8.19–10.04)	4.26 (3.67–4.93)	2.92 (2.44–3.49)	1.90 (1.52–2.37)
Comparison cohort				
Number of cases	150	77	38	35
Median length of follow-up (years)	4.93	4.93	4.93	4.93
Person-years	101,270	101,270	101,270	101,270
Incidence rate per 10,000 person-years (95% CI)	14.81 (12.62–17.38)	7.60 (6.08–9.51)	3.75 (2.73–5.16)	3.46 (2.48–4.81)

Table 22. Crude incidence rate of ICB per 10,000 person-years (95% CI) stratified by sex, age group and CVD prevention population (primary or secondary) for each study cohort.

	Men	**Women**	**Aged 40–64 years**	**Aged 65–74 years**	**Aged 75–89 years**
Primary prevention population					
Low-dose aspirin cohort					
Number of cases	253	255	146	216	146
Median length of follow-up (years)	5.71	5.81	6.04	5.88	4.62
Person-years	355,476	390,338	423,838	222,090	99,885
Incidence rate per 10,000 person-years (95% CI)	7.12 (6.29–8.05)	6.53 (5.78–7.39)	3.44 (2.93–4.05)	9.73 (8.51–11.11)	14.62 (12.43–17.19)
Comparison cohort					
Number of cases	296	284	183	214	183
Median length of follow-up (years)	5.11	5.31	5.54	5.18	4.18
Person-years	490,328	485,665	553,339	283,503	139,150
Incidence rate per 10,000 person-years (95% CI)	6.04 (5.39–6.77)	5.85 (5.21–6.57)	3.31 (2.86–3.82)	7.55 (6.60–8.63)	13.15 (11.38–15.20)
Secondary prevention population					
Low-dose aspirin cohort					
Number of cases	200	173	119	128	126
Person-years	234,668	176,631	208,942	128,072	74,285
Median length of follow-up (years)	5.18	5.23	5.71	5.88	4.07
Incidence rate per 10,000 person-years (95% CI)	8.52 (7.42–9.79)	9.79 (8.44–11.37)	5.70 (4.76–6.82)	9.99 (8.41–11.86)	16.96 (14.24–20.20)
Comparison cohort					
Number of cases	79	71	38	49	63
Median length of follow-up (years)	4.90	4.97	6.19	5.16	3.41
Person-years	56,235	45,035	39,440	37,388	24,442

	Men	**Women**	**Aged 40–64 years**	**Aged 65–74 years**	**Aged 75–89 years**
Incidence rate per 10,000 person-years (95% CI)	14.05 (11.27–17.51)	15.77 (12.49–19.89)	9.63 (7.01–13.24)	13.11 (9.91–17.34)	25.78 (20.14–32.99)

Table 23. Hazard ratios (95% CIs) for ICB associated with risk factors.

	ICB cases N=1611		**Non-cases N=396,358**		**HR (95% CI)***
	n	**%**	**n**	**%**	
Sex					
Male	828	51.4	203,965	51.5	1 (–)
Female	783	48.6	192,393	48.5	0.82 (0.74–0.91)
Age (years)					
50–64	486	30.2	204,875	51.7	1 (–)
65–74	607	37.7	117,515	29.6	2.31 (2.05–2.61)
≥75	518	32.2	73,968	18.7	4.10 (3.62–4.65)
PCP visits					
0–4	271	16.8	67,608	17.1	
5–9	458	28.4	117,218	29.6	1.04 (0.90–1.21)
10–14	613	38.1	149,684	37.8	1.17 (1.01–1.35)
≥20	269	16.7	61,848	15.6	1.41 (1.19–1.67)
Type of cohort					
Comparison	730	45.3	198,190	50.0	1 (–)
Low-dose ASA	881	54.7	198,168	50.0	1.11 (1.01–1.22)
Reason for low-dose ASA use					
Primary CVD prevention	1088	67.5	304,873	76.9	1 (–)
Secondary CVD prevention	523	32.5	91,485	23.1	1.41 (1.26–1.58)
BMI (kg/m^2)					
15–19	79	4.9	12,296	3.1	1.60 (1.26–2.03)
20–24	448	27.8	99,773	25.2	1
25–29	558	34.6	137,860	34.8	0.89 (0.78–1.00)
≥30	268	16.6	94,277	23.8	0.69 (0.60–0.81)
Unknown	258	16.0	52,152	13.2	1.05 (0.90–1.23)
Smoking					
Non-smoker	688	42.7	176,932	44.6	1 (–)
Current	318	19.7	75,094	18.9	1.38 (1.21–1.58)
Former	507	31.5	124,428	31.4	1.10 (0.98–1.23)
Unknown	98	6.1	19,904	5.0	0.99 (0.80–1.23)
Comorbidities					
Hypertension	772	47.9	164,296	41.5	1.03 (0.93–1.15)
Hypercholesterolemia	183	11.4	45,947	11.6	0.96 (0.82–1.12)
MI	82	5.1	19,033	4.8	1.02 (0.81–1.28)
IS	84	5.2	11,826	3.0	1.72 (1.38–2.15)

	ICB cases N=1611		**Non-cases N=396,358**		**HR (95% CI)***
	n	**%**	**n**	**%**	
IHD	109	6.8	25,256	6.4	0.84 (0.69–1.02)
Haemorrhagic stroke	46	2.9	1993	0.5	6.27 (4.68–8.41)
COPD	91	5.7	449	4.5	1.17 (0.95–1.45)
PU, complicated/ uncomplicated	104	6.5	20,784	5.2	1.12 (0.92–1.37)
Polypharmacy					
0–1	850	52.8	228,653	57.7	1 (–)
2–4	521	32.3	118,798	30.0	1.05 (0.93–1.17)
≥5	240	14.9	48,907	12.3	1.22 (1.04–1.42)
Warfarin					
Non-use	1483	92.1	381,487	96.2	1 (–)
Current use‡	97	6.0	9415	2.4	2.60 (2.09–3.22)
Past use§	31	1.9	5456	1.4	1.38 (0.97–1.97)
Clopidogrel					
Non-use	1590	98.7	390,699	98.6	1 (–)
Current use‡	13	0.8	4315	1.1	0.75 (0.44–1.30)
Past use§	8	0.5	1344	0.3	1.58 (0.79–3.16)

*Adjusted by age, sex, and number of PCP visits in the year prior to the start date and type of cohort.

†Excluding MI.

‡Use on the start date or in the previous 90 days.

§Use that ended at least 91 days before the start date.

PCP visits were ascertained in the year before the start date. BMI and smoking were ascertained any time before the start date the most recent status/value as appropriate. Comorbidities were ascertained any time before the start date. Polypharmacy was taken as the number of different medications in the month before the start date.

Table 24. Hazard ratios (95% CIs) for ICH associated with risk factors.

	ICH cases N=743		**Non-cases N=397,212**		**HR (95% CI)***
	n	**%**	**n**	**%**	
Sex					
Male	375	50.5	204,410	51.5	1 (–)
Female	368	49.5	192,802	48.5	0.83 (0.72–0.96)
Age (years)					
50–64	182	24.5	205,176	51.7	1 (–)
65–74	286	38.5	117,828	29.7	2.90 (2.41–3.50)
≥75	275	37.0	74,208	18.7	5.79 (4.79–7.00)
PCP visits					
0–4	126	17.0	67,749	17.1	1 (–)
5–9	218	29.3	117,452	29.6	1.05 (0.84–1.30)
10–14	292	39.3	150,002	37.8	1.17 (0.95–1.44)
≥20	107	14.4	62,009	15.6	1.16 (0.89–1.50)
Type of cohort					
Comparison cohort	336	45.2	198,584	50.0	1 (–)
Low-dose ASA	407	54.8	198,628	50.0	1.12 (0.97–1.29)
CVD prevention population					
Primary prevention	491	66.1	305,468	76.9	1 (–)
Secondary prevention	252	33.9	91,744	23.1	1.49 (1.27–1.75)
BMI (kg/m2)					
15–19	42	5.7	12,332	3.1	1.99 (1.42–2.79)
20–24	188	25.3	100,030	25.2	1
25–29	252	33.9	138,161	34.8	0.97 (0.80–1.17)
≥30	120	16.2	94,422	23.8	0.78 (0.62–0.99)
Unknown	141	19.0	52,267	13.2	1.37 (1.10–1.71)
Smoking					
Non-smoker	337	45.4	177,275	44.6	1 (–)
Current	129	17.4	75,281	19.0	1.20 (0.98–1.48)
Former	228	30.7	124,703	31.4	1.01 (0.85–1.20)
Unknown	49	6.6	19,953	5.0	0.99 (0.73–1.35)
Comorbidities					
Hypertension	364	49.0	164,697	41.5	1.05 (0.91–1.22)
Hypercholesterolemia	84	11.3	46,043	11.6	0.97 (0.77–1.22)
MI	40	5.4	19,075	4.8	1.09 (0.79–1.51)
IS	48	6.5	11,860	3.0	2.14 (1.60– 2.86)
IHD[†]	43	5.8	25,322	6.4	0.70 (0.52–0.96)
ICB	22	3.0	2016	0.5	6.50 (4.25– 9.94)
COPD	41	5.5	20,349	5.1	1.12 (0.81–1.54)
PU, complicated/uncomplicated	53	7.1	20835	5.2	1.24 (0.93–1.63)
Polypharmacy					
0–1	388	52.2	229,106	57.7	1 (–)
2–4	250	33.6	119,066	30.0	1.08 (0.92–1.28)
≥5	105	14.1	49,040	12.3	1.16 (0.92–1.46)

Warfarin[‡]					
Non-use	682	91.8	382,276	96.2	1 (–)
Current use[‡]	46	6.2	9465	2.4	2.77 (2.02–3.79)
Past use[§]	15	2.0	5471	1.4	1.44 (0.86–2.40)
Clopidogrel					
Non-use	733	98.7	391,542	98.6	1 (–)
Current use[‡]	6	0.8	4322	1.1	0.76 (0.34–1.71)
Past use[§]	4	0.5	1348	0.3	1.74 (0.65–4.65)

[*]Adjusted by age, sex, and number of PCP visits in the year prior to the start date and type of cohort.

[†]Excluding MI.

[‡]Use on the start date or in the previous 90 days.

[§]Use that ended at least 91 days before the start date.

PCP visits were ascertained in the year before the start date. BMI and smoking were ascertained any time before the start date the most recent status/value as appropriate. Comorbidities were ascertained any time before the start date. Polypharmacy was taken as the number of different medications in the month before the start date.

Table 25. Hazard ratios (95% CIs) for SDH associated with risk factors.

	SDH cases N=483		**Non-cases N=396,729**		**HR (95% CI)***
	n	**%**	**n**	**%**	
Sex					
Male	298	61.7	204,112	51.4	1 (–)
Female	185	38.3	192,617	48.6	0.49 (0.41–0.60)
Age (years)					
50–64	109	22.6	205,067	51.7	1 (–)
65–74	201	41.6	117,627	29.6	3.53 (2.80–4.46)
≥75	173	35.8	74,035	18.7	6.92 (5.42–8.82)
PCP visits					
0–4	66	13.7	67,683	17.1	
5–9	135	28.0	117,317	29.6	1.31 (0.98–1.76)
10–14	189	39.1	149,813	37.8	1.62 (1.22–2.14)
≥20	93	19.3	61,916	15.6	2.30 (1.67–3.17)
Type of cohort					
Comparison	200	41.4	198,384	50.0	1 (–)
Low-dose ASA	283	58.6	198,345	50.0	1.28 (1.07–1.53)
CVD prevention population					
Primary prevention	325	67.3	305,143	76.9	1 (–)
Secondary prevention	158	32.7	91,586	23.1	1.23 (1.01–1.51)
BMI (kg/m^2)					
15–19	19	3.9	12,313	3.1	1.24 (0.77–2.00)
20–24	153	31.7	99,877	25.2	1
25–29	169	35.0	137,992	34.8	0.75 (0.60–0.94)
≥30	85	17.6	94,337	23.8	0.67 (0.51–0.87)
Unknown	57	11.8	52,210	13.2	0.69 (0.51–0.94)
Smoking					
Non-smoker	214	44.3	177,061	44.6	1 (–)
Current	69	14.3	75,212	19.0	0.97 (0.74–1.28)
Former	176	36.4	124,527	31.4	1.10 (0.90–1.35)
Unknown	24	5.0	19,929	5.0	0.76 (0.49–1.16)
Comorbidities					
Hypertension	239	49.5	164,458	41.5	1.01 (0.84–1.21)
Hypercholesterolemia	55	11.4	45,988	11.6	0.95 (0.71–1.25)
MI	29	6.0	19,046	4.8	1.07 (0.73–1.57)
IS	26	5.4	11,834	3.0	1.62 (1.09–2.42)
IHD[†]	38	7.9	25,284	6.4	0.87 (0.62–1.21)
Haemorrhagic stroke	5	1.0	2011	0.5	2.21 (0.92–5.35)
COPD	24	5.0	20,325	5.1	0.93 (0.61–1.40)
PU, complicated/uncomplicated	27	5.6	20,808	5.2	0.85 (0.57–1.25)
Polypharmacy					
0–1	239	49.5	228867	57.7	1 (–)
2–4	156	32.3	118910	30.0	1.05 (0.85–1.29)
≥5	88	18.2	48,952	12.3	1.50 (1.15–1.94)

Warfarin					
Non-use	431	89.2	381,845	96.2	1 (–)
Current use[‡]	40	8.3	9425	2.4	3.14 (2.22–4.43)
Past use[§]	12	2.5	5459	1.4	1.66 (0.95–3.00)
Clopidogrel					
Non-use	478	99.0	391,064	98.6	1 (–)
Current use[‡]	3	0.6	4319	1.1	0.52 (0.17–1.63)
Past use[§]	2	0.4	1346	0.3	1.22 (0.30–4.90)

[*]Adjusted by age, sex, and number of PCP visits in the year prior to the start date and type of cohort.

[†]Excluding MI.

[‡]Use on the start date or in the previous 90 days.

[§]Use that ended at least 91 days before the start date.

PCP visits were ascertained in the year before the start date. BMI and smoking were ascertained any time before the start date the most recent status/value as appropriate. Comorbidities were ascertained any time before the start date. Polypharmacy was taken as the number of different medications in the month before the start date.

Table 26. Hazard ratios (95% CIs) for SAH associated with risk factors.

	SAH cases N=385		**Non-cases N=396,827**		**HR (95% CI)***
	n	**%**	**n**	**%**	
Sex					
Male	155	40.3	204,255	51.5	1 (–)
Female	230	59.7	192,572	48.5	1.50 (1.22–1.85)
Age (years)					
50–64	195	50.6	204,981	51.7	1 (–)
65–74	120	31.2	117,708	29.7	1.09 (0.87–1.37)
≥75	70	18.2	74,138	18.7	1.19 (0.91–1.57)
PCP visits					
0–4	79	20.5	67,670	17.1	
5–9	105	27.3	117,347	29.6	0.80 (0.60–1.07)
10–14	132	34.3	149,870	37.8	0.81 (0.61–1.07)
≥20	69	17.9	61,940	15.6	1.12 (0.81–1.55)
Type of cohort					
Comparison	194	50.4	198,390	50.0	1 (–)
Low-dose ASA	191	49.6	198,437	50.0	0.92 (0.75–1.12)
CVD prevention population					
Primary prevention	272	70.6	305,196	76.9	1 (–)
Secondary prevention	113	29.4	91,631	23.1	1.53 (1.21–1.93)
BMI (kg/m^2)					
15–19	18	4.7	12,314	3.1	1.44 (0.87–2.38)
20–24	107	27.8	99,923	25.2	1
25–29	137	35.6	138,024	34.8	0.95 (0.74–1.23)
≥30	63	16.4	94,359	23.8	0.61 (0.45–0.84)
Unknown	60	15.6	52,207	13.2	1.05 (0.76–1.45)
Smoking					
Non-smoker	137	35.6	177,138	44.6	1 (–)
Current	120	31.2	75,161	18.9	2.38 (1.85–3.05)
Former	103	26.8	124,600	31.4	1.27 (0.98–1.64)
Unknown	25	6.5	19,928	5.0	1.38 (0.89–2.14)
Comorbidities					
Hypertension	169	43.9	164,528	41.5	1.05 (0.85–1.30)
Hypercholesterolemia	13	3.4	19,062	4.8	0.99 (0.72–1.35)
MI	44	11.4	45,999	11.6	0.79 (0.45–1.38)
IS	10	2.6	11,850	3.0	0.99 (0.53–1.87)
IHD[†]	28	7.3	25,294	6.4	1.11 (0.75–1.64)
Haemorrhagic stroke	19	4.9	1997	0.5	11.29 (7.11–17.93)
COPD	26	6.8	20,323	5.1	1.73 (1.16– 2.60)
PU, complicated/uncomplicated	24	6.2	20811	5.2	1.30 (0.85–1.96)
Polypharmacy					
0–1	223	57.9	228,883	57.7	1 (–)
2–4	115	29.9	118,951	30.0	0.98 (0.78–1.24)
≥5	47	12.2	48,993	12.3	1.01 (0.72–1.41)

	SAH cases N=385		Non-cases N=396,827		HR (95% CI)*
Warfarin					
Non-use	370	96.1	381,906	96.2	1 (–)
Current use‡	11	2.9	9454	2.4	1.41 (0.76–2.61)
Past use§	4	1.0	5467	1.4	0.83 (0.31–2.22)
Clopidogrel‡					
Non-use	379	98.4	391,163	98.6	1 (–)
Current use‡	4	1.0	4318	1.1	1.13 (0.42–3.03)
Past use§	2	0.5	1346	0.3	1.82 (0.45–7.33)

*Adjusted by age, sex, and number of PCP visits in the year prior to the start date and type of cohort.

†Excluding MI.

‡Use on the start date or in the previous 90 days.

§Use that ended at least 91 days before the start date.

PCP visits were ascertained in the year before the start date. BMI and smoking were ascertained any time before the start date the most recent status/value as appropriate. Comorbidities were ascertained any time before the start date. Polypharmacy was taken as the number of different medications in the month before the start date.

Table 27. Frequency of demographics, lifestyle factors, healthcare use and polypharmacy among ICB cases and controls, and association (RRs with 95% CIs) with ICB.

	ICB cases N=1611		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	828	51.4	5164	51.6	NA	NA
Female	783	48.6	4836	48.4	NA	NA
Age (years)						
40–59	188	11.7	1174	11.7	NA	NA
60–69	355	22.0	2231	22.3	NA	NA
70–79	595	36.9	3708	37.1	NA	NA
80–89	473	29.4	2887	28.8	NA	NA
Calendar year						
2000–2004	264	16.4	1669	16.7	NA	NA
2005–2010	648	40.2	4973	49.7	NA	NA
2010 and beyond	699	43.4	3358	33.6	NA	NA
Cohort type						
Comparison	730	45.3	4790	47.9	1 (–)	1 (–)
Low-dose ASA	881	54.7	5210	52.1	0.99 (0.89–1.11)	0.94 (0.80–1.10)
Smoking						
Non-smoker	633	39.3	4403	44.0	1 (–)	1 (–)
Current	246	15.3	1193	11.9	1.47 (1.24–1.73)	1.38 (1.16–1.63)
Former	704	43.7	4215	42.1	1.08 (0.96–1.22)	1.09 (0.97–1.24)
Unknown	28	1.7	189	1.9	1.29 (0.85–1.97)	1.13 (0.71–1.78)
BMI (kg/m^2)						
15–19	96	6.0	355	3.5	1.50 (1.17–1.92)	1.48 (1.15–1.92)
20–24	486	30.2	2774	27.7	1 (–)	1 (–)
25–29	567	35.2	3712	37.1	0.86 (0.75–0.98)	0.86 (0.75–0.99)
≥30	315	19.6	2328	23.3	0.69 (0.59–0.81)	0.69 (0.58–0.81)
Unknown	147	9.1	831	8.3	1.14 (0.93–1.40)	1.12 (0.89–1.41)
Alcohol (u/w)						
None	342	21.2	1955	19.6	1 (–)	1 (–)
1–9	752	46.7	4867	48.7	0.91 (0.79–1.05)	0.92 (0.80–1.06)
10–20	225	14.0	1365	13.7	0.99 (0.82–1.19)	1.00 (0.82–1.22)
21–41	69	4.3	443	4.4	0.93 (0.70–1.24)	0.86 (0.64–1.16)
≥42	22	1.4	94	0.9	1.48 (0.91–2.41)	1.39 (0.84–2.28)
Unknown	201	12.5	1276	12.8	1.00 (0.82–1.21)	0.90 (0.73–1.11)

	ICB cases N=1611		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Polypharmacy (in month before the index date)						
0–1	602	37.4	3658	36.6	1 (–)	1 (–)
2–4	436	27.1	3039	30.4	0.73 (0.64–0.84)	0.70 (0.61–0.81)
≥5	573	35.6	3303	33.0	0.75 (0.65–0.86)	0.70 (0.61–0.82)
Polypharmacy (in month before the start date)						
0–1	850	52.8	5572	55.7	1 (–)	1 (–)
2–4	521	32.3	3231	32.3	0.95 (0.84–1.07)	0.95 (0.84–1.08)
≥5	240	14.9	1197	12.0	1.05 (0.89–1.23)	1.05 (0.88–1.24)
PCP visits						
0–4	142	8.9	1415	14.1	1 (–)	1 (–)
5–9	282	17.5	2319	23.2	1.23 (0.99–1.52)	1.23 (0.99–1.54)
10–15	305	18.9	2286	22.9	1.36 (1.10–1.68)	1.33 (1.06–1.66)
15–19	259	16.1	1584	15.8	1.68 (1.35–2.09)	1.56 (1.23–1.96)
≥20	623	38.7	2396	24.0	2.70 (2.22–3.29)	2.23 (1.79–2.77)
Referrals						
0–4	568	35.3	4669	46.7	1 (–)	1 (–)
5–9	445	27.6	2836	28.4	1.17 (1.01–1.34)	1.16 (1.00–1.34)
10–19	375	23.3	1781	17.8	1.39 (1.19–1.64)	1.41 (1.19–1.66)
≥20	223	13.8	714	7.1	1.78 (1.45–2.18)	1.78 (1.45–2.20)
Hospitalizations						
None	1055	65.5	8376	83.8	1 (–)	1 (–)
1	294	18.2	969	9.7	2.11 (1.81–2.45)	2.04 (1.75–2.38)
2	149	9.2	387	3.9	2.54 (2.07–3.12)	2.34 (1.89–2.90)
≥3	113	7.0	268	2.7	2.63 (2.07–3.33)	2.33 (1.81–2.98)
Townsend score						
Deprived 1 (least deprived)	398	24.7	2634	26.3	1 (–)	1 (–)
Deprived 2	375	23.3	2369	23.7	1.01 (0.87–1.18)	1.05 (0.90–1.22)
Deprived 3	308	19.1	2039	20.4	0.97 (0.83–1.14)	0.97 (0.82–1.15)
Deprived 4	251	15.6	1628	16.3	0.96 (0.81–1.14)	0.97 (0.81–1.15)
Deprived 5 (most deprived)	239	14.8	1036	10.4	1.44 (1.20–1.72)	1.45 (1.20–1.74)
Unknown	40	2.5	294	2.9	0.90 (0.63–1.27)	0.94 (0.66–1.34)
Urban/rural						
Urban	1023	63.5	6238	62.4	1 (–)	1 (–)
Town	194	12.0	1247	12.5	0.92 (0.78–1.09)	0.90 (0.76–1.07)
Rural	109	6.8	781	7.8	0.86 (0.69–1.06)	0.87 (0.70–1.08)
Unknown	285	17.7	1734	17.3	0.99 (0.86–1.15)	0.98 (0.84–1.13)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and previous ICB, clopidogrel, low-dose ASA and warfarin.
PCP visits were ascertained in the year before the index date. BMI, smoking and alcohol intake were ascertained any time before the index date using the most recent status/value as appropriate.
Polypharmacy refers to the number of different medications.

Table 28. Frequency of comorbidities among ICB cases and controls, and association (RRs with 95% CIs) with ICB.

Comorbidities	**Cases N=1611**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
MI	123	7.6	748	7.5	0.91 (0.75–1.12)	0.87 (0.69–1.09)
IS/TIA	297	18.4	884	8.8	2.12 (1.83–2.46)	1.86 (1.59–2.17)
IS	188	11.7	532	5.3	2.10 (1.76–2.51)	1.58 (1.30–1.92)
TIA	169	10.5	518	5.2	1.95 (1.62–2.35)	1.58 (1.29–1.94)
IHD†	200	12.4	1448	14.5	0.74 (0.63–0.87)	0.73 (0.61–0.87)
Prior ICB	64	4.0	48	0.5	9.02 (6.12–13.30)	8.42 (5.66–12.51)
COPD	143	8.9	746	7.5	1.01 (0.84–1.23)	0.94 (0.77–1.15)
Asthma	233	14.5	1544	15.4	0.79 (0.68–0.92)	0.82 (0.70–0.96)
Hypertension	980	60.8	5795	58.0	1.01 (0.90–1.13)	1.06 (0.94–1.19)
Hyperlipidemia	404	25.1	2495	24.9	0.93 (0.82–1.05)	0.95 (0.83–1.08)
Diabetes	304	18.9	1829	18.3	0.83 (0.72–0.96)	0.98 (0.85–1.14)
DVT	158	9.8	789	7.9	1.13 (0.94–1.36)	1.03 (0.85–1.26)
Anemia§	51	3.2	175	1.8	1.31 (0.95–1.81)	1.30 (0.93–1.81)
Atrial fibrillation	291	18.1	1014	10.1	1.64 (1.41–1.91)	1.09 (0.89–1.34)
Heart failure	117	7.3	491	4.9	1.24 (1.00–1.53)	1.05 (0.83–1.32)
Haemodialysis all	7	0.4	12	0.1	2.82 (1.09–7.28)	2.88 (1.08–7.70)
Haemodialysis extracorporeal	7	0.4	8	0.1	4.16 (1.48–11.68)	4.17 (1.42–12.19)
eGFR (mL/min/1.73 m^2)						
0–14	13	0.8	25	0.2	2.60 (1.31–5.15)	2.29 (1.13–4.67)
15–29	41	2.5	126	1.3	1.72 (1.19–2.48)	1.70 (1.16–2.48)
30–44	108	6.7	670	6.7	0.90 (0.72–1.12)	0.85 (0.68–1.07)
45–59	299	18.6	1881	18.8	0.96 (0.83–1.11)	0.96 (0.83–1.12)
≥60	953	59.2	5960	59.6	1 (–)	1 (–)
Unknown	197	12.2	1338	13.4	1.21(1.00–1.46)	1.19 (0.98–1.45)
PU, uncomplicated/ complicated	133	8.3	702	7.0	1.08 (0.89–1.32)	1.01 (0.82–1.23)
PU, uncomplicated	91	5.6	479	4.8	1.11 (0.88–1.40)	1.03 (0.81–1.31)
PU, complicated	65	4.0	302	3.0	1.19 (0.90–1.57)	1.08 (0.81–1.44)
IBD	27	1.7	142	1.4	1.04 (0.68–1.57)	1.07 (0.70–1.64)
Dyspepsia	441	27.4	2406	24.1	1.05 (0.93–1.18)	1.06 (0.94–1.21)
Gout	135	8.4	710	7.1	1.09 (0.90–1.33)	1.07 (0.87–1.31)
Osteoporosis	150	9.3	775	7.8	1.09 (0.90–1.32)	1.02 (0.84–1.25)
GERD	293	18.2	1724	17.2	0.95 (0.82–1.09)	0.99 (0.86–1.14)
Anxiety	307	19.1	1622	16.2	1.10 (0.96–1.27)	1.09 (0.95–1.26)
Depression	438	27.2	2061	20.6	1.30 (1.15–1.48)	1.29 (1.14–1.47)
Migraine	113	7.0	570	5.7	1.20 (0.97–1.48)	1.15 (0.92–1.44)
Epilepsy	62	3.8	156	1.6	2.28 (1.69–3.09)	1.96 (1.43–2.70)
Dementia	101	6.3	248	2.5	2.38 (1.86–3.04)	2.16 (1.67–2.78)
Falls§	144	8.9	270	2.7	3.01 (2.42–3.74)	3.05 (2.44–3.82)
Osteoarthritis	642	39.9	3991	39.9	0.90 (0.80–1.00)	0.95 (0.85–1.06)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and previous ICB, clopidogrel, low-dose ASA and warfarin.
[‡]IHD does not include myocardial infarction.
[§]In the year before the index date.
Comorbidities were ascertained in the year before the index date, unless otherwise specified.

Table 29. Frequency of specific medication use among ICB cases and controls, and association (RRs with 95% CIs) with ICB.

Medication use	ICB cases N=1611		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	474	29.4	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	614	38.1	3852	38.5	0.97 (0.85–1.11)	0.98 (0.84–1.13)
Recent use (8–90 days)	126	7.8	656	6.6	1.13 (0.91–1.40)	1.10 (0.88–1.37)
Past use (91–365)	112	7.0	492	4.9	1.29 (1.02–1.62)	1.17 (0.92–1.48)
Distant use (>365 days)	285	17.7	1656	16.6	1.03 (0.88–1.22)	0.89 (0.75–1.06)
Duration (continuous) of low-dose ASA among current users						
<3 months	71	4.4	362	3.6	1.19 (0.90–1.57)	1.13 (0.85–1.50)
3–<6 months	52	3.2	253	2.5	1.22 (0.89–1.69)	1.19 (0.86–1.65)
6 months–<1 year	81	5.0	432	4.3	1.08 (0.83–1.40)	1.04 (0.80–1.37)
1–<5 years	281	17.4	1949	19.5	0.90 (0.76–1.06)	0.88 (0.74–1.05)
≥5 years	129	8.0	856	8.6	0.92 (0.74–1.14)	0.97 (0.77–1.21)
Total use of low-dose ASA among current users						
<3 months	57	3.5	270	2.7	1.29 (0.95–1.76)	1.21 (0.88–1.67)
3–<6 months	37	2.3	220	2.2	0.98 (0.68–1.41)	0.91 (0.62–1.33)
6 months–<1 year	71	4.4	395	4.0	1.04 (0.79–1.37)	1.01 (0.76–1.35)
1–<5 years	320	19.9	2121	21.2	0.94 (0.81–1.10)	0.93 (0.79–1.10)
≥5 years	129	8.0	846	8.5	0.93 (0.75–1.16)	0.98 (0.78–1.23)
Time interval between start date and index date among current users of low-dose ASA						
<3 months	34	2.1	182	1.8	1.13 (0.77–1.66)	1.03 (0.69–1.53)
3–<6 months	29	1.8	135	1.4	1.24 (0.81–1.89)	1.14 (0.74–1.76)
6 months–<1 year	47	2.9	279	2.8	0.97 (0.70–1.35)	0.91 (0.65–1.29)
1–<5 years	267	16.6	1877	18.8	0.88 (0.75–1.04)	0.88 (0.74–1.05)
≥5 years	237	14.7	1379	13.8	1.06 (0.89–1.27)	1.09 (0.90–1.31)
Duration of low-dose ASA among recent users						
<3 months	28	1.7	143	1.4	1.15 (0.76–1.75)	1.13 (0.85–1.50)
3–<6 months	15	0.9	94	0.9	0.96 (0.55–1.68)	1.19 (0.86–1.65)
6 months–<1 year	19	1.2	98	1.0	1.10 (0.66–1.82)	1.04 (0.80–1.37)
1–<5 years	55	3.4	229	2.3	1.43 (1.04–1.96)	0.88 (0.74–1.05)
≥5 years	9	0.6	90	0.9	0.56 (0.28–1.12)	0.97 (0.77–1.21)

Medication use	ICB cases N=1611		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Low-dose ASA dose among current users						
75 mg	575	35.7	3,660	36.6	0.96 (0.84–1.10)	0.96 (0.83–1.11)
150 mg	31	1.9	164	1.6	1.16 (0.78–1.74)	1.10 (0.73–1.67)
300 mg	8	0.5	28	0.3	1.63 (0.73–3.63)	1.37 (0.60–3.16)
Among primary prevention cohort	1088		7469			
Current low-dose ASA users	352	32.3	2348	31.4	1.01 (0.86–1.18)	1.00 (0.84–1.18)
Among secondary prevention cohort						
Current low-dose ASA users	262	50.1	1504	59.4	0.60 (0.45–0.79)	0.87 (0.63–1.19)
Clopidogrel						
Never use	1438	89.3	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	71	4.4	326	3.3	1.16 (0.89–1.51)	1.13 (0.86–1.49)
Recent use (8–90 days)	15	0.9	55	0.5	1.47 (0.82–2.63)	1.36 (0.75–2.48)
Past use (91–365)	14	0.9	118	1.2	0.61 (0.35–1.07)	0.51 (0.29–0.91)
Distant use (>365 days)	73	4.5	389	3.9	1.10 (0.85–1.43)	1.06 (0.81–1.39)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	460	28.6	3289	32.9	1 (–)	1 (–)
DAT	28	1.7	139	1.4	1.04 (0.68–1.59)	1.10 (0.71–1.69)
Low-dose ASA monotherapy	573	35.6	3609	36.1	1.00 (0.87–1.14)	0.97 (0.84–1.13)
Clopidogrel monotherapy	28	1.7	144	1.4	1.15 (0.75–1.75)	0.94 (0.61–1.45)
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	736	45.7	4376	43.8	1 (–)	1 (–)
DAT	28	1.7	139	1.4	1.00 (0.66–1.51)	1.09 (0.71–1.66)
Low-dose ASA monotherapy	40	2.5	259	2.6	0.92 (0.65–1.30)	0.93 (0.65–1.32)
Clopidogrel monotherapy	28	1.7	144	1.4	1.10 (0.72–1.67)	0.93 (0.61–1.43)
Warfarin						
Never use	1307	81.1	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	214	13.3	535	5.4	2.15 (1.80–2.58)	2.04 (1.60–2.61)
Recent use (31–365 days)	27	1.7	83	0.8	1.73 (1.11–2.69)	1.68 (1.05–2.70)
Past use (>365 days)	63	3.9	262	2.6	1.59 (1.20–2.11)	1.49 (1.10–2.01)

Medication use	ICB cases N=1611		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to index date						
INR <3	91	5.7	275	2.8	1.69 (1.31–2.18)	1.55 (1.13–2.12)
INR ≥3	46	2.9	58	0.6	4.03 (2.70–6.00)	3.64 (2.36–5.60)
Unknown INR	77	4.8	202	2.0	2.24 (1.70–2.94)	2.12 (1.53–2.92)
Remaining anticoagulants‡						
Never use	1581	98.1	9902	99.0	1 (–)	1 (–)
Current use (0–7 days)	2	0.1	10	0.1	NA	NA
Recent use (8–90 days)	5	0.3	8	0.1	NA	NA
Past use (91–365)	4	0.2	22	0.2	NA	NA
Distant use (>365 days)	19	1.2	58	0.6	NA	NA
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	396	24.6	3159	31.6	1 (–)	1 (–)
Both drugs	25	1.6	51	0.5	2.69 (1.63–4.44)	2.31 (1.36–3.91)
INR <3	10	0.6	19	0.2	2.64 (1.21–5.77)	2.00 (0.88–4.55)
INR ≥3	7	0.4	5	0.05	6.79 (2.12–21.69)	4.17 (1.25–13.90)
Unknown INR	8	0.5	27	0.3	1.68 (0.75–3.75)	1.49 (0.66–3.38)
Low-dose ASA monotherapy	582	36.1	3760	37.6	1.08 (0.94–1.25)	1.00 (0.86–1.16)
Warfarin monotherapy	152	9.4	397	4.0	2.16 (1.72–2.72)	1.67 (1.27–2.19)
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	593	36.8	4573	45.7	1 (–)	1 (–)
Both drugs	25	1.6	51	0.5	2.73 (1.67–4.49)	2.42 (1.43–4.08)
Low-dose ASA monotherapy	582	36.1	3760	37.6	1.09 (0.96–1.23)	1.02 (0.89–1.16)
Warfarin monotherapy	152	9.4	397	4.0	2.18 (1.75–2.71)	1.75 (1.34–2.27)
PPI						
Never use	828	51.4	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	332	20.6	1895	18.9	0.99 (0.86–1.14)	1.00 (0.86–1.16)
Recent use (8–90 days)	82	5.1	381	3.8	1.23 (0.96–1.59)	1.28 (0.99–1.67)
Past use (91–365)	80	5.0	485	4.9	0.95 (0.74–1.22)	0.97 (0.75–1.26)
Distant use (>365 days)	289	17.9	1570	15.7	1.16 (1.00–1.35)	1.16 (0.99–1.35)

Medication use	ICB cases N=1611		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
H_2RA						
Never use	1226	76.1	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	41	2.5	218	2.2	1.08 (0.77–1.52)	1.14 (0.80–1.62)
Recent use (8–90 days)	10	0.6	75	0.8	0.74 (0.38–1.44)	0.72 (0.36–1.42)
Past use (91–365)	24	1.5	112	1.1	1.15 (0.73–1.80)	1.21 (0.77–1.91)
Distant use (>365 days)	310	19.2	1844	18.4	0.94 (0.82–1.08)	0.94 (0.82–1.09)
SSRI						
Never use	1211	75.2	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	113	7.0	441	4.4	1.53 (1.22–1.90)	1.50 (1.20–1.88)
Duration <91 days	22	1.4	67	0.7	1.84 (1.12–3.01)	1.66 (1.00–2.75)
Duration 90–365 days	28	1.7	97	1.0	1.56 (1.01–2.39)	1.53 (0.99–2.38)
Duration >365 days	63	3.9	277	2.8	1.43 (1.07–1.90)	1.43 (1.07–1.92)
Recent use (8–90 days)	37	2.3	106	1.1	2.00 (1.36–2.94)	1.97 (1.33–2.92)
Past use (91–365)	39	2.4	141	1.4	1.58 (1.09–2.27)	1.59 (1.09–2.31)
Distant use (>365 days)	211	13.1	1034	10.3	1.29 (1.09–1.52)	1.26 (1.06–1.49)
NSAIDs						
Never use	472	29.3	2856	28.6	1 (–)	1 (–)
Current use (0–7 days	115	7.1	642	6.4	0.98 (0.78–1.23)	1.17 (0.93–1.48)
Duration <91 days	43	2.7	186	1.9	1.32 (0.93–1.87)	1.53 (1.07–2.19)
Duration 90–365 days	26	1.6	148	1.5	0.96 (0.62–1.48)	1.16 (0.74–1.80)
Duration >365 days	46	2.9	308	3.1	0.81 (0.58–1.12)	0.99 (0.71–1.38)
Recent use (8–90 days)	64	4.0	454	4.5	0.72 (0.54–0.95)	0.87 (0.65–1.16)
Past use (91–365)	99	6.1	892	8.9	0.57 (0.45–0.72)	0.65 (0.51–0.83)
Distant use (>365 days)	861	53.4	5156	51.6	0.92 (0.82–1.05)	0.98 (0.86–1.11)
Acetaminophen						
Never use	424	26.3	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	313	19.4	1537	15.4	1.17 (0.99–1.38)	1.21 (1.01–1.43)
Duration <91 days	119	7.4	402	4.0	1.68 (1.33–2.13)	1.76 (1.38–2.24)
Duration 90–365 days	59	3.7	348	3.5	0.93 (0.69–1.26)	0.90 (0.66–1.23)
Duration >365 days	135	8.4	787	7.9	0.99 (0.80–1.23)	1.04 (0.83–1.30)
Recent use (8–90 days)	199	12.4	1140	11.4	1.03 (0.85–1.24)	1.05 (0.86–1.27)
Past use (91–365)	196	12.2	1061	10.6	1.09 (0.90–1.32)	1.11 (0.92–1.35)
Distant use (>365 days)	479	29.7	3212	32.1	0.98 (0.85–1.13)	0.96 (0.83–1.11)
Oral steroids						
Never use	1284	79.7	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	49	3.0	262	2.6	0.86 (0.63–1.18)	0.88 (0.63–1.21)
Recent use (8–90 days)	29	1.8	161	1.6	0.83 (0.55–1.24)	0.84 (0.55–1.27)
Past use (91–365)	49	3.0	284	2.8	0.83 (0.60–1.13)	0.82 (0.60–1.14)
Distant use (>365 days)	200	12.4	1254	12.5	0.87 (0.74–1.03)	0.87 (0.73–1.03)

Medication use	ICB cases N=1611		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Inhaled steroids						
Never use	1370	85.0	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	67	4.2	624	6.2	0.55 (0.42–0.72)	0.56 (0.43–0.74)
Recent use (8–90 days)	36	2.2	218	2.2	0.83 (0.58–1.20)	0.87 (0.60–1.26)
Past use (91–365)	30	1.9	150	1.5	0.99 (0.66–1.47)	1.05 (0.69–1.58)
Distant use (>365 days)	108	6.7	645	6.5	0.91 (0.73–1.13)	0.93 (0.75–1.16)
Antihypertensive medications						
Never use	298	18.5	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	919	57.0	6288	62.9	0.81 (0.70–0.94)	0.62 (0.51–0.75)
Recent use (8–90 days)	137	8.5	505	5.1	1.47 (1.16–1.85)	1.19 (0.91–1.55)
Past use (91–365)	80	5.0	224	2.2	2.01 (1.50–2.69)	1.74 (1.28–2.36)
Distant use (>365 days)	177	11.0	832	8.3	1.34 (1.09–1.65)	1.23 (0.99–1.53)
Statins						
Never use	723	44.9	4704	47.0	1 (–)	1 (–)
Current use (0–7days)	616	38.2	4038	40.4	0.84 (0.74–0.95)	0.75 (0.65–0.87)
Duration <91 days	56	3.5	297	3.0	1.02 (0.75–1.38)	0.92 (0.67–1.27)
Duration 90–365 days	109	6.8	630	6.3	0.90 (0.72–1.12)	0.78 (0.61–0.99)
Duration >365 days	451	28.0	3111	31.1	0.81 (0.71–0.93)	0.73 (0.63–0.85)
Recent use (8–90 days)	118	7.3	523	5.2	1.22 (0.98–1.53)	1.15 (0.90–1.45)
Past use (91–365)	57	3.5	224	2.2	1.35 (0.99–1.83)	1.25 (0.90–1.72)
Distant use (>365 days)	97	6.0	511	5.1	1.11 (0.87–1.41)	1.06 (0.83–1.36)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

‡Among two cases who were current users of 'remaining anticoagulants', one was using rivaroxaban and other dalteparim. Among ten controls who were current users of a 'remaining anticoagulant: four were using acenocoumarol, two were using rivaroxaban, two were using enoxaparin, one was using heparin and one was using dabigatran.

Table 30. Frequency of low-dose ASA use among ICB cases and controls, and association (RRs with 95% CIs) with ICB, stratified by sex.

Low-dose ASA Men	**ICB cases N=828**		**Controls N=5164**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	236	28.5	1639	31.7	1 (–)	1 (–)
Current and recent use (0–90 days)	396	47.8	2470	47.8	0.91 (0.76–1.09)	0.99 (0.82–1.21)
Current use (0–7 days)	334	40.3	2120	41.1	0.90 (0.75–1.09)	1.00 (0.81–1.22)
Recent use (8–90 days)	62	7.5	350	6.8	0.96 (0.71–1.31)	0.98 (0.71–1.36)
Past use (91–365)	61	7.4	249	4.8	1.25 (0.91–1.72)	1.21 (0.87–1.69)
Distant use (>365 days)	135	16.3	806	15.6	0.95 (0.75–1.21)	0.84 (0.65–1.08)
Low-dose ASA Women	**ICB cases N=783**		**Controls N=4836**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	238	30.4	1705	35.3	1 (–)	1 (–)
Current and recent use (0–90 days)	344	43.9	2038	42.1	1.10 (0.91–1.32)	1.00 (0.82–1.22)
Current use (0–7 days)	280	35.8	1732	35.8	1.06 (0.87–1.28)	0.95 (0.77–1.17)
Recent use (8–90 days)	64	8.2	306	6.3	1.33 (0.98–1.80)	1.24 (0.91–1.71)
Past use (91–365)	51	6.5	243	5.0	1.31 (0.94–1.84)	1.15 (0.81–1.63)
Distant use (>365 days)	150	19.2	850	17.6	1.13 (0.90–1.42)	0.94 (0.74–1.20)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 31. Frequency of low-dose ASA use among ICB cases and controls, and association (RRs with 95% CIs) with ICB, stratified by case-fatality status (fatal case = death within 30 days following the event).

Low-dose ASA Fatal cases	**ICB cases N=402**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	156	38.8	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	169	42.0	4508	45.1	0.67 (0.53–0.85)	0.67 (0.52–0.86)
Current use (0–7 days)	134	33.3	3852	38.5	0.63 (0.50–0.81)	0.63 (0.48–0.82)
Recent use (8–90 days)	35	8.7	656	6.6	0.89 (0.61–1.31)	0.85 (0.57–1.27)
Past use (91–365)	19	4.7	492	4.9	0.64 (0.39–1.05)	0.54 (0.32–0.89)
Distant use (>365 days)	58	14.4	1656	16.6	0.73 (0.53–1.01)	0.56 (0.40–0.78)
Duration among current users						
≤6 months	26	6.5	615	6.2	0.64 (0.41–0.98)	0.61 (0.39–0.95)
>6 months	108	26.9	3237	32.4	0.63 (0.49–0.82)	0.63 (0.48–0.83)
Low-dose ASA Non-fatal cases	**ICB cases N=1209**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	318	26.3	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	571	47.2	4508	45.1	1.16 (1.00–1.35)	1.16 (0.98–1.36)
Current use (0–7 days)	480	39.7	3852	38.5	1.15 (0.98–1.34)	1.14 (0.97–1.35)
Recent use (8–90 days)	91	7.5	656	6.6	1.25 (0.97–1.60)	1.22 (0.94–1.58)
Past use (91–365)	93	7.7	492	4.9	1.63 (1.26–2.10)	1.50 (1.15–1.95)
Distant use (>365 days)	227	18.8	1656	16.6	1.19 (0.99–1.43)	1.06 (0.87–1.28)
Duration among current users						
≤6 months	97	8.0	615	6.2	1.52 (1.18–1.95)	1.46 (1.12–1.89)
>6 months	383	31.7	3237	32.4	1.08 (0.92–1.27)	1.07 (0.90–1.28)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 32. Frequency of specific medication use among non-traumatic ICB cases and controls, and association (RRs with 95% CIs) with non-traumatic ICB.

Medication use	Non-traumatic ICB cases N=1176		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	363	30.9	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	423	36.0	3852	38.5	0.91 (0.78–1.06)	0.88 (0.74–1.03)
Recent use (8–90 days)	99	8.4	656	6.6	1.19 (0.93–1.51)	1.13 (0.88–1.45)
Past use (91–365)	82	7.0	492	4.9	1.27 (0.98–1.65)	1.13 (0.86–1.48)
Distant use (>365 days)	209	17.8	1656	16.6	1.06 (0.88–1.27)	0.90 (0.74–1.10)
Duration of low-dose ASA among current users						
<3 months	53	4.5	362	3.6	1.14 (0.83–1.55)	1.07 (0.77–1.48)
3–<6 months	34	2.9	253	2.5	1.05 (0.72–1.53)	1.00 (0.67–1.47)
6 months–<1 year	54	4.6	432	4.3	0.95 (0.69–1.29)	0.88 (0.64–1.21)
1–<5 years	204	17.3	1949	19.5	0.87 (0.73–1.05)	0.83 (0.68–1.01)
≥5 years	78	6.6	856	8.6	0.80 (0.62–1.05)	0.81 (0.62–1.07)
Duration of low-dose ASA among recent users						
<3 months	23	2.0	145	1.5	1.25 (0.79–1.97)	1.15 (0.72–1.85)
3–<6 months	14	1.2	94	0.9	1.16 (0.65–2.06)	1.19 (0.67–2.14)
6 months–<1 year	13	1.1	98	1.0	1.00 (0.55–1.81)	0.82 (0.44–1.52)
1–<5 years	41	3.5	229	2.3	1.43 (1.00–2.03)	1.39 (0.96–2.00)
≥5 years	8	0.7	90	0.9	0.73 (0.35–1.52)	0.73 (0.35–1.54)
Low-dose ASA dose among current users						
75 mg	399	33.9	3660	36.6	0.90 (0.77–1.05)	0.87 (0.74–1.03)
150–300 mg	24	2.0	192	1.9	1.01 (0.65–1.57)	0.89 (0.56–1.40)
Clopidogrel						
Never use	1056	89.8	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	43	3.7	326	3.3	0.99 (0.71–1.38)	0.94 (0.67–1.32)
Recent use (8–90 days)	12	1.0	55	0.5	1.70 (0.90–3.21)	1.52 (0.79–2.93)
Past use (91–365)	10	0.9	118	1.2	0.60 (0.31–1.15)	0.50 (0.26–0.98)
Distant use (>365 days)	55	4.7	389	3.9	1.20 (0.89–1.61)	1.16 (0.86–1.58)

Medication use	Non-traumatic ICB cases N=1176		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	353	30.0	3289	32.9	1 (–)	1 (–)
DAT	15	1.3	139	1.4	0.76 (0.44–1.31)	0.80 (0.46–1.39)
Low-dose ASA monotherapy	399	33.9	3609	36.1	0.93 (0.80–1.09)	0.89 (0.75–1.05)
Clopidogrel monotherapy	18	1.5	144	1.4	1.04 (0.63–1.73)	0.81 (0.48–1.36)
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	524	44.6	4376	43.8	1 (–)	1 (–)
DAT	15	1.3	139	1.4	0.76 (0.44–1.31)	0.85 (0.49–1.48)
Low-dose ASA monotherapy	31	2.6	259	2.6	1.07 (0.72–1.57)	1.07 (0.72–1.59)
Clopidogrel monotherapy	18	1.5	144	1.4	1.05 (0.63–1.73)	0.87 (0.52–1.45)
Warfarin						
Never use	960	81.6	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	152	12.9	535	5.3	2.23 (1.81–2.74)	1.96 (1.48–2.60)
Recent use (31–365 days)	21	1.8	83	0.8	1.92 (1.18–3.14)	1.79 (1.06–3.03)
Past use (>365 days)	43	3.7	262	2.6	1.54 (1.11–2.15)	1.40 (0.99–2.00)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	66	5.6	275	2.8	1.82 (1.36–2.44)	1.53 (1.07–2.19)
INR ≥3	36	3.1	58	0.6	4.66 (3.03–7.18)	3.92 (2.45–6.29)
Unknown INR	50	4.3	202	2.0	2.06 (1.50–2.85)	1.80 (1.23–2.62)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	311	26.4	3159	31.6	1 (–)	1 (–)
Both drugs	20	1.7	51	0.5	2.92 (1.70–5.02)	2.38 (1.33–4.25)
Low-dose ASA monotherapy	400	34.0	3760	37.6	0.98 (0.83–1.15)	0.87 (0.73–1.04)
Warfarin monotherapy	103	8.8	397	4.0	2.04 (1.57–2.66)	1.48 (1.08–2.03)

Medication use	Non-traumatic ICB cases N=1176		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	456	38.8	4573	45.7	1 (–)	1 (–)
Both drugs	20	1.7	51	0.5	2.98 (1.74–5.09)	2.51 (1.42–4.45)
Low-dose ASA monotherapy	400	34.0	3760	37.6	0.99 (0.85–1.14)	0.90 (0.77–1.05)
Warfarin monotherapy	103	8.8	397	4.0	2.07 (1.61–2.66)	1.56 (1.15–2.11)
PPI						
Never use	605	51.4	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	241	20.5	1895	18.9	1.05 (0.89–1.24)	1.07 (0.90–1.27)
Recent use (8–90 days)	67	5.7	381	3.8	1.46 (1.11–1.93)	1.54 (1.15–2.05)
Past use (91–365)	63	5.4	485	4.9	1.08 (0.81–1.43)	1.10 (0.82–1.46)
Distant use (>365 days)	200	17.0	1570	15.7	1.16 (0.98–1.39)	1.17 (0.98–1.40)
H_2RA						
Never use	900	76.5	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	30	2.6	218	2.2	1.09 (0.73–1.61)	1.15 (0.77–1.72)
Recent use (8–90 days)	7	0.6	75	0.8	0.71 (0.33–1.55)	0.66 (0.30–1.47)
Past use (91–365)	21	1.8	112	1.1	1.36 (0.85–2.19)	1.44 (0.88–2.33)
Distant use (>365 days)	218	18.5	1844	18.4	0.92 (0.78–1.08)	0.91 (0.77–1.08)
SSRI						
Never use	892	75.9	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	74	6.3	441	4.4	1.37 (1.05–1.77)	1.33 (1.02–1.75)
Duration <91 days	12	1.0	67	0.7	1.36 (0.73–2.54)	1.14 (0.60–2.19)
Duration 90–365 days	16	1.4	97	1.0	1.21 (0.70–2.07)	1.20 (0.69–2.08)
Duration >365 days	46	3.9	277	2.8	1.43 (1.03–1.97)	1.42 (1.02–1.99)
Recent use (8–90 days)	31	2.6	106	1.1	2.26 (1.50–3.42)	2.26 (1.48–3.44)
Past use (91–365)	30	2.6	141	1.4	1.62 (1.08–2.43)	1.60 (1.05–2.44)
Distant use (>365 days)	149	12.7	1034	10.3	1.23 (1.01–1.48)	1.18 (0.97–1.44)
NSAIDs						
Never use	363	30.9	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	98	8.3	642	6.4	1.07 (0.84–1.37)	1.30 (1.01–1.67)
Duration <91 days	34	2.9	186	1.9	1.34 (0.91–1.98)	1.56 (1.05–2.31)
Duration 90–365 days	21	1.8	148	1.5	0.99 (0.61–1.59)	1.19 (0.74–1.94)
Duration >365 days	43	3.7	308	3.1	0.97 (0.69–1.36)	1.21 (0.86–1.72)
Recent use (8–90 days)	48	4.1	454	4.5	0.69 (0.50–0.95)	0.83 (0.60–1.15)
Past use (91–365)	70	6.0	892	8.9	0.52 (0.40–0.68)	0.60 (0.45–0.79)
Distant use (>365 days)	597	50.8	5156	51.6	0.85 (0.74–0.98)	0.90 (0.77–1.04)

Medication use	Non-traumatic ICB cases N=1176		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Acetaminophen						
Never use	328	27.9	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	224	19.0	1537	15.4	1.14 (0.94–1.38)	1.15 (0.94–1.40)
Duration <91 days	81	6.9	402	4.0	1.55 (1.18–2.03)	1.61 (1.22–2.13)
Duration 90–365 days	44	3.7	348	3.5	0.95 (0.67–1.34)	0.91 (0.64–1.29)
Duration >365 days	99	8.4	787	7.9	0.99 (0.78–1.27)	1.01 (0.78–1.30)
Recent use (8–90 days)	141	12.0	1140	11.4	0.98 (0.79–1.22)	0.98 (0.79–1.23)
Past use (91–365)	138	11.7	1061	10.6	1.02 (0.82–1.27)	1.02 (0.81–1.27)
Distant use (>365 days)	345	29.3	3212	32.1	0.95 (0.80–1.11)	0.91 (0.77–1.07)
Oral steroids						
Never use	938	79.8	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	40	3.4	262	2.6	1.00 (0.71–1.42)	1.00 (0.70–1.43)
Recent use (8–90 days)	21	1.8	161	1.6	0.85 (0.54–1.36)	0.84 (0.52–1.35)
Past use (91–365)	35	3.0	284	2.8	0.84 (0.58–1.21)	0.82 (0.57–1.20)
Distant use (>365 days)	142	12.1	1254	12.5	0.88 (0.73–1.07)	0.87 (0.71–1.06)
Inhaled steroids						
Never use	1006	85.5	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	48	4.1	624	6.2	0.55 (0.41–0.75)	0.54 (0.39–0.73)
Recent use (8–90 days)	27	2.3	218	2.2	0.86 (0.57–1.29)	0.89 (0.59–1.35)
Past use (91–365)	20	1.7	150	1.5	0.89 (0.56–1.44)	1.02 (0.64–1.63)
Distant use (>365 days)	75	6.4	645	6.5	0.88 (0.68–1.13)	0.87 (0.67–1.12)
Antihypertensive medications						
Never use	235	20.0	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	655	55.7	6288	62.9	0.78 (0.66–0.93)	0.55 (0.40–0.75)
Recent use (8–90 days)	101	8.6	505	5.1	1.45 (1.12–1.89)	0.88 (0.58–1.34)
Past use (91–365)	64	5.4	224	2.2	2.16 (1.57–2.97)	0.94 (0.58–1.53)
Distant use (>365 days)	121	10.3	832	8.3	1.21 (0.95–1.53)	0.89 (0.69–1.15)
Statins						
Never use	547	46.5	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	424	36.1	4038	40.4	0.81 (0.70–0.93)	0.73 (0.62–0.86)
Duration <91 days	43	3.7	297	3.0	1.05 (0.75–1.48)	0.98 (0.69–1.40)
Duration 90–365 days	78	6.6	630	6.3	0.87 (0.67–1.13)	0.78 (0.59–1.02)
Duration >365 days	303	25.8	3111	31.1	0.77 (0.65–0.90)	0.69 (0.58–0.83)
Recent use (8–90 days)	90	7.7	523	5.2	1.30 (1.01–1.66)	1.19 (0.91–1.56)
Past use (91–365)	47	4.0	224	2.2	1.54 (1.10–2.15)	1.46 (1.03–2.07)
Distant use (>365 days)	68	5.8	511	5.1	1.11 (0.84–1.46)	1.05 (0.79–1.40)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 33. Frequency of specific medication use among traumatic ICB cases and controls, and association (RRs with 95% CIs) with traumatic ICB.

Medication use	Traumatic ICB cases N=435		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	111	25.5	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	191	43.9	3852	38.5	1.19 (0.93–1.53)	1.30 (1.00–1.68)
Recent use (8–90 days)	27	6.2	656	6.6	0.95 (0.62–1.47)	0.99 (0.64–1.54)
Past use (91–365)	30	6.9	492	4.9	1.36 (0.89–2.07)	1.26 (0.82–1.94)
Distant use (>365 days)	76	17.5	1656	16.6	0.99 (0.73–1.34)	0.86 (0.62–1.18)
Duration of low-dose ASA among current users						
<3 months	18	4.1	362	3.6	1.38 (0.82–2.32)	1.34 (0.79–2.27)
3–<6 months	18	4.1	253	2.5	1.83 (1.08–3.09)	1.83 (1.07–3.13)
6 months–<1 year	27	6.2	432	4.3	1.60 (1.02–2.49)	1.68 (1.06–2.64)
1–<5 years	77	17.7	1949	19.5	1.01 (0.74–1.36)	1.07 (0.78–1.47)
≥5 years	51	11.7	856	8.6	1.18 (0.83–1.67)	1.39 (0.96–1.99)
Duration of low-dose ASA among recent users						
<3 months	5	1.1	145	1.5	0.84 (0.34–2.10)	0.87 (0.34–2.19)
3–<6 months	1	0.2	94	0.9	0.28 (0.04–2.07)	0.29 (0.04–2.10)
6 months–<1 year	6	1.4	98	1.0	1.41 (0.60–3.32)	1.40 (0.59–3.35)
1–<5 years	14	3.2	229	2.3	1.46 (0.82–2.60)	1.51 (0.84–2.72)
≥5 years	1	0.2	90	0.9	0.20 (0.03–1.42)	0.20 (0.03–1.47)
Low-dose ASA dose among current users						
75 mg	176	40.5	3660	36.6	1.15 (0.90–1.48)	1.25 (0.96–1.63)
150–300 mg	15	3.4	192	1.9	1.98 (1.13–3.50)	2.24 (1.25–4.00)
Clopidogrel						
Never use	382	87.8	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	28	6.4	326	3.3	1.57 (1.05–2.35)	1.67 (1.10–2.54)
Recent use (8–90 days)	3	0.7	55	0.5	0.99 (0.30–3.19)	1.02 (0.31–3.34)
Past use (91–365)	4	0.9	118	1.2	0.62 (0.23–1.70)	0.50 (0.18–1.38)
Distant use (>365 days)	18	4.1	389	3.9	0.89 (0.54–1.45)	0.83 (0.50–1.36)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	107	24.6	3289	32.9	1 (–)	1 (–)
DAT	13	3.0	139	1.4	1.87 (1.01–3.44)	2.09 (1.13–3.89)
Low-dose ASA monotherapy	174	40.0	3609	36.1	1.19 (0.93–1.53)	1.27 (0.97–1.65)
Clopidogrel monotherapy	10	2.3	144	1.4	1.42 (0.72–2.79)	1.39 (0.69–2.78)

Medication use	**Traumatic ICB cases N=435**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	212	48.7	4376	43.8	1 (–)	1 (–)
DAT	13	3.0	139	1.4	1.56 (0.86–2.83)	1.68 (0.92–3.06)
Low-dose ASA monotherapy	9	2.1	259	2.6	0.62 (0.31–1.23)	0.63 (0.32–1.25)
Clopidogrel monotherapy	10	2.3	144	1.4	1.18 (0.61–2.29)	1.11 (0.57–2.17)
Warfarin						
Never use	347	79.8	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	62	14.3	535	5.3	1.93 (1.42–2.61)	2.23 (1.45–3.42)
Recent use (31–365 days)	6	1.4	83	0.8	1.29 (0.55–3.00)	1.45 (0.60–3.48)
Past use (>365 days)	20	4.6	262	2.6	1.75 (1.09–2.80)	1.72 (1.05–2.82)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	25	5.7	275	2.8	1.38 (0.89–2.15)	1.56 (0.91–2.69)
INR ≥3	10	2.3	58	0.6	2.66 (1.33–5.31)	2.84 (1.35–5.97)
Unknown INR	27	6.2	202	2.0	2.56 (1.67–3.91)	2.98 (1.78–5.01)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	85	19.5	3159	31.6	1 (–)	1 (–)
Both drugs	5	1.1	51	0.5	2.16 (0.83–5.64)	1.92 (0.70–5.25)
Low-dose ASA monotherapy	182	41.8	3760	37.6	1.43 (1.09–1.88)	1.45 (1.10–1.92)
Warfarin monotherapy	49	11.3	397	4.0	2.48 (1.68–3.67)	2.27 (1.40–3.67)
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	137	31.5	4573	45.7	1 (–)	1 (–)
Both drugs	5	1.1	51	0.5	2.14 (0.83–5.52)	1.96 (0.73–5.31)
Low-dose ASA monotherapy	182	41.8	3760	37.6	1.41 (1.11–1.78)	1.45 (1.14–1.84)
Warfarin monotherapy	49	11.3	397	4.0	2.44 (1.69–3.50)	2.32 (1.47–3.66)
PPI						
Never use	223	51.3	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	91	20.9	1895	18.9	0.84 (0.65–1.09)	0.85 (0.65–1.11)
Recent use (8–90 days)	15	3.4	381	3.8	0.71 (0.42–1.22)	0.76 (0.44–1.32)
Past use (91–365)	17	3.9	485	4.9	0.66 (0.39–1.09)	0.68 (0.41–1.14)
Distant use (>365 days)	89	20.5	1570	15.7	1.13 (0.87–1.47)	1.14 (0.87–1.48)

Medication use	Traumatic ICB cases N=435		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
H_2RA						
Never use	326	74.9	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	11	2.5	218	2.2	1.03 (0.56–1.92)	1.11 (0.59–2.08)
Recent use (8–90 days)	3	0.7	75	0.8	0.86 (0.27–2.76)	0.85 (0.26–2.76)
Past use (91–365)	3	0.7	112	1.1	0.55 (0.17–1.76)	0.61 (0.19–1.95)
Distant use (>365 days)	92	21.1	1844	18.4	1.01 (0.79–1.28)	1.01 (0.79–1.30)
SSRI						
Never use	319	73.3	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	39	9.0	441	4.4	2.00 (1.40–2.86)	2.02 (1.41–2.90)
Duration <91 days	10	2.3	67	0.7	3.17 (1.60–6.31)	3.01 (1.49–6.07)
Duration 90–365 days	12	2.8	97	1.0	2.63 (1.41–4.91)	2.62 (1.39–4.94)
Duration >365 days	17	3.9	277	2.8	1.45 (0.87–2.41)	1.51 (0.90–2.52)
Recent use (8–90 days)	6	1.4	106	1.1	1.29 (0.56–2.99)	1.25 (0.53–2.94)
Past use (91–365)	9	2.1	141	1.4	1.44 (0.72–2.87)	1.55 (0.77–3.11)
Distant use (>365 days)	62	14.3	1034	10.3	1.46 (1.10–1.95)	1.46 (1.09–1.95)
NSAIDs						
Never use	109	25.1	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	17	3.9	642	6.4	0.65 (0.39–1.10)	0.76 (0.45–1.29)
Duration <91 days	9	2.1	186	1.9	1.23 (0.61–2.48)	1.45 (0.71–2.96)
Duration 90–365 days	5	1.1	148	1.5	0.84 (0.33–2.10)	0.95 (0.38–2.40)
Duration >365 days	3	0.7	308	3.1	0.24 (0.07–0.75)	0.28 (0.09–0.89)
Recent use (8–90 days)	16	3.7	454	4.5	0.80 (0.47–1.37)	0.99 (0.58–1.71)
Past use (91–365)	29	6.7	892	8.9	0.73 (0.48–1.11)	0.81 (0.53–1.25)
Distant use (>365 days)	264	60.7	5156	51.6	1.16 (0.92–1.46)	1.23 (0.97–1.56)
Acetaminophen						
Never use	96	22.1	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	89	20.5	1537	15.4	1.25 (0.92–1.69)	1.39 (1.03–1.90)
Duration <91 days	38	8.7	402	4.0	2.06 (1.38–3.07)	2.20 (1.46–3.31)
Duration 90–365 days	15	3.4	348	3.5	0.90 (0.51–1.59)	0.94 (0.53–1.67)
Duration >365 days	36	8.3	787	7.9	0.98 (0.66–1.47)	1.14 (0.75–1.72)
Recent use (8–90 days)	58	13.3	1140	11.4	1.24 (0.87–1.78)	1.36 (0.95–1.96)
Past use (91–365)	58	13.3	1061	10.6	1.37 (0.97–1.93)	1.48 (1.05–2.10)
Distant use (>365 days)	134	30.8	3212	32.1	1.11 (0.84–1.46)	1.16 (0.88–1.53)
Oral steroids						
Never use	346	79.5	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	9	2.1	262	2.6	0.53 (0.27–1.04)	0.56 (0.28–1.11)
Recent use (8–90 days)	8	1.8	161	1.6	0.75 (0.37–1.56)	0.81 (0.39–1.70)
Past use (91–365)	14	3.2	284	2.8	0.81 (0.47–1.41)	0.85 (0.48–1.48)
Distant use (>365 days)	58	13.3	1254	12.5	0.84 (0.63–1.12)	0.85 (0.63–1.14)
Inhaled steroids						
Never use	364	83.7	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	19	4.4	624	6.2	0.56 (0.35–0.89)	0.59 (0.37–0.96)
Recent use (8–90 days)	9	2.1	218	2.2	0.77 (0.39–1.51)	0.83 (0.42–1.65)
Past use (91–365)	10	2.3	150	1.5	1.29 (0.67–2.49)	1.42 (0.73–2.76)
Distant use (>365 days)	33	7.6	645	6.5	0.98 (0.68–1.42)	1.04 (0.71–1.51)

Medication use	**Traumatic ICB cases N=435**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Antihypertensive medications						
Never use	63	14.5	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	264	60.7	6288	62.9	0.91 (0.68–1.22)	0.65 (0.45–0.94)
Recent use (8–90 days)	36	8.3	505	5.1	1.53 (0.99–2.36)	1.35 (0.83–2.18)
Past use (91–365)	16	3.7	224	2.2	1.59 (0.89–2.84)	1.27 (0.69–2.32)
Distant use (>365 days)	56	12.9	832	8.3	1.77 (1.21–2.58)	1.59 (1.08–2.35)
Statins						
Never use	176	40.5	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	192	44.1	4038	40.4	0.93 (0.75–1.16)	0.80 (0.62–1.03)
Duration <91 days	13	3.0	297	3.0	0.91 (0.51–1.63)	0.76 (0.42–1.39)
Duration 90–365 days	31	7.1	630	6.3	0.96 (0.64–1.43)	0.77 (0.51–1.18)
Duration >365 days	148	34.0	3111	31.1	0.93 (0.73–1.17)	0.81 (0.62–1.06)
Recent use (8–90 days)	28	6.4	523	5.2	1.05 (0.69–1.59)	1.02 (0.66–1.59)
Past use (91–365)	10	2.3	224	2.2	0.87 (0.45–1.67)	0.78 (0.40–1.53)
Distant use (>365 days)	29	6.7	511	5.1	1.10 (0.73–1.66)	1.06 (0.69–1.62)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 34. Frequency of specific medication use among ICH cases and controls, and association (RRs with 95% CIs) with ICH.

Medication use	**ICH Cases N=743 (%)**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Low-dose ASA						
Never use	210	28.3	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	282	38.0	3852	38.5	1.00 (0.82–1.21)	0.98 (0.80–1.20)
Recent use (8–90 days)	66	8.9	656	6.6	1.30 (0.97–1.75)	1.22 (0.90–1.66)
Past use (91–365)	56	7.5	492	4.9	1.47 (1.07–2.02)	1.28 (0.92–1.78)
Distant use (>365 days)	129	17.4	1656	16.6	1.08 (0.85–1.37)	0.90 (0.70–1.16)
Duration of low-dose ASA among current users						
<3 months	33	4.4	362	3.6	1.23 (0.83–1.81)	1.13 (0.76–1.69)
3–<6 months	20	2.7	253	2.5	1.02 (0.63–1.65)	0.97 (0.59–1.59)
6 months–<1 year	45	6.1	432	4.3	1.31 (0.93–1.85)	1.26 (0.89–1.80)
1–<5 years	133	17.9	1949	19.5	0.94 (0.75–1.19)	0.90 (0.71–1.15)
≥5 years	51	6.9	856	8.6	0.83 (0.60–1.15)	0.89 (0.63–1.24)
Duration of low-dose ASA among recent users						
<3 months	14	1.9	145	1.5	1.27 (0.72–2.25)	1.56 (0.92–2.65)
3–<6 months	8	1.1	94	0.9	1.13 (0.54–2.37)	1.53 (0.79–2.95)
6 months–<1 year	9	1.2	98	1.0	1.13 (0.56–2.28)	1.55 (0.86–2.81)
1–<5 years	29	3.9	229	2.3	1.65 (1.08–2.50)	2.16 (1.47–3.17)
≥5 years	6	0.8	90	0.9	0.85 (0.36–1.98)	1.50 (0.77–2.90)
Low-dose ASA dose among current users						
75 mg	266	35.8	3660	36.6	0.99 (0.81–1.20)	0.89 (0.73–1.09)
150 mg	12	1.6	164	1.6	0.99 (0.54–1.81)	0.79 (0.41–1.50)
300 mg	4	0.5	28	0.3	1.78 (0.61–5.18)	1.74 (0.69–4.44)
Clopidogrel						
Never use	671	90.3	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	28	3.8	326	3.3	1.00 (0.67–1.49)	0.95 (0.63–1.43)
Recent use (8–90 days)	8	1.1	55	0.5	1.79 (0.84–3.80)	1.64 (0.76–3.57)
Past use (91–365)	8	1.1	118	1.2	0.78 (0.38–1.62)	0.63 (0.30–1.33)
Distant use (>365 days)	28	3.8	389	3.9	0.94 (0.63–1.40)	0.90 (0.60–1.36)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	203	27.3	3289	32.9	1 (–)	1 (–)
DAT	9	1.2	139	1.4	0.80 (0.40–1.60)	0.85 (0.42–1.71)
Low-dose ASA monotherapy	268	36.1	3609	36.1	1.03 (0.85–1.25)	0.98 (0.80–1.21)
Clopidogrel monotherapy	12	1.6	144	1.4	1.10 (0.60–2.02)	0.83 (0.44–1.56)

Medication use	ICH Cases N=743 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	360	48.5	4376	43.8	1 (–)	1 (–)
DAT	9	1.2	139	1.4	0.70 (0.35–1.40)	0.80 (0.40–1.60)
Low-dose ASA monotherapy	14	1.9	259	2.6	0.71 (0.41–1.23)	0.75 (0.43–1.32)
Clopidogrel monotherapy	12	1.6	144	1.4	0.97 (0.53–1.77)	0.79 (0.43–1.46)
Warfarin						
Never use	593	79.8	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	106	14.3	535	5.3	2.30 (1.81–2.92)	1.87 (1.35–2.61)
Recent use (31–365 days)	14	1.9	83	0.8	1.91 (1.07–3.41)	1.62 (0.87–3.01)
Past use (>365 days)	30	4.0	262	2.6	1.66 (1.12–2.45)	1.37 (0.91–2.08)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	42	5.5	275	2.8	1.77 (1.25–2.50)	1.38 (0.90–2.10)
INR ≥3	29	3.8	58	0.6	5.22 (3.24–8.40)	4.31 (2.54–7.30)
Unknown INR	36	4.8	202	2.0	2.16 (1.49–3.15)	1.72 (1.11–2.67)
Remaining anticoagulants						
Never use	730	98.3	9902	99.0	NA	NA
Current use (0–7 days)	1	0.1	10	0.1	NA	NA
Past use (8–90 days)	2	0.3	8	0.1	NA	NA
Recent (91–365)	2	0.3	22	0.2	NA	NA
Distant use (>365 days)	8	1.1	58	0.6	NA	NA
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	178	24.0	3159	31.6	1 (–)	1 (–)
Both drugs	12	1.6	51	0.5	2.74 (1.42–5.30)	2.01 (1.00–4.07)
Low-dose ASA monotherapy	267	35.9	3760	37.6	1.08 (0.88–1.32)	0.97 (0.79–1.20)
Warfarin monotherapy	71	9.6	397	4.0	2.18 (1.59–2.98)	1.42 (0.97–2.07)
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	260	35.0	4573	45.7	1 (–)	1 (–)
Both drugs	12	1.6	51	0.5	2.84 (1.48–5.46)	2.18 (1.09–4.36)
Low-dose ASA monotherapy	267	35.9	3760	37.6	1.10 (0.92–1.33)	1.02 (0.84–1.23)
Warfarin monotherapy	71	9.6	397	4.0	2.24 (1.66–3.01)	1.54 (1.07–2.20)

Medication use	ICH Cases N=743 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
PPI						
Never use	391	52.6	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	157	21.1	1895	18.9	1.01 (0.82–1.23)	1.03 (0.84–1.27)
Recent use (8–90 days)	32	4.3	381	3.8	1.06 (0.72–1.55)	1.10 (0.74–1.63)
Past use (91–365)	33	4.4	485	4.9	0.86 (0.59–1.24)	0.87 (0.60–1.28)
Distant use (>365 days)	130	17.5	1570	15.7	1.14 (0.92–1.41)	1.18 (0.95–1.47)
H_2RA						
Never use	556	74.8	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	23	3.1	218	2.2	1.30 (0.83–2.02)	1.31 (0.83–2.08)
Recent use (8–90 days)	6	0.8	75	0.8	0.95 (0.41–2.20)	0.92 (0.39–2.16)
Past use (91–365)	12	1.6	112	1.1	1.27 (0.69–2.33)	1.36 (0.73–2.51)
Distant use (>365 days)	146	19.7	1844	18.4	0.98 (0.81–1.19)	1.00 (0.82–1.21)
SSRI						
Never use	573	77.1	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	45	6.1	441	4.4	1.34 (0.97–1.85)	1.30 (0.93–1.81)
Duration <91 days	10	1.3	67	0.7	1.78 (0.90–3.51)	1.53 (0.76–3.10)
Duration 90–365 days	13	1.7	97	1.0	1.60 (0.88–2.89)	1.59 (0.87–2.92)
Duration >365 days	22	3.0	277	2.8	1.11 (0.71–1.74)	1.11 (0.70–1.75)
Recent use (8–90 days)	21	2.8	106	1.1	2.61 (1.61–4.24)	2.66 (1.62–4.36)
Past use (91–365)	14	1.9	141	1.4	1.22 (0.69–2.14)	1.25 (0.70–2.23)
Distant use (>365 days)	90	12.1	1034	10.3	1.22 (0.96–1.54)	1.17 (0.92–1.50)
NSAIDs						
Never use	235	31.6	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	59	7.9	642	6.4	1.03 (0.76–1.39)	1.26 (0.93–1.72)
Duration <91 days	20	2.7	186	1.9	1.28 (0.79–2.07)	1.50 (0.91–2.47)
Duration 90–365 days	13	1.7	148	1.5	0.97 (0.54–1.75)	1.17 (0.64–2.12)
Duration >365 days	26	3.5	308	3.1	0.93 (0.61–1.42)	1.19 (0.77–1.84)
Recent use (8–90 days)	29	3.9	454	4.5	0.67 (0.45–1.00)	0.85 (0.57–1.28)
Past use (91–365)	40	5.4	892	8.9	0.48 (0.34–0.67)	0.56 (0.39–0.80)
Distant use (>365 days)	380	51.1	5156	51.6	0.84 (0.71–1.00)	0.91 (0.76–1.08)
Acetaminophen						
Never use	218	29.3	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	131	17.6	1537	15.4	0.89 (0.70–1.13)	0.93 (0.73–1.19)
Duration <91 days	45	6.1	402	4.0	1.18 (0.83–1.67)	1.24 (0.87–1.76)
Duration 90–365 days	25	3.4	348	3.5	0.72 (0.47–1.12)	0.71 (0.46–1.12)
Duration >365 days	61	8.2	787	7.9	0.82 (0.60–1.11)	0.86 (0.63–1.18)
Recent use (8–90 days)	89	12.0	1140	11.4	0.83 (0.64–1.09)	0.84 (0.64–1.10)
Past use (91–365)	96	12.9	1061	10.6	0.99 (0.76–1.28)	0.99 (0.76–1.29)
Distant use (>365 days)	209	28.1	3212	32.1	0.83 (0.68–1.01)	0.81 (0.66–1.00)
Oral steroids						
Never use	938	79.8	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	40	3.4	262	2.6	1.06 (0.71–1.58)	1.15 (0.76–1.72)
Recent use (8–90 days)	21	1.8	161	1.6	0.67 (0.36–1.26)	0.69 (0.37–1.31)
Past use (91–365)	35	3.0	284	2.8	0.67 (0.41–1.09)	0.67 (0.40–1.10)
Distant use (>365 days)	142	12.1	1254	12.5	0.86 (0.68–1.09)	0.86 (0.68–1.09)

Medication use	**ICH Cases N=743 (%)**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Inhaled steroids						
Never use	1006	85.5	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	48	4.1	624	6.2	0.53 (0.36–0.77)	0.54 (0.37–0.80)
Recent use (8–90 days)	27	2.3	218	2.2	0.88 (0.54–1.44)	0.89 (0.54–1.47)
Past use (91–365)	20	1.7	150	1.5	0.86 (0.47–1.57)	0.97 (0.53–1.78)
Distant use (>365 days)	75	6.4	645	6.5	0.79 (0.57–1.09)	0.81 (0.58–1.12)
Antihypertensive medications						
Never use	235	20.0	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	655	55.7	6288	62.9	0.84 (0.68–1.05)	0.63 (0.47–0.83)
Recent use (8–90 days)	101	8.6	505	5.1	1.64 (1.19–2.25)	1.24 (0.86–1.78)
Past use (91–365)	64	5.4	224	2.2	2.60 (1.79–3.78)	2.15 (1.44–3.20)
Distant use (>365 days)	121	10.0	832	8.3	1.31 (0.97–1.76)	1.17 (0.85–1.60)
Statins						
Never use	547	46.5	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	424	36.1	4040	40.4	0.82 (0.69–0.98)	0.73 (0.59–0.89)
Duration <91 days	22	3.0	297	3.0	0.91 (0.58–1.43)	0.81 (0.51–1.30)
Duration 90–365 days	56	7.5	630	6.3	1.00 (0.74–1.36)	0.85 (0.61–1.17)
Duration >365 days)	192	25.8	3111	31.1	0.77 (0.64–0.94)	0.69 (0.55–0.86)
Recent use (8–90 days)	90	7.7	521	5.2	1.34 (0.99–1.81)	1.19 (0.86–1.65)
Past use (91–365)	47	4.0	224	2.2	1.33 (0.86–2.06)	1.24 (0.78–1.95)
Distant use (>365 days)	68	5.8	511	5.1	1.37 (1.00–1.87)	1.31 (0.94–1.81)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 35. Frequency of specific medication use among ICH cases and controls, and association (RRs with 95% CIs) with ICH, stratified by sex.

Low-dose ASA Men	**ICH cases N=375**		**Controls N=5164**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	115	30.7	1639	31.7	1 (–)	1 (–)
Current and recent use (0–90 days)	172	45.9	2470	47.8	0.58 (0.38–0.89)	0.87 (0.67–1.15)
Current use (0–7 days)	138	36.8	2120	41.1	0.78 (0.60–1.01)	0.84 (0.63–1.12)
Recent use (8–90 days)	34	9.1	350	6.8	1.09 (0.73–1.64)	1.04 (0.68–1.60)
Past use (91–365)	31	8.3	249	4.8	1.35 (0.88–2.07)	1.23 (0.78–1.92)
Distant use (>365 days)	57	15.2	806	15.6	0.86 (0.61–1.20)	0.68 (0.47–0.97)
Low-dose ASA Women	**ICH cases N=368**		**Controls N=4836**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	95	25.8	1705	35.3	1 (–)	1 (–)
Current and recent use (0–90 days)	176	47.8	2038	42.1	1.33 (1.02–1.73)	1.20 (0.90–1.60)
Current use (0–7 days)	144	39.1	1732	35.8	1.29 (0.98–1.69)	1.16 (0.86–1.56)
Recent use (8–90 days)	32	8.7	306	6.3	1.55 (1.01–2.37)	1.43 (0.92–2.22)
Past use (91–365)	25	6.8	243	5.0	1.57 (0.98–2.50)	1.38 (0.85–2.26)
Distant use (>365 days)	72	19.6	850	17.6	1.36 (0.98–1.88)	1.17 (0.83–1.65)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 36. Frequency of specific medication use among ICH cases and controls, and association (RRs with 95% CIs) with ICH, stratified by case-fatality status (fatal case = death within 30 days following the event).

Low-dose ASA Fatal cases	**ICH cases N=241**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	88	36.5	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	104	43.2	4508	45.1	0.67 (0.50–0.90)	0.66 (0.48–0.91)
Current use (0–7 days)	87	36.1	3852	38.5	0.67 (0.49–0.91)	0.66 (0.48–0.92)
Recent use (8–90 days)	17	7.1	656	6.6	0.69 (0.40–1.18)	0.64 (0.37–1.11)
Past use (91–365)	13	5.4	492	4.9	0.70 (0.39–1.28)	0.59 (0.32–1.10)
Distant use (>365 days)	36	14.9	1656	16.6	0.73 (0.49–1.10)	0.55 (0.36–0.85)
Duration among current users						
≤6 months	11	4.6	615	6.2	0.44 (0.23–0.84)	0.41 (0.22–0.80)
>6 months	76	31.5	3237	32.4	0.72 (0.52–0.99)	0.73 (0.52–1.03)
Low-dose ASA Non-fatal cases	**ICH cases N=502**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**	**n**	**%**
Never use	122	24.3	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	244	48.6	4508	45.1	1.32 (1.05–1.67)	1.30 (1.02–1.66)
Current use (0–7 days)	195	38.8	3852	38.5	1.24 (0.98–1.58)	1.22 (0.95–1.58)
Recent use (8–90 days)	49	9.8	656	6.6	1.78 (1.26–2.52)	1.68 (1.18–2.41)
Past use (91–365)	43	8.6	492	4.9	2.08 (1.44–3.00)	1.84 (1.26–2.70)
Distant use (>365 days)	93	18.5	1656	16.6	1.34 (1.01–1.78)	1.18 (0.88–1.59)
Duration among current users						
≤6 months	42	8.4	615	6.2	1.73 (1.19–2.51)	1.62 (1.10–2.37)
>6 months	153	30.5	3237	32.4	1.15 (0.90–1.48)	1.13 (0.87–1.47)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 37. Frequency of specific medication use among non-traumatic ICH cases and controls, and association (RRs with 95% CIs) with non-traumatic ICH.

Medication use	Non-traumatic ICH cases N=660		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	187	28.3	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	252	38.2	3852	38.5	1.01 (0.83–1.24)	0.97 (0.78–1.20)
Recent use (8–90 days)	60	9.1	656	6.6	1.34 (0.99–1.83)	1.23 (0.89–1.69)
Past use (91–365)	49	7.4	492	4.9	1.46 (1.05–2.05)	1.26 (0.89–1.79)
Distant use (>365 days)	112	17.0	1656	16.6	1.07 (0.84–1.38)	0.91 (0.70–1.18)
Duration of low-dose ASA among current users						
<3 months	30	4.5	362	3.6	1.25 (0.83–1.88)	1.13 (0.74–1.71)
3–<6 months	17	2.6	253	2.5	0.98 (0.58–1.64)	0.90 (0.53–1.53)
6 months–<1 year	40	6.1	432	4.3	1.32 (0.91–1.89)	1.23 (0.84–1.78)
1–<5 years	122	18.5	1949	19.5	0.98 (0.77–1.25)	0.92 (0.71–1.18)
≥5 years	43	6.5	856	8.6	0.81 (0.57–1.15)	0.83 (0.58–1.20)
Duration of low-dose ASA among recent users						
<3 months	12	1.8	145	1.5	1.23 (0.67–2.27)	1.06 (0.56–1.99)
3–<6 months	8	1.2	94	0.9	1.27 (0.61–2.68)	1.24 (0.59–2.63)
6 months–<1 year	8	1.2	98	1.0	1.14 (0.54–2.39)	0.86 (0.39–1.89)
1–<5 years	26	3.9	229	2.3	1.67 (1.08–2.59)	1.61 (1.03–2.53)
≥5 years	6	0.9	90	0.9	0.98 (0.42–2.30)	1.00 (0.43–2.36)
Low-dose ASA dose among current users						
75 mg	238	36.1	3660	36.6	1.00 (0.82–1.23)	0.91 (0.73–1.13)
150 mg	10	1.5	164	1.6	0.93 (0.48–1.79)	0.72 (0.35–1.45)
300 mg	4	0.6	28	0.3	2.04 (0.70–5.93)	1.96 (0.77–5.01)
Clopidogrel						
Never use	599	90.8	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	25	3.8	326	3.3	1.01 (0.66–1.53)	0.92 (0.60–1.42)
Recent use (8–90 days)	7	1.1	55	0.5	1.78 (0.80–3.96)	1.55 (0.68–3.52)
Past use (91–365)	6	0.9	118	1.2	0.66 (0.29–1.51)	0.52 (0.22–1.21)
Distant use (>365 days)	23	3.5	389	3.9	0.88 (0.57–1.35)	0.84 (0.54–1.31)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	182	27.6	3289	32.9	1 (–)	
DAT	9	1.4	139	1.4	0.90 (0.45–1.80)	1 (–) 1.13 (0.74–1.71)
Low-dose ASA monotherapy	239	36.2	3609	36.1	1.04 (0.84–1.27)	0.90 (0.53–1.53)
Clopidogrel monotherapy	11	1.7	144	1.4	1.15 (0.61–2.18)	1.23 (0.84–1.78)

Medication use	Non-traumatic ICH cases N=660		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	323	48.9	4376	43.8	1 (–)	1 (–)
DAT	9	1.4	139	1.4	0.78 (0.39–1.56)	0.92 (0.45–1.86)
Low-dose ASA monotherapy	13	2.0	259	2.6	0.74 (0.41–1.31)	0.95 (0.77–1.19)
Clopidogrel monotherapy	11	1.7	144	1.4	1.01 (0.54–1.88)	0.83 (0.43–1.59)
Warfarin						
Never use	533	80.8	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	84	12.7	535	5.3	2.05 (1.58–2.67)	1.51 (1.06–2.17)
Recent use (31–365 days)	14	2.1	83	0.8	2.15 (1.20–3.85)	1.68 (0.90–3.13)
Past use (>365 days)	29	4.4	262	2.6	1.80 (1.21–2.67)	1.43 (0.93–2.18)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	37	5.6	275	2.8	1.69 (1.17–2.45)	1.19 (0.76–1.87)
INR ≥3	22	3.3	58	0.6	4.81 (2.89–8.03)	3.64 (2.07–6.42)
Unknown INR	25	3.8	202	2.0	1.73 (1.13–2.66)	1.24 (0.76–2.04)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	162	24.5	3159	31.6	1 (–)	1 (–)
Both drugs	10	1.5	51	0.5	2.54 (1.25–5.17)	1.76 (0.82–3.77)
Low-dose ASA monotherapy	239	36.2	3760	37.6	1.07 (0.86–1.32)	0.95 (0.76–1.19)
Warfarin monotherapy	55	8.3	397	4.0	1.89 (1.34–2.66)	1.13 (0.75–1.70)
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	236	35.8	4573	45.7	1 (–)	1 (–)
Both drugs	10	1.5	51	0.5	2.64 (1.31–5.32)	1.91 (0.90–4.05)
Low-dose ASA monotherapy	239	36.2	3760	37.6	1.09 (0.90–1.32)	1.00 (0.82–1.22)
Warfarin monotherapy	55	8.3	397	4.0	1.94 (1.40–2.69)	1.23 (0.83–1.81)
PPI						
Never use	347	52.6	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	142	21.5	1895	18.9	1.04 (0.84–1.29)	1.06 (0.85–1.32)
Recent use (8–90 days)	31	4.7	381	3.8	1.17 (0.79–1.72)	1.22 (0.82–1.82)
Past use (91–365)	31	4.7	485	4.9	0.92 (0.63–1.35)	0.93 (0.63–1.38)
Distant use (>365 days)	109	16.5	1570	15.7	1.09 (0.87–1.37)	1.14 (0.90–1.44)

Medication use	Non-traumatic ICH cases N=660		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
H_2RA						
Never use	493	74.7	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	21	3.2	218	2.2	1.34 (0.85–2.12)	1.35 (0.84–2.18)
Recent use (8–90 days)	4	0.6	75	0.8	0.72 (0.26–1.98)	0.68 (0.24–1.91)
Past use (91–365)	12	1.8	112	1.1	1.44 (0.78–2.64)	1.52 (0.82–2.81)
Distant use (>365 days)	130	19.7	1844	18.4	0.99 (0.81–1.21)	1.01 (0.82–1.24)
SSRI						
Never use	513	77.7	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	36	5.5	441	4.4	1.19 (0.83–1.70)	1.14 (0.79–1.64)
Duration <91 days	8	1.2	67	0.7	1.58 (0.75–3.34)	1.28 (0.59–2.78)
Duration 90–365 days	11	1.7	97	1.0	1.50 (0.79–2.84)	1.53 (0.80–2.93)
Duration >365 days	17	2.6	277	2.8	0.95 (0.58–1.57)	0.93 (0.56–1.56)
Recent use (8–90 days)	21	3.2	106	1.1	2.89 (1.78–4.69)	2.90 (1.77–4.78)
Past use (91–365)	14	2.1	141	1.4	1.36 (0.77–2.38)	1.36 (0.76–2.44)
Distant use (>365 days)	76	11.5	1034	10.3	1.14 (0.88–1.47)	1.07 (0.83–1.40)
NSAIDs						
Never use	208	31.5	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	57	8.6	642	6.4	1.12 (0.82–1.52)	1.34 (0.98–1.84)
Duration <91 days	18	2.7	186	1.9	1.28 (0.77–2.13)	1.47 (0.87–2.48)
Duration 90–365 days	13	2.0	148	1.5	1.09 (0.60–1.96)	1.27 (0.70–2.32)
Duration >365 days	26	3.9	308	3.1	1.05 (0.68–1.60)	1.32 (0.85–2.04)
Recent use (8–90 days)	25	3.8	454	4.5	0.65 (0.42–0.99)	0.81 (0.52–1.25)
Past use (91–365)	37	5.6	892	8.9	0.49 (0.34–0.71)	0.58 (0.40–0.84)
Distant use (>365 days)	333	50.5	5156	51.6	0.84 (0.70–1.00)	0.90 (0.74–1.08)
Acetaminophen						
Never use	197	29.8	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	115	17.4	1537	15.4	0.88 (0.68–1.13)	0.90 (0.70–1.17)
Duration <91 days	37	5.6	402	4.0	1.09 (0.75–1.58)	1.13 (0.77–1.66)
Duration 90–365 days	24	3.6	348	3.5	0.78 (0.50–1.22)	0.76 (0.48–1.20)
Duration >365 days	54	8.2	787	7.9	0.81 (0.59–1.12)	0.84 (0.60–1.18)
Recent use (8–90 days)	75	11.4	1140	11.4	0.79 (0.59–1.05)	0.80 (0.60–1.07)
Past use (91–365)	88	13.3	1061	10.6	1.01 (0.77–1.33)	1.00 (0.76–1.32)
Distant use (>365 days)	185	28.0	3212	32.1	0.82 (0.66–1.01)	0.80 (0.64–0.99)
Oral steroids						
Never use	530	80.3	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	27	4.1	262	2.6	1.13 (0.74–1.70)	1.20 (0.79–1.84)
Recent use (8–90 days)	9	1.4	161	1.6	0.63 (0.32–1.25)	0.63 (0.31–1.27)
Past use (91–365)	15	2.3	284	2.8	0.63 (0.37–1.08)	0.62 (0.36–1.07)
Distant use (>365 days)	79	12.0	1254	12.5	0.85 (0.66–1.09)	0.84 (0.65–1.08)
Inhaled steroids						
Never use	573	86.8	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	26	3.9	624	6.2	0.51 (0.34–0.77)	0.53 (0.35–0.79)
Recent use (8–90 days)	15	2.3	218	2.2	0.82 (0.48–1.41)	0.82 (0.47–1.41)
Past use (91–365)	9	1.4	150	1.5	0.73 (0.37–1.43)	0.82 (0.41–1.63)
Distant use (>365 days)	37	5.6	645	6.5	0.78 (0.55–1.10)	0.79 (0.55–1.12)

Medication use	**Non-traumatic ICH cases N=660**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Antihypertensive medications						
Never use	118	17.9	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	372	56.4	6288	62.9	0.82 (0.66–1.04)	0.60 (0.45–0.81)
Recent use (8–90 days)	61	9.2	505	5.1	1.64 (1.17–2.29)	1.21 (0.82–1.78)
Past use (91–365)	45	6.8	224	2.2	2.84 (1.94–4.15)	2.31 (1.54–3.48)
Distant use (>365 days)	64	9.7	832	8.3	1.23 (0.90–1.70)	1.10 (0.79–1.54)
Statins						
Never use	303	45.9	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	237	35.9	4038	40.4	0.81 (0.67–0.98)	0.71 (0.57–0.88)
Duration <91 days	21	3.2	297	3.0	0.96 (0.61–1.53)	0.85 (0.52–1.38)
Duration 90–365 days	51	7.7	630	6.3	1.02 (0.74–1.40)	0.86 (0.61–1.20)
Duration >365 days	165	25.0	3111	31.1	0.75 (0.61–0.92)	0.66 (0.53–0.83)
Recent use (8–90 days)	52	7.9	523	5.2	1.37 (1.00–1.88)	1.20 (0.85–1.69)
Past use (91–365)	23	3.5	224	2.2	1.38 (0.88–2.17)	1.29 (0.81–2.07)
Distant use (>365 days)	45	6.8	511	5.1	1.32 (0.94–1.85)	1.26 (0.89–1.79)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 38. Frequency of specific medication use among SDH cases and controls, and association (RRs with 95% CIs) with SDH.

Medication use	Cases N=483		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	117	24.2	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	206	42.7	3852	38.5	1.14 (0.90–1.45)	1.23 (0.95–1.59)
Recent use (8–90 days)	31	6.4	656	6.6	0.95 (0.63–1.43)	0.95 (0.62–1.45)
Past use (91–365)	37	7.7	492	4.9	1.45 (0.98–2.14)	1.30 (0.86–1.95)
Distant use (>365 days)	92	19.0	1656	16.6	1.09 (0.82–1.45)	0.92 (0.68–1.25)
Duration of low-dose ASA among current users						
<3 months	20	4.1	362	3.6	1.35 (0.82–2.22)	1.30 (0.78–2.17)
3–<6 months	18	3.7	253	2.5	1.59 (0.94–2.68)	1.57 (0.92–2.69)
6 months–<1 year	21	4.3	432	4.3	1.08 (0.66–1.75)	1.11 (0.67–1.82)
1–<5 years	92	19.0	1949	19.5	1.06 (0.80–1.41)	1.13 (0.84–1.53)
≥5 years	55	11.4	856	8.6	1.13 (0.81–1.59)	1.33 (0.93–1.90)
Duration of low-dose ASA among recent users						
<3 months	5	1.0	145	1.5	0.73 (0.29–1.82)	0.71 (0.28–1.80)
3–<6 months	3	0.6	94	0.9	0.75 (0.23–2.42)	0.76 (0.23–2.50)
6 months–<1 year	7	1.4	98	1.0	1.41 (0.63–3.14)	1.34 (0.59–3.07)
1–<5 years	14	2.9	229	2.3	1.28 (0.71–2.27)	1.25 (0.69–2.26)
≥5 years	2	0.4	90	0.9	0.34 (0.08–1.40)	0.35 (0.08–1.48)
Low-dose ASA dose among current users						
75 mg	195	40.4	3660	36.6	1.13 (0.89–1.44)	1.22 (0.95–1.58)
150 mg	9	1.9	164	1.6	1.25 (0.62–2.52)	1.25 (0.61–2.59)
300 mg	2	0.4	28	0.3	1.36 (0.31–5.91)	1.63 (0.37–7.15)
Clopidogrel						
Never use	420	87.0	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	27	5.6	326	3.3	1.28 (0.85–1.94)	1.32 (0.86–2.01)
Recent use (8–90 days)	6	1.2	55	0.5	1.62 (0.69–3.85)	1.61 (0.67–3.89)
Past use (91–365)	3	0.6	118	1.2	0.38 (0.12–1.21)	0.27 (0.08–0.88)
Distant use (>365 days)	27	5.6	389	3.9	1.16 (0.77–1.75)	1.08 (0.71–1.64)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	113	23.4	3289	32.9	1 (–)	1 (–)
DAT	12	2.5	139	1.4	1.44 (0.77–2.71)	1.63 (0.86–3.10)
Low-dose ASA monotherapy	188	38.9	3609	36.1	1.14 (0.89–1.45)	1.21 (0.93–1.56)
Clopidogrel monotherapy	11	2.3	144	1.4	1.36 (0.71–2.61)	1.26 (0.64–2.47)

Medication use	Cases N=483		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	229	47.4	4376	43.8	1 (–)	1 (–)
DAT	12	2.5	139	1.4	1.26 (0.68–2.33)	1.39 (0.75–2.59)
Low-dose ASA monotherapy	16	3.3	259	2.6	1.03 (0.60–1.74)	1.06 (0.62–1.81)
Clopidogrel monotherapy	11	2.3	144	1.4	1.19 (0.63–2.25)	1.08 (0.56–2.06)
Warfarin						
Never use	361	74.7	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	87	18.0	535	5.3	2.30 (1.76–3.01)	2.47 (1.67–3.63)
Recent use (31–365 days)	12	2.5	83	0.8	2.31 (1.23–4.32)	2.63 (1.35–5.11)
Past use (>365 days)	23	4.8	262	2.6	1.91 (1.22–2.98)	1.88 (1.18–2.99)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	40	8.3	275	2.8	1.87 (1.30–2.70)	1.94 (1.21–3.10)
INR ≥3	15	3.1	58	0.6	3.27 (1.81–5.90)	3.06 (1.61–5.84)
Unknown INR	32	6.6	202	2.0	2.63 (1.77–3.92)	2.87 (1.76–4.68)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	80	16.6	3159	31.6	1 (–)	1 (–)
Both drugs	13	2.7	51	0.5	4.87 (2.49–9.51)	4.43 (2.16–9.09)
Low-dose ASA monotherapy	190	39.3	3760	37.6	1.48 (1.12–1.94)	1.43 (1.08–1.90)
Warfarin monotherapy	64	13.3	397	4.0	2.93 (2.03–4.24)	2.42 (1.55–3.78)
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	139	28.8	4573	45.7	1 (–)	1 (–)
Both drugs	13	2.7	51	0.5	4.51 (2.35–8.66)	4.18 (2.07–8.43)
Low-dose ASA monotherapy	190	39.3	3760	37.6	1.35 (1.08–1.70)	1.32 (1.04–1.68)
Warfarin monotherapy	64	13.3	397	4.0	2.69 (1.92–3.75)	2.27 (1.50–3.44)
PPI						
Never use	223	46.2	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	117	24.2	1895	18.9	1.05 (0.82–1.33)	1.06 (0.83–1.36)
Recent use (8–90 days)	23	4.8	381	3.8	1.06 (0.68–1.67)	1.16 (0.73–1.84)
Past use (91–365)	27	5.6	485	4.9	1.02 (0.67–1.55)	1.03 (0.67–1.58)
Distant use (>365 days)	93	19.3	1570	15.7	1.19 (0.92–1.54)	1.18 (0.91–1.54)
H_2RA						
Never use	358	74.1	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	10	2.1	218	2.2	0.85 (0.44–1.62)	0.92 (0.48–1.79)
Recent use (8–90 days)	2	0.4	75	0.8	0.51 (0.12–2.09)	0.49 (0.12–2.05)
Past use (91–365)	9	1.9	112	1.1	1.44 (0.72–2.90)	1.57 (0.77–3.19)
Distant use (>365 days)	104	21.5	1844	18.4	1.02 (0.81–1.28)	1.00 (0.79–1.26)

Medication use	Cases N=483		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
SSRI						
Never use	377	78.1	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	35	7.2	441	4.4	1.52 (1.05–2.19)	1.57 (1.08–2.29)
Duration <91 days	8	1.7	67	0.7	2.00 (0.94–4.26)	1.83 (0.84–3.97)
Duration 90–365 days	8	1.7	97	1.0	1.44 (0.69–3.02)	1.56 (0.74–3.30)
Duration >365 days	19	3.9	277	2.8	1.40 (0.86–2.28)	1.49 (0.91–2.43)
Recent use (8–90 days)	9	1.9	106	1.1	1.56 (0.77–3.14)	1.52 (0.74–3.11)
Past use (91–365)	11	2.3	141	1.4	1.45 (0.77–2.74)	1.59 (0.83–3.02)
Distant use (>365 days)	51	10.6	1034	10.3	1.02 (0.75–1.38)	1.00 (0.73–1.37)
NSAIDs						
Never use	116	24.0	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	25	5.2	642	6.4	0.88 (0.56–1.37)	1.05 (0.67–1.67)
Duration <91 days	14	2.9	186	1.9	1.79 (1.00–3.21)	2.18 (1.20–3.97)
Duration 90–365 days	5	1.0	148	1.5	0.78 (0.31–1.95)	0.89 (0.35–2.26)
Duration >365 days	6	1.2	308	3.1	0.43 (0.19–0.99)	0.52 (0.22–1.22)
Recent use (8–90 days)	12	2.5	454	4.5	0.55 (0.30–1.01)	0.70 (0.38–1.29)
Past use (91–365)	31	6.4	892	8.9	0.71 (0.47–1.07)	0.82 (0.54–1.25)
Distant use (>365 days)	299	61.9	5156	51.6	1.22 (0.97–1.52)	1.29 (1.03–1.63)
Acetaminophen						
Never use	108	22.4	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	115	23.8	1537	15.4	1.38 (1.04–1.84)	1.54 (1.15–2.07)
Duration <91 days	51	10.6	402	4.0	2.33 (1.62–3.36)	2.55 (1.76–3.70)
Duration 90–365 days	22	4.6	348	3.5	1.11 (0.69–1.81)	1.12 (0.68–1.85)
Duration >365 days	42	8.7	787	7.9	0.99 (0.68–1.45)	1.16 (0.79–1.71)
Recent use (8–90 days)	62	12.8	1140	11.4	1.09 (0.78–1.52)	1.17 (0.83–1.64)
Past use (91–365)	59	12.2	1061	10.6	1.12 (0.80–1.57)	1.23 (0.87–1.73)
Distant use (>365 days)	139	28.8	3212	32.1	0.99 (0.76–1.29)	1.01 (0.77–1.32)
Oral steroids						
Never use	381	78.9	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	11	2.3	262	2.6	0.54 (0.29–1.01)	0.56 (0.30–1.05)
Recent use (8–90 days)	8	1.7	161	1.6	0.62 (0.30–1.28)	0.63 (0.30–1.31)
Past use (91–365)	18	3.7	284	2.8	0.89 (0.54–1.47)	0.91 (0.55–1.51)
Distant use (>365 days)	65	13.5	1254	12.5	0.83 (0.63–1.10)	0.83 (0.63–1.10)
Inhaled steroids						
Never use	406	84.1	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	23	4.8	624	6.2	0.56 (0.36–0.87)	0.58 (0.37–0.90)
Recent use (8–90 days)	5	1.0	218	2.2	0.35 (0.14–0.87)	0.37 (0.15–0.91)
Past use (91–365)	11	2.3	150	1.5	1.18 (0.63–2.21)	1.32 (0.69–2.51)
Distant use (>365 days)	38	7.9	645	6.5	1.00 (0.70–1.41)	1.04 (0.73–1.48)
Antihypertensive medications						
Never use	67	13.9	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	306	63.4	6288	62.9	0.89 (0.67–1.19)	0.73 (0.52–1.04)
Recent use (8–90 days)	43	8.9	505	5.1	1.55 (1.03–2.33)	1.49 (0.95–2.35)
Past use (91–365)	22	4.6	224	2.2	1.90 (1.13–3.18)	1.66 (0.97–2.86)
Distant use (>365 days)	45	9.3	832	8.3	1.30 (0.88–1.93)	1.19 (0.79–1.79)

Medication use	**Cases N=483**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Statins						
Never use	183	37.9	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	209	43.3	4038	40.4	0.89 (0.72–1.11)	0.77 (0.61–0.99)
Duration (<91 days)	17	3.5	297	3.0	1.04 (0.62–1.75)	0.88 (0.51–1.52)
Duration (90–365 days)	29	6.0	630	6.3	0.77 (0.51–1.16)	0.63 (0.41–0.97)
Duration (>365 days)	163	33.7	3111	31.1	0.90 (0.72–1.14)	0.79 (0.61–1.03)
Recent use (8–90 days)	39	8.1	523	5.2	1.31 (0.90–1.89)	1.27 (0.86–1.89)
Past use (91–365)	21	4.3	224	2.2	1.61 (0.99–2.61)	1.53 (0.92–2.54)
Distant use (>365 days)	31	6.4	511	5.1	1.12 (0.75–1.67)	1.08 (0.71–1.64)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 39. Frequency of specific medication use among SDH cases and controls, and association (RRs with 95% CIs) with SDH, stratified by sex.

Low-dose ASA Men	**SDH cases N=298**		**Controls N=5164**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	74	24.8	1639	31.7	1 (–)	1 (–)
Current and recent use (0–90 days)	149	50.0	2470	47.8	0.98 (0.73–1.32)	1.12 (0.81–1.53)
Current use (0–7 days)	132	44.3	2120	41.1	1.03 (0.76–1.39)	1.18 (0.86–1.64)
Recent use (8–90 days)	17	5.7	350	6.8	0.74 (0.42–1.27)	0.78 (0.44–1.37)
Past use (91–365)	21	7.0	249	4.8	1.18 (0.70–1.97)	1.15 (0.67–1.95)
Distant use (>365 days)	54	18.1	806	15.6	1.02 (0.70–1.48)	0.89 (0.60–1.32)
Low-dose ASA Women	**SDH cases N=185**		**Controls N=4836**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	43	23.2	1705	35.3	1 (–)	1 (–)
Current and recent use (0–90 days)	88	47.6	2038	42.1	1.34 (0.92–1.96)	1.30 (0.87–1.94)
Current use (0–7 days)	74	40.0	1732	35.8	1.33 (0.90–1.97)	1.29 (0.85–1.95)
Recent use (8–90 days)	14	7.6	306	6.3	1.38 (0.74–2.58)	1.34 (0.71–2.56)
Past use (91–365)	16	8.6	243	5.0	2.01 (1.10–3.67)	1.72 (0.91–3.22)
Distant use (>365 days)	38	20.5	850	17.6	1.19 (0.76–1.88)	0.96 (0.59–1.56)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 40. Frequency of specific medication use among SDH cases and controls, and association (RRs with 95% CIs) with SDH, stratified by case-fatality (fatal case = death within 30 days following the event).

Low-dose ASA Fatal cases	**SDH cases N=44**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	12	27.3	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	22	50.0	4508	45.1	1.11 (0.54–2.29)	1.10 (0.51–2.37)
Current use (0–7 days)	18	40.9	3852	38.5	1.08 (0.51–2.28)	1.08 (0.48–2.40)
Recent use (8–90 days)	4	9.1	656	6.6	1.30 (0.41–4.09)	1.17 (0.35–3.85)
Past use (91–365)	2	4.5	492	4.9	0.85 (0.19–3.85)	0.56 (0.12–2.67)
Distant use (>365 days)	8	18.2	1656	16.6	0.99 (0.40–2.47)	0.56 (0.20–1.53)
Duration among current users						
≤6 months	4	9.1	615	6.2	1.52 (0.48–4.87)	1.27 (0.38–4.21)
>6 months	14	31.8	3237	32.4	1.00 (0.45–2.19)	1.02 (0.44–2.39)
Low-dose ASA Non-fatal cases	**SDH cases N=439**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	105	23.9	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	215	49.0	4508	45.1	1.11 (0.87–1.42)	1.19 (0.92–1.55)
Current use (0–7 days)	188	42.8	3852	38.5	1.15 (0.89–1.47)	1.25 (0.95–1.63)
Recent use (8–90 days)	27	6.2	656	6.6	0.91 (0.59–1.42)	0.92 (0.59–1.45)
Past use (91–365)	35	8.0	492	4.9	1.51 (1.01–2.27)	1.39 (0.91–2.10)
Distant use (>365 days)	84	19.1	1656	16.6	1.10 (0.81–1.49)	0.96 (0.70–1.32)
Duration among current users						
≤6 months	34	7.7	615	6.2	1.45 (0.96–2.18)	1.43 (0.94–2.18)
>6 months	154	35.1	3237	32.4	1.10 (0.84–1.42)	1.21 (0.92–1.59)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 41. Frequency of specific medication use among non-traumatic SDH cases and controls, and association (RRs with 95% CIs) with non-traumatic SDH.

Medication use	Non-traumatic SDH N=205		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	53	25.9	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	80	39.0	3852	38.5	0.93 (0.65–1.33)	1.03 (0.70–1.52)
Recent use (8–90 days)	13	6.3	656	6.6	0.80 (0.43–1.49)	0.78 (0.41–1.49)
Past use (91–365)	18	8.8	492	4.9	1.41 (0.81–2.46)	1.21 (0.68–2.17)
Distant use (>365 days)	41	20.0	1656	16.6	1.04 (0.68–1.59)	0.84 (0.54–1.33)
Duration of low-dose ASA among current users						
<3 months	8	3.9	362	3.6	1.11 (0.51–2.39)	1.79 (0.94–3.42)
3–<6 months	6	2.9	253	2.5	1.05 (0.44–2.51)	1.02 (0.42–2.46)
6 months–<1 year	5	2.4	432	4.3	0.51 (0.20–1.31)	0.43 (0.16–1.13)
1–<5 years	40	19.5	1949	19.5	0.97 (0.63–1.48)	0.90 (0.58–1.40)
≥5 years	21	10.2	856	8.6	0.93 (0.55–1.57)	0.94 (0.54–1.63)
Duration of low-dose ASA among recent users						
<3 months	2	1.0	145	1.5	0.57 (0.14–2.38)	0.55 (0.13–2.35)
3–<6 months	2	1.0	94	0.9	0.98 (0.23–4.15)	0.99 (0.23–4.29)
6 months–<1 year	3	1.5	98	1.0	1.19 (0.36–3.93)	0.94 (0.27–3.29)
1–<5 years	5	2.4	229	2.3	0.93 (0.36–2.37)	1.36 (0.62–3.00)
≥5 years	1	0.5	90	0.9	0.36 (0.05–2.62)	0.75 (0.18–3.20)
Low-dose ASA dose among current users						
75 mg	78	38.0	3660	36.6	0.95 (0.66–1.36)	0.97 (0.66–1.41)
150 mg	1	0.5	164	1.6	0.28 (0.04–2.05)	0.26 (0.04–1.95)
300 mg	1	0.5	28	0.3	1.27 (0.16–9.74)	0.98 (0.13–7.64)
Clopidogrel						
Never use	175	85.4	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	8	3.9	326	3.3	0.87 (0.42–1.79)	0.92 (0.44–1.94)
Recent use (8–90 days)	4	2.0	55	0.5	2.47 (0.87–7.03)	2.69 (0.91–7.94)
Past use (91–365)	1	0.5	118	1.2	0.27 (0.04–1.98)	0.17 (0.02–1.27)
Distant use (>365 days)	17	8.3	389	3.9	1.72 (1.02–2.90)	1.67 (0.97–2.85)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	51	24.9	3289	32.9	1 (–)	1 (–)
DAT	3	1.5	139	1.4	0.71 (0.22–2.34)	0.90 (0.27–2.99)
Low-dose ASA monotherapy	74	36.1	3609	36.1	0.94 (0.65–1.37)	1.07 (0.72–1.59)
Clopidogrel monotherapy	4	2.0	144	1.4	1.03 (0.36–2.93)	1.04 (0.35–3.03)

Medication use	**Non-traumatic SDH N=205**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	90	43.9	4376	43.8	1 (–)	1 (–)
DAT	3	1.5	139	1.4	0.76 (0.24–2.47)	0.90 (0.28–2.91)
Low-dose ASA monotherapy	9	4.4	259	2.6	1.51 (0.74–3.07)	1.62 (0.79–3.32)
Clopidogrel monotherapy	4	2.0	144	1.4	1.11 (0.40–3.10)	1.04 (0.37–2.94)
Warfarin						
Never use	140	68.3	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	51	24.9	535	5.3	3.16 (2.20–4.55)	4.15 (2.42–7.13)
Recent use (31–365 days)	7	3.4	83	0.8	3.27 (1.46–7.34)	4.85 (2.04–11.51)
Past use (>365 days)	7	3.4	262	2.6	1.51 (0.70–3.28)	1.59 (0.72–3.53)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	24	11.7	275	2.8	2.64 (1.63–4.25)	3.23 (1.71–6.09)
INR ≥3	10	4.9	58	0.6	4.90 (2.40–10.02)	4.96 (2.20–11.15)
Unknown INR	17	8.3	202	2.0	3.31 (1.93–5.68)	4.42 (2.24–8.75)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	31	15.1	3159	31.6	1 (–)	1 (–)
Both drugs	10	4.9	51	0.5	8.11 (3.64–18.10)	8.63 (3.57–20.86)
Low-dose ASA monotherapy	70	34.1	3760	37.6	1.35 (0.87–2.09)	1.25 (0.79–1.96)
Warfarin monotherapy	35	17.1	397	4.0	3.71 (2.18–6.31)	3.53 (1.85–6.75)
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	54	26.3	4573	45.7	1 (–)	1 (–)
Both drugs	10	4.9	51	0.5	7.50 (3.49–16.13)	8.02 (3.44–18.71)
Low-dose ASA monotherapy	70	34.1	3760	37.6	1.23 (0.85–1.78)	1.13 (0.77–1.65)
Warfarin monotherapy	35	17.1	397	4.0	3.39 (2.12–5.41)	3.27 (1.81–5.92)
PPI						
Never use	85	41.5	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	53	25.9	1893	18.9	1.24 (0.87–1.79)	1.31 (0.90–1.90)
Recent use (8–90 days)	12	5.9	381	3.8	1.44 (0.77–2.69)	1.71 (0.90–3.25)
Past use (91–365)	14	6.8	485	4.9	1.40 (0.78–2.52)	1.40 (0.77–2.57)
Distant use (>365 days)	41	20.0	1570	15.7	1.43 (0.97–2.11)	1.46 (0.98–2.17)

Medication use	Non-traumatic SDH N=205		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
H_2RA						
Never use	155	75.6	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	3	1.5	218	2.2	0.59 (0.18–1.86)	0.64 (0.20–2.07)
Recent use (8–90 days)	1	0.5	75	0.8	0.56 (0.08–4.13)	0.51 (0.07–3.90)
Past use (91–365)	6	2.9	112	1.1	2.14 (0.91–5.02)	2.34 (0.96–5.70)
Distant use (>365 days)	40	19.5	1844	18.4	0.88 (0.62–1.26)	0.83 (0.58–1.21)
SSRI						
Never use	168	82.0	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	12	5.9	441	4.4	1.20 (0.65–2.20)	1.33 (0.72–2.48)
Duration <91 days	1	0.5	67	0.7	0.54 (0.07–3.94)	0.51 (0.07–3.83)
Duration 90–365 days	1	0.5	96	1.0	0.39 (0.05–2.86)	0.50 (0.07–3.68)
Duration >365 days	10	4.9	276	2.8	1.78 (0.91–3.46)	1.96 (0.99–3.88)
Recent use (8–90 days)	4	2.0	106	1.1	1.53 (0.55–4.28)	1.71 (0.60–4.85)
Past use (91–365)	4	2.0	141	1.4	1.19 (0.43–3.28)	1.37 (0.49–3.85)
Distant use (>365 days)	17	8.3	1034	10.3	0.77 (0.46–1.29)	0.81 (0.48–1.36)
NSAIDs						
Never use	56	27.3	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	12	5.9	642	6.4	0.87 (0.46–1.65)	1.17 (0.61–2.25)
Duration <91 days	8	3.9	186	1.9	2.13 (0.98–4.60)	2.84 (1.29–6.26)
Duration 90–365 days	1	0.5	148	1.5	0.33 (0.04–2.38)	0.40 (0.05–3.00)
Duration >365 days	3	1.5	306	3.1	0.44 (0.14–1.42)	0.61 (0.19–1.99)
Recent use (8–90 days)	6	2.9	454	4.5	0.56 (0.24–1.31)	0.78 (0.33–1.86)
Past use (91–365)	12	5.9	892	8.9	0.54 (0.29–1.03)	0.68 (0.35–1.30)
Distant use (>365 days)	119	58.0	5156	51.6	1.00 (0.72–1.39)	1.06 (0.76–1.49)
Acetaminophen						
Never use	49	23.9	3050	30.5	1 (–)	
Current use (0–7 days)	56	27.3	1537	15.4	1.49 (0.99–2.25)	1.64 (1.07–2.51)
Duration <91 days	25	12.2	402	4.1	2.48 (1.48–4.14)	2.74 (1.61–4.65)
Duration 90–365 days	11	5.4	346	3.5	1.22 (0.61–2.41)	1.19 (0.58–2.42)
Duration >365 days	20	9.8	783	7.9	1.05 (0.61–1.82)	1.25 (0.71–2.20)
Recent use (8–90 days)	29	14.1	1140	11.4	1.15 (0.71–1.86)	1.22 (0.74–2.00)
Past use (91–365)	19	9.3	1061	10.6	0.79 (0.46–1.36)	0.84 (0.48–1.48)
Distant use (>365 days)	52	25.4	3212	32.1	0.83 (0.56–1.24)	0.82 (0.54–1.23)
Oral steroids						
Never use	159	77.6	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	6	2.9	262	2.6	0.67 (0.29–1.54)	0.69 (0.29–1.64)
Recent use (8–90 days)	4	2.0	161	1.6	0.69 (0.25–1.92)	0.69 (0.24–1.95)
Past use (91–365)	8	3.9	284	2.8	0.91 (0.44–1.90)	0.94 (0.44–1.97)
Distant use (>365 days)	28	13.7	1254	12.5	0.86 (0.57–1.30)	0.84 (0.55–1.29)
Inhaled steroids						
Never use	171	83.4	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	10	4.9	624	6.2	0.55 (0.29–1.06)	0.53 (0.27–1.02)
Recent use (8–90 days)	0	0.0	218	2.2	NA	NA
Past use (91–365)	5	2.4	150	1.5	1.21 (0.49–3.04)	1.38 (0.54–3.55)
Distant use (>365 days)	19	9.3	645	6.5	1.19 (0.73–1.94)	1.23 (1.95–11.11)

Medication use	**Non-traumatic SDH N=205**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Antihypertensive medications						
Never use	29	14.1	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	135	65.9	6288	62.9	0.86 (0.56–1.32)	0.84 (0.50–1.43)
Recent use (8–90 days)	19	9.3	505	5.1	1.46 (0.79–2.68)	1.60 (0.81–3.14)
Past use (91–365)	9	4.4	224	2.2	1.75 (0.80–3.83)	1.67 (0.74–3.81)
Distant use (>365 days)	13	6.3	832	8.3	0.86 (0.44–1.68)	0.82 (0.41–1.64)
Statins						
Never use	72	35.1	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	86	42.0	4038	40.4	0.89 (0.64–1.24)	0.80 (0.55–1.16)
Duration <91 days	8	3.9	297	3.0	1.16 (0.55–2.47)	1.11 (0.51–2.43)
Duration 90–365 days	11	5.4	630	6.3	0.68 (0.36–1.31)	0.60 (0.30–1.19)
Duration >365 days	67	32.7	3111	31.1	0.91 (0.64–1.29)	0.82 (0.55–1.22)
Recent use (8–90 days)	20	9.8	523	5.2	1.61 (0.96–2.71)	1.65 (0.94–2.91)
Past use (91–365)	14	6.8	224	2.2	2.52 (1.37–4.62)	2.57 (1.34–4.95)
Distant use (>365 days)	13	6.3	511	5.1	1.21 (0.65–2.23)	1.19 (0.63–2.27)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 42. Frequency of specific medication use among traumatic SDH cases and controls, and association (RRs with 95% CIs) with traumatic SDH.

Medication use	Traumatic SDH cases N=278 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	64	23.0	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	126	45.3	3852	38.5	1.32 (0.97–1.81)	1.39 (1.00–1.93)
Recent use (8–90 days)	18	6.5	656	6.6	1.07 (0.62–1.83)	1.06 (0.61–1.83)
Past use (91–365)	19	6.8	492	4.9	1.45 (0.85–2.46)	1.34 (0.78–2.30)
Distant use (>365 days)	51	18.3	1656	16.6	1.12 (0.77–1.64)	0.99 (0.67–1.47)
Duration of low-dose ASA among current users						
<3 months	12	4.3	362	3.6	1.57 (0.83–2.97)	1.96 (1.10–3.48)
3–<6 months	12	4.3	253	2.5	2.07 (1.09–3.93)	1.60 (0.80–3.21)
6 months–<1 year	16	5.8	432	4.3	1.62 (0.92–2.86)	1.46 (0.81–2.62)
1–<5 years	52	18.7	1949	19.5	1.14 (0.78–1.66)	0.99 (0.67–1.47)
≥5 years	34	12.2	856	8.6	1.30 (0.84–2.01)	1.35 (0.86–2.11)
Duration of low-dose ASA among recent users						
<3 months	3	1.1	145	1.5	0.86 (0.26–2.78)	1.05 (0.37–2.98)
3–<6 months	1	0.4	94	0.9	0.49 (0.07–3.58)	1.46 (0.44–4.81)
6 months–<1 year	4	1.4	98	1.0	1.59 (0.56–4.50)	1.44 (0.50–4.14)
1–<5 years	9	3.2	229	2.3	1.56 (0.76–3.21)	1.91 (0.98–3.72)
≥5 years	1	0.4	90	0.9	0.32 (0.04–2.37)	0.63 (0.15–2.66)
Low-dose ASA dose among current users						
75 mg	117	42.1	3660	36.6	1.29 (0.94–1.77)	1.23 (0.89–1.71)
150 mg	8	2.9	164	1.6	2.15 (1.00–4.59)	1.78 (0.79–4.03)
300 mg	1	0.4	28	0.3	1.35 (0.18–10.21)	1.08 (0.14–8.26)
Clopidogrel						
Never use	245	88.1	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	19	6.8	326	3.3	1.60 (0.99–2.61)	1.63 (0.99–2.70)
Recent use (8–90 days)	2	0.7	55	0.5	1.00 (0.24–4.15)	0.98 (0.23–4.14)
Past use (91–365)	2	0.7	118	1.2	0.47 (0.11–1.92)	0.36 (0.09–1.50)
Distant use (>365 days)	10	3.6	389	3.9	0.75 (0.39–1.42)	0.67 (0.35–1.29)

Medication use	Traumatic SDH cases N=278 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	62	22.3	3289	32.9	1 (–)	1 (–)
DAT	9	3.2	139	1.4	2.13 (1.02–4.42)	2.29 (1.09–4.80)
Low-dose ASA monotherapy	114	41.0	3609	36.1	1.30 (0.95–1.80)	1.31 (0.94–1.84)
Clopidogrel monotherapy	7	2.5	144	1.4	1.64 (0.73–3.67)	1.50 (0.65–3.44)
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	139	50.0	4376	43.8	1 (–)	1 (–)
DAT	9	3.2	139	1.4	1.62 (0.80–3.27)	1.76 (0.86–3.58)
Low-dose ASA monotherapy	7	2.5	259	2.6	0.73 (0.34–1.59)	0.73 (0.34–1.60)
Clopidogrel monotherapy	7	2.5	144	1.4	1.24 (0.57–2.72)	1.15 (0.52–2.55)
Warfarin						
Never use	221	79.5	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	36	12.9	535	5.3	1.66 (1.13–2.44)	1.48 (0.87–2.52)
Recent use (31–365 days)	5	1.8	83	0.8	1.63 (0.65–4.10)	1.54 (0.58–4.04)
Past use (>365 days)	16	5.8	262	2.6	2.16 (1.27–3.66)	1.97 (1.13–3.44)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	16	5.8	275	2.8	1.31 (0.76–2.26)	1.14 (0.59–2.22)
INR ≥3	5	1.8	58	0.6	1.97 (0.77–5.03)	1.76 (0.65–4.77)
Unknown INR	15	5.4	202	2.0	2.12 (1.22–3.69)	1.95 (1.00–3.77)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	49	17.6	3159	31.6	1 (–)	1 (–)
Both drugs	3	1.1	51	0.5	2.07 (0.62–6.99)	1.55 (0.43–5.56)
Low-dose ASA monotherapy	120	43.2	3760	37.6	1.57 (1.11–2.22)	1.59 (1.11–2.27)
Warfarin monotherapy	29	10.4	397	4.0	2.35 (1.43–3.88)	1.74 (0.95–3.16)

Medication use	Traumatic SDH cases N=278 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	85	30.6	4573	45.7	1 (–)	1 (–)
Both drugs	3	1.1	51	0.5	1.92 (0.58–6.36)	1.47 (0.42–5.20)
Low-dose ASA monotherapy	120	43.2	3760	37.6	1.45 (1.08–1.93)	1.48 (1.10–2.00)
Warfarin monotherapy	29	10.4	397	4.0	2.16 (1.37–3.41)	1.64 (0.94–2.88)
PPI						
Never use	138	49.6	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	64	23.0	1895	18.9	0.93 (0.68–1.28)	0.94 (0.68–1.29)
Recent use (8–90 days)	11	4.0	381	3.8	0.83 (0.44–1.55)	0.87 (0.46–1.64)
Past use (91–365)	13	4.7	485	4.9	0.79 (0.44–1.41)	0.80 (0.45–1.45)
Distant use (>365 days)	52	18.7	1570	15.7	1.05 (0.75–1.46)	1.04 (0.74–1.45)
H_2RA						
Never use	203	73.0	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	7	2.5	218	2.2	1.04 (0.48–2.24)	1.11 (0.51–2.41)
Recent use (8–90 days)	1	0.4	75	0.8	0.46 (0.06–3.37)	0.46 (0.06–3.34)
Past use (91–365)	3	1.1	112	1.1	0.88 (0.28–2.82)	0.96 (0.30–3.08)
Distant use (>365 days)	64	23.0	1844	18.4	1.12 (0.84–1.49)	1.12 (0.83–1.50)
SSRI						
Never use	209	75.2	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	23	8.3	441	4.4	1.78 (1.14–2.80)	1.79 (1.13–2.83)
Duration <91 days	7	2.5	67	0.7	3.33 (1.49–7.45)	3.03 (1.33–6.91)
Duration 90–365 days	7	2.5	97	1.0	2.34 (1.06–5.18)	2.34 (1.05–5.23)
Duration >365 days	9	3.2	277	2.8	1.15 (0.58–2.29)	1.20 (0.60–2.39)
Recent use (8–90 days)	5	1.8	106	1.1	1.61 (0.64–4.04)	1.48 (0.58–3.80)
Past use (91–365)	7	2.5	141	1.4	1.69 (0.77–3.69)	1.76 (0.80–3.88)
Distant use (>365 days)	34	12.2	1034	10.3	1.21 (0.83–1.76)	1.17 (0.80–1.71)
NSAIDs						
Never use	60	21.6	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	13	4.7	642	6.4	0.90 (0.49–1.65)	1.01 (0.54–1.89)
Duration <91 days	6	2.2	186	1.9	1.50 (0.64–3.54)	1.70 (0.71–4.06)
Duration 90–365 days	4	1.4	148	1.5	1.21 (0.43–3.40)	1.33 (0.47–3.78)
Duration >365 days	3	1.1	308	3.1	0.42 (0.13–1.37)	0.49 (0.15–1.59)
Recent use (8–90 days)	6	2.2	454	4.5	0.54 (0.23–1.26)	0.65 (0.28–1.52)
Past use (91–365)	19	6.8	892	8.9	0.86 (0.51–1.45)	0.94 (0.55–1.60)
Distant use (>365 days)	180	64.7	5156	51.6	1.42 (1.05–1.91)	1.49 (1.10–2.02)

Medication use	Traumatic SDH cases N=278 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Acetaminophen						
Never use	59	21.2	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	59	21.2	1537	15.4	1.30 (0.88–1.91)	1.46 (0.98–2.16)
Duration <91 days	26	9.4	402	4.0	2.20 (1.35–3.59)	2.37 (1.45–3.89)
Duration 90–365 days	11	4.0	348	3.5	1.04 (0.53–2.02)	1.06 (0.54–2.10)
Duration >365 days	22	7.9	787	7.9	0.94 (0.56–1.57)	1.10 (0.66–1.86)
Recent use (8–90 days)	33	11.9	1140	11.4	1.05 (0.67–1.64)	1.15 (0.73–1.80)
Past use (91–365)	40	14.4	1061	10.6	1.40 (0.92–2.13)	1.53 (1.00–2.35)
Distant use (>365 days)	87	31.3	3212	32.1	1.12 (0.80–1.58)	1.16 (0.82–1.64)
Oral steroids						
Never use	222	79.9	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	5	1.8	262	2.6	0.44 (0.18–1.09)	0.47 (0.19–1.16)
Recent use (8–90 days)	4	1.4	161	1.6	0.56 (0.20–1.54)	0.58 (0.21–1.60)
Past use (91–365)	10	3.6	284	2.8	0.88 (0.46–1.68)	0.89 (0.46–1.73)
Distant use (>365 days)	37	13.3	1254	12.5	0.82 (0.57–1.17)	0.82 (0.57–1.19)
Inhaled steroids						
Never use	235	84.5	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	13	4.7	624	6.2	0.58 (0.33–1.02)	0.61 (0.35–1.09)
Recent use (8–90 days)	5	1.8	218	2.2	0.64 (0.26–1.57)	0.67 (0.27–1.66)
Past use (91–365)	6	2.2	150	1.5	1.18 (0.51–2.71)	1.27 (0.54–2.95)
Distant use (>365 days)	19	6.8	645	6.5	0.87 (0.54–1.40)	0.91 (0.56–1.47)
Antihypertensive medications						
Never use	38	13.7	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	171	61.5	6288	62.9	0.92 (0.63–1.34)	0.66 (0.41–1.04)
Recent use (8–90 days)	24	8.6	505	5.1	1.60 (0.94–2.74)	1.40 (0.77–2.54)
Past use (91–365)	13	4.7	224	2.2	2.03 (1.05–3.92)	1.58 (0.79–3.17)
Distant use (>365 days)	32	11.5	832	8.3	1.62 (1.00–2.63)	1.41 (0.85–2.32)
Statins						
Never use	111	39.9	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	123	44.2	4038	40.4	0.90 (0.68–1.18)	0.76 (0.56–1.04)
Duration <91 days	9	3.2	297	3.0	0.95 (0.47–1.90)	0.76 (0.37–1.57)
Duration 90–365 days	18	6.5	630	6.3	0.84 (0.50–1.41)	0.66 (0.38–1.12)
Duration >365 days	96	34.5	3111	31.1	0.91 (0.68–1.21)	0.79 (0.57–1.09)
Recent use (8–90 days)	19	6.8	523	5.2	1.08 (0.65–1.79)	1.00 (0.59–1.71)
Past use (91–365)	7	2.5	224	2.2	0.93 (0.43–2.04)	0.85 (0.38–1.89)
Distant use (>365 days)	18	6.5	511	5.1	1.05 (0.63–1.76)	0.99 (0.58–1.69)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.
[‡]IHD does not include myocardial infarction.

Table 43. Frequency of specific medication use among SAH cases and controls, and association (RRs with 95% CIs) with SAH.

Medication use	Cases of SAH N=385 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	147	38.2	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	126	32.7	3852	38.5	0.81 (0.63–1.05)	0.77 (0.58–1.01)
Recent use (8–90 days)	29	7.5	656	6.6	1.09 (0.72–1.66)	1.11 (0.73–1.70)
Past use (91–365)	19	4.9	492	4.9	0.86 (0.52–1.42)	0.85 (0.51–1.41)
Distant use (>365 days)	64	16.6	1656	16.6	0.93 (0.68–1.27)	0.90 (0.65–1.24)
Duration of low-dose ASA among current users						
<3 months	18	4.7	362	3.6	1.01 (0.61–1.69)	1.01 (0.60–1.70)
3–<6 months	14	3.6	253	2.5	1.31 (0.74–2.34)	1.23 (0.68–2.25)
6 months–<1 year	15	3.9	432	4.3	0.77 (0.44–1.33)	0.71 (0.40–1.26)
1–<5 years	56	14.5	1949	19.5	0.72 (0.52–0.99)	0.67 (0.47–0.94)
≥5 years	23	6.0	856	8.6	0.79 (0.50–1.25)	0.73 (0.45–1.18)
Duration of low-dose ASA among recent users						
<3 months	9	2.3	145	1.5	1.39 (0.69–2.82)	1.42 (0.69–2.91)
3–<6 months	4	1.0	94	0.9	0.90 (0.32–2.51)	0.99 (0.35–2.79)
6 months–<1 year	3	0.8	98	1.0	0.75 (0.23–2.42)	0.73 (0.22–2.37)
1–<5 years	12	3.1	229	2.3	1.39 (0.75–2.57)	1.43 (0.77–2.67)
≥5 years	1	0.3	90	0.9	0.35 (0.05–2.53)	0.32 (0.04–2.38)
Low-dose ASA dose among current users						
75 mg	114	29.6	3660	36.6	0.77 (0.60–1.00)	0.73 (0.56–0.97)
150 mg	10	2.6	164	1.6	1.52 (0.78–2.97)	1.37 (0.69–2.74)
300 mg	2	0.5	28	0.3	1.65 (0.38–7.17)	1.26 (0.23–6.99)
Clopidogrel						
Never use	347	90.1	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	16	4.2	326	3.3	1.34 (0.80–2.26)	1.33 (0.78–2.28)
Recent use (8–90 days)	1	0.3	55	0.5	0.52 (0.07–3.84)	0.41 (0.05–3.17)
Past use (91–365)	3	0.8	118	1.2	0.58 (0.18–1.85)	0.57 (0.18–1.84)
Distant use (>365 days)	18	4.7	389	3.9	1.38 (0.84–2.26)	1.39 (0.84–2.32)

Medication use	**Cases of SAH N=385 (%)**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	144	37.4	3289	32.9	1 (–)	1 (–)
DAT	7	1.8	139	1.4	1.07 (0.48–2.36)	1.09 (0.49–2.45)
Low-dose ASA monotherapy	117	30.4	3609	36.1	0.82 (0.63–1.07)	0.78 (0.59–1.03)
Clopidogrel monotherapy	5	1.3	144	1.4	0.98 (0.39–2.44)	0.83 (0.32–2.12)
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	147	38.2	4376	43.8	1 (–)	1 (–)
DAT	7	1.8	139	1.4	1.28 (0.58–2.82)	1.35 (0.61–3.00)
Low-dose ASA monotherapy	10	2.6	259	2.6	1.27 (0.66–2.46)	1.14 (0.58–2.25)
Clopidogrel monotherapy	5	1.3	144	1.4	1.17 (0.47–2.93)	1.03 (0.41–2.60)
Warfarin						
Never use	353	91.7	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	21	5.5	535	5.3	1.27 (0.79–2.03)	1.79 (0.97–3.29)
Recent use (31–365 days)	1	0.3	83	0.8	0.37 (0.05–2.66)	0.52 (0.07–3.91)
Past use (>365 days)	10	2.6	262	2.6	1.15 (0.60–2.19)	1.25 (0.64–2.43)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	7	1.8	275	2.8	0.84 (0.39–1.83)	1.23 (0.51–2.98)
INR ≥3	4	1.0	58	0.6	2.19 (0.77–6.22)	2.76 (0.91–8.38)
Unknown INR	10	2.6	202	2.0	1.57 (0.81–3.02)	2.16 (1.02–4.60)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	138	35.8	3159	31.6	1 (–)	1 (–)
Both drugs	0	0.0	51	0.5	NA	NA
Low-dose ASA monotherapy	125	32.5	3760	37.6	0.84 (0.65–1.09)	0.78 (0.59–1.03)
Warfarin monotherapy	17	4.4	397	4.0	1.28 (0.74–2.20)	1.71 (0.89–3.32)

Medication use	Cases of SAH N=385 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA/warfarin (no use in the year before the index date as reference)						
No low-dose ASA, no warfarin	194	50.4	4573	45.7	1 (–)	1 (–)
Both drugs	0	0.0	51	0.5	NA	NA
Low-dose ASA monotherapy	125	32.5	3760	37.6	0.86 (0.67–1.09)	0.81 (0.63–1.04)
Warfarin monotherapy	17	4.4	397	4.0	1.31 (0.77–2.23)	1.81 (0.95–3.45)
PPI						
Never use	214	55.6	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	58	15.1	1895	18.9	0.87 (0.64–1.19)	0.85 (0.61–1.17)
Recent use (8–90 days)	27	7.0	381	3.8	1.92 (1.25–2.94)	1.97 (1.27–3.07)
Past use (91–365)	20	5.2	485	4.9	1.08 (0.67–1.74)	1.13 (0.70–1.84)
Distant use (>365 days)	66	17.1	1570	15.7	1.17 (0.88–1.57)	1.11 (0.82–1.49)
H_2RA						
Never use	312	81.0	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	8	2.1	218	2.2	0.94 (0.45–1.93)	1.02 (0.49–2.11)
Recent use (8–90 days)	2	0.5	75	0.8	0.65 (0.16–2.66)	0.54 (0.12–2.32)
Past use (91–365)	3	0.8	112	1.1	0.59 (0.18–1.88)	0.58 (0.18–1.88)
Distant use (>365 days)	60	15.6	1844	18.4	0.80 (0.60–1.06)	0.75 (0.56–1.01)
SSRI						
Never use	261	67.8	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	33	8.6	441	4.4	1.97 (1.34–2.89)	1.84 (1.23–2.74)
Duration <91 days	4	1.0	67	0.7	1.63 (0.58–4.55)	1.31 (0.44–3.91)
Duration 90–365 days	7	1.8	97	1.0	1.69 (0.77–3.74)	1.44 (0.63–3.29)
Duration >365 days	22	5.7	277	2.8	2.15 (1.35–3.41)	2.15 (1.33–3.45)
Recent use (8–90 days)	7	1.8	106	1.1	1.58 (0.72–3.47)	1.52 (0.69–3.39)
Past use (91–365)	14	3.6	141	1.4	2.53 (1.42–4.50)	2.21 (1.21–4.02)
Distant use (>365 days)	70	18.2	1034	10.3	1.75 (1.32–2.33)	1.63 (1.22–2.17)
NSAIDs						
Never use	121	31.4	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	31	8.1	642	6.4	0.99 (0.66–1.50)	1.08 (0.71–1.65)
Duration <91 days	9	2.3	186	1.9	1.00 (0.50–2.02)	1.08 (0.53–2.20)
Duration 90–365 days	8	2.1	148	1.5	1.03 (0.49–2.18)	1.20 (0.56–2.56)
Duration >365 days	14	3.6	308	3.1	0.97 (0.54–1.71)	1.04 (0.58–1.86)
Recent use (8–90 days)	23	6.0	454	4.5	0.98 (0.61–1.56)	0.99 (0.61–1.59)
Past use (91–365)	28	7.3	892	8.9	0.61 (0.40–0.94)	0.61 (0.39–0.94)
Distant use (>365 days)	182	47.3	5156	51.6	0.79 (0.62–1.01)	0.79 (0.62–1.01)

Medication use	Cases of SAH N=385 (%)		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Acetaminophen						
Never use	98	25.5	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	67	17.4	1537	15.4	1.57 (1.12–2.20)	1.49 (1.05–2.11)
Duration <91 days	23	6.0	402	4.0	2.00 (1.24–3.24)	1.97 (1.20–3.24)
Duration 90–365 days	12	3.1	348	3.5	1.21 (0.65–2.25)	1.17 (0.62–2.20)
Duration >365 days	32	8.3	787	7.9	1.49 (0.98–2.28)	1.35 (0.87–2.10)
Recent use (8–90 days)	48	12.5	1140	11.4	1.46 (1.01–2.12)	1.43 (0.98–2.08)
Past use (91–365)	41	10.6	1061	10.6	1.25 (0.85–1.83)	1.19 (0.80–1.75)
Distant use (>365 days)	131	34.0	3212	32.1	1.33 (1.01–1.75)	1.25 (0.94–1.65)
Oral steroids						
Never use	309	80.3	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	9	2.3	262	2.6	0.90 (0.45–1.79)	0.85 (0.42–1.72)
Recent use (8–90 days)	10	2.6	161	1.6	1.62 (0.83–3.15)	1.52 (0.77–2.99)
Past use (91–365)	13	3.4	284	2.8	1.10 (0.62–1.96)	1.06 (0.59–1.91)
Distant use (>365 days)	44	11.4	1254	12.5	0.95 (0.69–1.32)	0.90 (0.65–1.26)
Inhaled steroids						
Never use	323	83.9	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	14	3.6	624	6.2	0.54 (0.31–0.95)	0.56 (0.32–0.98)
Recent use (8–90 days)	13	3.4	218	2.2	1.59 (0.91–2.79)	1.51 (0.84–2.74)
Past use (91–365)	7	1.8	150	1.5	1.15 (0.55–2.38)	0.95 (0.43–2.09)
Distant use (>365 days)	28	7.3	645	6.5	1.03 (0.69–1.53)	1.05 (0.70–1.58)
Antihypertensive medications						
Never use	102	26.5	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	188	48.8	6288	62.9	0.68 (0.52–0.89)	0.48 (0.33–0.70)
Recent use (8–90 days)	26	6.8	505	5.1	1.28 (0.83–1.97)	0.82 (0.49–1.38)
Past use (91–365)	12	3.1	224	2.2	1.14 (0.61–2.13)	0.92 (0.48–1.79)
Distant use (>365 days)	57	14.8	832	8.3	1.37 (0.97–1.93)	1.27 (0.89–1.83)
Statins						
Never use	202	52.5	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	137	35.6	4038	40.4	0.83 (0.65–1.05)	0.83 (0.62–1.09)
Duration <91 days	17	4.4	297	3.0	1.22 (0.72–2.05)	1.31 (0.76–2.26)
Duration 90–365 days	24	6.2	630	6.3	0.87 (0.56–1.36)	0.89 (0.56–1.43)
Duration >365 days	96	24.9	3111	31.1	0.78 (0.60–1.01)	0.75 (0.56–1.02)
Recent use (8–90 days)	22	5.7	523	5.2	1.08 (0.69–1.68)	0.92 (0.56–1.50)
Past use (91–365)	11	2.9	224	2.2	1.21 (0.66–2.23)	1.07 (0.55–2.07)
Distant use (>365 days)	13	3.4	511	5.1	0.69 (0.39–1.20)	0.59 (0.32–1.06)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 44. Frequency of specific medication use among SAH cases and controls, and association (RRs with 95% CIs) with SAH, stratified by sex.

Low-dose ASA Men	**SAH cases N=155**		**Controls N=5164**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	47	30.3	1639	31.7	1 (–)	1 (–)
Current and recent use (0–90 days)	75	48.4	2470	47.8	1.03 (0.69–1.53)	1.14 (0.74–1.74)
Current use (0–7 days)	64	41.3	2120	41.1	1.02 (0.68–1.53)	1.13 (0.73–1.74)
Recent use (8–90 days)	11	7.1	350	6.8	1.07 (0.54–2.13)	1.20 (0.60–2.42)
Past use (91–365)	9	5.8	249	4.8	1.03 (0.49–2.17)	1.12 (0.52–2.39)
Distant use (>365 days)	24	15.5	806	15.6	1.05 (0.63–1.75)	1.12 (0.66–1.91)
Low-dose ASA Women	**SAH cases N=230**		**Controls N=4836**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	100	43.5	1705	35.3	1 (–)	1 (–)
Current and recent use (0–90 days)	80	34.8	2038	42.1	0.74 (0.54–1.02)	0.65 (0.46–0.91)
Current use (0–7 days)	62	27.0	1732	35.8	0.68 (0.48–0.95)	0.57 (0.39–0.82)
Recent use (8–90 days)	18	7.8	306	6.3	1.12 (0.66–1.90)	1.09 (0.63–1.88)
Past use (91–365)	10	4.3	243	5.0	0.73 (0.37–1.44)	0.70 (0.35–1.39)
Distant use (>365 days)	40	17.4	850	17.6	0.89 (0.60–1.31)	0.79 (0.52–1.19)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 45. Frequency of specific medication use among SAH cases and controls, and association (RRs with 95% CIs) with SAH, stratified by case-fatality status (fatal case = death within 30 days following the event).

Low-dose ASA Fatal cases	**SAH cases N=117**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	56	47.9	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	43	36.8	4508	45.1	0.58 (0.38–0.89)	0.58 (0.37–0.92)
Current use (0–7 days)	29	24.8	3852	38.5	0.46 (0.29–0.74)	0.45 (0.27–0.74)
Recent use (8–90 days)	14	12.0	656	6.6	1.27 (0.69–2.34)	1.29 (0.69–2.43)
Past use (91–365)	4	3.4	492	4.9	0.46 (0.16–1.29)	0.41 (0.14–1.18)
Distant use (>365 days)	14	12.0	1656	16.6	0.68 (0.37–1.24)	0.60 (0.32–1.13)
Duration among current users						
≤6 months	11	9.4	615	6.2	0.82 (0.42–1.61)	0.84 (0.42–1.68)
>6 months	18	15.4	3237	32.4	0.36 (0.21–0.63)	0.34 (0.19–0.61)
Low-dose ASA Non-fatal cases	**SAH cases N=268**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	91	34.0	3344	33.4	1 (–)	1 (–)
Current and recent use (0–90 days)	112	41.8	4508	45.1	1.01 (0.75–1.37)	0.95 (0.69–1.31)
Current use (0–7 days)	97	36.2	3852	38.5	1.03 (0.76–1.39)	0.95 (0.69–1.33)
Recent use (8–90 days)	15	5.6	656	6.6	0.94 (0.54–1.66)	0.95 (0.54–1.69)
Past use (91–365)	15	5.6	492	4.9	1.11 (0.63–1.96)	1.14 (0.64–2.02)
Distant use (>365 days)	50	18.7	1656	16.6	1.08 (0.75–1.55)	1.07 (0.73–1.55)
Duration among current users						
≤6 months	21	7.8	615	6.2	1.32 (0.80–2.17)	1.25 (0.75–2.09)
>6 months	76	28.4	3237	32.4	0.97 (0.70–1.34)	0.89 (0.63–1.26)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 46. Frequency of specific medication use among non-traumatic SAH cases and controls, and association (RRs with 95% CIs) with non-traumatic SAH.

Medication use	**Non-traumatic SAH cases N=311**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Low-dose ASA						
Never use	123	39.5	3344	33.4	1 (–)	1 (–)
Current use (0–7 days)	91	29.3	3852	38.5	0.73 (0.54–0.97)	0.66 (0.48–0.90)
Recent use (8–90 days)	26	8.4	656	6.6	1.22 (0.78–1.91)	1.23 (0.78–1.94)
Past use (91–365)	15	4.8	492	4.9	0.83 (0.48–1.45)	0.80 (0.46–1.42)
Distant use (>365 days)	56	18.0	1656	16.6	1.06 (0.76–1.48)	1.01 (0.71–1.43)
Duration of low-dose ASA among current users						
<3 months	15	4.8	362	3.6	0.98 (0.56–1.72)	0.96 (0.54–1.70)
3–<6 months	11	3.5	253	2.5	1.23 (0.64–2.35)	1.18 (0.60–2.32)
6 months–<1 year	9	2.9	432	4.3	0.55 (0.27–1.10)	0.48 (0.23–1.00)
1–<5 years	42	13.5	1949	19.5	0.66 (0.46–0.95)	0.58 (0.39–0.86)
≥5 years	14	4.5	856	8.6	0.67 (0.38–1.20)	0.59 (0.32–1.06)
Duration of low-dose ASA among recent users						
<3 months	9	2.9	145	1.5	1.69 (0.83–3.46)	1.69 (0.82–3.50)
3–<6 months	4	1.3	94	0.9	1.06 (0.38–2.98)	1.18 (0.42–3.36)
6 months–<1 year	2	0.6	98	1.0	0.61 (0.15–2.55)	0.58 (0.14–2.44)
1–<5 years	10	3.2	229	2.3	1.48 (0.76–2.90)	1.55 (0.78–3.07)
≥5 years	1	0.3	90	0.9	0.51 (0.07–3.70)	0.46 (0.06–3.38)
Low-dose ASA dose among current users						
75 mg	83	26.7	3660	36.6	0.70 (0.52–0.94)	0.64 (0.46–0.88)
150 mg	7	2.3	164	1.6	1.30 (0.59–2.87)	1.09 (0.48–2.47)
300 mg	1	0.3	28	0.3	1.03 (0.13–7.82)	0.51 (0.04–5.93)
Clopidogrel						
Never use	282	90.7	9112	91.1	1 (–)	1 (–)
Current use (0–7 days)	10	3.2	326	3.3	1.14 (0.59–2.18)	1.09 (0.56–2.12)
Recent use (8–90 days)	1	0.3	55	0.5	0.69 (0.09–5.08)	0.51 (0.06–3.96)
Past use (91–365)	3	1.0	118	1.2	0.73 (0.23–2.35)	0.76 (0.23–2.47)
Distant use (>365 days)	15	4.8	389	3.9	1.55 (0.91–2.67)	1.63 (0.93–2.86)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	120	38.6	3289	32.9	1 (–)	1 (–)
DAT	3	1.0	139	1.4	0.60 (0.19–1.95)	0.62 (0.19–2.03)
Low-dose ASA monotherapy	86	27.7	3609	36.1	0.75 (0.56–1.01)	0.69 (0.51–0.95)
Clopidogrel monotherapy	3	1.0	144	1.4	0.81 (0.25–2.61)	0.64 (0.19–2.10)

Medication use	**Non-traumatic SAH cases N=311**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Low-dose ASA/clopidogrel (no use in the year prior as reference)						
No low-dose ASA, no clopidogrel	111	35.7	4376	43.8	1 (–)	1 (–)
DAT	3	1.0	139	1.4	0.77 (0.24–2.49)	0.84 (0.26–2.73)
Low-dose ASA monotherapy	9	2.9	259	2.6	1.66 (0.82–3.35)	1.51 (0.73–3.12)
Clopidogrel monotherapy	3	1.0	144	1.4	1.04 (0.33–3.35)	0.87 (0.27–2.84)
Warfarin						
Never use	287	92.3	9120	91.2	1 (–)	1 (–)
Current use (0–30 days)	17	5.5	535	5.3	1.45 (0.86–2.44)	1.80 (0.91–3.58)
Recent use (31–365 days)	0	0.0	83	0.8	NA	NA
Past use (>365 days)	7	2.3	262	2.6	1.04 (0.48–2.24)	1.07 (0.48–2.38)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	5	1.6	275	2.8	0.88 (0.35–2.20)	1.16 (0.41–3.24)
INR ≥3	4	1.3	58	0.6	3.15 (1.10–9.07)	3.62 (1.15–11.37)
Unknown INR	8	2.6	202	2.0	1.68 (0.81–3.49)	2.04 (0.87–4.77)
Low-dose ASA/warfarin (never use as reference)						
No low-dose ASA, no warfarin	118	37.9	3159	31.6	1 (–)	1 (–)
Both drugs	0	0.0	51	0.5	NA	NA
Low-dose ASA monotherapy	91	29.3	3760	37.6	0.74 (0.55–1.00)	0.65 (0.47–0.89)
Warfarin monotherapy	13	4.2	397	4.0	1.34 (0.72–2.48)	1.61 (0.77–3.40)
Low-dose ASA/warfarin (no use in the year prior as reference)						
No low-dose ASA, no warfarin	166	53.4	4573	45.7	1 (–)	1 (–)
Both drugs	0	0.0	51	0.5	NA	NA
Low-dose ASA monotherapy	91	29.3	3760	37.6	0.74 (0.56–0.97)	0.66 (0.49–0.89)
Warfarin monotherapy	13	4.2	397	4.0	1.34 (0.73–2.45)	1.66 (0.80–3.44)
PPI						
Never use	173	55.6	5669	56.7	1 (–)	1 (–)
Current use (0–7 days)	46	14.8	1895	18.9	0.95 (0.67–1.35)	0.93 (0.65–1.34)
Recent use (8–90 days)	24	7.7	381	3.8	2.35 (1.49–3.70)	2.37 (1.47–3.82)
Past use (91–365)	18	5.8	485	4.9	1.30 (0.78–2.15)	1.36 (0.81–2.28)
Distant use (>365 days)	50	16.1	1570	15.7	1.19 (0.85–1.65)	1.11 (0.79–1.56)

Medication use	Non-traumatic SAH cases N=311		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
H_2RA						
Never use	252	81.0	7751	77.5	1 (–)	1 (–)
Current use (0–7 days)	6	1.9	218	2.2	0.89 (0.39–2.05)	1.02 (0.44–2.36)
Recent use (8–90 days)	2	0.6	75	0.8	0.81 (0.19–3.34)	0.65 (0.15–2.89)
Past use (91–365)	3	1.0	112	1.1	0.72 (0.23–2.32)	0.73 (0.23–2.37)
Distant use (>365 days)	48	15.4	1844	18.4	0.81 (0.59–1.11)	0.76 (0.55–1.06)
SSRI						
Never use	211	67.8	8278	82.8	1 (–)	1 (–)
Current use (0–7 days)	26	8.4	441	4.4	1.92 (1.24–2.95)	1.78 (1.13–2.80)
Duration <91 days	3	1.0	67	0.7	1.50 (0.46–4.88)	1.09 (0.30–3.94)
Duration 90–365 days	4	1.3	97	1.0	1.15 (0.41–3.20)	0.91 (0.31–2.68)
Duration >365 days	19	6.1	277	2.8	2.33 (1.42–3.84)	2.39 (1.43–4.00)
Recent use (8–90 days)	6	1.9	106	1.1	1.65 (0.70–3.86)	1.59 (0.67–3.76)
Past use (91–365)	12	3.9	141	1.4	2.65 (1.42–4.94)	2.29 (1.19–4.40)
Distant use (>365 days)	56	18.0	1034	10.3	1.71 (1.25–2.34)	1.55 (1.12–2.14)
NSAIDs						
Never use	99	31.8	2856	28.6	1 (–)	1 (–)
Current use (0–7 days)	29	9.3	642	6.4	1.11 (0.72–1.71)	1.24 (0.80–1.93)
Duration <91 days	8	2.6	186	1.9	1.07 (0.51–2.25)	1.15 (0.54–2.46)
Duration 90–365 days	7	2.3	148	1.5	1.06 (0.48–2.35)	1.27 (0.56–2.87)
Duration >365 days	14	4.5	308	3.1	1.17 (0.65–2.10)	1.29 (0.71–2.34)
Recent use (8–90 days)	17	5.5	454	4.5	0.87 (0.51–1.49)	0.87 (0.50–1.51)
Past use (91–365)	21	6.8	892	8.9	0.56 (0.34–0.91)	0.55 (0.34–0.91)
Distant use (>365 days)	145	46.6	5156	51.6	0.79 (0.61–1.03)	0.78 (0.60–1.03)
Acetaminophen						
Never use	82	26.4	3050	30.5	1 (–)	1 (–)
Current use (0–7 days)	53	17.0	1537	15.4	1.59 (1.09–2.31)	1.46 (0.99–2.15)
Duration <91 days	19	6.1	402	4.0	2.11 (1.24–3.58)	2.07 (1.20–3.57)
Duration 90–365 days	9	2.9	348	3.5	1.14 (0.56–2.33)	1.09 (0.53–2.27)
Duration >365 days	25	8.0	787	7.9	1.51 (0.94–2.44)	1.30 (0.80–2.13)
Recent use (8–90 days)	37	11.9	1140	11.4	1.42 (0.94–2.14)	1.37 (0.90–2.09)
Past use (91–365)	31	10.0	1061	10.6	1.17 (0.76–1.81)	1.08 (0.69–1.68)
Distant use (>365 days)	108	34.7	3212	32.1	1.36 (1.01–1.83)	1.24 (0.91–1.68)
Oral steroids						
Never use	249	80.1	8039	80.4	1 (–)	1 (–)
Current use (0–7 days)	7	2.3	262	2.6	0.95 (0.44–2.07)	0.89 (0.40–1.97)
Recent use (8–90 days)	8	2.6	161	1.6	1.71 (0.81–3.60)	1.54 (0.72–3.29)
Past use (91–365)	12	3.9	284	2.8	1.34 (0.73–2.46)	1.25 (0.68–2.33)
Distant use (>365 days)	35	11.3	1254	12.5	0.97 (0.67–1.40)	0.93 (0.64–1.36)
Inhaled steroids						
Never use	262	84.2	8363	83.6	1 (–)	1 (–)
Current use (0–7 days)	12	3.9	624	6.2	0.64 (0.36–1.16)	0.62 (0.34–1.13)
Recent use (8–90 days)	12	3.9	218	2.2	1.75 (0.95–3.21)	1.77 (0.95–3.29)
Past use (91–365)	6	1.9	150	1.5	1.06 (0.46–2.45)	0.95 (0.41–2.24)
Distant use (>365 days)	19	6.1	645	6.5	0.88 (0.55–1.43)	0.90 (0.55–1.47)

Medication use	**Non-traumatic SAH cases N=311**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
Antihypertensive medications						
Never use	88	28.3	2151	21.5	1 (–)	1 (–)
Current use (0–7 days)	148	47.6	6288	62.9	0.69 (0.51–0.93)	0.47 (0.31–0.71)
Recent use (8–90 days)	21	6.8	505	5.1	1.13 (0.69–1.88)	0.74 (0.41–1.33)
Past use (91–365)	10	3.2	224	2.2	1.18 (0.60–2.35)	0.97 (0.47–2.00)
Distant use (>365 days)	44	14.1	832	8.3	1.29 (0.89–1.89)	1.12 (0.75–1.68)
Statins						
Never use	172	55.3	4704	47.0	1 (–)	1 (–)
Current use (0–7 days)	101	32.5	4038	40.4	0.78 (0.59–1.01)	0.79 (0.57–1.07)
Duration <91 days	14	4.5	297	3.0	1.23 (0.69–2.17)	1.41 (0.77–2.55)
Duration 90–365 days	16	5.1	630	6.3	0.71 (0.42–1.21)	0.76 (0.43–1.32)
Duration >365 days	71	22.8	3111	31.1	0.73 (0.54–0.99)	0.72 (0.51–1.01)
Recent use (8–90 days)	18	5.8	523	5.2	1.03 (0.62–1.70)	0.88 (0.51–1.53)
Past use (91–365)	10	3.2	224	2.2	1.27 (0.65–2.46)	1.20 (0.59–2.44)
Distant use (>365 days)	10	3.2	511	5.1	0.64 (0.33–1.23)	0.55 (0.28–1.07)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension, ischemic stroke, TIA and prior ICB, clopidogrel, low-dose ASA and warfarin.

Table 47. Crude incidence rate of UGIB and LGIB per 1000 person-years overall and by study cohort, and IRR (low-dose ASA versus comparison cohort).

Characteristics	UGIB	LGIB
Overall (both cohorts)		
Number of cases	1843	2763
Median years	5.38	5.38
Person-years	2,233,315	2,233,334
Incidence rate per 1000 person-years (95% CI)	0.83 (0.79–0.86)	1.24 (1.19–1.28)
Low-dose ASA cohort		
Number of cases	1115	1936
Median years	5.56	5.56
Person-years	1,154,032	1,154,033
Incidence rate per 1000 person-years (95% CI)	0.97 (0.91–1.02)	1.68 (1.60–1.75)
Comparison cohort		
Number of cases	728	827
Median years	5.20	5.20
Person-years	1,079,283	1,079,302
Incidence rate per 1000 person-years (95% CI)	0.67 (0.63–0.75)	0.76 (0.72–0.82)
IRR (95% CI) low-dose ASA vs. comparison cohort*	1.42 (1.29–1.56)	2.17 (2.00–2.35)

*Adjusted by age, sex and number of PCP visits in the year before the start date.

Table 48. Crude incidence rate of UGIB and LGIB per 1000 person-years during the first year of follow-up, overall and by study cohort, and IRR (low-dose ASA versus comparison cohort).

	UGIB	**LGIB**
Overall (both cohorts)		
Number of cases	386	531
Total person-years	380,639	380,639
Incidence rate per 1000 person-years (95% CI)	1.01 (0.98–1.12)	1.40 (1.28–1.52)
Low-dose ASA		
Number of cases	251	375
Total person-years	192,024	192,024
Incidence rate per 1000 person-years (95% CI)	1.31 (1.16–1.48)	1.95 (1.76–2.16)
Comparison cohort		
Number of cases	135	156
Total person-years	188,616	188,616
Incidence rate per 1000 person-years (95% CI)	0.72 (0.60–0.85)	0.83 (0.71–0.97)
IRR (95% CI) low-dose ASA vs. comparison cohort*	1.80 (1.46–2.22)	2.30 (1.91–2.77)

*Adjusted by age, sex and number of PCP visits in the year prior to the start date.

Table 49. Crude incidence rate of UGIB and LGIB per 1000 person-years by healthcare assistance (i.e. hospital/referral), overall and according to each cohort.

Characteristics	UGIB*	LGIB†
Overall (both cohorts)		
Median years	5.38	5.38
Person-years	2,233,315	2,233,334
Hospitalized		
Number of cases	1106	771
Incidence rate per 1000 person-years (95% CI)	0.49 (0.47–0.53)	0.35 (0.32–0.37)
Referred		
Number of cases	729	1989
Incidence rate per 1000 person-years (95% CI)	0.33 (0.30–0.35)	0.89 (0.85–0.93)
Low-dose ASA cohort		
Median years	5.56	5.56
Person-years	1,154,032	1,154,033
Hospitalized		
Number of cases	657	523
Incidence rate per 1000 person-years (95% CI)	0.57 (0.53–0.61)	0.45 (0.42–0.49)
Referred		
Number of cases	452	1410
Incidence rate per 1000 person-years (95% CI)	0.39 (0.36–0.43)	1.22 (1.16–1.29)
Comparison cohort		
Median years	5.20	5.20
Person-years	1,079,283	1,079,302
Hospitalized		
Number of cases	4.49	248
Incidence rate per 1000 person-years (95% CI)	0.42 (0.38–0.46)	0.23 (0.20–0.26)
Referred		
Number of cases	277	579
Incidence rate per 1000 person-years (95% CI)	0.26 (0.23–0.29)	0.54 (0.49–0.58)

*Eight cases were neither hospitalized nor referred but died at home.
†Three cases were neither hospitalized nor referred but died at home.

Table 50. Crude incidence rate of UGIB per 1000 person-years by sex and age group, overall and by study cohort.

	Men	**Women**	**Aged <65 years**	**Aged 65–74 years**	**Aged ≥75 years**
Overall (both cohorts)					
Number of cases	970	873	605	629	609
Median person-years	5.30	5.46	5.77	5.43	4.18
Total person-years	1,135,897	1,097,418	1,227,772	669,744	335,799
Incidence rate per 1000 person-years (95% CI)	0.85 (0.80–0.91)	0.80 (0.74–0.85)	0.49 (0.46–0.54)	0.94 (0.87–1.02)	1.81 (1.68–1.96)
Low-dose ASA					
Number of cases	605	510	393	378	344
Median person-years	5.50	5.63	5.94	5.68	4.32
Total person-years	588,279	566,971	632,725	348,673	172,634
Incidence rate per 1000 person-years (95% CI)	1.03 (0.95–1.11)	0.90 (0.83–0.98)	0.62 (0.56–0.69)	1.08 (0.80–1.20)	1.99 (1.79–2.21)
Comparison cohort					
Number of cases	365	363	212	251	265
Median person-years	5.10	5.30	5.59	5.18	4.04
Total person-years	547,617	530,700	595,047	321,071	163,165
Incidence rate per 1000 person-years (95% CI)	0.67 (0.60–0.74)	0.68 (0.62–0.76)	0.36 (0.31–0.41)	0.78 (0.69–0.88)	1.62 (1.44–1.83)
IRR (95% CI) low-dose ASA vs. comparison cohort*	1.53 (1.34–1.74)	1.31 (1.15–1.50)	1.72 (1.46–2.03)	1.38 (1.17–1.61)	1.22 (1.04–1.43)

*Adjusted by age, sex and number of PCP visits in the year prior to the start date.

Table 51. Crude incidence rate of LGIB per 1000 person-years by sex and age group, overall and by study cohort.

	Men	**Women**	**Aged <65 years**	**Aged 65–74 years**	**Aged ≥75 years**
Overall (both cohorts)					
Number of cases	1336	1427	1255	912	599
Median person-years	5.30	5.46	5.77	5.43	4.18
Total person-years	1,135,898	1,097,436	1,227,772	669,752	335,811
Incidence rate per 1000 person-years (95% CI)	1.18 (1.11–1.24)	1.30 (1.23–1.37)	1.02 (0.96–1.08)	1.36 (1.28–1.45)	1.78 (1.65–1.93)
Low-dose ASA					
Number of cases	941	995	889	635	412
Median person-years	5.50	5.63	5.94	5.68	4.32
Total person-years	588,281	565,752	632,725	348,673	174,170
Incidence rate per 1000 person-years (95% CI)	1.60 (1.50–1.71)	1.76 (1.65–1.87)	1.41 (1.32–1.51)	1.82 (1.68–1.97)	2.39 (2.17–2.63)
Comparison cohort					
Number of cases	395	432	363	277	187
Median person-years	5.10	5.30	5.59	5.18	4.04
Total person-years	547,617	531,684	603,977	321,079	163,176
Incidence rate per 1000 person-years (95% CI)	0.72 (0.65–0.80)	0.81 (0.74–0.89)	0.61 (0.55–0.68)	0.86 (0.77–0.97)	1.15 (0.99–1.32)
IRR (95% CI) low-dose ASA vs. comparison cohort*	2.19 (1.95–2.46)	2.15 (1.92–2.41)	2.28 (2.01–2.57)	2.10 (1.82–2.42)	2.07 (1.74–2.46)

*Adjusted by age, sex and number of PCP visits in the year prior to the start date.

Table 52. Crude incidence rate of UGIB and LGIB per 1000 person-years by case-fatality status (fatal case = death within 30 days following the event), overall and by study cohort.

	UGIB		**LGIB**	
	Fatal cases	**Non-fatal cases**	**Fatal cases**	**Non-fatal cases**
Overall (both cohorts)				
Number of cases	128	1715	25	2738
Total person-years	2,233,315	2,233,315	2,233,334	2,233,334
Incidence rate per 1000 person-years (95% CI)	0.06 (0.05–0.07)	0.77 (0.73–0.81)	0.01 (0.008–0.02)	1.23 (1.18–1.27)
Low-dose ASA				
Number of cases	64	1051	15	1921
Total person-years	1,154,032	1,154,032	1,154,033	1,154,033
Incidence rate per 1000 person-years (95% CI)	0.06 (0.04–0.07)	0.91 (0.86–0.97)	0.01 (0.008–0.02)	1.66 (1.59–1.74)
Comparison cohort				
Number of cases	64	664	10	817
Total person-years	1,079,283	1,079,283	1,079,302	1,079,302
Incidence rate per 1000 person-years (95% CI)	0.06 (0.05–0.08)	0.62 (0.57–0.66)	0.009 (0.005–0.02)	0.76 (0.71–0.81)
IRR (95% CI) low-dose ASA vs. comparison cohort*	0.93 (0.66–1.31)	1.47 (1.33–1.62)	1.41 (0.63–3.14)	2.18 (2.01–2.37)

*Adjusted by age, sex and number of PCP visits in the year prior to the start date.

Table 53. Frequency of demographics, lifestyle factors, healthcare use and polypharmacy among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB.

	UGIB cases N=1843		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	970	52.6	2632	52.6	NA	NA
Female	873	47.4	2368	47.4	NA	NA
Age (years)						
40–59	237	12.9	661	13.2	NA	NA
60–69	431	23.4	1165	23.3	NA	NA
70–79	666	36.1	1805	36.1	NA	NA
80–89	509	27.6	1369	27.4	NA	NA
Calendar year						
2000–2004	388	21.1	1060	21.2	NA	NA
2005–2010	841	45.6	2280	45.6	NA	NA
2010 and beyond	614	33.3	1660	33.2	NA	NA
Cohort type						
Comparison	728	39.5	2451	49.0	1 (–)	1 (–)
Low-dose ASA	1115	60.5	2549	51.0	1.27 (1.14–1.42)	1.13 (0.96–1.33)
Smoking						
Non-smoker	703	38.1	2166	43.3	1 (–)	1 (–)
Current	282	15.3	615	12.3	1.45 (1.22–1.72)	1.36 (1.14–1.63)
Former	814	44.2	2082	41.6	1.07 (0.94–1.21)	1.02 (0.89–1.16)
Unknown	44	2.4	137	2.7	1.36 (0.94–1.98)	1.15 (0.76–1.72)
BMI (kg/m^2)						
15–19	94	5.1	183	3.7	1.30 (0.99–1.72)	1.24 (0.93–1.66)
20–24	478	25.9	1330	26.6	1 (–)	1 (–)
25–29	645	35.0	1863	37.3	0.93 (0.80–1.07)	0.90 (0.78–1.04)
≥30	465	25.2	1170	23.4	0.96 (0.82–1.12)	0.91 (0.77–1.07)
Unknown	161	8.7	454	9.1	1.19 (0.96–1.48)	1.12 (0.87–1.44)
Alcohol (u/w)						
None	391	21.2	906	18.1	1 (–)	1 (–)
1–9	826	44.8	2429	48.6	0.84 (0.73–0.98)	0.87 (0.75–1.02)
10–20	246	13.3	728	14.6	0.88 (0.72–1.07)	0.93 (0.75–1.14)
21–41	104	5.6	226	4.5	1.18 (0.89–1.55)	1.12 (0.84–1.49)
≥42	32	1.7	43	0.9	1.97 (1.20–3.23)	1.96 (1.18–3.26)
Unknown	244	13.2	668	13.4	1.06 (0.87–1.29)	1.04 (0.84–1.29)

	UGIB cases N=1843		Controls N=5000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Polypharmacy						
0–1	458	24.9	1858	37.2	1 (–)	1 (–)
2–4	531	28.8	1562	31.2	1.17 (1.01–1.35)	1.06 (0.91–1.24)
≥5	854	46.3	1580	31.6	1.50 (1.30–1.73)	1.20 (1.03–1.40)
PCP visits						
0–4	95	5.2	713	14.3	1 (–)	1 (–)
5–9	279	15.1	1233	24.7	1.77 (1.38–2.28)	1.52 (1.17–1.98)
10–15	330	17.9	1110	22.2	2.36 (1.84–3.03)	1.81 (1.39–2.35)
15–19	333	18.1	765	15.3	3.50 (2.72–4.51)	2.50 (1.91–3.28)
≥20	806	43.7	1179	23.6	5.63 (4.44–7.13)	3.70 (2.86–4.80)
Referrals						
0–4	601	32.6	2466	49.3	1 (–)	1 (–)
5–9	538	29.2	1401	28.0	1.25 (1.08–1.44)	1.19 (1.03–1.38)
10–19	451	24.5	809	16.2	1.54 (1.31–1.81)	1.41 (1.19–1.67)
≥20	253	13.7	324	6.5	1.79 (1.44–2.21)	1.60 (1.28–1.99)
Hospitalizations						
None	1182	64.1	4225	84.5	1 (–)	1 (–)
1	346	18.8	477	9.5	2.17 (1.85–2.54)	2.02 (1.71–2.37)
2	168	9.1	179	3.6	2.65 (2.10–3.33)	2.30 (1.82–2.92)
≥3	147	8.0	119	2.4	3.28 (2.52–4.26)	2.67 (2.03–3.51)
Townsend score						
Deprived 1 (least deprived)	54	2.9	137	2.7	1 (–)	1 (–)
Deprived 2	434	23.5	1276	25.5	0.82 (0.58–1.16)	0.94 (0.66–1.35)
Deprived 3	392	21.3	1160	23.2	0.81 (0.57–1.14)	0.89 (0.62–1.27)
Deprived 4	371	20.1	989	19.8	0.88 (0.62–1.24)	0.97 (0.68–1.40)
Deprived 5 (most deprived)	350	19.0	905	18.1	0.88 (0.62–1.25)	0.92 (0.64–1.32)
Unknown	242	13.1	533	10.7	1.01 (0.70–1.45)	1.02 (0.70–1.49)
Urban/rural						
Urban	1185	64.3	3222	64.4	1 (–)	1 (–)
Town	246	13.3	591	11.8	1.11 (0.94–1.32)	1.10 (0.93–1.31)
Rural	114	6.2	351	7.0	0.90 (0.71–1.12)	0.91 (0.72–1.16)
Unknown	298	16.2	836	16.7	0.94 (0.81–1.10)	0.83 (0.71–0.97)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated peptic ulcer problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. Alcohol, BMI and smoking were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy was taken as the number of different medications in the month before the index date.

Table 54. Frequency of comorbidities among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB.

Comorbidities	**UGIB cases N=1843**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
MI	187	10.1	392	7.8	1.11 (0.92–1.35)	0.86 (0.70–1.07)
IS	162	8.8	279	5.6	1.40 (1.13–1.72)	1.20 (0.97–1.49)
TIA	145	7.9	303	6.1	1.15 (0.93–1.42)	0.98 (0.78–1.22)
IHD‡	342	18.6	711	14.2	1.16 (1.00–1.34)	0.97 (0.83–1.14)
COPD	193	10.5	392	7.8	1.09 (0.91–1.32)	1.05 (0.86–1.28)
Asthma	327	17.7	770	15.4	0.96 (0.82–1.11)	0.96 (0.82–1.12)
Hypertension	1116	60.6	2855	57.1	0.98 (0.87–1.10)	0.98 (0.87–1.11)
Hyperlipidemia	455	24.7	1164	23.3	0.96 (0.84–1.09)	0.92 (0.81–1.06)
Diabetes	413	22.4	915	18.3	0.91 (0.80–1.05)	0.90 (0.78–1.05)
DVT	172	9.3	369	7.4	1.10 (0.90–1.34)	1.02 (0.83–1.26)
Anemia§	92	5.0	78	1.6	2.29 (1.67–3.14)	2.23 (1.61–3.10)
Atrial fibrillation	254	13.8	493	9.9	1.12 (0.94–1.33)	0.92 (0.74–1.14)
Heart failure	154	8.4	239	4.8	1.33 (1.07–1.66)	1.27 (1.01–1.61)
All hemodialysis	14	0.8	5	0.1	5.94 (2.07-17.03)	6.02 (2.08-17.46)
Hemodialysis extracorporeal	11	0.6	4	0.1	5.85 (1.79-19.14)	6.19 (1.88-20.45)
Hemodialysis Peritoneal	3	0.2	3	0.1	2.17 (0.42-11.32)	1.75 (0.31-9.86)
eGFR						
0–14	19	1.0	11	0.2	3.73 (1.73–8.03)	4.30 (1.96–9.39)
15–29	56	3.0	69	1.4	1.75 (1.20–2.54)	1.67 (1.14–2.46)
30-44	193	10.5	314	6.3	1.57 (1.28–1.93)	1.51 (1.22–1.87)
45–59	335	18.2	928	18.6	1.00 (0.86–1.17)	1.00 (0.85–1.17)
≥60	1047	56.8	2940	58.8	1 (–)	1
Unknown	193	10.5	738	14.8	1.09 (0.89–1.33)	1.07 (0.87–1.32)
PU, uncomplicated/ complicated	302	16.4	317	6.3	2.62 (2.20–3.12)	2.36 (1.93–2.87)
PU, uncomplicated	209	11.3	234	4.7	2.42 (1.97–2.96)	2.12 (1.71–2.62)
PU, complicated	133	7.2	123	2.5	2.69 (2.07–3.49)	1.84 (1.29–2.64)
IBD	30	1.6	64	1.3	1.07 (0.68–1.68)	1.12 (0.70–1.78)
IBS	140	7.6	289	5.8	1.18 (0.95–1.46)	1.16 (0.93–1.46)
Dyspepsia	605	32.8	1164	23.3	1.37 (1.21–1.54)	1.19 (1.04–1.37)
Constipation	440	23.9	739	14.8	1.47 (1.28–1.69)	1.39 (1.20–1.60)
Gout	173	9.4	340	6.8	1.23 (1.01–1.50)	1.16 (0.94–1.43)
Pancreatic disease	24	1.3	31	0.6	1.84 (1.06–3.20)	1.78 (1.00–3.18)
GERD	410	22.2	854	17.1	1.19 (1.04–1.37)	1.03 (0.89–1.20)
Prior UGIB	60	3.3	57	1.1	2.46 (1.68–3.61)	1.74 (1.16–2.61)
Prior LGIB	183	9.9	306	6.1	1.45 (1.19–1.77)	1.44 (1.18–1.77)
Prior GIB unspecified	58	3.1	51	1.0	2.97 (2.00–4.40)	2.41 (1.60–3.63)
Depression	496	26.9	1076	21.5	1.13 (0.99–1.29)	1.09 (0.95–1.25)
Rheumatoid arthritis	81	4.4	152	3.0	1.14 (0.86–1.51)	0.93 (0.69–1.26)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated PU problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.
[‡]IHD does not include MI.
[§]In the year before the index date.
Comorbidities were ascertained any time before the index date.

Table 55. Frequency of medication use among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB.

Medication	UGIB cases N=1843		Controls N=5000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	421	22.8	1710	34.2	1 (–)	1 (–)
Current use (0–30 days)	987	53.6	2160	43.2	1.48 (1.29–1.69)	1.62 (1.40–1.87)
Recent use (31–90 days)	83	4.5	181	3.6	1.42 (1.06–1.90)	1.50 (1.11–2.03)
Past use (91–365)	101	5.5	247	4.9	1.23 (0.95–1.60)	1.15 (0.87–1.51)
Distant use (>365 days)	251	13.6	702	14.0	1.13 (0.94–1.36)	1.05 (0.87–1.28)
Duration (continuous) of low-dose ASA among current users						
<3 months	172	9.3	286	5.7	1.93 (1.54–2.42)	1.99 (1.57–2.52)
3–<6 months	110	6.0	203	4.1	1.65 (1.26–2.15)	1.81 (1.38–2.39)
6 months–<1 year	150	8.1	320	6.4	1.41 (1.12–1.77)	1.46 (1.15–1.86)
1–<5 years	442	24.0	1043	20.9	1.40 (1.19–1.65)	1.56 (1.32–1.85)
≥5 years	113	6.1	308	6.2	1.25 (0.97–1.61)	1.45 (1.12–1.87)
Total use of low-dose ASA among current users						
<3 months	116	6.3	156	3.1	2.56 (1.95–3.37)	2.59 (1.95–3.44)
3–<6 months	84	4.6	156	3.1	1.59 (1.18–2.15)	1.79 (1.31–2.45)
6 months–<1 year	127	6.9	261	5.2	1.47 (1.15–1.89)	1.52 (1.18–1.97)
1–<5 years	512	27.8	1202	24.0	1.39 (1.19–1.63)	1.53 (1.30–1.80)
≥5 years	148	8.0	385	7.7	1.27 (1.01–1.59)	1.45 (1.14–1.84)
Low-dose ASA dose among current users						
75 mg	912	49.5	2028	40.6	1.45 (1.26–1.66)	1.58 (1.37–1.83)
150–300 mg	75	4.1	132	2.6	1.90 (1.39–2.60)	2.12 (1.53–2.93)
150 mg	63	3.4	111	2.2	1.87 (1.34–2.63)	2.06 (1.46–2.92)
300 mg	12	0.7	21	0.4	2.04 (0.97–4.30)	2.44 (1.14–5.25)
Among primary prevention cohort	**N=1200**		**N=3663**			
Current low-dose ASA users	572	47.8	1262	34.4	1.55 (1.32–1.83)	1.74 (1.47–2.06)
Among secondary prevention cohort	**N=643**		**N=1337**			
Current low-dose ASA users	415	64.5	898	67.2	0.89 (0.66–1.22)	1.14 (0.82–1.59)

Medication	UGIB cases N=1843		Controls N=5000		RR (95% CI)*	RR (95% CI)†
Clopidogrel						
Never use	1591	86.3	4608	92.2	1 (–)	1 (–)
Current use (0–30 days)	152	8.2	159	3.2	2.15 (1.70–2.73)	2.07 (1.62–2.65)
Recent use (31–90 days)	9	0.5	19	0.4	0.96 (0.43–2.16)	0.86 (0.37–1.98)
Past use (91–365)	22	1.2	47	0.9	0.97 (0.58–1.64)	0.80 (0.47–1.37)
Distant use (>365 days)	68	3.7	166	3.3	0.95 (0.71–1.28)	0.78 (0.57–1.06)
ASA/clopidogrel (never use as reference)						
No ASA no clopidogrel	400	21.7	1677	33.5	1 (–)	
DAT	89	4.8	72	1.4	3.58 (2.55–5.02)	3.87 (2.73–5.50)
ASA monotherapy	877	47.6	2038	40.8	1.44 (1.25–1.66)	1.58 (1.36–1.83)
Clopidogrel monotherapy	45	2.4	63	1.3	2.03 (1.35–3.05)	2.00 (1.32–3.05)
Warfarin						
Never use	1601	86.9	4596	91.9	1 (–)	1 (–)
Current use (0–30 days)	162	8.8	241	4.8	1.28 (1.03–1.59)	1.74 (1.38–2.20)
Duration <91 days	34	1.8	30	0.6	2.23 (1.35–3.71)	2.34 (1.37–3.99)
Duration 90–365 days	35	1.9	43	0.9	1.54 (0.97–2.44)	2.02 (1.25–3.27)
Duration >365 days	93	5.0	168	3.4	1.04 (0.80–1.36)	1.52 (1.13–2.03)
Recent use (31–365 days)	28	1.5	42	0.8	1.26 (0.77–2.06)	1.42 (0.85–2.37)
Past use (>365 days)	52	2.8	121	2.4	1.07 (0.76–1.50)	0.87 (0.61–1.24)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to index date						
INR <3	59	3.4	112	2.2	0.96 (0.69–1.33)	1.25 (0.88–1.76)
INR ≥3	28	1.6	12	0.2	4.09 (2.07–8.06)	5.76 (2.87–11.58)
Unknown INR	66	3.8	117	2.3	1.28 (0.94–1.75)	1.78 (1.29–2.47)
Remaining anticoagulants‡						
Never use	1812	98.3	4956	99.1	1 (–)	1 (–)
Current and recent use (<91 days)	10	0.5	9	0.2	2.33 (0.92–5.90)	2.47 (0.92–6.61)
Past use (91–365)	3	0.2	12	0.2	0.41 (0.12–1.46)	0.44 (0.12–1.59)
Distant use (>365 days)	18	1.0	23	0.5	1.85 (0.98–3.50)	1.51 (0.77–2.96)

Medication	UGIB cases N=1843		Controls N=5000		RR (95% CI)*	RR (95% CI)†
ASA/warfarin (never use as reference)						
No ASA no warfarin	364	19.8	1616	32.3	1 (–)	1 (–)
Both drugs	41	2.2	33	0.7	3.02 (1.86–4.90)	3.35 (2.01–5.60)
ASA monotherapy	931	50.5	2108	42.2	1.53 (1.32–1.76)	1.62 (1.40–1.89)
Warfarin monotherapy	91	4.9	170	3.4	1.38 (1.03–1.84)	1.71 (1.26–2.31)
PPI						
Never use	822	44.6	2945	58.9	1 (–)	1 (–)
Current use (0–30 days)	533	28.9	971	19.4	1.51 (1.31–1.74)	1.27 (1.09–1.47)
Duration <91 days	165	9.0	139	2.8	3.25 (2.54–4.16)	2.77 (2.15–3.59)
Duration 90–365 days	77	4.2	187	3.7	1.03 (0.78–1.37)	0.80 (0.60–1.08)
Duration >365 days	291	15.8	645	12.9	1.26 (1.07–1.49)	1.07 (0.90–1.28)
Recent use (31–90 days)	72	3.9	119	2.4	1.70 (1.24–2.32)	1.63 (1.17–2.26)
Past use (91–365)	121	6.6	224	4.5	1.61 (1.26–2.05)	1.60 (1.24–2.06)
Distant use (>365 days)	295	16.0	741	14.8	1.35 (1.15–1.59)	1.23 (1.04–1.46)
H_2RA						
Never use	1310	71.1	3927	78.5	1 (–)	1 (–)
Current use (0–30 days)	80	4.3	114	2.3	1.75 (1.27–2.42)	1.40 (1.02–1.92)
Duration <91 days	26	1.4	25	0.5	2.38 (1.35–4.22)	1.89 (1.04–3.44)
Duration 90–365 days	22	1.2	21	0.4	2.34 (1.26–4.33)	1.75 (0.93–3.32)
Duration >365 days	32	1.7	68	1.4	1.31 (0.85–2.03)	1.06 (0.67–1.67)
Recent use (31–90 days)	14	0.8	19	0.4	2.03 (1.17–3.53)	1.81 (0.85–3.86)
Past use (91–365)	32	1.7	63	1.3	1.18 (0.76–1.84)	0.93 (0.58–1.49)
Distant use (>365 days)	407	22.1	877	17.5	1.21 (1.05–1.39)	1.00 (0.86–1.17)
Antacids						
Never use	1261	68.4	3713	74.3	1 (–)	1 (–)
Current use (0–30 days)	135	7.3	258	5.2	1.26 (1.00–1.57)	1.08 (0.85–1.37)
Duration <91 days	41	2.2	64	1.3	1.58 (1.05–2.38)	1.38 (0.90–2.11)
Duration 90–365 days	39	2.1	67	1.3	1.37 (0.91–2.08)	1.13 (0.73–1.74)
Duration >365 days	55	3.0	127	2.5	1.03 (0.74–1.44)	0.91 (0.64–1.28)
Recent use (31–90 days)	17	0.9	37	0.7	1.08 (0.60–1.96)	0.95 (0.52–1.74)
Past use (91–365)	52	2.8	120	2.4	0.99 (0.71–1.40)	0.81 (0.56–1.16)
Distant use (>365 days)	378	20.5	872	17.4	1.11 (0.96–1.27)	0.98 (0.85–1.14)

Medication	UGIB cases N=1843		Controls N=5000		RR (95% CI)*	RR (95% CI)†
SSRI						
Never use	1403	76.1	4135	82.7	1 (–)	1 (–)
Current use (0–30 days)	144	7.8	256	5.1	1.29 (1.03–1.60)	1.22 (0.97–1.54)
Duration <91 days	36	2.0	31	0.6	2.51 (1.53–4.13)	2.54 (1.53–4.23)
Duration 90–365 days	31	1.7	66	1.3	0.96 (0.61–1.49)	0.95 (0.60–1.50)
Duration >365 days	77	4.2	159	3.2	1.18 (0.89–1.57)	1.07 (0.79–1.44)
Recent use (31–90 days)	19	1.0	35	0.7	1.22 (0.68–2.18)	1.19 (0.65–2.17)
Past use (91–365)	38	2.1	73	1.5	1.14 (0.76–1.72)	1.08 (0.71–1.65)
Distant use (>365 days)	239	13.0	501	10.0	1.28 (1.07–1.52)	1.21 (1.01–1.45)
NSAIDs						
Never use	465	25.2	1488	29.8	1 (–)	1 (–)
Current use (0–30 days)	307	16.7	394	7.9	2.09 (1.73–2.52)	2.11 (1.73–2.56)
Duration <91 days	124	6.7	145	2.9	2.34 (1.78–3.06)	2.33 (1.76–3.08)
Duration 90–365 days	61	3.3	89	1.8	1.75 (1.23–2.50)	1.69 (1.17–2.43)
Duration >365 days	122	6.6	160	3.2	2.05 (1.57–2.68)	2.15 (1.64–2.83)
Recent use (31–90 days)	65	3.5	163	3.3	0.98 (0.71–1.34)	1.04 (0.75–1.43)
Past use (91–365)	149	8.1	431	8.6	0.89 (0.72–1.12)	0.86 (0.69–1.09)
Distant use (>365 days)	857	46.5	2524	50.5	0.95 (0.83–1.09)	0.92 (0.80–1.06)
tNSAIDs						
Never use	500	27.1	1555	31.1	1 (–)	1 (–)
Current use (0–30 days)	268	14.5	345	6.9	2.05 (1.69–2.49)	2.13 (1.74–2.62)
Duration <91 days	113	6.1	135	2.7	2.27 (1.72–3.00)	2.34 (1.75–3.12)
Duration 90–365 days	55	3.0	76	1.5	1.82 (1.25–2.64)	1.80 (1.23–2.64)
Duration >365 days	100	5.4	134	2.7	1.97 (1.48–2.63)	2.14 (1.59–2.87)
Recent use (31–90 days)	58	3.1	156	3.1	0.90 (0.65–1.25)	0.97 (0.69–1.35)
Past use (91–365)	148	8.0	397	7.9	0.96 (0.77–1.19)	0.93 (0.73–1.17)
Distant use (>365 days)	869	47.2	2547	50.9	0.94 (0.82–1.07)	0.91 (0.79–1.05)
COXIBs						
Never use	1508	81.8	4291	85.8	1 (–)	1 (–)
Current use (0–30 days)	44	2.4	51	1.0	2.09 (1.36–3.19)	2.09 (1.34–3.25)
Duration <91 days	16	0.9	16	0.3	2.21 (1.08–4.56)	1.93 (0.91–4.09)
Duration 90–365 days	14	0.8	18	0.4	1.84 (0.89–3.82)	2.09 (0.99–4.42)
Duration >365 days	14	0.8	17	0.3	2.23 (1.07–4.62)	2.28 (1.08–4.82)
Recent use (31–90 days)	10	0.5	14	0.3	1.48 (0.64–3.43)	1.21 (0.49–2.96)
Past use (91–365)	26	1.4	67	1.3	0.88 (0.55–1.41)	0.75 (0.46–1.23)
Distant use (>365 days	255	13.8	577	11.5	1.05 (0.89–1.24)	0.93 (0.78–1.11)

Medication	UGIB cases N=1843		Controls N=5000		RR (95% CI)*	RR (95% CI)†
Acetaminophen						
Never use	382	20.7	1565	31.3	1 (–)	1 (–)
Current use (0–30 days)	588	31.9	991	19.8	1.81 (1.53–2.13)	1.52 (1.27–1.82)
Duration <91 days	206	11.2	314	6.3	1.98 (1.60–2.47)	1.75 (1.39–2.20)
Duration 90–365 days	132	7.2	214	4.3	1.76 (1.37–2.28)	1.48 (1.13–1.94)
Duration >365 days	250	13.6	463	9.3	1.69 (1.38–2.07)	1.37 (1.10–1.70)
Recent use (31–90 days)	133	7.2	298	6.0	1.40 (1.10–1.78)	1.27 (0.99–1.64)
Past use (91–365)	215	11.7	557	11.1	1.16 (0.95–1.42)	1.06 (0.86–1.32)
Distant use (>365 days	525	28.5	1589	31.8	1.22 (1.04–1.42)	1.15 (0.98–1.36)
Oral steroids						
Never use	1389	75.4	4056	81.1	1 (–)	1 (–)
Current use (0–30 days)	107	5.8	169	3.4	1.29 (0.99–1.67)	1.19 (0.91–1.56)
Recent use (31–90 days)	27	1.5	66	1.3	0.79 (0.50–1.25)	0.81 (0.50–1.30)
Past use (91–365)	69	3.7	148	3.0	0.95 (0.70–1.28)	0.92 (0.67–1.27)
Distant use (>365 days)	251	13.6	561	11.2	1.09 (0.92–1.29)	1.07 (0.90–1.28)
Inhaled steroids						
Never use	1511	82.0	4217	84.3	1 (–)	1 (–)
Current use (0–7 days)	147	8.0	361	7.2	0.87 (0.71–1.07)	0.88 (0.71–1.09)
Recent use (8–90 days)	30	1.6	49	1.0	1.38 (0.86–2.20)	1.38 (0.85–2.25)
Past use (91–365)	36	2.0	81	1.6	0.92 (0.61–1.38)	0.91 (0.59–1.39)
Distant use (>365 days)	119	6.5	292	5.8	0.99 (0.79–1.24)	0.98 (0.77–1.24)
Antihypertensive medications						
Never use	265	14.4	1106	22.1	1 (–)	1 (–)
Current use (0–30 days)	1340	72.7	3296	65.9	1.19 (1.01–1.39)	1.01 (0.85–1.20)
Recent use (31–90 days)	51	2.8	79	1.6	1.86 (1.26–2.75)	1.69 (1.12–2.56)
Past use (91–365)	40	2.2	113	2.3	1.05 (0.70–1.56)	0.87 (0.57–1.31)
Distant use (>365 days)	147	8.0	406	8.1	1.21 (0.95–1.54)	1.17 (0.91–1.50)
Statins						
Never use	777	42.2	2464	49.3	1 (–)	1 (–)
Current use (0 –30 days)	896	48.6	2065	41.3	1.08 (0.96–1.22)	0.88 (0.77–1.01)
Duration <91 days	102	5.5	172	3.4	1.40 (1.07–1.83)	1.13 (0.85–1.50)
Duration 90–365 days	201	10.9	333	6.7	1.38 (1.13–1.69)	1.10 (0.88–1.37)
Duration >365 days	593	32.2	1560	31.2	0.97 (0.85–1.11)	0.80 (0.68–0.93)
Recent use (31–90 days)	48	2.6	95	1.9	1.17 (0.81–1.69)	1.05 (0.71–1.56)
Past use (91–365)	39	2.1	131	2.6	0.72 (0.49–1.05)	0.62 (0.42–0.93)
Distant use (>365 days)	83	4.5	245	4.9	0.93 (0.70–1.21)	0.88 (0.66–1.16)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated PU problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA. ‡This variable included acenocoumarol, dabigatran, dalteraparan, enoxaparin, phenindione, tinzaparin, apixaban, rivaroxaban and heparin. Owing to low numbers current and recent users were merged into one category (there were 10 current/recent users among cases: acenocoumarol [n=2], heparin sodium [n=1], enoxaparin [n=6] and phenindione [n=1]; there were 9 current users among controls: dabigatran [n=2], enoxaparin [n=2], phenindione [n=2] and acenocoumarol [n=3]). Warfarin was excluded from the model.

Table 56. Sensitivity analyses: frequency of low-dose ASA and PPI use among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB, after removing any user of anticoagulants or other antiplatelets (other than low-dose ASA: 516 cases and 873 controls removed).

Medication	UGIB cases N=1327		Controls N=4127		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
Low-dose ASA						
Never use	346	26.1	1578	38.2	1 (–)	1 (–)
Current use (0–30 days)	724	54.6	1723	41.7	1.52 (1.30–1.77)	1.64 (1.40–1.93)
Recent use (31–90 days)	57	4.3	149	3.6	1.38 (0.99–1.94)	1.54 (1.09–2.17)
Past use (91–365)	55	4.1	184	4.5	1.04 (0.75–1.45)	1.05 (0.75–1.48)
Distant use (>365 days)	145	10.9	493	11.9	1.10 (0.88–1.38)	1.11 (0.88–1.40)
Duration (continuous) of low-dose ASA among current users						
<3 months	117	8.8	236	5.7	1.79 (1.38–2.32)	1.93 (1.48–2.52)
3–<6 months	79	6.0	166	4.0	1.63 (1.21–2.21)	1.90 (1.39–2.59)
6 months–<1 year	112	8.4	256	6.2	1.47 (1.14–1.92)	1.53 (1.16–2.00)
1–<5 years	331	24.9	832	20.2	1.46 (1.22–1.75)	1.56 (1.30–1.89)
≥5 years	85	6.4	233	5.6	1.40 (1.06–1.87)	1.93 (1.48–2.52)
PPIs						
Never use	646	48.7	2542	61.6	1 (–)	1 (–)
Current use (0–30 days)	338	25.5	710	17.2	1.47 (1.25–1.74)	1.25 (1.05–1.49)
Duration <91 days	118	8.9	111	2.7	3.22 (2.43–4.27)	2.72 (2.02–3.64)
Duration 90–365 days	49	3.7	134	3.2	1.03 (0.73–1.46)	0.84 (0.58–1.21)
Duration >365 days	171	12.9	465	11.3	1.17 (0.95–1.44)	1.01 (0.81–1.25)
Recent use (31–90 days)	44	3.3	99	2.4	1.41 (0.97–2.06)	1.40 (0.95–2.08)
Past use (91–365)	85	6.4	171	4.1	1.66 (1.25–2.20)	1.65 (1.23–2.21)
Distant use (>365 days)	214	16.1	605	14.7	1.34 (1.11–1.61)	1.18 (0.97–1.43)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated PU problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

Table 57. Frequency of low-dose ASA use among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB, stratified by case-fatality status (fatal case = death within 30 days following the event).

Fatal cases	**UGIB cases N=128**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	47	36.7	1710	34.2	1.0 (–)	1.0 (–)
Current use (0–30 days)	59	46.1	2160	43.2	0.66 (0.44–0.99)	0.75 (0.49–1.15)
Recent use (31–90 days)	7	5.5	181	3.6	0.88 (0.38–2.02)	0.95 (0.39–2.28)
Past (91–365)	2	1.6	247	4.9	0.20 (0.05–0.82)	0.19 (0.04–0.82)
Distant (>365 days)	13	10.2	702	14.0	0.52 (0.28–0.99)	0.60 (0.31–1.15)
Non-fatal cases	**UGIB cases N=1715**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	374	21.8	1710	34.2	1.0 (–)	1.0 (–)
Current use (0–30 days)	833	48.6	2001	40.0	1.58 (1.37–1.82)	1.73 (1.49–2.01)
Recent use (31–90 days)	171	10.0	340	6.8	1.47 (1.09–1.98)	1.54 (1.13–2.11)
Past (91–365)	99	5.8	247	4.9	1.36 (1.04–1.78)	1.26 (0.95–1.66)
Distant (>365 days)	238	13.9	702	14.0	1.20 (0.99–1.46)	1.10 (0.90–1.34)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated peptic ulcer problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

Table 58. Frequency of low-dose ASA use among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB, stratified by level of healthcare assistance.

Hospitalized cases	**UGIB cases N=1106**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	257	23.2	1710	34.2	1.0 (–)	1.0 (–)
Current use (0–30 days)	596	53.9	2160	43.2	1.43 (1.21–1.70)	1.58 (1.33–1.89)
Recent use (31–90 days)	45	4.1	181	3.6	1.24 (0.86–1.78)	1.26 (0.86–1.85)
Past (91–365)	68	6.1	247	4.9	1.35 (0.99–1.84)	1.29 (0.93–1.77)
Distant (>365 days)	140	12.7	702	14.0	1.02 (0.80–1.28)	0.95 (0.74–1.21)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	99	9.0	286	5.7	1.78 (1.36–2.35)	1.88 (1.41–2.50)
3–<6 months	65	5.9	203	4.1	1.59 (1.15–2.18)	1.79 (1.29–2.50)
6 months–<1 year	81	7.3	320	6.4	1.21 (0.91–1.61)	1.23 (0.91–1.66)
1–<5 years	277	25.0	1043	20.9	1.41 (1.16–1.72)	1.59 (1.29–1.94)
≥5 years	74	6.7	308	6.2	1.32 (0.98–1.77)	1.54 (1.13–2.10)
Referred cases	**UGIB cases N=729**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	162	22.2	1710	34.2	1.0 (–)	1.0 (–)
Current use (0 –30days)	385	52.8	2160	43.2	1.53 (1.25–1.87)	1.69 (1.37–2.09)
Recent use (31–90 days)	38	5.2	181	3.6	1.70 (1.15–2.53)	1.79 (1.19–2.69)
Past (91–365)	33	4.5	247	4.9	1.07 (0.71–1.60)	0.95 (0.63–1.44)
Distant (>365 days)	111	15.2	702	14.0	1.32 (1.02–1.72)	1.22 (0.93–1.61)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	73	10.0	286	5.7	2.13 (1.56–2.92)	2.26 (1.64–3.13)
3–<6 months	45	6.2	203	4.1	1.82 (1.25–2.64)	1.96 (1.34–2.89)
6 months–<1 year	68	9.3	320	6.4	1.71 (1.24–2.35)	1.80 (1.30–2.50)
1–<5 years	160	21.9	1043	20.9	1.35 (1.06–1.71)	1.51 (1.18–1.94)
≥5 years	39	5.3	308	6.2	1.17 (0.80–1.72)	1.34 (0.91–1.99)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated PU problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

Table 59. Frequency of low-dose ASA use among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB, stratified by bleeding location.

Duodenal ulcer cases	**UGIB Cases N=299**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	61	20.4	1710	34.2	1.0 (–)	1.0 (–)
Current use (0–30 days)	186	62.2	2160	43.2	1.95 (1.44–2.66)	2.33 (1.69–3.21)
Recent use (31–90 days)	11	3.7	181	3.6	1.31 (0.67–2.55)	1.44 (0.72–2.89)
Past (91–365)	13	4.3	247	4.9	1.13 (0.61–2.11)	1.02 (0.53–1.93)
Distant (>365 days)	28	9.4	702	14.0	0.91 (0.57–1.45)	0.81 (0.50–1.32)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	30	10.0	286	5.7	2.29 (1.44–3.65)	2.61 (1.61–4.24)
3–<6 months	14	4.7	203	4.1	1.45 (0.79–2.66)	1.68 (0.89–3.17)
6 months–<1 year	26	8.7	320	6.4	1.68 (1.03–2.74)	1.81 (1.09–3.02)
1–<5 years	90	30.1	1043	20.9	1.99 (1.41–2.81)	2.44 (1.71–3.50)
≥5 years	26	8.7	308	6.2	2.12 (1.30–3.47)	2.66 (1.60–4.44)
Gastric ulcer cases	**Cases N=370**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	85	23.0	1710	34.2	1.0 (–)	1.0 (–)
Current use (0 –30days)	218	58.9	2160	43.2	1.63 (1.25–2.14)	1.94 (1.46–2.58)
Recent use (31–90 days)	19	5.1	181	3.6	1.65 (0.97–2.81)	1.86 (1.06–3.27)
Past (91–365)	12	3.2	247	4.9	0.78 (0.42–1.46)	0.80 (0.42–1.53)
Distant (>365 days)	36	9.7	702	14.0	0.88 (0.59–1.33)	0.83 (0.54–1.28)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	44	11.9	286	5.7	2.43 (1.64–3.61)	2.60 (1.70–3.95)
3–<6 months	30	8.1	203	4.1	2.24 (1.42–3.52)	2.47 (1.52–3.99)
6 months–<1 year	39	10.5	320	6.4	1.85 (1.23–2.78)	2.12 (1.38–3.25)
1–<5 years	88	23.8	1043	20.9	1.39 (1.01–1.91)	1.73 (1.23–2.41)
≥5 years	17	4.6	308	6.2	0.97 (0.56–1.68)	1.20 (0.68–2.12)

Mucosal erosion cases	**UGIB cases N=551**		**Controls N=5000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	117	21.2	1710	34.2	1.0 (–)	1.0 (–)
Current use (0 –30days)	285	51.7	2160	43.2	1.47 (1.17–1.86)	1.59 (1.25–2.02)
Recent use (31–90 days)	24	4.4	181	3.6	1.42 (0.88–2.28)	1.46 (0.90–2.39)
Past (91–365)	30	5.4	247	4.9	1.26 (0.82–1.95)	1.10 (0.71–1.72)
Distant (>365 days)	95	17.2	702	14.0	1.52 (1.14–2.04)	1.39 (1.03–1.89)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	44	8.0	286	5.7	1.64 (1.12–2.39)	1.78 (1.21–2.62)
3–<6 months	33	6.0	203	4.1	1.68 (1.10–2.57)	1.79 (1.15–2.77)
6 months–<1 year	44	8.0	320	6.4	1.39 (0.95–2.03)	1.43 (0.97–2.11)
1–<5 years	133	24.1	1043	20.9	1.46 (1.11–1.91)	1.58 (1.19–2.08)
≥5 years	31	5.6	308	6.2	1.31 (0.85–2.01)	1.47 (0.95–2.27)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated PU problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

Table 60. Frequency of demographics, lifestyle factors, healthcare use and polypharmacy among LGIB cases and controls, and association (RRs with 95% CIs) with LGIB.

	LGIB cases N=2763		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	1336	48.4	4844	48.4	NA	NA
Female	1427	51.6	5156	51.6	NA	NA
Age (years)						
40–59	502	18.2	1837	18.4	NA	NA
60–69	841	30.4	3036	30.4	NA	NA
70–79	927	33.6	3341	33.4	NA	NA
80–89	493	17.8	1786	17.9	NA	NA
Calendar year						
2000–2004	466	16.9	1701	17.0	NA	NA
2005–2010	1252	45.3	4527	45.3	NA	NA
2010 and beyond	1045	37.8	3772	37.7	NA	NA
Cohort type					NA	NA
Comparison	827	29.9	4808	48.1	1 (–)	1 (–)
Low-dose ASA	1936	70.1	5192	51.9	1.87 (1.71–2.06)	1.60 (1.39–1.84)
Smoking						
Non–smoker	1117	40.4	4387	43.9	1 (–)	1 (–)
Current	336	12.2	1362	13.6	0.96 (0.83–1.10)	0.93 (0.80–1.07)
Former	1287	46.6	4027	40.3	1.15 (1.05–1.27)	1.10 (1.00–1.21)
Unknown	23	0.8	224	2.2	0.57 (0.36–0.89)	0.61 (0.38–0.98)
BMI (kg/m^2)						
15–19	105	3.8	347	3.5	1.16 (0.91–1.47)	1.25 (0.97–1.60)
20–24	646	23.4	2568	25.7	1 (–)	1 (–)
25–29	1077	39.0	3636	36.4	1.16 (1.04–1.30)	1.12 (1.00–1.26)
≥30	795	28.8	2662	26.6	1.05 (0.93–1.18)	0.99 (0.87–1.12)
Unknown	140	5.1	787	7.9	0.87 (0.71–1.06)	1.00 (0.80–1.25)
Polypharmacy (no. drugs)						
0–1	837	30.3	3915	39.1	1 (–)	1 (–)
2–4	833	30.1	2992	29.9	1.06 (0.95–1.18)	0.96 (0.85–1.07)
≥5	1093	39.6	3093	30.9	1.12 (1.00–1.25)	0.86 (0.76–0.97)

	LGIB cases N=2763		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Alcohol (u/w)						
None	512	18.5	1860	18.6	1 (–)	1 (–)
1–9	1419	51.4	4757	47.6	1.13 (1.01–1.27)	1.14 (1.01–1.29)
10–20	374	13.5	1532	15.3	0.96 (0.82–1.13)	1.00 (0.85–1.18)
21–41	148	5.4	486	4.9	1.24 (1.00–1.55)	1.24 (0.99–1.56)
≥42	38	1.4	96	1.0	1.55 (1.04–2.31)	1.47 (0.97–2.22)
Unknown	272	9.8	1269	12.7	0.92 (0.78–1.09)	1.07 (0.89–1.28)
PCP visits						
0–4	152	5.5	1500	15.0	1 (–)	1 (–)
5–9	457	16.5	2420	24.2	1.90 (1.56–2.31)	1.39 (1.13–1.70)
10–15	594	21.5	2346	23.5	2.58 (2.13–3.12)	1.65 (1.35–2.02)
15–19	555	20.1	1538	15.4	3.70 (3.05–4.50)	2.17 (1.77–2.67)
≥20	1005	36.4	2196	22.0	4.75 (3.95–5.71)	2.48 (2.03–3.03)
Referrals						
0–4	907	32.8	4947	49.5	1 (–)	1 (–)
5–9	859	31.1	2760	27.6	1.35 (1.21–1.51)	1.27 (1.13–1.42)
10–19	648	23.5	1638	16.4	1.51 (1.33–1.72)	1.34 (1.17–1.53)
≥20	349	12.6	655	6.6	1.78 (1.51–2.11)	1.47 (1.23–1.75)
Hospitalizations						
None	2035	73.7	8486	84.9	1 (–)	1 (–)
1	414	15.0	949	9.5	1.45 (1.27–1.65)	1.33 (1.17–1.53)
2	181	6.6	339	3.4	1.63 (1.35–1.97)	1.48 (1.22–1.81)
≥3	133	4.8	226	2.3	1.68 (1.34–2.10)	1.48 (1.17–1.88)
Townsend score						
Deprived 1 (least deprived)	61	2.2	268	2.7	1 (–)	1 (–)
Deprived 2	761	27.5	2656	26.6	1.30 (0.97–1.75)	1.30 (0.96–1.76)
Deprived 3	637	23.1	2350	23.5	1.22 (0.91–1.64)	1.21 (0.89–1.65)
Deprived 4	560	20.3	2008	20.1	1.23 (0.91–1.66)	1.23 (0.91–1.68)
Deprived 5 (most deprived)	443	16.0	1659	16.6	1.12 (0.83–1.51)	1.09 (0.80–1.49)
Unknown	301	10.9	1059	10.6	1.20 (0.88–1.63)	1.13 (0.82–1.56)
Urban/rural						
Urban	1787	64.7	6414	64.1	1 (–)	1 (–)
Town	363	13.1	1238	12.4	1.03 (0.91–1.18)	1.07 (0.94–1.23)
Rural	223	8.1	665	6.7	1.20 (1.02–1.41)	1.20 (1.01–1.42)
Unknown	390	14.1	1683	16.8	0.81 (0.72–0.92)	0.78 (0.69–0.89)

*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, BMI, history of polyps, history of LGIB, history of unspecified GIB, PU diseases (complicated and uncomplicated), GORD, IBD, IBS, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.
PCP visits, referrals and hospitalizations were ascertained in the year before the index date. Alcohol, BMI and smoking were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy was taken as the number of different medications in the month before the index date.

Table 61. Frequency of comorbidities among LGIB cases and controls, and association (RRs with 95% CIs) with LGIB.

Comorbidities	**LGIB cases N=2763**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
MI	247	8.9	707	7.1	1.10 (0.94–1.28)	0.89 (0.75–1.06)
IS	179	6.5	504	5.0	1.11 (0.93–1.33)	1.00 (0.83–1.20)
TIA	195	7.1	464	4.6	1.34 (1.12–1.60)	1.13 (0.94–1.36)
IHD‡	548	19.8	1278	12.8	1.45 (1.30–1.63)	1.19 (1.05–1.35)
COPD	228	8.3	694	6.9	0.96 (0.81–1.12)	0.92 (0.78–1.09)
Asthma	541	19.6	1597	16.0	1.07 (0.96–1.20)	1.05 (0.94–1.18)
Hypertension	1619	58.6	5564	55.6	0.94 (0.86–1.03)	0.91 (0.82–1.00)
Hyperlipidemia	736	26.6	2403	24.0	1.03 (0.93–1.14)	0.95 (0.86–1.05)
Diabetes	493	17.8	1906	19.1	0.68 (0.61–0.76)	0.67 (0.59–0.75)
DVT	282	10.2	693	6.9	1.31 (1.13–1.52)	1.23 (1.05–1.44)
Anemia§	104	3.8	131	1.3	2.05 (1.57–2.67)	1.77 (1.34–2.34)
Atrial fibrillation	337	12.2	803	8.0	1.25 (1.09–1.44)	1.24 (1.07–1.44)
Heart failure	158	5.7	365	3.6	1.23 (1.01–1.50)	1.19 (0.97–1.46)
All hemodialysis	10	0.4	16	0.2	2.28 (1.03–5.02)	1.52 (0.65–3.56)
Hemodialysis extracorporeal	7	0.3	13	0.1	1.96 (0.78–4.91)	1.31 (0.49–3.53)
Hemodialysis Peritoneal	5	0.2	5	0.1	3.66 (1.06–12.65)	2.36 (0.63–8.86)
eGFR						
0–14	11	0.4	17	0.2	2.16 (1.01–4.62)	1.54 (0.69–3.42)
15–29	48	1.7	120	1.2	1.36 (0.96–1.91)	1.06 (0.74–1.51)
30-44	171	6.2	497	5.0	1.16 (0.96–1.41)	0.99 (0.81–1.21)
45–59	425	15.4	1582	15.8	0.90 (0.80–1.02)	0.89 (0.78–1.01)
≥60	1896	68.6	6370	63.7	1 (–)	1 (–)
Unknown	212	7.7	1414	14.1	0.48 (0.41–0.56)	0.83 (0.70–0.99)
PU, uncomplicated/ complicated	251	9.1	574	5.7	1.45 (1.24–1.70)	1.15 (0.95–1.38)
PU, uncomplicated	163	5.9	424	4.2	1.26 (1.04–1.52)	1.02 (0.83–1.25)
PU, complicated	115	4.2	202	2.0	1.86 (1.47–2.37)	1.51 (1.09–2.11)
IBD	147	5.3	142	1.4	3.48 (2.74–4.43)	3.03 (2.35–3.89)
IBS	346	12.5	700	7.0	1.72 (1.50–1.98)	1.50 (1.29–1.74)
Dyspepsia	905	32.8	2337	23.4	1.38 (1.25–1.51)	1.09 (0.98–1.21)
Constipation	570	20.6	1288	12.9	1.47 (1.31–1.64)	1.25 (1.11–1.41)
Gout	206	7.5	632	6.3	1.03 (0.87–1.21)	0.94 (0.79–1.12)

Pancreatic disease	25	0.9	69	0.7	1.13 (0.71–1.81)	1.08 (0.66–1.77)
GERD	696	25.2	1692	16.9	1.43 (1.29–1.59)	1.19 (1.06–1.33)
Prior UGIB	42	1.5	108	1.1	1.21 (0.84–1.74)	1.06 (0.72–1.55)
Prior LGIB	480	17.4	740	7.4	2.36 (2.08–2.68)	1.98 (1.73–2.26)
Prior GIB unspecified	52	1.9	81	0.8	2.10 (1.46–3.00)	1.52 (1.01–2.30)
Melena	59	2.1	78	0.8	2.56 (1.80–3.63)	2.00 (1.12–3.59)
Polyps	162	5.9	225	2.2	2.32 (1.88–2.87)	1.94 (1.56–2.41)
Depression	807	29.2	2225	22.2	1.26 (1.14–1.39)	1.13 (1.01–1.25)
RA	105	3.8	321	3.2	0.97 (0.77–1.21)	0.81 (0.63–1.02)

[*]Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, BMI, history of polyps, history of LGIB, history of unspecified GIB, PU diseases (complicated and uncomplicated), GORD, IBD, IBS, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

[‡]IHD does not include MI.[§]In the year before the index date.

Comorbidities were ascertained any time before the index date.

Table 62. Frequency of medication use among LGIB cases and controls, and association (RRs with 95% CIs) with LGIB.

Medication use	**LGIB cases N=2763**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Low-dose ASA						
Never use	520	18.8	3540	35.4	1 (–)	1 (–)
Current use (0–30 days)	1428	51.7	4100	41.0	1.93 (1.72–2.16)	1.97 (1.75–2.22)
Recent use (31–90 days)	118	4.3	286	2.9	2.14 (1.69–2.72)	2.15 (1.68–2.75)
Past use (91–365)	185	6.7	512	5.1	1.91 (1.57–2.32)	1.93 (1.57–2.36)
Distant use (>365 days)	512	18.5	1562	15.6	1.88 (1.63–2.16)	1.79 (1.55–2.06)
Duration (continuous) of low-dose ASA among current users						
<3 months	207	7.5	558	5.6	2.01 (1.66–2.43)	2.02 (1.66–2.45)
3–<6 months	146	5.3	378	3.8	2.00 (1.61–2.49)	2.00 (1.60–2.50)
6 months–<1 year	215	7.8	548	5.5	2.05 (1.70–2.48)	2.11 (1.74–2.56)
1–<5 years	678	24.5	2000	20.0	1.93 (1.69–2.20)	1.97 (1.72–2.25)
≥5 years	182	6.6	616	6.2	1.66 (1.37–2.02)	1.75 (1.43–2.14)
Total use among current users						
<3 months	136	4.9	341	3.4	2.18 (1.74–2.73)	2.20 (1.75–2.78)
3–<6 months	110	4.0	297	3.0	1.86 (1.45–2.37)	1.86 (1.44–2.39)
6 months–<1 year	189	6.8	458	4.6	2.19 (1.79–2.67)	2.27 (1.85–2.79)
1–<5 years	767	27.8	2245	22.4	1.94 (1.70–2.20)	1.96 (1.71–2.24)
≥5 years	226	8.2	759	7.6	1.65 (1.38–1.98)	1.72 (1.42–2.07)
Low-dose ASA dose among current users						
75 mg	1344	48.6	3869	38.7	1.92 (1.71–2.16)	1.97 (1.74–2.22)
150–300 mg	84	3.0	231	2.3	1.97 (1.50–2.58)	1.98 (1.50–2.62)
150 mg	75	2.7	192	1.9	2.12 (1.59–2.82)	2.09 (1.55–2.82)
300 mg	9	0.3	39	0.4	1.25 (0.60–2.61)	1.31 (0.62–2.76)
Among primary prevention cohort	**N=1908**		**N=7619**			
Current low-dose ASA users	816	42.8	2540	33.3	1.83 (1.60–2.08)	1.93 (1.68–2.21)
Among secondary prevention cohort	**N=855**		**N=2381**			
Current low-dose ASA users	612	71.6	1560	65.5	1.93 (1.42–264)	1.90 (1.38–2.62)

Medication use	LGIB cases N=2763		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Clopidogrel						
Never use	2427	87.8	9216	92.2	1 (–)	1 (–)
Current use (0–30 days)	159	5.8	289	2.9	1.67 (1.35–2.07)	1.41 (1.14–1.75)
Recent use (31–90 days)	8	0.3	29	0.3	1.12 (0.69–1.82)	0.69 (0.31–1.56)
Past use (91–365)	36	1.3	88	0.9	1.20 (0.81–1.78)	0.95 (0.63–1.43)
Distant use (>365 days)	133	4.8	378	3.8	1.17 (0.95–1.44)	1.00 (0.80–1.23)
Low-dose ASA/clopidogrel (never use as reference)						
No low-dose ASA, no clopidogrel	508	18.4	3485	34.8	1 (–)	1 (–)
DAT	91	3.3	132	1.3	3.30 (2.48–4.41)	3.33 (2.47–4.48)
Low-dose ASA monotherapy	1306	47.3	3878	38.8	1.88 (1.67–2.12)	1.93 (1.71–2.17)
Clopidogrel monotherapy	46	1.7	111	1.1	2.07 (1.44–2.97)	1.80 (1.24–2.62)
Warfarin						
Never use	2465	89.2	9263	92.6	1 (–)	1 (–)
Current use (0–30 days)	180	6.5	444	4.4	1.05 (0.87–1.26)	1.27 (1.04–1.55)
Duration <91 days	30	1.1	46	0.5	1.66 (1.04–2.65)	1.94 (1.20–3.15)
Duration 90–365 days	52	1.9	86	0.9	1.47 (1.04–2.10)	1.79 (1.24–2.58)
Duration >365 days	98	3.5	312	3.1	0.83 (0.65–1.05)	1.00 (0.77–1.28)
Recent use (31–365 days)	29	1.0	69	0.7	1.08 (0.70–1.68)	1.11 (0.71–1.76)
Past use (>365 days)	89	3.2	224	2.2	1.37 (1.06–1.76)	1.18 (0.91–1.54)
INR (ascertained in the 2 months prior) among current users prioritizing the closest value to the index date						
INR <3	108	3.9	261	2.6	1.00 (0.79–1.27)	1.23 (0.96–1.58)
INR ≥3	1	0.0	1	0.0	2.67 (0.17–43.10)	7.37 (0.39–139.91)
Unknown INR	71	2.6	182	1.8	1.11 (0.84–1.48)	1.30 (0.97–1.75)
ASA/warfarin (never use as reference)						
No ASA no warfarin	475	17.2	3376	33.8	1 (–)	1 (–)
Both drugs	42	1.5	53	0.5	3.42 (2.24–5.23)	3.76 (2.43–5.82)
ASA monotherapy	1373	49.7	4019	40.2	1.94 (1.72–2.19)	2.00 (1.77–2.27)
Warfarin monotherapy	110	4.0	331	3.3	1.49 (1.16–1.91)	1.70 (1.32–2.18)

Medication use	LGIB cases N=2763		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Remaining anticoagulants‡						
Never use	2719	98.4	9901	99.1	1 (–)	1 (–)
Current and recent use (<91 days)	11	0.4	12	0.1	2.38 (1.04–5.47)	3.10 (1.32–7.26)
Past use (91–365)	12	0.4	23	0.2	1.35 (0.67–2.74)	1.52 (0.74–3.15)
Distant use (>365 days)	21	0.8	64	0.6	0.95 (0.57–1.56)	0.93 (0.55–1.56)
PPI						
Never use	1205	43.6	5765	57.6	1 (–)	1 (–)
Current use (0–30 days)	822	29.8	1937	19.4	1.59 (1.43–1.78)	1.25 (1.10–1.41)
Duration <91 days	155	5.6	300	3.0	1.95 (1.58–2.40)	1.52 (1.22–1.90)
Duration 90–365 days	154	5.6	373	3.7	1.44 (1.18–1.77)	1.17 (0.94–1.45)
Duration >365 days	513	18.6	1264	12.6	1.55 (1.37–1.76)	1.20 (1.04–1.38)
Recent use (31–90 days)	81	2.9	200	2.0	1.54 (1.18–2.02)	1.29 (0.97–1.72)
Past use (91–365)	161	5.8	453	4.5	1.40 (1.15–1.70)	1.16 (0.95–1.43)
Distant use (>365 days)	494	17.9	1645	16.4	1.32 (1.17–1.49)	1.14 (1.00–1.30)
H_2RA						
Never use	1972	71.4	7879	78.8	1 (–)	1 (–)
Current use (0–30 days)	94	3.4	278	2.8	1.17 (0.92–1.49)	1.03 (0.80–1.33)
Duration <91 days	22	0.8	59	0.6	1.32 (0.80–2.19)	1.06 (0.63–1.78)
Duration 90–365 days	25	0.9	66	0.7	1.14 (0.71–1.82)	0.96 (0.59–1.56)
Duration >365 days	47	1.7	153	1.5	1.13 (0.80–1.57)	1.06 (0.75–1.50)
Recent use (31–90 days)	15	0.5	39	0.4	1.14 (0.62–2.09)	0.98 (0.52–1.83)
Past use (91–365)	28	1.0	100	1.0	0.87 (0.57–1.33)	0.75 (0.48–1.17)
Distant use (>365 days)	654	23.7	1704	17.0	1.35 (1.21–1.50)	1.06 (0.94–1.19)
Antacids						
Never use	1906	69.0	7674	76.7	1 (–)	1 (–)
Current use (0–30 days)	187	6.8	429	4.3	1.47 (1.22–1.77)	1.23 (1.01–1.49)
Duration <91 days	41	1.5	93	0.9	1.43 (0.98–2.09)	1.11 (0.74–1.64)
Duration 90–365 days	56	2.0	112	1.1	1.65 (1.18–2.29)	1.34 (0.95–1.90)
Duration >365 days	90	3.3	224	2.2	1.39 (1.08–1.80)	1.22 (0.94–1.59)
Recent use (31–90 days)	36	1.3	78	0.8	1.56 (1.04–2.35)	1.30 (0.86–1.98)
Past use (91–365)	78	2.8	195	1.9	1.29 (0.98–1.69)	1.04 (0.78–1.38)
Distant use (>365 days)	556	20.1	1624	16.2	1.21 (1.09–1.36)	0.97 (0.86–1.10)

Medication use	LGIB cases N=2763		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
SSRI						
Never use	2069	74.9	8096	81.0	1 (–)	1 (–)
Current use (0–30 days)	192	6.9	547	5.5	1.09 (0.92–1.30)	0.98 (0.82–1.18)
Duration <91 days	31	1.1	88	0.9	1.04 (0.69–1.58)	0.96 (0.62–1.50)
Duration 90–365 days	50	1.8	122	1.2	1.19 (0.85–1.67)	1.13 (0.79–1.60)
Duration >365 days	111	4.0	337	3.4	1.07 (0.85–1.34)	0.93 (0.74–1.18)
Recent use (31–90 days)	27	1.0	48	0.5	1.75 (1.08–2.83)	1.72 (1.04–2.85)
Past use (91–365)	57	2.1	162	1.6	1.12 (0.82–1.53)	1.09 (0.79–1.51)
Distant use (>365 days)	418	15.1	1147	11.5	1.26 (1.11–1.43)	1.15 (1.01–1.32)
NSAIDs						
Never use	593	21.5	2893	28.9	1 (–)	1 (–)
Current use (0–30 days)	359	13.0	841	8.4	1.69 (1.44–1.97)	1.61 (1.37–1.89)
Duration <91 days	134	4.8	317	3.2	1.68 (1.34–2.11)	1.59 (1.26–2.00)
Duration 90–365 days	83	3.0	170	1.7	1.85 (1.40–2.45)	1.87 (1.40–2.50)
Duration >365 days	142	5.1	354	3.5	1.61 (1.29–2.00)	1.48 (1.18–1.86)
Recent use (31–90 days)	105	3.8	316	3.2	1.33 (1.04–1.70)	1.23 (0.96–1.58)
Past use (91–365)	302	10.9	874	8.7	1.40 (1.19–1.64)	1.29 (1.09–1.52)
Distant use (>365 days)	1404	50.8	5076	50.8	1.20 (1.07–1.34)	1.08 (0.97–1.21)
tNSAIDs						
Never use	632	22.9	3019	30.2	1 (–)	1 (–)
Current use (0–30 days)	316	11.4	747	7.5	1.66 (1.42–1.96)	1.59 (1.35–1.88)
Duration <91 days	128	4.6	301	3.0	1.69 (1.34–2.12)	1.58 (1.25–2.00)
Duration 90–365 days	81	2.9	158	1.6	1.93 (1.45–2.57)	2.01 (1.50–2.70)
Duration >365 days	107	3.9	288	2.9	1.49 (1.17–1.89)	1.37 (1.06–1.76)
Recent use (31–90 days)	99	3.6	310	3.1	1.26 (0.99–1.62)	1.19 (0.92–1.53)
Past use (91–365)	285	10.3	818	8.2	1.39 (1.18–1.64)	1.29 (1.09–1.54)
Distant use (>365 days)	1431	51.8	5106	51.1	1.19 (1.07–1.33)	1.09 (0.97–1.21)
COXIBS						
Never use	2293	83.0	8693	86.9	1 (–)	1 (–)
Current use (0–30 days)	49	1.8	103	1.0	1.48 (1.04–2.10)	1.46 (1.02–2.11)
Duration <91 days	14	0.5	38	0.4	1.06 (0.57–1.98)	1.15 (0.61–2.17)
Duration 90–365 days	13	0.5	17	0.2	2.42 (1.16–5.06)	2.45 (1.15–5.27)
Duration >365 days	22	0.8	48	0.5	1.48 (0.88–2.49)	1.37 (0.80–2.35)
Recent use (31–90 days)	10	0.4	19	0.2	1.48 (0.68–3.21)	1.33 (0.59–3.01)
Past use (91–365)	47	1.7	118	1.2	1.26 (0.89–1.78)	1.18 (0.83–1.69)
Distant use (>365 days	364	13.2	1067	10.7	1.10 (0.97–1.26)	0.99 (0.86–1.14)

Medication use	LGIB cases N=2763		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
Acetaminophen						
Never use	613	22.2	3337	33.4	1 (–)	1 (–)
Current use (0–30 days)	665	24.1	1884	18.8	1.44 (1.26–1.64)	1.13 (0.98–1.31)
Duration <91 days	222	8.0	614	6.1	1.49 (1.24–1.78)	1.20 (0.99–1.45)
Duration 90–365 days	146	5.3	409	4.1	1.40 (1.13–1.73)	1.07 (0.85–1.34)
Duration >365 days	297	10.7	861	8.6	1.41 (1.19–1.66)	1.11 (0.93–1.33)
Recent use (31–90 days)	206	7.5	560	5.6	1.51 (1.25–1.82)	1.25 (1.02–1.52)
Past use (91–365)	333	12.1	941	9.4	1.47 (1.25–1.72)	1.19 (1.01–1.41)
Distant use (>365 days	946	34.2	3278	32.8	1.37 (1.22–1.53)	1.20 (1.06–1.35)
Oral steroids						
Never use	2048	74.1	8019	80.2	1 (–)	1 (–)
Current use (0–30 days)	137	5.0	305	3.0	1.22 (0.99–1.51)	1.09 (0.87–1.36)
Recent use (31–90 days)	47	1.7	110	1.1	1.21 (0.85–1.71)	0.99 (0.68–1.44)
Past use (91–365)	102	3.7	320	3.2	0.93 (0.74–1.17)	0.85 (0.67–1.09)
Distant use (>365 days)	429	15.5	1246	12.5	1.17 (1.04–1.33)	1.02 (0.89–1.16)
Inhaled steroids						
Never use	2198	79.6	8413	84.1	1 (–)	1 (–)
Current use (0–7 days)	219	7.9	693	6.9	0.97 (0.82–1.14)	0.96 (0.81–1.13)
Recent use (8–90 days)	52	1.9	121	1.2	1.33 (0.95–1.86)	1.41 (1.00–1.99)
Past use (91–365)	66	2.4	171	1.7	1.21 (0.90–1.62)	1.16 (0.86–1.57)
Distant use (>365 days)	228	8.3	602	6.0	1.27 (1.08–1.49)	1.19 (1.01–1.41)
Antihypertensive medications						
Never use	464	16.8	2405	24.1	1 (–)	1 (–)
Current use (0–30 days)	1921	69.5	6405	64.0	1.09 (0.97–1.24)	0.89 (0.78–1.02)
Recent use (31–90 days)	56	2.0	159	1.6	1.31 (0.95–1.82)	1.14 (0.81–1.61)
Past use (91–365)	59	2.1	216	2.2	0.96 (0.70–1.31)	0.83 (0.60–1.15)
Distant use (>365 days)	263	9.5	815	8.2	1.39 (1.17–1.66)	1.17 (0.97–1.40)
Statins						
Never use	1121	40.6	4724	47.2	1 (–)	1 (–)
Current use (0 –30 days)	1345	48.7	4414	44.1	1.01 (0.92–1.11)	0.77 (0.69–0.85)
Duration <91 days	133	4.8	329	3.3	1.01 (0.92–1.11)	0.99 (0.79–1.24)
Duration 90–365 days	220	8.0	770	7.7	1.30 (0.98–1.73)	0.64 (0.53–0.76)
Duration >365 days	992	35.9	3315	33.1	1.05 (0.80–1.38)	0.77 (0.69–0.87)
Recent use (31–90 days)	74	2.7	176	1.8	1.30 (0.98–1.73)	1.02 (0.76–1.39)
Past use (91–365)	76	2.8	237	2.4	1.05 (0.80–1.38)	0.85 (0.64–1.13)
Distant use (>365 days)	147	5.3	449	4.5	1.19 (0.97–1.46)	0.93 (0.75–1.15)

*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, BMI, history of polyps, history of LGIB, history of unspecified GIB, PU diseases (complicated and uncomplicated), GORD, IBD, IBS, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

[‡]Owing to low numbers current and recent users were merged into one category (there were 11 current/recent users among cases: acenocoumarol [n=1], dalteparin [n=3], enoxaparin [n=4], phenindione [n=1] and tinazparin [n=2]; there were 12 current users among controls: dabigatran [n=2], enoxaparin [n=4], dalteparin [n=2] and phenindione [n=4]). Warfarin was excluded from the model.

Table 63. Sensitivity analyses: frequency of low-dose ASA and PPI use among UGIB cases and controls, and association (RRs with 95% CIs) with UGIB, after removing any user of anticoagulants or other antiplatelets (other than low-dose ASA: 687 cases and 1670 controls removed).

Medication	**LGIB cases N=2076**		**Controls N=8330**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Low-dose ASA						
Never use	461	22.2	3302	39.6	1 (-)	1 (-)
Current use (0–30 days)	1046	50.4	3284	39.4	1.85 (1.63-2.10)	1.94 (1.70-2.21)
Recent use (31–90 days)	88	4.2	223	2.7	2.20 (1.68-2.88)	2.27 (1.72-2.99)
Past use (91–365)	131	(6.3	394	4.7	1.89 (1.51-2.37)	1.96 (1.56-2.47)
Distant use (>365 days)	350	16.9	1127	13.5	1.93 (1.65-2.26)	1.85 (1.57-2.18)
Duration (continuous) of low-dose ASA among current users						
<3 months	155	7.5	465	5.6	1.92 (1.55-2.37)	1.99 (1.60-2.47)
3–<6 months	108	5.2	312	3.7	1.90 (1.49-2.43)	1.96 (1.52-2.53)
6 months–<1 year	159	7.7	447	5.4	2.00 (1.62-2.47)	2.10 (1.69-2.61)
1–<5 years	492	23.7	1584	19.0	1.85 (1.60-2.14)	1.93 (1.66-2.24)
≥5 years	132	6.4	476	5.7	1.61 (1.29-2.01)	1.74 (1.39-2.19)
PPIs						
Never use	972	46.8	5079)	61.0	1 (-)	1 (-)
Current use (0–30 days)	558	26.9	1411	16.9	1.62 (1.43-1.84)	1.25 (1.08-1.45)
Duration <91 days	120	5.8	252	3.0	1.95 (1.55-2.46)	1.49 (1.17-1.91)
Duration 90–365 days	104	5.0	274	3.3	1.47 (1.16-1.87)	1.20 (0.93-1.54)
Duration >365 days	334	16.1	885	10.6	1.58 (1.36-1.83)	1.19 (1.01-1.41)
Recent use (31–90 days)	49	2.4	153	1.8	1.35 (0.97-1.89)	1.14 (0.80-1.61)
Past use (91–365)	126	6.1	362	4.3	1.50 (1.20-1.86)	1.26 (1.00-1.58)
Distant use (>365 days)	371	17.9	1325	15.9	1.33 (1.16-1.53)	1.14 (0.98-1.32)

*Adjusted by age, sex, calendar year and number of GP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of GP visits in the year prior to the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated PU problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

Table 64. Frequency of low-dose ASA use among LGIB cases and controls, and association (RRs with 95% CIs) with LGIB, stratified by case–fatality status.

Fatal cases	**LGIB cases N=24**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	7	29.2	3540	35.4	1 (–)	1 (–)
Current use (0–30 days)	13	54.2	4100	41.0	1.04 (0.41–2.63)	1.06 (0.40–2.81)
Recent use (31–90 days)	2	8.3	286	2.9	2.02 (0.40–10.08)	2.04 (0.38–11.01)
Past (91–365)	1	4.2	512	5.1	0.56 (0.07–4.62)	0.47 (0.05–4.18)
Distant (>365 days)	1	4.2	1562	15.6	0.25 (0.03–2.06)	0.21 (0.02–1.98)
Non–fatal cases	**LGIB cases N=2738**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	513	18.7	3540	35.4	1 (–)	1 (–)
Current use (0–30 days)	1414	51.6	4100	41.0	1.94 (1.73–2.17)	1.98 (1.76–2.23)
Recent use (31–90 days)	116	4.2	286	2.9	2.14 (1.68–2.72)	2.15 (1.68–2.75)
Past (91–365)	184	6.7	512	5.1	1.93 (1.59–2.35)	1.95 (1.59–2.39)
Distant (>365 days)	511	18.7	1562	15.6	1.90 (1.65–2.19)	1.81 (1.56–2.09)

*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, history of UGIB, history of LGIB, history of unspecified GIB, pancreatic disease, uncomplicated PU problems, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

Table 65. Frequency of low-dose ASA use among LGIB cases and controls, and association (RRs with 95% CIs) with LGIB, stratified by level of healthcare assistance.

Hospitalized cases	**LGIB cases N=771**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	146	18.9	3540	35.4	1 (–)	1 (–)
Current use (0–30 days)	428	55.5	4100	41.0	1.85 (1.51–2.26)	1.93 (1.57–2.36)
Recent use (31–90 days)	34	4.4	286	2.9	1.92 (1.29–2.87)	1.88 (1.25–2.84)
Past (91–365)	46	6.0	512	5.1	1.45 (1.02–2.07)	1.50 (1.05–2.15)
Distant (>365 days)	117	15.2	1562	15.6	1.35 (1.05–1.75)	1.31 (1.01–1.70)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	65	8.4	558	5.6	2.04 (1.49–2.79)	2.13 (1.55–2.93)
3–<6 months	51	6.6	378	3.8	2.23 (1.58–3.15)	2.27 (1.60–3.22)
6 months–<1 year	59	7.7	548	5.5	1.76 (1.28–2.44)	1.87 (1.34–2.60)
1–<5 years	199	25.8	2000	20.0	1.82 (1.45–2.28)	1.88 (1.49–2.37)
≥5 years	54	7.0	616	6.2	1.60 (1.15–2.23)	1.68 (1.19–2.37)
Referred cases	**LGIB cases N=1989**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	374	18.8	3540	35.4	1 (–)	1 (–)
Current use (0–30 days)	997	50.1	4100	41.0	1.95 (1.71–2.23)	1.98 (1.73–2.28)
Recent use (31–90 days)	84	4.2	286	2.9	2.23 (1.70–2.92)	2.24 (1.70–2.95)
Past (91–365)	139	7.0	512	5.1	2.11 (1.69–2.63)	2.11 (1.69–2.65)
Distant (>365 days)	395	19.9	1562	15.6	2.09 (1.78–2.44)	1.98 (1.69–2.33)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	141	7.1	558	5.6	1.98 (1.59–2.46)	1.96 (1.56–2.45)
3–<6 months	95	4.8	378	3.8	1.90 (1.48–2.46)	1.89 (1.45–2.45)
6 months–<1 year	156	7.8	548	5.5	2.18 (1.76–2.70)	2.23 (1.79–2.78)
1–<5 years	477	24.0	2000	20.0	1.97 (1.69–2.29)	2.00 (1.71–2.34)
≥5 years	128	6.4	616	6.2	1.69 (1.35–2.12)	1.76 (1.40–2.22)

*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, BMI, history of polyps, history of LGIB, history of unspecified GIB, PU diseases (complicated and uncomplicated), GORD, IBD, IBS, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

Table 66. Frequency of low-dose ASA use among LGIB cases and controls, and association (RRs with 95% CIs) with LGIB, stratified by bleeding location.

Diverticular disease cases	**Cases N=1189**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	199	16.7	3540	35.4	1 (–)	1 (–)
Current use (0–30 days)	653	54.9	4100	41.0	2.31 (1.94–2.73)	2.33 (1.96–2.77)
Recent use (31–90 days)	42	3.5	286	2.9	2.07 (1.45–2.96)	1.98 (1.38–2.86)
Past (91–365)	73	6.1	512	5.1	2.01 (1.51–2.69)	2.01 (1.50–2.70)
Distant (>365 days)	222	18.7	1562	15.6	2.13 (1.74–2.61)	2.01 (1.63–2.48)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	91	7.7	558	5.6	2.40 (1.83–3.15)	2.41 (1.81–3.21)
3–<6 months	61	5.1	378	3.8	2.28 (1.67–3.11)	2.25 (1.62–3.14)
6 months–<1 year	100	8.4	548	5.5	2.58 (1.99–3.36)	2.32 (1.74–3.08)
1–<5 years	307	25.8	2000	20.0	2.27 (1.87–2.75)	2.24 (1.84–2.73)
≥5 years	94	7.9	616	6.2	2.14 (1.64–2.79)	2.23 (1.69–2.95)
Polyp cases	**Cases N=296**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Never use	38	12.8	3540	35.4	1 (–)	1 (–)
Current use (0 –30 days)	164	55.4	4100	41.0	3.15 (2.18–4.55)	3.09 (2.13–4.50)
Recent use (31–90 days)	9	3.0	286	2.9	2.34 (1.11–4.93)	2.23 (1.05–4.73)
Past (91–365)	19	6.4	512	5.1	2.87 (1.63–5.07)	2.78 (1.56–4.93)
Distant (>365 days)	66	22.3	1562	15.6	3.34 (2.21–5.04)	3.24 (2.14–4.90)
Duration of low-dose ASA among current users (continuous duration)						
<3 months	26	8.8	558	5.6	3.63 (2.16–6.10)	3.43 (2.03–5.80)
3–<6 months	16	5.4	378	3.8	3.06 (1.67–5.62)	3.01 (1.63–5.55)
6 months–<1 year	20	6.8	548	5.5	2.78 (1.59–4.88)	2.76 (1.57–4.87)
1–<5 years	82	27.7	2000	20.0	3.38 (2.27–5.05)	3.34 (2.22–5.02)
≥5 years	20	6.8	616	6.2	2.48 (1.41–4.35)	2.46 (1.39–4.36)

*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, BMI, history of polyps, history of LGIB, history of unspecified GIB, PU diseases (complicated and uncomplicated), GORD, IBD, IBS, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

11. Discussion

11.1 Key Results

Incidence rates (95% CIs) of bleeding outcomes over the whole follow-up period in the low-dose ASA and comparison cohort, respectively, were 7.61 vs. 6.78 cases per 10,000 person-years for ICB (3.52 vs. 3.12 per 10,000 person-years for ICH, 2.45 vs. 1.86 per 10,000 person-years for SDH and 1.65 vs. 1.80 per 10,000 person-years for SAH), 0.97 vs. 0.67 per 1000 person-years for UGIB and 1.68 vs. 0.76 per 1000 person-years for LGIB. Incidence rate ratios (low-dose ASA vs. comparison cohort) over the whole duration of the follow-up were 1.11 (95% CI: 1.01–1.22) for all ICB, 1.12 (95% CI: 0.97–1.29) for ICH, 1.28 (95% CI: 1.07–1.53) for SDH, 0.92 (95% CI: 0.75–1.13) for SAH, 1.42 (95% CI: 1.29–1.56) for UGIB and 2.17 (95% CI: 2.00–2.35) for LGIB. The IRR in the first year of follow-up was 1.02 (95% CI: 0.81–1.29) for all cases of ICB, 1.80 (95% CI: 1.46–2.22) for UGIB and 2.30 (95% CI: 1.91–2.77) for LGIB.

Compared with individuals who had never used low-dose ASA, no significant change in risk of ICB was seen among current users of low-dose ASA (RR 0.98, 95% CI: 0.84–1.13); this lack of association was observed for both sexes for ICH and SDH, whereas a significant 43% decreased risk of SAH was seen among women (RR 0.57, 95% CI: 0.39–0.82; no association apparent in men). For GIB, current users of low-dose ASA had an increased risk of UGIB (RR 1.62, 95% CI:1.40–1.87) and LGIB (1.97, 95% CI: 1.75–2.22) compared with never users.

Analyses stratified by case-fatality status showed that, compared with never users of low-dose ASA, current use was not associated with a significant change in risk of fatal UGIB or LGIB, and was associated with a significant 37% decreased risk of fatal ICB (RR 0.63, 95% CI: 0.48–0.82). No significant change in the risk of non-fatal ICB was seen with current use of low-dose ASA (compared with never use) while the risk of non-fatal UGIB and non-fatal LGIB was significantly raised, approaching a two-fold increased risk: RR 1.73 (95% CI: 1.49–2.01) for non-fatal UGIB and RR 1.98 (95% CI: 1.76–2.23) for non-fatal LGIB.

Among current users of low-dose ASA, short-, medium- or long-term use was not associated with a significant change in risk of ICB, when considering all cases types of ICB as a single group, and compared with never users. Some duration of use associations were seen when evaluating current use of low-dose ASA and risk of individual ICB subtypes or after stratification by trauma/non-trauma-related status. For example, a significant 33% decrease in risk of SAH was seen with long-term use (1–<5 years; RR 0.67, 95% CI: 0.47–0.94), while a two-fold significant increase in risk was seen for traumatic SDH with short-term use (<3 months; RR 1.96, 95% CI: 1.10–3.48), and a borderline significant increased risk of all traumatic cases of ICB was seen with medium-term use (RR 1.83, 95% CI: 1.07–3.13 for 3–<6 months and

RR 1.68, 95% CI: 1.06–2.64 for 6 months–<1 year). Current use of low-dose ASA was associated with significantly increased risks of UGIB and LGIB when used either in the short- medium- or long-term, and no clear relationships between duration of low-dose ASA and risk of UGIB or LGIB were apparent. No significant dose–response relationship between current use of low-dose ASA and risk of ICB or LGIB for the doses of ASA evaluated in this study (75 mg–300 mg per day), however, the results were suggestive of a dose–response relationship between low-dose ASA and UGIB (RR 1.30, 95% CI: 0.93–1.83) for current user of low-dose ASA at a dose or 75 mg/day compared with current use of low-dose ASA at a dose of more than 75 mg/day).

For all bleeding outcomes, use of DAT always carried a greater risk than the sum of each antiplatelet used in monotherapy. Current use of DAT was associated with a two-fold risk of traumatic ICB (RR 2.09, 95% CI: 1.13–3.89); the effect being restricted to cases of traumatic SDH (RR 2.29, 95% CI: 1.09–4.80), and a three-to-four-fold risk of GIB; RR 3.87 (95% CI: 2.73–5.50) for UGIB and 3.33 (95% CI: 2.47–4.48) for LGIB, when compared with never use of either medication. Compared with never use of either medication, concomitant current use of low-dose ASA and warfarin was associated with a two-fold significantly increased risk of ICB (RR 2.31, 95% CI: 1.36–3.91); the effect being restricted to cases of SDH (RR 4.43, 95% CI: 2.16–9.09) with an eight-fold increased risk seen among non-traumatic cases of SDH (RR 8.63, 95% CI: 3.57–20.86), when compared with never users of either low-dose ASA or warfarin. Similar to the findings for DAT, current use of low-dose ASA and warfarin was associated with a three to four-fold increased risk of UGIB (RR 3.35, 95% CI: 2.01–5.60) and LGIB (RR 3.76, 95% CI: 2.43–5.82).

11.2 Limitations

The lack of detailed clinical information for all cases might have introduced some minor misclassification of the study outcomes, yet the prospective nature of the data collection prevents this information bias being differential between low-dose ASA exposed cases and non-exposed cases. We have previously shown that low-dose ASA can sometimes obtained over-the counter but the frequency of non-prescription low-dose ASA was found to be very small.(24) and therefore should have little or no impact on our measures of association. Although we did not evaluate prevouis use of high-dose ASA in our analyses, any residual confounding is likely to be very minimal. The numbers of cases and controls using high-dose ASA as an analgesic were small in each nested case–control analysis, with nearly all using the medication more than a year before the index date (8 cases and 29 controls in the ICB analysis, 4 cases and 15 controls in the UGIB case–control analysis, and 9 cases and 39 controls in the LGIB case–control analysis).

11.3 Interpretation

While use of low-dose ASA has been linked to a small increased risk of ICB in RCTs,(25) previous evidence from observational studies regarding use of low-dose ASA has been equivocal (26, 27) with some (28) albeit not all, (27) reporting a decreased risk of SAH with long term low-dose ASA use. This present study did not find a significantly increased risk of ICB among current users of low-dose ASA compared with never users of the medication, in line with previous observational research, and also found a significant 33% decreased risk of SAH with long-term use. (28) This present study also found a different effect of low-dose ASA on the risk of SAH between the sexes, with no effect seen in men and a significant 43% decreased risk among women. While low-dose ASA was clearly associated with a significant increase in GIB in this study, in line with previous findings from RCTs (29) and observational studies, (26) the increase in risk was restricted to non-fatal events of UGIB and LGIB, with no significant increase risk observed for fatal UGIB or LGIB. Importantly, when low-dose ASA was used concomitantly with certain other medications, the risk of bleeding events, were found to be greater than those with low-dose ASA monotherapy, as found in previous research. (26) In particular, the risk of non-traumatic SDH was raised eight-fold when low-dose ASA was used concomitantly with warfarin.

11.4 Generalizability

THIN is representative of the UK population with regards to age, sex and geographic distribution and major disease prevalence(19, 20), giving our results good external validity. The study population also included a broad range of patients, including those with GI disorders or antecedents, and both primary and secondary CVD prevention populations who may have been excluded from ASA clinical trials, and thereby representing individuals using low-dose ASA in the real-world.

12. Other information

None.

13. Conclusion

New use of low-dose ASA is not associated with a significant increase in the risk of ICB overall compared with never use, and may be associated with a significantly decreased risk of fatal ICB, and of SAH in women or when used for a long duration. The risk of non-fatal UGIB and LGIB events is significantly higher among new users of low-dose ASA compared with never users, but not significantly different for fatal cases of UGIB or LGIB when compared with never users. These estimates should be weighed against the cardiovascular and CRC benefits of low-dose ASA to make an informed risk–benefit evaluation of low-dose ASA use in the general population.

14. References

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15. Appendices

15.1 Appendix tables

Appendix Table 1. Read codes for ICB.

Read	Descriptor
7004100	Evacuation of haematoma from temporal lobe of brain
7004200	Evacuation of haematoma from cerebellum
7004300	Evacuation of intracerebral haematoma NEC
7008200	Aspiration of haematoma of brain tissue
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G619.00	Lobar cerebral haemorrhage
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G681.00	Sequelae of intracerebral haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
7017000	Evacuation of subdural haematoma
7034.00	Drainage of subdural space
7034y00	Other specified drainage of subdural space
7034z00	Drainage of subdural space NOS
G621.00	Subdural haemorrhage - nontraumatic
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
S62..13	Subdural haemorrhage following injury
S622.00	Closed traumatic subdural haemorrhage
S622000	Subdural h'ge inj no open intracranial wnd + unspec consc
S622100	Subdural h'ge inj no open intracranial wound+no loss consc
S622200	Subdural h'ge inj no open intracranial wound+<1hr loss consc
S622300	Subdural h'ge inj no open intracran wnd+1-24hr loss consc
S622400	Subdural h'ge inj no open intracranial wnd+>24 LOC +recovery

Read	Descriptor
S622500	Subdural h'ge inj no open intracran wnd+>24hr LOC -restored
S622600	Subdural h'ge inj no open intracran wnd+LOC unspec duration
S622z00	Subdural h'ge inj no open intracran wound+concussion unspec
S623.00	Open traumatic subdural haemorrhage
S623000	Subdural h'ge inj + open intracranial wound + unspec consc
S623100	Subdural h'ge inj + open intracranial wound+no loss consc
S623200	Subdural h'ge inj + open intracranial wound+<1hr loss consc
S623300	Subdural h'ge inj + open intracranial wnd+1-24hr loss consc
S623400	Subdural h'ge inj + open intracran wound+>24hr LOC +recovery
S623500	Subdural h'ge inj + open intracran wnd+>24hr LOC -restored
S623600	Subdural h'ge inj + open intracran wnd+LOC unspec duration
S623z00	Subdural h'ge inj + open intracranial wnd+concussion unspec
S628.00	Traumatic subdural haemorrhage
S629.00	Traumatic subdural haematoma
S629000	Traumatic subdural haematoma without open intracranial wound
S629100	Traumatic subdural haematoma with open intracranial wound
G60..00	Subarachnoid haemorrhage
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G680.00	Sequelae of subarachnoid haemorrhage
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
S62..12	Subarachnoid haemorrhage following injury
S620.00	Closed traumatic subarachnoid haemorrhage
S620000	Subarachnoid h'ge inj no open intracran wound + unspec consc
S620100	Subarachnoid h'ge inj no open intracran wnd+no loss consc
S620200	Subarachnoid h'ge inj no open intracran wnd+<1hr loss consc
S620300	Subarachnoid h'ge inj no open intracran wound + 1-24hr LOC
S620400	Subarachnoid h'ge inj no open intracran wnd+>24 LOC+recovery
S620500	Subarach h'ge inj no open intracran wnd+>24hrs LOC-restored
S620600	Subarach h'ge inj no open intracran wnd+LOC unspec duration
S620z00	Subarach h'ge inj no open intracran wnd + concussion unspec
S621.00	Open traumatic subarachnoid haemorrhage
S621000	Subarachnoid h'ge inj + open intracran wound + unspec consc
S621100	Subarachnoid h'ge inj + open intracranial wound + no LOC

Read	Descriptor
S621200	Subarachnoid h'ge inj + open intracran wound+<1hr loss consc
S621300	Subarachnoid h'ge inj + open intracran wnd+1-24hr loss consc
S621400	Subarach h'ge inj + open intracran wnd +>24hr LOC + recovery
S621500	Subarach h'ge inj + open intracran wnd+>24hr LOC -restored
S621600	Subarach h'ge inj + open intracran wnd+LOC unspec duration
S621z00	Subarachnoid h'ge inj + open intracran wnd+concussion unspec
S627.00	Traumatic subarachnoid haemorrhage
7032000	Evacuation of extradural haematoma
G600.00	Ruptured berry aneurysm
G62..00	Other and unspecified intracranial haemorrhage
G620.00	Extradural haemorrhage - nontraumatic
G62z.00	Intracranial haemorrhage NOS
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage
S62..00	Cerebral haemorrhage following injury
S62..11	Extradural haemorrhage following injury
S62..14	Traumatic cerebral haemorrhage
S620.11	Middle meningeal haemmorhage following injury
S624.00	Closed traumatic extradural haemorrhage
S624.11	Epidural haematoma following injury
S624000	Extradural h'ge inj no open intracranial wnd + unspec consc
S624100	Extradural h'ge inj no open intracranial wnd + no loss consc
S624200	Extradural h'ge inj no open intracranial wnd+<1hr loss consc
S624300	Extradural h'ge inj no open intracran wnd+1-24hr loss consc
S624400	Extradural h'ge inj no open intracran wnd+>24hr LOC+recovery
S624500	Extradural h'ge inj no open intracran wnd+>24hr LOC-restored
S624600	Extradural h'ge inj no open intracra wnd+LOC unspec duration
S624z00	Extradural h'ge inj no open intracran wnd+concussion unspec
S625.00	Open traumatic extradural haemorrhage
S625000	Extradural h'ge inj + open intracranial wnd + unspec consc
S625100	Extradural h'ge inj + open intracranial wound+no loss consc
S625200	Extradural h'ge inj + open intracranial wnd+<1hr loss consc
S625300	Extradural h'ge inj + open intracran wnd+1-24hr loss consc
S625400	Extradural h'ge inj + open intracran wnd+>24hr LOC+recovery
S625500	Extradural h'ge inj + open intracran wnd+>24hr LOC -restored
S625600	Extradural h'ge inj + open intracran wnd+LOC unspec duration
S625z00	Extradural h'ge inj + open intracran wnd+concussion unspec
S626.00	Epidural haemorrhage
S62A.00	Traumatic extradural haematoma
S62A000	Traumatic extradural haemat without open intracranial wound
S62A100	Traumatic extradural haematoma with open intracranial wound
S62z.00	Cerebral haemorrhage following injury NOS

Read	Descriptor
S63..00	Other cerebral haemorrhage following injury
S630.00	Other cerebral h'ge after injury no open intracranial wound
S630.11	Cerebral compression due to injury
S630.12	Intracranial haematoma following injury
S630000	Oth cerebral h'ge inj no open intracran wnd+unspec consc
S630100	Oth cerebral h'ge inj no open intracranial wnd+no loss consc
S630200	Oth cerebral h'ge inj no open intracran wnd+<1hr loss consc
S630300	Oth cerebral h'ge inj no open intracran wnd+1-24hr LOC
S630400	Oth cereb h'ge inj no open intracran wnd+>24hr LOC +recovery
S630500	Oth cereb h'ge inj no open intracran wnd+>24hr LOC -restored
S630600	Oth cereb h'ge inj no open intracran wnd+LOC unspec duration
S630z00	Oth cereb h'ge inj no open intracran wnd+concussion unspec
S631.00	Other cerebral h'ge after injury + open intracranial wound
S631000	Oth cerebral h'ge inj + open intracran wnd + unspec consc
S631100	Oth cerebral h'ge inj + open intracranial wnd+no loss consc
S631200	Oth cerebral h'ge inj + open intracran wnd+<1hr loss consc
S631300	Oth cerebral h'ge inj + open intracran wnd+1-24hr loss consc
S631400	Oth cereb h'ge inj + open intracran wnd+>24hr LOC + recovery
S631500	Oth cereb h'ge inj + open intracran wnd+>24hr LOC -restored
S631600	Oth cereb h'ge inj + open intracran wnd+LOC unspec duration
S631z00	Oth cereb h'ge inj + open intracran wnd+concussion unspec
S63z.00	Other cerebral haemorrhage following injury NOS

Appendix Table 2. Read codes for UGIB.

Read	Descriptor
14C8.00	H/O: haematemesis
14C9.00	H/O: melaena
1994.11	Blood in vomit - symptom
19E4.12	C/O - melaena
4737.11	Melaena - O/E of faeces
4A23.00	Vomit: frank blood present
4A23.11	Blood in vomit O/E
4A24.00	Vomit: coffee ground
4A24.11	Coffee ground vomit
4A5..00	Vomit occult blood
4A5..11	Occult blood in vomit
4A51.00	Vomit occult blood positive
4A5Z.00	Vomit occult blood NOS
J110100	Acute gastric ulcer with haemorrhage
J110111	Bleeding acute gastric ulcer
J110300	Acute gastric ulcer with haemorrhage and perforation
J110400	Acute gastric ulcer with obstruction
J111100	Chronic gastric ulcer with haemorrhage
J111111	Bleeding chronic gastric ulcer
J111300	Chronic gastric ulcer with haemorrhage and perforation
J111400	Chronic gastric ulcer with obstruction
J11y100	Unspecified gastric ulcer with haemorrhage
J11y300	Unspecified gastric ulcer with haemorrhage and perforation
J11y400	Unspecified gastric ulcer with obstruction
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J120100	Acute duodenal ulcer with haemorrhage
J120300	Acute duodenal ulcer with haemorrhage and perforation
J120400	Acute duodenal ulcer with obstruction
J121100	Chronic duodenal ulcer with haemorrhage
J121111	Bleeding chronic duodenal ulcer
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J121400	Chronic duodenal ulcer with obstruction
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12y400	Unspecified duodenal ulcer with obstruction
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J130100	Acute peptic ulcer with haemorrhage
J130300	Acute peptic ulcer with haemorrhage and perforation
J130400	Acute peptic ulcer with obstruction
J131100	Chronic peptic ulcer with haemorrhage
J131300	Chronic peptic ulcer with haemorrhage and perforation
J131400	Chronic peptic ulcer with obstruction
J13y100	Unspecified peptic ulcer with haemorrhage
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J13y400	Unspecified peptic ulcer with obstruction
J13yy00	Unspec peptic ulcer; unspec haemorrhage and/or perforation
J140100	Acute gastrojejunal ulcer with haemorrhage
J140300	Acute gastrojejunal ulcer with haemorrhage and perforation

Read	Descriptor
J140400	Acute gastrojejunal ulcer with obstruction
J141100	Chronic gastrojejunal ulcer with haemorrhage
J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation
J141400	Chronic gastrojejunal ulcer with obstruction
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y300	Unspec gastrojejunal ulcer with haemorrhage and perforation
J14y400	Unspecified gastrojejunal ulcer with obstruction
J14yy00	Unspec gastrojejunal ulcer; unspec haemorrhage/perforation
J150000	Acute haemorrhagic gastritis
J68..00	Gastrointestinal haemorrhage
J680.00	Haematemesis
J680.11	Vomiting of blood
J681.00	Melaena
J681.11	Blood in stool
J681.12	Altered blood in stools
J681.13	Blood in stools altered
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB - Gastrointestinal bleeding
J68z000	Gastric haemorrhage NOS
J68z100	Intestinal haemorrhage NOS
J68z200	Upper gastrointestinal haemorrhage
J68zz00	Gastrointestinal tract haemorrhage NOS
1994.00	Vomiting blood - fresh
1995.00	Vomiting blood - coffee ground
J110200	Acute gastric ulcer with perforation
J111200	Chronic gastric ulcer with perforation
J111211	Perforated chronic gastric ulcer
J11y200	Unspecified gastric ulcer with perforation
J120200	Acute duodenal ulcer with perforation
J121200	Chronic duodenal ulcer with perforation
J121211	Perforated chronic duodenal ulcer
J12y200	Unspecified duodenal ulcer with perforation
J130200	Acute peptic ulcer with perforation
J131200	Chronic peptic ulcer with perforation
J13y200	Unspecified peptic ulcer with perforation
J13yy00	Unspec peptic ulcer; unspec haemorrhage and/or perforation
J140200	Acute gastrojejunal ulcer with perforation
J141200	Chronic gastrojejunal ulcer with perforation
J14y200	Unspecified gastrojejunal ulcer with perforation

Appendix Table 3. Read codes for LGIB.

Read	Descriptor
4737.11	Melaena - O/E of faeces
14C9.00	H/O: melaena
19E4.12	C/O - melaena
J140100	Acute gastrojejunal ulcer with haemorrhage
J140400	Acute gastrojejunal ulcer with obstruction
J141100	Chronic gastrojejunal ulcer with haemorrhage
J141400	Chronic gastrojejunal ulcer with obstruction
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y400	Unspecified gastrojejunal ulcer with obstruction
J510900	Bleeding diverticulosis
J573.00	Haemorrhage of rectum and anus
J573.11	Bleeding PR
J573000	Rectal haemorrhage
J573011	Rectal bleeding
J573012	PRB - Rectal bleeding
J573100	Anal haemorrhage
J573z00	Haemorrhage of rectum and anus NOS
J68..00	Gastrointestinal haemorrhage
J681.00	Melaena
J681.11	Blood in stool
J681.12	Altered blood in stools
J681.13	Blood in stools altered
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB - Gastrointestinal bleeding
J68z100	Intestinal haemorrhage NOS
J68zz00	Gastrointestinal tract haemorrhage NOS

Appendix Table 4. ICD-10 codes for ICB.

ICD-10	Descriptor
I60	Subarachnoid haemorrhage
I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
I601	Subarachnoid haemorrhage from middle cerebral artery
I602	Subarachnoid haemorrhage from anterior communicating artery
I603	Subarachnoid haemorrhage from posterior communicating artery
I604	Subarachnoid haemorrhage from basilar artery
I605	Subarachnoid haemorrhage from vertebral artery
I606	Subarachnoid haemorrhage from other intracranial arteries
I607	Subarachnoid haemorrhage from intracranial artery, unspecified
I608	Other subarachnoid haemorrhage
I609	Subarachnoid haemorrhage, unspecified
I61	Intracerebral haemorrhage
I610	Intracerebral haemorrhage in hemisphere, subcortical
I611	Intracerebral haemorrhage in hemisphere, cortical
I612	Intracerebral haemorrhage in hemisphere, unspecified
I613	Intracerebral haemorrhage in brain stem
I614	Intracerebral haemorrhage in cerebellum
I615	Intracerebral haemorrhage, intraventricular
I616	Intracerebral haemorrhage, multiple localized
I618	Other intracerebral haemorrhage
I619	Intracerebral haemorrhage, unspecified
I62	Other nontraumatic intracranial haemorrhage
I620	Subdural haemorrhage (acute)(nontraumatic)
I621	Nontraumatic extradural haemorrhage
I629	Intracranial haemorrhage (nontraumatic), unspecified
I690	Sequelae of subarachnoid haemorrhage
I691	Sequelae of intracerebral haemorrhage
I692	Sequelae of other nontraumatic intracranial haemorrhage
S064	Epidural haemorrhage
S0640	Epidural haemorrhage :without open intracranial wound
S0641	Epidural haemorrhage :with open intracranial wound
S065	Traumatic subdural haemorrhage
S0650	Traumatic subdural haemorrhage :without open intracranial wound
S0651	Traumatic subdural haemorrhage :with open intracranial wound
S066	Traumatic subarachnoid haemorrhage
S0660	Traumatic subarachnoid haemorrhage :without open intracranial wound
S0661	Traumatic subarachnoid haemorrhage :with open intracranial wound

Appendix Table 5. Read codes related to cerebrovascular diseases.

Read	Descriptor
1477.00	H/O: cerebrovascular disease
14A7.00	H/O: CVA/stroke
14A7.11	H/O: CVA
14A7.12	H/O: stroke
14AF.00	H/O sub-arachnoid haemorrhage
14AK.00	H/O: Stroke in last year
662M.00	Stroke monitoring
7004100	Evacuation of haematoma from temporal lobe of brain
7004200	Evacuation of haematoma from cerebellum
7004300	Evacuation of intracerebral haematoma NEC
7008200	Aspiration of haematoma of brain tissue
7A24400	Open embolectomy of cerebral artery
7A24500	Open embolectomy of circle of Willis
7A24600	Open embolisation of cerebral artery
7A24700	Open embolisation of circle of Willis
7A25000	Percutaneous transluminal embolisation of cerebral artery
7A25100	Percutaneous transluminal embolisation of circle of Willis
7A25200	Embolisation of cerebral artery NEC
7A25300	Embolisation of circle of Willis NEC
8H2..00	Emergency hospital admission
8H2Z.00	Admit hospital emergency NOS
8H3..00	Non-urgent hospital admission
8H3Z.00	Other hospital admission NOS
8HBJ.00	Stroke / transient ischaemic attack referral
8HC..00	Refer to hospital casualty
8HCZ.00	Refer to hospital casualty NOS
8HTQ.00	Referral to stroke clinic
8Hd..00	Admission to hospital
8Hd0.00	Admission to community hospital
9H1..00	Form 4-admit to hosp-assess
9N19.00	Seen in hospital casualty
9Om..00	Stroke/transient ischaemic attack monitoring administration
9Om0.00	Stroke/transient ischaemic attack monitoring first letter
9Om1.00	Stroke/transient ischaemic attack monitoring second letter
9Om2.00	Stroke/transient ischaemic attack monitoring third letter
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
9b0K.00	Hospital admission note
A270300	Listerial cerebral arteritis
F11x200	Cerebral degeneration due to cerebrovascular disease
F285.00	Cerebral oedema

Read	Descriptor
F404500	Intra-ocular haemorrhage
Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
G6...00	Cerebrovascular disease
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
G620.00	Extradural haemorrhage - nontraumatic
G621.00	Subdural haemorrhage - nontraumatic
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
G62z.00	Intracranial haemorrhage NOS
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion

Read	Descriptor
G633.00	Multiple and bilateral precerebral arterial occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G64z400	Infarction of basal ganglia
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS
G66..00	Stroke and cerebrovascular accident unspecified

Read	Descriptor
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G672.00	Hypertensive encephalopathy
G672.11	Hypertensive crisis
G673.00	Cerebral aneurysm, nonruptured
G673000	Dissection of cerebral arteries, nonruptured
G673100	Carotico-cavernous sinus fistula
G673200	Carotid artery dissection
G673300	Vertebral artery dissection
G674.00	Cerebral arteritis
G674000	Cerebral amyloid angiopathy
G675.00	Moyamoya disease
G676.00	Nonpyogenic venous sinus thrombosis
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G679.00	Small vessel cerebrovascular disease
G67A.00	Cerebral vein thrombosis
G67y.00	Other cerebrovascular disease OS

Read	Descriptor
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease
G680.00	Sequelae of subarachnoid haemorrhage
G681.00	Sequelae of intracerebral haemorrhage
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6800	[X]Cerebral arteritis in infectious and parasitic diseases
Gyu6900	[X]Cerebral arteritis in other diseases CE
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
L417.00	Obstetric cerebral venous thrombosis
L417000	Cerebral venous thrombosis in pregnancy
L417100	Cerebral venous thrombosis in the puerperium
L440.11	CVA - cerebrovascular accident in the puerperium
L440.12	Stroke in the puerperium
Q200.00	Subdural and cerebral haemorrhage due to birth trauma
Q200000	Cerebral haemorrhage unspecified, due to birth trauma
Q200011	Intracerebral haemorrhage in fetus or newborn
Q200012	Intracranial haemorrhage in fetus or newborn
Q200700	Cerebral haemorrhage due to birth injury
Q200y00	Subdural or cerebral haemorrhage due to birth trauma OS
Q200z00	Subdural or cerebral haemorrhage due to birth trauma NOS
Q208.00	Cerebral oedema due to birth injury
Q313100	Perinatal lung intra-alveolar haemorrhage
Q412.00	Perinatal subarachnoid haemorrhage
Q412000	Subarachnoid haemorrhage due to birth injury
Q417.00	Intracranial nontraumatic haemorrhage of fetus and newborn

Read	Descriptor
Q417000	Intracerebral (nontraumatic) haemorrhage of fet and newborn
Q488.00	Neonatal cerebral ischaemia
Qyu5F00	[X]Intracranial nontraumatic haemorrhage fetus newborn unsp
S62..00	Cerebral haemorrhage following injury
S62..12	Subarachnoid haemorrhage following injury
S62..14	Traumatic cerebral haemorrhage
S620.00	Closed traumatic subarachnoid haemorrhage
S621.00	Open traumatic subarachnoid haemorrhage
S627.00	Traumatic subarachnoid haemorrhage
S62z.00	Cerebral haemorrhage following injury NOS
S63..00	Other cerebral haemorrhage following injury
S63z.00	Other cerebral haemorrhage following injury NOS
S642.00	Traumatic cerebral oedema
S642000	Traumatic cerebral oedema without open intracranial wound
S642100	Traumatic cerebral oedema with open intracranial wound
ZLEP.00	Discharge from stroke serv
ZV12511	[V]Personal history of stroke
ZV12512	[V]Personal history of cerebrovascular accident (CVA)
G619.00	Lobar cerebral haemorrhage
7017000	Evacuation of subdural haematoma
7034	Drainage of subdural space
7034y00	Other specified drainage of subdural space
7034z00	Drainage of subdural space NOS
S62..13	Subdural haemorrhage following injury
S622.00	Closed traumatic subdural haemorrhage
S622000	Subdural h'ge inj no open intracranial wnd + unspec consc
S622100	Subdural h'ge inj no open intracranial wound+no loss consc
S622200	Subdural h'ge inj no open intracranial wound+<1hr loss consc
S622300	Subdural h'ge inj no open intracran wnd+1-24hr loss consc
S622400	Subdural h'ge inj no open intracranial wnd+>24 LOC +recovery
S622500	Subdural h'ge inj no open intracran wnd+>24hr LOC -restored
S622600	Subdural h'ge inj no open intracran wnd+LOC unspec duration
S622z00	Subdural h'ge inj no open intracran wound+concussion unspec
S623.00	Open traumatic subdural haemorrhage
S623000	Subdural h'ge inj + open intracranial wound + unspec consc
S623100	Subdural h'ge inj + open intracranial wound+no loss consc
S623200	Subdural h'ge inj + open intracranial wound+<1hr loss consc
S623300	Subdural h'ge inj + open intracranial wnd+1-24hr loss consc
S623400	Subdural h'ge inj + open intracran wound+>24hr LOC +recovery
S623500	Subdural h'ge inj + open intracran wnd+>24hr LOC -restored
S623600	Subdural h'ge inj + open intracran wnd+LOC unspec duration
S623z00	Subdural h'ge inj + open intracranial wnd+concussion unspec
S628.00	Traumatic subdural haemorrhage

Read	Descriptor
S629.00	Traumatic subdural haematoma
S629000	Traumatic subdural haematoma without open intracranial wound
S629100	Traumatic subdural haematoma with open intracranial wound
S620000	Subarachnoid h'ge inj no open intracran wound + unspec consc
S620100	Subarachnoid h'ge inj no open intracran wnd+no loss consc
S620200	Subarachnoid h'ge inj no open intracran wnd+<1hr loss consc
S620300	Subarachnoid h'ge inj no open intracran wound + 1-24hr LOC
S620400	Subarachnoid h'ge inj no open intracran wnd+>24 LOC+recovery
S620500	Subarach h'ge inj no open intracran wnd+>24hrs LOC-restored
S620600	Subarach h'ge inj no open intracran wnd+LOC unspec duration
S620z00	Subarach h'ge inj no open intracran wnd + concussion unspec
S621000	Subarachnoid h'ge inj + open intracran wound + unspec consc
S621100	Subarachnoid h'ge inj + open intracranial wound + no LOC
S621200	Subarachnoid h'ge inj + open intracran wound+<1hr loss consc
S621300	Subarachnoid h'ge inj + open intracran wnd+1-24hr loss consc
S621400	Subarach h'ge inj + open intracran wnd +>24hr LOC + recovery
S621500	Subarach h'ge inj + open intracran wnd+>24hr LOC -restored
S621600	Subarach h'ge inj + open intracran wnd+LOC unspec duration
S621z00	Subarachnoid h'ge inj + open intracran wnd+concussion unspec
S62..11	Extradural haemorrhage following injury
S620.11	Middle meningeal haemmorhage following injury
S624.00	Closed traumatic extradural haemorrhage
S624.11	Epidural haematoma following injury
S624000	Extradural h'ge inj no open intracranial wnd + unspec consc
S624100	Extradural h'ge inj no open intracranial wnd + no loss consc
S624200	Extradural h'ge inj no open intracranial wnd+<1hr loss consc
S624300	Extradural h'ge inj no open intracran wnd+1-24hr loss consc
S624400	Extradural h'ge inj no open intracran wnd+>24hr LOC+recovery
S624500	Extradural h'ge inj no open intracran wnd+>24hr LOC-restored
S624600	Extradural h'ge inj no open intracra wnd+LOC unspec duration
S624z00	Extradural h'ge inj no open intracran wnd+concussion unspec
S625.00	Open traumatic extradural haemorrhage
S625000	Extradural h'ge inj + open intracranial wnd + unspec consc
S625100	Extradural h'ge inj + open intracranial wound+no loss consc
S625200	Extradural h'ge inj + open intracranial wnd+<1hr loss consc
S625300	Extradural h'ge inj + open intracran wnd+1-24hr loss consc
S625400	Extradural h'ge inj + open intracran wnd+>24hr LOC+recovery
S625500	Extradural h'ge inj + open intracran wnd+>24hr LOC -restored
S625600	Extradural h'ge inj + open intracran wnd+LOC unspec duration
S625z00	Extradural h'ge inj + open intracran wnd+concussion unspec
S626.00	Epidural haemorrhage
S62A.00	Traumatic extradural haematoma

Read	Descriptor
S62A000	Traumatic extradural haemat without open intracranial wound
S62A100	Traumatic extradural haematoma with open intracranial wound
S630.00	Other cerebral h'ge after injury no open intracranial wound
S630.11	Cerebral compression due to injury
S630.12	Intracranial haematoma following injury
S630000	Oth cerebral h'ge inj no open intracran wnd+unspec consc
S630100	Oth cerebral h'ge inj no open intracranial wnd+no loss consc
S630200	Oth cerebral h'ge inj no open intracran wnd+<1hr loss consc
S630300	Oth cerebral h'ge inj no open intracran wnd+1-24hr LOC
S630400	Oth cereb h'ge inj no open intracran wnd+>24hr LOC +recovery
S630500	Oth cereb h'ge inj no open intracran wnd+>24hr LOC -restored
S630600	Oth cereb h'ge inj no open intracran wnd+LOC unspec duration
S630z00	Oth cereb h'ge inj no open intracran wnd+concussion unspec
S631.00	Other cerebral h'ge after injury + open intracranial wound
S631000	Oth cerebral h'ge inj + open intracran wnd + unspec consc
S631100	Oth cerebral h'ge inj + open intracranial wnd+no loss consc
S631200	Oth cerebral h'ge inj + open intracran wnd+<1hr loss consc
S631300	Oth cerebral h'ge inj + open intracran wnd+1-24hr loss consc
S631400	Oth cereb h'ge inj + open intracran wnd+>24hr LOC + recovery
S631500	Oth cereb h'ge inj + open intracran wnd+>24hr LOC -restored
S631600	Oth cereb h'ge inj + open intracran wnd+LOC unspec duration
S631z00	Oth cereb h'ge inj + open intracran wnd+concussion unspec
1837.00	Pitting oedema
2BC3.00	O/E - homonymous hemianopia
388c.00	Glasgow coma scale
567..11	CAT scan
6A1..00	Patient reviewed at hospital
7A23.00	Cerebral artery and circle of Willis aneurysm operations
7A23.11	Cerebral artery aneurysm operations
7A23200	Clipping of aneurysm of cerebral artery
7A23800	Percutaneous coil embolisation of cerebral artery aneurysm
7J01.11	Craniotomy
7J01.12	Exploratory craniotomy
7J01000	Exploratory open craniotomy
893..00	Post operative monitoring
8H2X.00	Emergency hospital admission from walk-in centre
8HE..00	Discharged from hospital
8HE2.00	Discharged from inpatient care
9N1R.00	Seen in neurology clinic
9N2R.00	Seen by co-operative doctor
F22z.00	Hemiplegia NOS

Read	Descriptor
ZL91.00	Seen by accident and emergency doctor
ZL91.11	Seen by A & E doctor
ZRLA.00	Glasgow coma scale
ZRLA.11	GCS - Glasgow coma scale

Appendix Table 6. Additional health data (ADH) codes related to cerebrovascular diseases.

AHD code	Descriptor
1001400087	Other Diagnostic Imaging
1001400172	CAT scan
1001400165	Tomography
1001400298	Electroencephalography
1016500000	Cause of death
1016000000	Death administration
1001400177	Carotid angiogram

Appendix Table 7. ICD-10 codes for GIB.

ICD-10	Descriptor
K250	Gastric ulcer :Acute with haemorrhage
K252	Gastric ulcer :Acute with both haemorrhage and perforation
K254	Gastric ulcer :Chronic or unspecified with haemorrhage
K256	Gastric ulcer :Chronic or unspecified with both haemorrhage and perforation
K260	Duodenal ulcer :Acute with haemorrhage
K262	Duodenal ulcer :Acute with both haemorrhage and perforation
K264	Duodenal ulcer :Chronic or unspecified with haemorrhage
K266	Duodenal ulcer :Chronic or unspecified with both haemorrhage and perforation
K270	Peptic ulcer, site unspecified :Acute with haemorrhage
K272	Peptic ulcer, site unspecified :Acute with both haemorrhage and perforation
K274	Peptic ulcer, site unspecified :Chronic or unspecified with haemorrhage
K276	Peptic ulcer, site unspecified :Chronic or unspecified with both haemorrhage and perforation
K280	Gastrojejunal ulcer :Acute with haemorrhage
K282	Gastrojejunal ulcer :Acute with both haemorrhage and perforation
K284	Gastrojejunal ulcer :Chronic or unspecified with haemorrhage
K286	Gastrojejunal ulcer :Chronic or unspecified with both haemorrhage and perforation
K290	Acute haemorrhagic gastritis
K625	Haemorrhage of anus and rectum
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage, unspecified

Appendix Table 8. Classification of UGIB and LGIB cases following GIB case ascertainment phase VI by study cohort.

	Low-dose ASA (N=3456) Confirmed cases (1925, 55.7%)		**Comparison cohort (N=1611) Confirmed cases (897, 55.7%)**	
	Upper[*]	**Lower**[*]	**Upper**[†]	**Lower**[†]
N	610	1315	467	430
Site	Duodenal ulcer=107 Gastric ulcer=98 Peptic ulcer=5 Hiatus hernia=43 Gastritis/dyspepsia=166 *Helicobacter pylori*=8 Duodenitis=12 Gastritis/duodenitis=8 Other =24 Unknown=139	Diverticular diseases=634 Polyps=178 Divert/polyps=77 Colitis=107 Colitis/Polyps=2 Diverticular/colitis=1 Crohn's=8 IBS=42 Angiodysplasia=5 Coeliac diseases=1 Other=23 Unknown=237	Duodenal ulcer=85 Gastric ulcer=65 Duodenal/gastric=2 Peptic ulcer=1 Hiatus hernia=36 Gastritis/dyspepsia=109 *Helicobacter pylori* =11 Duodenitis=4 Gastritis/duodenitis=13 Other =22 Unknown=119	Diverticular diseases=231 Polyps=20 Divert/polyps=40 Colitis=60 Crohn's =7 IBS=30 Angiodysplasia=4 Celiac diseases=1 Other=9 Unknown=28

[*]There was one patient who fell in both episodes of both UGIB and LGIB on different dates.

[†]There were two patients who fell in both episodes of both UGIB and LGIB on different dates.

Appendix Table 9. Classification of UGIB and LGIB cases following GIB case ascertainment phase VIII by study cohort.

	Low-dose ASA		**Comparison cohort**	
	Upper[*]	**Lower**[*]	**Upper**[†]	**Lower**[†]
N	1125	1943	734	832
Site	Duodenal ulcer=225 Gastric ulcer=192 DU/GU=9 Peptic ulcer=21 DU/PU=2 Hiatus hernia=57 Gastritis/dyspepsia=250 *Helicobacter pylori*=19 Duodenitis=33 Gastritis/duodenitis=29 Other=44 Unknown=244	Diverticular diseases=842 Polyps=236 Divert/polyps=107 Colitis=157 Colitis/divert =1 Colitis/polyps=2 Colitis/ Crohn's =1 Crohn's=9 IBS=49 Angiodysplasia=7 Celiac diseases=1 Other=25 Unknown=506	Duodenal ulcer=146 Gastric ulcer=110 Duodenal/Gastric=7 Peptic ulcer=11 Hiatus hernia=44 Gastritis/dyspepsia=174 *Helicobacter pylori*=15 Duodenitis=16 Gastritis/duodenitis=23 Other=26 Unknown=163	Diverticular diseases=351 Polyps=61 Divert/polyps=52 Colitis=80 Colitis/divert =1 Crohn's =17 IBS=36 Angiodysplasia=5 Celiac diseases=1 Other=12 Unknown=216

[*]There was one patient who fell in both episodes of both UGIB and LGIB on different dates.

[†]There were two patients who fell in both episodes of both UGIB and LGIB on different dates.

Appendix Table 10. Classification of UGIB and LGIB cases following GIB case ascertainment phase IX by study cohort.

	Low-dose ASA, confirmed cases N=3052		**Comparison cohort, confirmed cases N=1557**	
	Upper*	**Lower***	**Upper†**	**Lower†**
Non-fatal case	**1051 (94.3%)**	**1921 (99.2%)**	**664 (91.2%)**	**817 (98.8%)**
Hospitalization	615 (58.6%)	513 (26.7%)	401 (60.5%)	241 (29.6%)
Referral	436 (41.4%)	1408 (73.3%)	263 (39.5%)	576 (70.4%)
Fatal-case	**64 (5.7%)**	**15 (0.8%)**	**64 (8.8%)**	**10 (1.2%)**
Hospitalization	42 (65.6%)	10 (66.7%)	48 (75.0%)	7 (70.0%)
Referral	16 (25%)	2 (13.3%)	14 (21.9%)	3 (30.0%)
Home	6 (9.4%)	3 (20.0%)	2 (3.1%)	–

*There was one patient who fell in both episodes of both UGIB and LGIB on different dates.

†There were two patients who fell in both episodes of both UGIB and LGIB on different dates.

Appendix Table 11a. Read code for MI.

Read	Descriptor
G30..00	Acute myocardial infarction
G30..13	Cardiac rupture following myocardial infarction (MI)
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G30..11	Attack - heart
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G31..00	Other acute and subacute ischaemic heart disease
G311500	Acute coronary syndrome
G310.00	Postmyocardial infarction syndrome
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
3232.00	ECG: old myocardial infarction
3235.00	ECG: subendocardial infarct
323Z.00	ECG: myocardial infarct NOS
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
G307100	Acute non-ST segment elevation myocardial infarction
G312.00	Coronary thrombosis not resulting in myocardial infarction
G36..00	Certain current complication follow acute myocardial infarct

Read	Descriptor
G360.00	Haemopericardium/current comp folow acut myocard infarct
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G384.00	Postoperative subendocardial myocardial infarction
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site

Appendix Table 11b. Read code for unstable angina.

Read code	Descriptor
G311.11	Crescendo angina
G311.13	Unstable angina
G311.14	Angina at rest
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris

Appendix Table 11c. Read codes for revascularization.

Read code	Descriptor
ZV45700	[V]Presence of aortocoronary bypass graft
7920000	Saphenous vein graft replacement of one coronary artery
7920.00	Saphenous vein graft replacement of coronary artery
792..00	Coronary artery operations
7920100	Saphenous vein graft replacement of two coronary arteries
7920.11	Saphenous vein graft bypass of coronary artery
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921000	Autograft replacement of one coronary artery NEC
7921.00	Other autograft replacement of coronary artery
7921100	Autograft replacement of two coronary arteries NEC
7921.11	Other autograft bypass of coronary artery
792..11	Coronary artery bypass graft operations
7921200	Autograft replacement of three coronary arteries NEC
7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922000	Allograft replacement of one coronary artery
7922.00	Allograft replacement of coronary artery
7922100	Allograft replacement of two coronary arteries
7922.11	Allograft bypass of coronary artery
7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7923000	Prosthetic replacement of one coronary artery
7923.00	Prosthetic replacement of coronary artery
7923100	Prosthetic replacement of two coronary arteries
7923.11	Prosthetic bypass of coronary artery
7923200	Prosthetic replacement of three coronary arteries
7923300	Prosthetic replacement of four or more coronary arteries
7923y00	Other specified prosthetic replacement of coronary artery
7923z00	Prosthetic replacement of coronary artery NOS
7924000	Revision of bypass for one coronary artery

Read code	Descriptor
7924.00	Revision of bypass for coronary artery
7924100	Revision of bypass for two coronary arteries
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery
7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925000	Double anastomosis of mammary arteries to coronary arteries
7925.00	Connection of mammary artery to coronary artery
7925100	Double implant of mammary arteries into coronary arteries
7925.11	Creation of bypass from mammary artery to coronary artery
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926.00	Connection of other thoracic artery to coronary artery
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS
7927000	Repair of arteriovenous fistula of coronary artery
7927.00	Other open operations on coronary artery
7927100	Repair of aneurysm of coronary artery
7927200	Transection of muscle bridge of coronary artery
7927300	Transposition of coronary artery NEC
7927400	Exploration of coronary artery
7927500	Open angioplasty of coronary artery
7927y00	Other specified other open operation on coronary artery
7927z00	Other open operation on coronary artery NOS
7928000	Percut transluminal balloon angioplasty one coronary artery
7928.00	Transluminal balloon angioplasty of coronary artery
7928100	Percut translum balloon angioplasty mult coronary arteries
7928.11	Percutaneous balloon coronary angioplasty
7928200	Percut translum balloon angioplasty bypass graft coronary a
7928y00	Transluminal balloon angioplasty of coronary artery OS

Read code	Descriptor
7928z00	Transluminal balloon angioplasty of coronary artery NOS
7929000	Percutaneous transluminal laser coronary angioplasty
7929.00	Other therapeutic transluminal operations on coronary artery
7929100	Percut transluminal coronary thrombolysis with streptokinase
7929111	Percut translum coronary thrombolytic therapy- streptokinase
7929200	Percut translum inject therap subst to coronary artery NEC
7929300	Rotary blade coronary angioplasty
7929400	Insertion of coronary artery stent
7929y00	Other therapeutic transluminal op on coronary artery OS
7929z00	Other therapeutic transluminal op on coronary artery NOS
792B000	Endarterectomy of coronary artery NEC
792B.00	Repair of coronary artery NEC
792By00	Other specified repair of coronary artery
792Bz00	Repair of coronary artery NOS
792C000	Replacement of coronary arteries using multiple methods
792C.00	Other replacement of coronary artery
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS
792y.00	Other specified operations on coronary artery
792z.00	Coronary artery operations NOS
ZV45800	[V]Presence of coronary angioplasty implant and graft
ZV45K00	[V]Presence of coronary artery bypass graft
ZV45K11	[V]Presence of coronary artery bypass graft - CABG
ZV45L00	[V]Status following coronary angioplasty NOS
790H300	Revascularisation of wall of heart
88A8.00	Thrombolytic therapy
SP00300	Mechanical complication of coronary bypass

Appendix Table 11d. Read codes for ischaemic stroke.

Read code	Descriptor
G6...00	Cerebrovascular disease
G68..00	Late effects of cerebrovascular disease
G683.00	Sequelae of cerebral infarction
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G6W..00	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..00	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
G6y..00	Other specified cerebrovascular disease
G6z..00	Cerebrovascular disease NOS
G68W.00	Sequelae/other + unspecified cerebrovascular diseases
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
14A7.00	H/O: CVA/stroke
14A7.11	H/O: CVA
14A7.12	H/O: stroke
1477.00	H/O: cerebrovascular disease
Gyu6.00	[X]Cerebrovascular diseases
Gyu6300	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu6400	[X]Other cerebral infarction
Gyu6500	[X]Occlusion and stenosis of other precerebral arteries
Gyu6600	[X]Occlusion and stenosis of other cerebral arteries
Gyu6700	[X]Other specified cerebrovascular diseases
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
Gyu6G00	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
14AK.00	H/O: Stroke in last year
662e.00	Stroke/CVA annual review
662e.11	Stroke annual review
662M.00	Stroke monitoring
662M100	Stroke 6 month review
662M200	Stroke initial post discharge review
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
L440.12	Stroke in the puerperium
ZV12511	[V]Personal history of stroke
ZV12512	[V]Personal history of cerebrovascular accident (CVA)
7A24400	Open embolectomy of cerebral artery
7A24500	Open embolectomy of circle of Willis
7A24600	Open embolisation of cerebral artery

Read code	Descriptor
7A24700	Open embolisation of circle of Willis
7A25000	Percutaneous transluminal embolisation of cerebral artery
7A25100	Percutaneous transluminal embolisation of circle of Willis
7A25200	Embolisation of cerebral artery NEC
7A25300	Embolisation of circle of Willis NEC
8HBJ.00	Stroke / transient ischaemic attack referral
8HTQ.00	Referral to stroke clinic
ZLEP.00	Discharge from stroke serv
9Om..00	Stroke/transient ischaemic attack monitoring administration
9Om0.00	Stroke/transient ischaemic attack monitoring first letter
9Om1.00	Stroke/transient ischaemic attack monitoring second letter
9Om2.00	Stroke/transient ischaemic attack monitoring third letter
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte
G63..00	Precerebral arterial occlusion
G63..11	Infarction - precerebral
G63..12	Stenosis of precerebral arteries
G630.00	Basilar artery occlusion
G631.00	Carotid artery occlusion
G631.11	Stenosis, carotid artery
G631.12	Thrombosis, carotid artery
G632.00	Vertebral artery occlusion
G633.00	Multiple and bilateral precerebral arterial occlusion
G634.00	Carotid artery stenosis
G63y.00	Other precerebral artery occlusion
G63y000	Cerebral infarct due to thrombosis of precerebral arteries
G63y100	Cerebral infarction due to embolism of precerebral arteries
G63z.00	Precerebral artery occlusion NOS
G64..00	Cerebral arterial occlusion
G64..11	CVA - cerebral artery occlusion
G64..12	Infarction - cerebral
G64..13	Stroke due to cerebral arterial occlusion
G640.00	Cerebral thrombosis
G640000	Cerebral infarction due to thrombosis of cerebral arteries
G641.00	Cerebral embolism
G641.11	Cerebral embolus
G641000	Cerebral infarction due to embolism of cerebral arteries
G64z.00	Cerebral infarction NOS

Read code	Descriptor
G64z.11	Brainstem infarction NOS
G64z.12	Cerebellar infarction
G64z000	Brainstem infarction
G64z100	Wallenberg syndrome
G64z111	Lateral medullary syndrome
G64z200	Left sided cerebral infarction
G64z300	Right sided cerebral infarction
G66..00	Stroke and cerebrovascular accident unspecified
G66..11	CVA unspecified
G66..12	Stroke unspecified
G66..13	CVA - Cerebrovascular accident unspecified
G660.00	Middle cerebral artery syndrome
G661.00	Anterior cerebral artery syndrome
G662.00	Posterior cerebral artery syndrome
G663.00	Brain stem stroke syndrome
G664.00	Cerebellar stroke syndrome
G665.00	Pure motor lacunar syndrome
G666.00	Pure sensory lacunar syndrome
G667.00	Left sided CVA
G668.00	Right sided CVA
G669.00	Cerebral palsy, not congenital or infantile, acute
G67..00	Other cerebrovascular disease
G670.00	Cerebral atherosclerosis
G670.11	Precerebral atherosclerosis
G671.00	Generalised ischaemic cerebrovascular disease NOS
G671000	Acute cerebrovascular insufficiency NOS
G671100	Chronic cerebral ischaemia
G671z00	Generalised ischaemic cerebrovascular disease NOS
G676.00	Nonpyogenic venous sinus thrombosis
G676000	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G677.00	Occlusion/stenosis cerebral arts not result cerebral infarct
G677000	Occlusion and stenosis of middle cerebral artery
G677100	Occlusion and stenosis of anterior cerebral artery
G677200	Occlusion and stenosis of posterior cerebral artery
G677300	Occlusion and stenosis of cerebellar arteries
G677400	Occlusion+stenosis of multiple and bilat cerebral arteries
G678.00	Cereb autosom dominant arteriop subcort infarcts leukoenceph
G679.00	Small vessel cerebrovascular disease

Read code	Descriptor
G67A.00	Cerebral vein thrombosis
G67y.00	Other cerebrovascular disease OS
G67z.00	Other cerebrovascular disease NOS
G68..00	Late effects of cerebrovascular disease

Appendix Table 11e. Read codes for TIA.

Read code	Descriptor
8HBJ.00	Stroke / transient ischaemic attack referral
9Om..00	Stroke/transient ischaemic attack monitoring administration
9Om0.00	Stroke/transient ischaemic attack monitoring first letter
9Om1.00	Stroke/transient ischaemic attack monitoring second letter
9Om2.00	Stroke/transient ischaemic attack monitoring third letter
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte
Fyu5500	[X]Other transnt cerebral ischaemic attacks+related syndroms
G65..00	Transient cerebral ischaemia
G65..11	Drop attack
G65..12	Transient ischaemic attack
G65..13	Vertebro-basilar insufficiency
G650.00	Basilar artery syndrome
G650.11	Insufficiency - basilar artery
G651.00	Vertebral artery syndrome
G651000	Vertebro-basilar artery syndrome
G652.00	Subclavian steal syndrome
G653.00	Carotid artery syndrome hemispheric
G654.00	Multiple and bilateral precerebral artery syndromes
G655.00	Transient global amnesia
G656.00	Vertebrobasilar insufficiency
G65y.00	Other transient cerebral ischaemia
G65z.00	Transient cerebral ischaemia NOS
G65z000	Impending cerebral ischaemia
G65z100	Intermittent cerebral ischaemia
G65zz00	Transient cerebral ischaemia NOS

Appendix Table 11f. Read codes for PAD.

Read codes	Descriptor
14AE.00	H/O: aortic aneurysm
14NB.00	H/O: Peripheral vascular disease procedure
2456.00	O/E - arterial wall - aneurysm
2I16.00	O/E - gangrene
33C5.00	Peripheral vasc. resistance
A3A0F00	Gas gangrene-foot
A930.00	Syphilitic aortic aneurysm
C107.00	Diabetes mellitus with peripheral circulatory disorder
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107300	IDDM with peripheral circulatory disorder
C107400	NIDDM with peripheral circulatory disorder
C107y00	Other specified diabetes mellitus with periph circ comps
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108G11	Type I diabetes mellitus with peripheral angiopathy
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109F11	Type II diabetes mellitus with peripheral angiopathy
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
F161100	Myelopathy due to arterial thrombosis of spinal cord
F371100	Polyneuropathy in polyarteritis nodosa
F396300	Myopathy due to polyarteritis nodosa
F423200	Retinal arterial branch occlusion
F423500	Retinal partial arterial occlusion NOS
F423700	Retinal transient arterial occlusion NOS
G420.00	Arteriovenous fistula of pulmonary vessels
G7...00	Arterial, arteriole and capillary disease
G7...11	Capillary disease
G70..00	Atherosclerosis
G70..11	Arteriosclerosis
G700.00	Aortic atherosclerosis
G700.11	Aorto-iliac disease
G701.00	Renal artery atherosclerosis
G701000	Atherosclerotic renal artery stenosis
G701011	ARAS - Atherosclerotic renal artery stenosis
G702.00	Extremity artery atheroma

Read codes	Descriptor
G702000	Monckeberg's medial sclerosis
G702z00	Extremity artery atheroma NOS
G703.00	Acquired renal artery stenosis
G70y.00	Other specified artery atheroma
G70y000	Carotid artery atherosclerosis
G70y011	Carotid artery disease
G70z.00	Arteriosclerotic vascular disease NOS
G71..00	Aortic aneurysm
G710.00	Dissecting aortic aneurysm
G711.00	Thoracic aortic aneurysm which has ruptured
G711.11	Ruptured thoracic aortic aneurysm
G712.00	Thoracic aortic aneurysm without mention of rupture
G713.00	Abdominal aortic aneurysm which has ruptured
G713.11	Ruptured abdominal aortic aneurysm
G713000	Ruptured suprarenal aortic aneurysm
G714.00	Abdominal aortic aneurysm without mention of rupture
G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
G714000	Juxtarenal aortic aneurysm
G714100	Inflammatory abdominal aortic aneurysm
G714200	Infrarenal abdominal aortic aneurysm
G714300	Aneurysm of suprarenal aorta
G715.00	Ruptured aortic aneurysm NOS
G715000	Thoracoabdominal aortic aneurysm, ruptured
G716.00	Aortic aneurysm without mention of rupture NOS
G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
G717.00	Aortic aneurysm - syphilitic
G718.00	Leaking abdominal aortic aneurysm
G719.00	Abscess of aortic root
G71A.00	Aortic root dilatation
G71z.00	Aortic aneurysm NOS
G72..00	Other aneurysm
G720.00	Aneurysm of artery of arm
G720000	Aneurysm of brachial artery
G720100	Aneurysm of radial artery
G720200	Aneurysm of ulnar artery
G720z00	Aneurysm of arm artery NOS
G721.00	Aneurysm of renal artery
G721000	Acquired renal artery aneurysm

Read codes	Descriptor
G722.00	Aneurysm of iliac artery
G722000	Aneurysm of common iliac artery
G722100	Aneurysm of external iliac artery
G722200	Aneurysm of internal iliac artery
G722z00	Aneurysm of iliac artery NOS
G723.00	Aneurysm of leg artery
G723000	Aneurysm of femoral artery
G723100	Aneurysm of popliteal artery
G723200	Aneurysm of anterior tibial artery
G723300	Aneurysm of dorsalis pedis artery
G723400	Aneurysm of posterior tibial artery
G723500	Ruptured popliteal artery aneurysm
G723600	Post radiological femoral false aneurysm
G723z00	Aneurysm of leg artery NOS
G724.00	Arterial false aneurysm
G724.11	False aneurysm
G725.00	Dissection of artery of upper extremity
G725.11	Dissection of artery of arm
G726.00	Dissection of renal artery
G727.00	Dissection of iliac artery
G728.00	Dissection of artery of lower extremity
G728.11	Dissection of artery of leg
G729.00	Aneurysm and dissection of precerebral artery
G72A.00	Dissection of other specified arteries
G72B.00	Dissection of artery
G72C.00	Ruptured aneurysm of dialysis vascular access
G72D.00	Aneurysm of dialysis arteriovenous fistula
G72D000	Aneurysm of superficialised artery of dialysis AV fistula
G72D100	Aneurysm of needle site of dialysis arteriovenous fistula
G72D200	Aneurysm of anastomotic site of dialysis AV fistula
G72E.00	Aneurysm of dialysis vascular access
G72y.00	Aneurysm of other artery
G72y000	Aneurysm of common carotid art
G72y100	Aneurysm of external carotid artery
G72y200	Aneurysm of internal carotid artery
G72y300	Aneurysm of neck artery NOS
G72y400	Aneurysm of subclavian artery
G72y500	Aneurysm of splenic artery

Read codes	Descriptor
G72y600	Aneurysm of axillary artery
G72y700	Aneurysm of coeliac artery
G72y800	Aneurysm of superior mesenteric artery
G72y900	Aneurysm of inferior mesenteric artery
G72yA00	Aneurysm of hepatic artery
G72yB00	Aneurysm of other visceral artery
G72yz00	Other aneurysm NOS
G72z.00	Aneurysm NOS
G73..00	Other peripheral vascular disease
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia
G730.00	Raynaud's syndrome
G730000	Raynaud's disease
G730100	Raynaud's phenomenon
G730111	Vibratory white finger
G730z00	Raynaud's syndrome NOS
G731.00	Thromboangiitis obliterans
G731000	Buerger's disease
G731100	Presenile gangrene
G731z00	Thromboangiitis obliterans NOS
G732.00	Peripheral gangrene
G732000	Gangrene of toe
G732100	Gangrene of foot
G732200	Gangrene of finger
G732300	Gangrene of thumb
G732400	Gangrene of hand
G733.00	Ischaemic foot
G734.00	Peripheral arterial disease
G73y.00	Other specified peripheral vascular disease
G73y000	Diabetic peripheral angiopathy
G73y100	Peripheral angiopathic disease EC NOS
G73y200	Acrocyanosis
G73y400	Acroparaesthesia - Schultze's type
G73y411	Schultze's simple acroparaesthesia
G73y500	Acroparaesthesia - Nothnagel's type
G73y511	Nothnagel's vasomotor acroparaesthesia
G73y600	Acroparaesthesia - unspecified

Read codes	Descriptor
G73y700	Erythrocyanosis
G73y800	Erythromelalgia
G73y811	Erythralgia
G73yz00	Other specified peripheral vascular disease NOS
G73z.00	Peripheral vascular disease NOS
G73z000	Intermittent claudication
G73z011	Claudication
G73z012	Vascular claudication
G73z100	Spasm of peripheral artery
G73zz00	Peripheral vascular disease NOS
G74..00	Arterial embolism and thrombosis
G74..11	Arterial embolus and thrombosis
G74..12	Thrombosis - arterial
G74..13	Arterial embolic and thrombotic occlusion
G740.00	Embolism and thrombosis of the abdominal aorta
G740.11	Aortic bifurcation syndrome
G740.12	Aortoiliac obstruction
G740.13	Leriche's syndrome
G740.14	Saddle embolus
G741.00	Embolism and thrombosis of the thoracic aorta
G742.00	Embolism and thrombosis of an arm or leg artery
G742000	Embolism and thrombosis of the brachial artery
G742100	Embolism and thrombosis of the radial artery
G742200	Embolism and thrombosis of the ulnar artery
G742300	Embolism and thrombosis of an arm artery NOS
G742400	Embolism and thrombosis of the femoral artery
G742500	Embolism and thrombosis of the popliteal artery
G742600	Embolism and thrombosis of the anterior tibial artery
G742700	Embolism and thrombosis of the dorsalis pedis artery
G742800	Embolism and thrombosis of the posterior tibial artery
G742900	Embolism and thrombosis of a leg artery NOS
G742A00	Post radiological embolism of upper limb artery
G742B00	Post radiological embolism of lower limb artery
G742z00	Peripheral arterial embolism and thrombosis NOS
G743.00	Embolism and thrombosis of other and unspec parts aorta
G74y.00	Embolism and thrombosis of other specified artery
G74y000	Embolism and/or thrombosis of the common iliac artery
G74y100	Embolism and/or thrombosis of the internal iliac artery

Read codes	Descriptor
G74y200	Embolism and/or thrombosis of the external iliac artery
G74y300	Embolism and thrombosis of the iliac artery unspecified
G74y500	Embolism and thrombosis of the subclavian artery
G74y600	Embolism and thrombosis of the splenic artery
G74y700	Embolism and thrombosis of the axillary artery
G74y800	Embolism and thrombosis of the coeliac artery
G74y900	Embolism and thrombosis of the hepatic artery
G74yz00	Embolism and thrombosis of other arteries NOS
G74z.00	Arterial embolism and thrombosis NOS
G75..00	Polyarteritis nodosa and allied conditions
G750.00	Polyarteritis nodosa
G750.11	Necrotising angiitis
G751.00	Acute febrile mucocutaneous lymph node syndrome
G751000	Kawasaki disease
G751z00	Acute febrile mucocutaneous lymph node syndrome NOS
G752.00	Hypersensitivity angiitis
G752.11	Hypersensitivity arteritis
G752000	Goodpasture's syndrome
G752100	Goodpasture's disease
G752111	Antiglomerular basement membrane disease
G752112	Anti GBM disease - Antiglomerular basement membrane disease
G752z00	Hypersensitivity angiitis NOS
G753.00	Lethal midline granuloma
G754.00	Wegener's granulomatosis
G755.00	Giant cell arteritis
G755000	Cranial arteritis
G755100	Temporal arteritis
G755200	Horton's disease
G755z00	Giant cell arteritis NOS
G756.00	Thrombotic microangiopathy
G756000	Moschcowitz syndrome
G756100	Thrombotic thrombocytopenic purpura
G756z00	Thrombotic microangiopathy NOS
G757.00	Takayasu's disease
G757.11	Aortic arch arteritis
G757.12	Pulseless disease
G758.00	Churg-Strauss vasculitis
G759.00	Juvenile polyarteritis

Read codes	Descriptor
G75A.00	Microscopic polyangiitis
G75X.00	Necrotising vasculopathy, unspecified
G75z.00	Polyarteritis nodosa and allied conditions NOS
G76..00	Other disorders of arteries and arterioles
G760.00	Acquired arteriovenous fistula
G761.00	Stricture of artery
G762.00	Rupture of artery
G762000	Aorto-duodenal fistula
G763.00	Hyperplasia of renal artery
G764.00	Coeliac artery compression syndrome
G764.11	Marable's syndrome
G765.00	Necrosis of artery
G766.00	Arteritis unspecified
G766.11	Aortitis
G767.00	Aortitis - syphilitic
G768.00	Other disorders of arteries and arterioles
G768000	Fibromuscular hyperplasia of arteries NOS
G768100	Arterial fibromuscular dysplasia
G768z00	Other disorders of arteries and arterioles NOS
G769.00	Anterior spinal and vertebral artery compression syndromes
G76A.00	Arterial insufficiency
G76B.00	Vasculitis
G76z.00	Disorders of arteries and arterioles NOS
G76z000	Iliac artery occlusion
G76z100	Femoral artery occlusion
G76z200	Popliteal artery occlusion
G77..00	Diseases of capillaries
G770.00	Hereditary haemorrhagic telangiectasia
G770.11	Rendu - Osler - Weber disease
G7y..00	Other specified arterial, arteriole or capillary disease
G7z..00	Arterial, arteriole and capillary diseases NOS
Gyu7100	[X]Aortic aneurysm of unspecified site, ruptured
Gyu7200	[X]Aortic aneurysm of unspecified site, nonruptured
Gyu7400	[X]Other specified peripheral vascular diseases
Gyu7A00	[X]Peripheral angiopathy in diseases classified elsewhere
J420.18	Mesenteric thrombosis
K138000	Renal artery embolism
N200.00	Giant cell arteritis with polymyalgia rheumatica

Read codes	Descriptor
Nyu4100	[X]Other giant cell arteritis
P76..00	Other peripheral vascular system anomalies
P76..11	Other congenital anomalies of peripheral arteries
P76..12	Other congenital anomalies of peripheral veins
P76y.00	Congenital anomaly of peripheral vascular system OS
P76yz00	Other congenital anomaly of peripheral vascular system NOS
P76z.00	Peripheral vascular system anomaly NOS
Pyu2B00	[X]Oth specified cong malform of peripheral vascular system
R054.00	[D]Gangrene
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
R055000	[D]Failure of peripheral circulation
R055011	[D]Peripheral circulatory failure
SP12.00	Peripheral vascular complications of care
SP12z00	Peripheral vascular complications of care NOS

Appendix Table 11g. Read codes for IHD.

Read code	Descriptor
G3...00	Ischaemic heart disease
G3...11	Arteriosclerotic heart disease
G3...12	Atherosclerotic heart disease
G3...13	IHD - Ischaemic heart disease
G30..00	Acute myocardial infarction
G30..11	Attack - heart
G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS

Read code	Descriptor
G31..00	Other acute and subacute ischaemic heart disease
G310.00	Postmyocardial infarction syndrome
G310.11	Dressler's syndrome
G311.00	Preinfarction syndrome
G311.11	Crescendo angina
G311.12	Impending infarction
G311.13	Unstable angina
G311.14	Angina at rest
G311000	Myocardial infarction aborted
G311011	MI - myocardial infarction aborted
G311100	Unstable angina
G311200	Angina at rest
G311300	Refractory angina
G311400	Worsening angina
G311500	Acute coronary syndrome
G311z00	Preinfarction syndrome NOS
G312.00	Coronary thrombosis not resulting in myocardial infarction
G31y.00	Other acute and subacute ischaemic heart disease
G31y000	Acute coronary insufficiency
G31y100	Microinfarction of heart
G31y200	Subendocardial ischaemia
G31y300	Transient myocardial ischaemia
G31yz00	Other acute and subacute ischaemic heart disease NOS
G32..00	Old myocardial infarction
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
G33..00	Angina pectoris
G330.00	Angina decubitus
G330000	Nocturnal angina
G330z00	Angina decubitus NOS
G331.00	Prinzmetal's angina
G331.11	Variant angina pectoris
G332.00	Coronary artery spasm
G33z.00	Angina pectoris NOS
G33z000	Status anginosus
G33z100	Stenocardia
G33z200	Syncope anginosa
G33z300	Angina on effort

Read code	Descriptor
G33z400	Ischaemic chest pain
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
G34..00	Other chronic ischaemic heart disease
G340.00	Coronary atherosclerosis
G340.11	Triple vessel disease of the heart
G340.12	Coronary artery disease
G340000	Single coronary vessel disease
G340100	Double coronary vessel disease
G341.00	Aneurysm of heart
G341.11	Cardiac aneurysm
G341000	Ventricular cardiac aneurysm
G341100	Other cardiac wall aneurysm
G341111	Mural cardiac aneurysm
G341200	Aneurysm of coronary vessels
G341300	Acquired atrioventricular fistula of heart
G341z00	Aneurysm of heart NOS
G342.00	Atherosclerotic cardiovascular disease
G343.00	Ischaemic cardiomyopathy
G344.00	Silent myocardial ischaemia
G34y.00	Other specified chronic ischaemic heart disease
G34y000	Chronic coronary insufficiency
G34y100	Chronic myocardial ischaemia
G34yz00	Other specified chronic ischaemic heart disease NOS
G34z.00	Other chronic ischaemic heart disease NOS
G34z000	Asymptomatic coronary heart disease
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI

Read code	Descriptor
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G37..00	Cardiac syndrome X
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G382.00	Postoperative transmural myocardial infarction other sites
G383.00	Postoperative transmural myocardial infarction unspec site
G384.00	Postoperative subendocardial myocardial infarction
G38z.00	Postoperative myocardial infarction, unspecified
G39..00	Coronary microvascular disease
G3y..00	Other specified ischaemic heart disease
G3z..00	Ischaemic heart disease NOS
14A3.00	H/O: myocardial infarct
14A4.00	H/O: myocardial infarct >60
14A5.00	H/O: angina pectoris
14AJ.00	H/O: Angina in last year
14AL.00	H/O: Treatment for ischaemic heart disease
322..00	ECG: myocardial ischaemia
3222.00	ECG:shows myocardial ischaemia
322Z.00	ECG: myocardial ischaemia NOS
3232.00	ECG: old myocardial infarction
3235.00	ECG: subendocardial infarct
323Z.00	ECG: myocardial infarct NOS
3889.00	Euroscore for angina
388E.00	Canadian Cardiovascular Society classification of angina
388F.00	Cardiovascular Limitations and Symptoms Profile angina score
662K.00	Angina control
662K000	Angina control - good
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662Kz00	Angina control NOS
68B2.00	Ischaemic heart disease screen
790H300	Revascularisation of wall of heart
792..00	Coronary artery operations
792..11	Coronary artery bypass graft operations

Read code	Descriptor
7920.00	Saphenous vein graft replacement of coronary artery
7920.11	Saphenous vein graft bypass of coronary artery
7920000	Saphenous vein graft replacement of one coronary artery
7920100	Saphenous vein graft replacement of two coronary arteries
7920200	Saphenous vein graft replacement of three coronary arteries
7920300	Saphenous vein graft replacement of four+ coronary arteries
7920y00	Saphenous vein graft replacement of coronary artery OS
7920z00	Saphenous vein graft replacement coronary artery NOS
7921.00	Other autograft replacement of coronary artery
7921.11	Other autograft bypass of coronary artery
7921000	Autograft replacement of one coronary artery NEC
7921100	Autograft replacement of two coronary arteries NEC
7921200	Autograft replacement of three coronary arteries NEC
7921300	Autograft replacement of four of more coronary arteries NEC
7921y00	Other autograft replacement of coronary artery OS
7921z00	Other autograft replacement of coronary artery NOS
7922.00	Allograft replacement of coronary artery
7922.11	Allograft bypass of coronary artery
7922000	Allograft replacement of one coronary artery
7922100	Allograft replacement of two coronary arteries
7922200	Allograft replacement of three coronary arteries
7922300	Allograft replacement of four or more coronary arteries
7922y00	Other specified allograft replacement of coronary artery
7922z00	Allograft replacement of coronary artery NOS
7923.00	Prosthetic replacement of coronary artery
7923.11	Prosthetic bypass of coronary artery
7923000	Prosthetic replacement of one coronary artery
7923100	Prosthetic replacement of two coronary arteries
7923200	Prosthetic replacement of three coronary arteries
7923300	Prosthetic replacement of four or more coronary arteries
7923y00	Other specified prosthetic replacement of coronary artery
7923z00	Prosthetic replacement of coronary artery NOS
7924.00	Revision of bypass for coronary artery
7924000	Revision of bypass for one coronary artery
7924100	Revision of bypass for two coronary arteries
7924200	Revision of bypass for three coronary arteries
7924300	Revision of bypass for four or more coronary arteries
7924400	Revision of connection of thoracic artery to coronary artery

Read code	Descriptor
7924y00	Other specified revision of bypass for coronary artery
7924z00	Revision of bypass for coronary artery NOS
7925.00	Connection of mammary artery to coronary artery
7925.11	Creation of bypass from mammary artery to coronary artery
7925000	Double anastomosis of mammary arteries to coronary arteries
7925100	Double implant of mammary arteries into coronary arteries
7925200	Single anast mammary art to left ant descend coronary art
7925300	Single anastomosis of mammary artery to coronary artery NEC
7925400	Single implantation of mammary artery into coronary artery
7925y00	Connection of mammary artery to coronary artery OS
7925z00	Connection of mammary artery to coronary artery NOS
7926.00	Connection of other thoracic artery to coronary artery
7926000	Double anastom thoracic arteries to coronary arteries NEC
7926100	Double implant thoracic arteries into coronary arteries NEC
7926200	Single anastomosis of thoracic artery to coronary artery NEC
7926300	Single implantation thoracic artery into coronary artery NEC
7926y00	Connection of other thoracic artery to coronary artery OS
7926z00	Connection of other thoracic artery to coronary artery NOS
7927.00	Other open operations on coronary artery
7927000	Repair of arteriovenous fistula of coronary artery
7927100	Repair of aneurysm of coronary artery
7927200	Transection of muscle bridge of coronary artery
7927300	Transposition of coronary artery NEC
7927400	Exploration of coronary artery
7927500	Open angioplasty of coronary artery
7927y00	Other specified other open operation on coronary artery
7927z00	Other open operation on coronary artery NOS
7928.00	Transluminal balloon angioplasty of coronary artery
7928.11	Percutaneous balloon coronary angioplasty
7928000	Percut transluminal balloon angioplasty one coronary artery
7928100	Percut translum balloon angioplasty mult coronary arteries
7928200	Percut translum balloon angioplasty bypass graft coronary a
7928y00	Transluminal balloon angioplasty of coronary artery OS
7928z00	Transluminal balloon angioplasty of coronary artery NOS
7929.00	Other therapeutic transluminal operations on coronary artery
7929000	Percutaneous transluminal laser coronary angioplasty
7929100	Percut transluminal coronary thrombolysis with streptokinase
7929111	Percut translum coronary thrombolytic therapy- streptokinase

Read code	Descriptor
7929200	Percut translum inject therap subst to coronary artery NEC
7929300	Rotary blade coronary angioplasty
7929400	Insertion of coronary artery stent
7929y00	Other therapeutic transluminal op on coronary artery OS
7929z00	Other therapeutic transluminal op on coronary artery NOS
792B.00	Repair of coronary artery NEC
792B000	Endarterectomy of coronary artery NEC
792By00	Other specified repair of coronary artery
792Bz00	Repair of coronary artery NOS
792C.00	Other replacement of coronary artery
792C000	Replacement of coronary arteries using multiple methods
792Cy00	Other specified replacement of coronary artery
792Cz00	Replacement of coronary artery NOS
792D.00	Other bypass of coronary artery
792Dy00	Other specified other bypass of coronary artery
792Dz00	Other bypass of coronary artery NOS
792y.00	Other specified operations on coronary artery
792z.00	Coronary artery operations NOS
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
88A8.00	Thrombolytic therapy
8B27.00	Antianginal therapy
G5y2.00	Cardiovascular arteriosclerosis unspecified
Gyu3000	[X]Other forms of angina pectoris
Gyu3100	[X]Other current complicatns following acute myocard infarct
Gyu3200	[X]Other forms of acute ischaemic heart disease
Gyu3300	[X]Other forms of chronic ischaemic heart disease
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
Q494.00	Transient myocardial ischaemia of newborn
SP00300	Mechanical complication of coronary bypass
ZR37.00	Canadian Cardiovascular Society classification of angina
ZR3P.00	CLASP angina score
ZR3P.11	CLASP angina score
ZRB1.00	Euroscore for angina
ZV45700	[V]Presence of aortocoronary bypass graft
ZV45800	[V]Presence of coronary angioplasty implant and graft
ZV45K00	[V]Presence of coronary artery bypass graft
ZV45K11	[V]Presence of coronary artery bypass graft - CABG
ZV45L00	[V]Status following coronary angioplasty NOS

Appendix Table 11h. Read codes for stable angina.

Read code	Descriptor
14A5.00	H/O: angina pectoris
14AJ.00	H/O: Angina in last year
3889.00	Euroscore for angina
388E.00	Canadian Cardiovascular Society classification of angina
388F.00	Cardiovascular Limitations and Symptoms Profile angina score
662K000	Angina control - good
662K.00	Angina control
662K100	Angina control - poor
662K200	Angina control - improving
662K300	Angina control - worsening
662Kz00	Angina control NOS
8B27.00	Antianginal therapy
G33..00	Angina pectoris
G33z.00	Angina pectoris NOS
G33z300	Angina on effort
G33z500	Post infarct angina
G33z600	New onset angina
G33z700	Stable angina
G33zz00	Angina pectoris NOS
Gyu3000	[X]Other forms of angina pectoris
ZR37.00	Canadian Cardiovascular Society classification of angina
ZR3P.00	CLASP angina score
ZR3P.11	CLASP angina score
ZRB1.00	Euroscore for angina

Appendix Table 12. Distribution of follow-up time (time between start date and index date) among ICB cases and controls and the association between follow-up time and ICB.

Follow-up time	UGIB cases N= 1611 n (%)	Controls N= 10,000 n (%)	RR (95% CI)*	RR (95%CI) †
<6 months	156 (9.7)	816 (8.2)	1 (–)	1 (–)
6 months–<1year	134 (8.3)	787 (7.9)	0.89 (0.69–1.15)	0.89 (0.68–1.15)
1–<2 years	227 (14.1)	1420 (14.2)	0.85 (0.68–1.06)	0.88 (0.70–1.11)
2–<3 years	214 (13.3)	1288 (12.9)	0.88 (0.70–1.11)	0.92 (0.72–1.16)
3–<5 years	311 (19.3)	2198 (22.0)	0.73 (0.59–0.91)	0.75 (0.60–0.95)
≥5 years	569 (35.3)	3491 (34.9)	0.79 (0.64–0.99)	0.83 (0.66–1.05)

*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

Appendix Table 13. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic ICB cases and controls, and their association with non-traumatic ICB.

	Non-traumatic ICB cases N=1176		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	586	49.8	5164	51.6	NA	NA
Female	590	50.2	4836	48.4	NA	NA
Age (years)						
40–59	147	12.5	1174	11.7	NA	NA
60–69	286	24.3	2231	22.3	NA	NA
70–79	428	36.4	3708	37.1	NA	NA
80–89	315	26.8	2887	28.9	NA	NA
Calendar year						
2000–2004	219	18.6	1669	16.7	NA	NA
2005–2010	493	41.9	3988	39.9	NA	NA
2010 and beyond	464	39.5	4343	43.4	NA	NA
Cohort type						
Comparison	545	46.3	4790	47.9	1 (–)	1 (–)
Low-dose ASA	631	53.7	5210	52.1	0.97 (0.86–1.10)	0.92 (0.77–1.10)
Smoking						
Non-smoker	443	37.7	4403	44.0	1 (–)	1 (–)
Current	198	16.8	1193	11.9	1.63 (1.36–1.96)	1.53 (1.26–1.85)
Former	510	43.4	4215	42.1	1.16 (1.01–1.33)	1.18 (1.02–1.36)
Unknown	25	2.1	189	1.9	1.47 (0.94–2.29)	1.23 (0.75–2.01)
BMI (kg/m^2)						
15–19	68	5.8	355	3.5	1.52 (1.14–2.02)	1.50 (1.12–2.02)
20–24	342	29.1	2774	27.7	1	1
25–29	404	34.4	3712	37.1	0.87 (0.74–1.01)	0.87 (0.75–1.02)
≥30	243	20.7	2328	23.3	0.75 (0.63–0.89)	0.75 (0.63–0.91)
Unknown	119	10.1	831	8.3	1.24 (0.99–1.56)	1.23 (0.95–1.58)
Polypharmacy (in month before the index date)						
0–1	463	39.4	3658	36.6	1 (–)	1 (–)
2–4	318	27.0	3039	30.4	0.71 (0.61–0.84)	0.69 (0.58–0.81)
≥5	395	33.6	3303	33.0	0.71 (0.61–0.83)	0.68 (0.57–0.80)

	Non-traumatic ICB cases N=1176		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Polypharmacy (in month before the start date)						
0–1	628	53.4	5572	55.7	1 (–)	1 (–)
2–4	374	31.8	3231	32.3	0.94 (0.82–1.08)	0.94 (0.82–1.09)
≥5	174	14.8	1197	12.0	1.05 (0.87–1.27)	1.04 (0.86–1.27)
Alcohol (u/w)						
None	255	21.7	1955	19.6	1 (–)	1 (–)
1–9	558	47.4	4867	48.7	0.90 (0.76–1.05)	0.90 (0.77–1.07)
10–20	149	12.7	1365	13.7	0.86 (0.69–1.08)	0.88 (0.70–1.10)
21–41	43	3.7	443	4.4	0.77 (0.54–1.09)	0.69 (0.48–0.98)
≥42	18	1.5	94	0.9	1.55 (0.91–2.63)	1.40 (0.81–2.41)
Unknown	153	13.0	1276	12.8	0.98 (0.79–1.22)	0.84 (0.66–1.08)
PCP visits						
0–4	122	10.4	1415	14.1	1 (–)	1 (–)
5–9	207	17.6	2320	23.2	1.07 (0.85–1.35)	1.09 (0.86–1.39)
10–15	231	19.6	2285	22.9	1.24 (0.98–1.56)	1.22 (0.96–1.56)
15–19	175	14.9	1584	15.8	1.37 (1.07–1.75)	1.29 (0.99–1.67)
≥20	441	37.5	2396	24.0	2.34 (1.89–2.91)	1.94 (1.53–2.47)
Referrals						
0–4	441	37.5	4669	46.7	1 (–)	1 (–)
5–9	316	26.9	2836	28.4	1.12 (0.95–1.32)	1.12 (0.95–1.32)
10–19	261	22.2	1781	17.8	1.35 (1.12–1.63)	1.36 (1.13–1.65)
≥20	158	13.4	714	7.1	1.79 (1.42–2.26)	1.81 (1.42–2.30)
Hospitalizations						
None	796	67.7	8376	83.8	1 (–)	1 (–)
1	210	17.9	969	9.7	2.03 (1.71–2.41)	1.97 (1.65–2.35)
2	96	8.2	387	3.9	2.23 (1.75–2.84)	2.01 (1.56–2.59)
≥3	74	6.3	268	2.7	2.41 (1.82–3.18)	2.14 (1.60–2.87)

	Non-traumatic ICB cases N=1176		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Townsend score						
Deprived 1 (least deprived)	272	23.1	2634	26.3	1 (–)	1 (–)
Deprived 2	289	24.6	2369	23.7	1.15 (0.96–1.37)	1.18 (0.98–1.41)
Deprived 3	223	19.0	2039	20.4	1.03 (0.85–1.24)	1.01 (0.83–1.22)
Deprived 4	187	15.9	1628	16.3	1.05 (0.86–1.28)	1.03 (0.84–1.26)
Deprived 5 (most deprived)	176	15.0	1036	10.4	1.53 (1.25–1.88)	1.49 (1.20–1.84)
Unknown	29	2.5	294	2.9	0.92 (0.61–1.37)	0.95 (0.63–1.43)
Urban/rural						
Urban	738	6238	6238	62.4	1 (–)	1 (–)
Town	142	1247	1247	12.5	0.93 (0.77–1.13)	0.91 (0.75–1.11)
Rural	78	781	781	7.8	0.85 (0.67–1.09)	0.87 (0.68–1.12)
Unknown	218	1734	1734	17.3	1.05 (0.89–1.23)	1.03 (0.87–1.21)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 14. The frequency of comorbidities among non-traumatic ICB cases and controls, and their association with non-traumatic ICB.

Comorbidity	Non-traumatic ICB cases N=1176		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
MI	85	7.2	748	7.5	0.89 (0.70–1.13)	0.88 (0.67–1.15)
IS/TIA	224	19.03	884	8.8	2.31 (1.96–2.73)	2.05 (1.72–2.44)
IS	144	12.2	532	5.3	2.32 (1.90–2.83)	1.71 (1.37–2.13)
TIA	131	11.1	518	5.2	2.18 (1.78–2.68)	1.73 (1.38–2.17)
IHD‡	126	10.7	1448	14.5	0.64 (0.52–0.78)	0.63 (0.51–0.78)
Prior ICB	53	4.5	46	0.5	10.34 (6.89–15.51)	9.43 (6.21–14.31)
COPD	143	8.9	746	7.5	1.04 (0.83–1.29)	0.92 (0.73–1.16)
Asthma	233	14.5	1544	15.4	0.79 (0.66–0.94)	0.80 (0.67–0.96)
Hypertension	703	59.8	5795	58.0	1.00 (0.88–1.14)	1.05 (0.91–1.20)
Hyperlipidemia	280	23.8	2495	24.9	0.88 (0.76–1.01)	0.90 (0.77–1.04)
Diabetes	204	17.3	1829	18.3	0.76 (0.65–0.90)	0.91 (0.77–1.08)
DVT	118	10.0	789	7.9	1.18 (0.96–1.46)	1.10 (0.88–1.38)
Anaemia§	31	2.6	175	1.8	1.13 (0.76–1.67)	1.09 (0.73–1.64)
Atrial fibrillation	207	17.6	1014	10.1	1.69 (1.42–2.01)	1.11 (0.88–1.41)
Heart failure	73	6.2	491	4.9	1.09 (0.84–1.41)	0.89 (0.68–1.18)
PU, uncomplicated/ complicated	102	8.7	702	7.0	1.18 (0.95–1.47)	1.08 (0.86–1.36)
PU, uncomplicated	74	6.3	479	4.8	1.28 (0.99–1.65)	1.18 (0.91–1.54)
PU, complicated	46	3.9	302	3.0	1.20 (0.87–1.66)	1.05 (0.75–1.47)
IBD	22	1.9	142	1.4	1.18 (0.75–1.87)	1.24 (0.78–1.98)
Dyspepsia	441	27.4	2406	24.1	1.11 (0.96–1.27)	1.12 (0.97–1.29)
Gout	95	8.1	710	7.1	1.10 (0.88–1.39)	1.10 (0.87–1.39)
Osteoporosis	102	8.7	775	7.8	1.04 (0.83–1.30)	0.97 (0.76–1.22)
GERD	209	17.8	1724	17.2	0.94 (0.80–1.11)	0.98 (0.83–1.16)
Anxiety	307	19.1	1622	16.2	1.12 (0.96–1.32)	1.11 (0.95–1.31)
Depression	321	27.3	2061	20.6	1.30 (1.12–1.50)	1.27 (1.09–1.47)
Migraine	84	7.1	570	5.7	1.20 (0.94–1.52)	1.15 (0.89–1.47)
Epilepsy	36	3.1	156	1.6	3.43 (2.22–5.29)	3.13 (2.00–4.91))
Dementia	46	217	217	2.2	1.90 (1.40–2.58)	1.66 (1.21–2.29)
Falls§	57	4.8	270	2.7	1.56 (1.16–2.11)	1.58 (1.15–2.15)
Osteoarthritis	450	38.3	3991	39.9	0.86 (0.76–0.98)	0.91 (0.80–1.04)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.
[‡]Excluding MI.[§]In the year before the index date.
Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 15. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among traumatic ICB cases and controls, and their association with traumatic ICB.

	Traumatic ICB cases N=435		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	242	55.6	5164	51.6	NA	NA
Female	193	44.4	4836	48.4	NA	NA
Age (years)						
40–59	41	9.4	1174	11.7	NA	NA
60–69	69	15.9	2231	22.3	NA	NA
70–79	167	38.4	3708	37.1	NA	NA
80–89	158	36.3	2887	28.9	NA	NA
Calendar year						
2000–2004	45	10.3	1669	16.7	NA	NA
2005–2010	155	35.6	3988	39.9	NA	NA
2010 and beyond	235	54.0	4343	43.4	NA	NA
Cohort type					NA	NA
Comparison cohort	185	42.5	4790	47.9	1 (–)	1 (–)
Low-dose ASA cohort	250	57.5	5210	52.1	1.06 (0.87–1.29)	0.97 (0.74–1.28)
Smoking						
Non-smoker	190	43.7	4403	44.0	1 (–)	1 (–)
Current	48	11.0	1193	11.9	1.03 (0.74–1.43)	0.97 (0.70–1.36)
Former	194	44.6	4215	42.1	0.91 (0.73–1.12)	0.89 (0.72–1.11)
Unknown	3	0.7	189	1.9	0.70 (0.22–2.28)	0.70 (0.21–2.36)
BMI (kg/m^2)						
15–19	28	6.4	355	3.5	1.45 (0.95–2.23)	1.47 (0.95–2.26)
20–24	144	33.1	2774	27.7	1	1
25–29	163	37.5	3712	37.1	0.83 (0.66–1.05)	0.81 (0.64–1.03)
≥30	72	16.6	2328	23.3	0.54 (0.40–0.73)	0.53 (0.39–0.71)
Unknown	28	6.4	831	8.3	0.88 (0.58–1.33)	0.87 (0.56–1.37)
Polypharmacy (in month before the index date)						
0–1	139	32.0	3658	36.6	1 (–)	1 (–)
2–4	118	27.1	3039	30.4	0.79 (0.61–1.03)	0.75 (0.58–0.97)
≥5	178	40.9	3303	33.0	0.86 (0.68–1.11)	0.77 (0.59–1.00)

	Traumatic ICB cases N=435		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Polypharmacy (in month before the start date)						
0–1	222	51.0	5572	55.7	1 (–)	1 (–)
2–4	147	33.8	3231	32.3	0.97 (0.78–1.20)	1.00 (0.80–1.24)
≥5	66	15.2	1197	12.0	1.03 (0.77–1.37)	1.08 (0.80–1.46)
Alcohol (u/w)						
None	87	20.0	1955	19.6	1 (–)	1 (–)
1–9	194	44.6	4867	48.7	0.94 (0.72–1.22)	0.99 (0.76–1.30)
10–20	76	17.5	1365	13.7	1.37 (0.98–1.91)	1.44 (1.03–2.01)
21–41	26	6.0	443	4.4	1.44 (0.90–2.30)	1.52 (0.94–2.45)
≥42	4	0.9	94	0.9	1.20 (0.42–3.40)	1.34 (0.47–3.83)
Unknown	48	11.0	1276	12.8	1.04 (0.72–1.50)	1.09 (0.74–1.60)
PCP visits						
0–4	20	4.6	1415	14.1	1 (–)	1 (–)
5–9	75	17.2	2320	23.2	2.20 (1.34–3.63)	2.10 (1.26–3.49)
10–15	74	17.0	2285	22.9	2.16 (1.31–3.56)	1.99 (1.19–3.32)
15–19	84	19.3	1584	15.8	3.47 (2.12–5.71)	3.12 (1.87–5.21)
≥20	182	41.8	2396	24.0	4.84 (3.02–7.76)	3.93 (2.39–6.48)
Referrals						
0–4	127	29.2	4669	46.7	1 (–)	1 (–)
5–9	129	29.7	2836	28.4	1.29 (0.99–1.68)	1.27 (0.98–1.66)
10–19	114	26.2	1781	17.8	1.49 (1.12–2.00)	1.47 (1.10–1.98)
≥20	65	14.9	714	7.1	1.77 (1.24–2.53)	1.72 (1.19–2.49)
Hospitalizations						
None	259	59.5	8376	83.8	1 (–)	1 (–)
1	84	19.3	969	9.7	2.29 (1.76–2.99)	2.20 (1.68–2.87)
2	53	12.2	387	3.9	3.32 (2.40–4.60)	3.15 (2.25–4.40)
≥3	39	9.0	268	2.7	3.28 (2.25–4.78)	2.99 (2.03–4.41)

	Traumatic ICB cases N=435		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Townsend score						
Deprived 1 (least deprived)	126	29.0	2634	26.3	1 (–)	1 (–)
Deprived 2	86	19.8	2369	23.7	0.72 (0.54–0.96)	0.76 (0.57–1.01)
Deprived 3	85	19.5	2039	20.4	0.83 (0.63–1.11)	0.88 (0.66–1.18)
Deprived 4	64	14.7	1628	16.3	0.77 (0.56–1.05)	0.81 (0.59–1.11)
Deprived 5 (most deprived)	63	14.5	1036	10.4	1.21 (0.88–1.65)	1.34 (0.97–1.85)
Unknown	11	2.5	294	2.9	0.87 (0.46–1.64)	0.89 (0.47–1.69)
Urban/rural						
Urban	285	65.5	6238	62.4	1 (–)	1 (–)
Town	52	12.0	1247	12.5	0.89 (0.66–1.21)	0.86 (0.63–1.17)
Rural	31	7.1	781	7.8	0.90 (0.61–1.31)	0.87 (0.59–1.28)
Unknown	67	15.4	1734	17.3	0.84 (0.64–1.11)	0.84 (0.64–1.11)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 16. The frequency of comorbidities among traumatic ICB cases and controls, and their association with traumatic ICB.

Comorbidities	**Traumatic cases N=435**		**Controls N=10,000**		**RR (95% CI)**[*]	**RR (95% CI)**[†]
	n	**%**	**n**	**%**		
MI	38	8.7	748	7.5	0.98 (0.69–1.39)	0.86 (0.58–1.27)
IS/TIA	73	16.8	884	8.8	1.68 (1.29–2.20)	1.40 (1.06–1.85)
IS	44	10.1	532	5.3	1.58 (1.14–2.19)	1.20 (0.84–1.71)
TIA	38	8.8	518	5.2	1.43 (1.01–2.03)	1.22 (0.85–1.77)
IHD[‡]	74	17.0	1448	14.5	1.02 (0.79–1.32)	0.96 (0.72–1.28)
Prior ICB	11	2.5	46	0.5	5.17 (2.63–10.18)	5.28 (2.63–10.60)
COPD	40	9.2	746	7.5	0.93 (0.66–1.31)	0.96 (0.67–1.36)
Asthma	66	15.2	1544	15.4	0.79 (0.60–1.04)	0.85 (0.65–1.12)
Hypertension	277	63.7	5795	58.0	1.02 (0.83–1.26)	1.04 (0.84–1.29)
Hyperlipidemia	124	28.5	2495	24.9	1.06 (0.86–1.32)	1.06 (0.85–1.33)
Diabetes	100	23.0	1829	18.3	1.01 (0.79–1.28)	1.18 (0.92–1.52)
DVT	40	9.2	789	7.9	0.98 (0.70–1.38)	0.88 (0.61–1.26)
Anaemia[§]	20	4.6	175	1.8	1.83 (1.13–2.96)	1.82 (1.11–2.99)
Atrial fibrillation	84	19.3	1014	10.1	1.52 (1.17–1.97)	1.01 (0.70–1.45)
Heart failure	44	10.1	491	4.9	1.61 (1.15–2.24)	1.43 (1.01–2.04)
PU, uncomplicated/ complicated	31	7.1	702	7.0	0.84 (0.58–1.23)	0.82 (0.56–1.20)
PU, uncomplicated	19	4.4	302	3.0	0.69 (0.42–1.13)	0.65 (0.39–1.07)
PU, complicated	17	3.9	479	4.8	1.17 (0.73–1.90)	1.13 (0.69–1.84)
IBD	5	1.1	142	1.4	0.67 (0.27–1.66)	0.70 (0.28–1.75)
Dyspepsia	111	25.5	2406	24.1	0.89 (0.71–1.12)	0.93 (0.74–1.17)
Gout	40	9.2	710	7.1	1.05 (0.75–1.48)	1.01 (0.71–1.44)
Osteoporosis	48	11.0	775	7.8	1.22 (0.88–1.69)	1.12 (0.80–1.56)
GERD	84	19.3	1724	17.2	0.95 (0.75–1.22)	1.03 (0.80–1.32)
Anxiety	79	18.2	1622	16.2	1.04 (0.80–1.35)	1.04 (0.80–1.35)
Depression	117	26.9	2061	20.6	1.32 (1.06–1.66)	1.34 (1.07–1.69)
Migraine	29	6.7	570	5.7	1.20 (0.81–1.78)	1.19 (0.80–1.78)
Epilepsy	26	6.0	156	1.6	3.43 (2.22–5.29)	3.13 (2.00–4.91)
Dementia	45	10.3	248	2.5	3.46 (2.44–4.91)	3.24 (2.26–4.63)
Falls[§]	87	20.0	270	2.7	7.41 (5.60–9.80)	7.64 (5.72–10.21)
Osteoarthritis	192	44.1	3991	39.9	1.04 (0.85–1.27)	1.02 (0.84–1.25)

[*]Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

[‡]Excluding MI.

[§]In the year before the index date.

Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 17. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among ICH cases and controls, and their association with ICH.

	ICH cases N=743		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	375	50.5	5164	51.6	NA	NA
Female	368	49.5	4836	48.4	NA	NA
Age (years)						
40–59	55	7.4	1174	11.7	NA	NA
60–69	159	21.4	2231	22.3	NA	NA
70–79	281	37.8	3708	37.1	NA	NA
80–89	248	33.4	2887	28.9	NA	NA
Calendar year						
2000–2004	137	18.4	1669	16.7	NA	NA
2005–2010	311	41.9	3988	39.9	NA	NA
2010 and beyond	295	39.7	4343	43.4	NA	NA
Cohort type						
Comparison	336	45.2	4790	47.9	1 (–)	1 (–)
Low-dose ASA	407	54.8	5210	52.1	1.01 (0.87–1.18)	0.89 (0.72–1.11)
Smoking						
Non-smoker	307	41.3	4403	44.0	1 (–)	1 (–)
Current	89	12.0	1193	11.9	1.14 (0.89–1.47)	1.08 (0.83–1.39)
Former	328	44.1	4215	42.1	1.04 (0.88–1.23)	1.08 (0.91–1.28)
Unknown	19	2.6	189	1.9	1.63 (0.98–2.71)	1.27 (0.73–2.23)
BMI (kg/m^2)						
15–19	50	6.7	355	3.5	1.71 (1.23–2.39)	1.77 (1.26–2.48)
20–24	215	28.9	2774	27.7	1 (–)	1 (–)
25–29	245	33.0	3712	37.1	0.86 (0.71–1.04)	0.84 (0.69–1.03)
≥30	149	20.1	2328	23.3	0.79 (0.63–0.99)	0.77 (0.61–0.97)
Unknown	84	11.3	831	8.3	1.44 (1.10–1.89)	1.41 (1.04–1.90)
Polypharmacy (in month before the index date)						
0–1	281	37.8	3658	36.6	1 (–)	1 (–)
2–4	198	26.6	3039	30.4	0.98 (0.83–1.16)	0.66 (0.54–0.81)
≥5	264	35.5	3303	33.0	0.97 (0.77–1.22)	0.68 (0.55–0.83)

	ICH cases N=743		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Polypharmacy (in month before the start date)						
0–1	388	52.2	5572	55.7	1 (–)	1 (–)
2–4	250	33.6	3231	32.3	0.69 (0.57–0.84)	0.99 (0.83–1.17)
≥5	105	14.1	1197	12.0	0.72 (0.59–0.87)	0.96 (0.75–1.22)
Alcohol (u/w)						
None	179	24.1	1955	19.6	1 (–)	1 (–)
1–9	345	46.4	4867	48.7	0.80 (0.66–0.97)	0.81 (0.67–0.99)
10–20	85	11.4	1365	13.7	0.73 (0.56–0.97)	0.74 (0.56–0.99)
21–41	24	3.2	443	4.4	0.63 (0.40–0.99)	0.59 (0.37–0.93)
≥42	10	1.3	94	0.9	1.36 (0.69–2.69)	1.28 (0.64–2.57)
Unknown	100	13.5	1276	12.8	0.94 (0.72–1.22)	0.78 (0.58–1.04)
PCP visits						
0–4	69	9.3	1415	14.1	1 (–)	1 (–)
5–9	126	17.0	2320	23.2	1.09 (0.80–1.47)	1.11 (0.81–1.51)
10–15	137	18.4	2285	22.9	1.20 (0.89–1.62)	1.17 (0.85–1.60)
15–19	123	16.6	1584	15.8	1.57 (1.16–2.13)	1.43 (1.03–1.98)
≥20	288	38.8	2396	24.0	2.46 (1.86–3.24)	1.96 (1.44–2.65)
Referrals						
0–4	277	37.3	4669	46.7	1 (–)	1 (–)
5–9	218	29.3	2836	28.4	1.16 (0.96–1.42)	1.19 (0.97–1.45)
10–19	155	20.9	1781	17.8	1.16 (0.92–1.46)	1.17 (0.92–1.48)
≥20	93	12.5	714	7.1	1.48 (1.11–1.97)	1.46 (1.08–1.96)
Hospitalizations						
None	496	66.8	8376	83.8	1 (–)	1 (–)
1	141	19.0	969	9.7	2.11 (1.72–2.59)	2.02 (1.63–2.49)
2	62	8.3	387	3.9	2.15 (1.61–2.89)	1.93 (1.42–2.62)
≥3	44	5.9	268	2.7	2.11 (1.49–2.97)	1.73 (1.21–2.48)
Townsend score						
Deprived 1 (least deprived)	176	23.7	2634	26.3	1 (–)	1 (–)
Deprived 2	184	24.8	2369	23.7	1.12 (0.90–1.39)	1.16 (0.93–1.45)
Deprived 3	143	19.2	2039	20.4	1.01 (0.81–1.28)	1.02 (0.81–1.29)
Deprived 4	114	15.3	1628	16.3	0.98 (0.77–1.26)	0.99 (0.77–1.28)
Deprived 5 (most deprived)	104	14.0	1036	10.4	1.41 (1.09–1.82)	1.45 (1.11–1.89)
Unknown	22	3.0	294	2.9	1.09 (0.69–1.74)	1.17 (0.73–1.87)

	ICH cases N=743		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Urban/rural						
Urban	487	65.5	6238	62.4	1 (–)	1 (–)
Town	95	12.8	1247	12.5	0.69 (0.50–0.95)	0.90 (0.71–1.14)
Rural	42	5.7	781	7.8	0.89 (0.72–1.09)	0.68 (0.49–0.95)
Unknown	119	16.0	1734	17.3	0.93 (0.74–1.17)	0.87 (0.70–1.08)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 18. The frequency of comorbidities of ICH cases and controls, and their association with ICH.

Comorbidities	ICH cases N=743		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
MI	61	8.2	748	7.5	1.01 (0.76–1.33)	1.04 (0.76–1.42)
IS/TIA	157	21.1	884	8.8	2.41 (1.99–2.93)	2.09 (1.70–2.57)
IS	103	13.9	532	5.3	2.41 (1.99–2.93)	1.86 (1.44–2.39)
TIA	85	11.4	518	5.2	2.07 (1.61–2.64)	1.56 (1.19–2.04)
IHD‡	85	11.4	1448	14.5	0.67 (0.53–0.85)	0.68 (0.53–0.88)
Prior ICB	28	3.8	46	0.5	8.35 (5.15–13.56)	7.56 (4.59–12.45)
COPD	66	8.9	746	7.5	0.99 (0.76–1.29)	0.95 (0.71–1.25)
Asthma	94	12.7	1544	15.4	0.69 (0.55–0.86)	0.71 (0.57–0.90)
Hypertension	464	62.4	5795	58.0	1.05 (0.89–1.23)	1.07 (0.91–1.26)
Hyperlipidemia	180	24.2	2495	24.9	0.91 (0.76–1.08)	0.92 (0.77–1.11)
Diabetes	140	18.8	1829	18.3	0.86 (0.71–1.05)	0.99 (0.81–1.22)
DVT	71	9.6	789	7.9	1.07 (0.83–1.39)	0.99 (0.75–1.31)
Anaemia§	21	2.8	175	1.8	1.13 (0.71–1.80)	1.03 (0.64–1.68)
Atrial fibrillation	155	20.9	1014	10.1	1.89 (1.55–2.30)	1.27 (0.97–1.67)
Heart failure	62	8.3	491	4.9	1.37 (1.03–1.82)	1.11 (0.82–1.50)
PU, uncomplicated/ complicated	66	8.9	702	7.0	1.13 (0.86–1.47)	1.05 (0.79–1.38)
PU, uncomplicated	42	5.7	479	4.8	1.07 (0.77–1.49)	0.99 (0.71–1.39)
PU, complicated	39	5.2	302	3.0	1.52 (1.07–2.15)	1.37 (0.95–1.97)
IBD	16	2.2	142	1.4	1.37 (0.81–2.31)	1.46 (0.86–2.50)
Dyspepsia	210	28.3	2406	24.1	1.10 (0.93–1.31)	1.12 (0.97–1.37)
Gout	71	9.6	710	7.1	1.25 (0.97–1.63)	1.23 (0.94–1.62)
Osteoporosis	79	10.6	775	7.8	1.22 (0.94–1.27)	1.14 (0.87–1.48)
GERD	147	19.8	1724	17.2	1.07 (0.88–1.30)	1.16 (0.95–1.41)
Anxiety	133	17.9	1622	16.2	1.05 (0.86–1.29)	1.05 (0.86–1.29)
Depression	193	26.0	2061	20.6	1.27 (1.06–1.52)	1.27 (1.06–1.52)
Migraine	49	6.6	570	5.7	1.19 (0.88–1.62)	1.16 (0.84–1.59)
Epilepsy	21	2.8	156	1.6	1.70 (1.07–2.71)	1.35 (0.83–2.20)
Dementia	42	5.7	248	2.5	1.96 ((1.39–2.77)	1.69 (1.18–2.42)
Falls§	55	7.4	270	2.7	2.22 (1.63–3.03)	2.22 (1.61–3.06)
Osteoarthritis	303	40.8	3991	39.9	0.89 (0.76–1.04)	0.96 (0.81–1.12)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

‡Excluding MI.

§In the year before the index date.

Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 19. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic ICH cases and controls, and their association with non-traumatic ICH.

	Non-traumatic ICH cases N=660		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	331	50.2	5164	51.6	NA	NA
Female	329	49.8	4836	48.4	NA	NA
Age (years)						
40–59	51	7.7	1174	11.7	NA	NA
60–69	149	22.6	2231	22.3	NA	NA
70–79	247	37.4	3708	37.1	NA	NA
80–89	213	32.3	2887	28.9	NA	NA
Calendar year						
2000–2004	124	18.8	1669	16.7	NA	NA
2005–2010	279	42.3	3988	39.9	NA	NA
2010 and beyond	257	38.9	4343	43.4	NA	NA
Cohort type						
Comparison	301	45.6	4790	47.9	1 (–)	1 (–)
Low-dose ASA	359	54.4	5210	52.1	1.00 (0.85–1.18)	0.8 (0.69–1.09)
Smoking						
Non-smoker	266	40.3	4403	44.0	1 (–)	1 (–)
Current	82	12.4	1193	11.9	1.20 (0.92–1.56)	1.14 (0.87–1.49)
Former	293	44.4	4215	42.1	1.08 (0.91–1.29)	1.12 (0.93–1.34)
Unknown	19	2.9	189	1.9	1.86 (1.11–3.10)	1.47 (0.83–2.60)
BMI (kg/m^2)						
15–19	42	6.4	355	3.5	1.75 (1.23–2.50)	1.73 (1.20–2.49)
20–24	183	27.7	2774	27.7	1 (–)	1 (–)
25–29	224	33.9	3712	37.1	0.93 (0.76–1.13)	0.91 (0.74–1.12)
≥30	136	20.6	2328	23.3	0.92 (0.73–1.16)	0.82 (0.64–1.04)
Unknown	75	11.4	831	8.3	1.32 (0.98–1.78)	1.41 (1.02–1.95)
Polypharmacy (in month before index date)						
0–1	350	53.0	5572	55.7	1 (–)	1 (–)
2–4	216	32.7	3231	32.3	0.63 (0.51–0.78)	0.60 (0.49–0.74)
≥5	94	14.2	1197	12.0	0.69 (0.56–0.84)	0.65 (0.52–0.80)
Polypharmacy (in month before start date)						
0–1	261	39.5	3658	36.6	1 (–)	1 (–)
2–4	167	25.3	3039	30.4	0.95 (0.79–1.13)	0.95 (0.79–1.14)
≥5	232	35.2	3303	33.0	0.97 (0.76–1.24)	0.95 (0.74–1.23)

Alcohol (u/w)						
None	157	23.8	1955	19.6	1 (–)	1 (–)
1–9	311	47.1	4867	48.7	0.82 (0.67–1.01)	0.83 (0.68–1.03)
10–20	70	10.6	1365	13.7	0.68 (0.51–0.92)	0.70 (0.51–0.95)
21–41	21	3.2	443	4.4	0.63 (0.39–1.01)	0.58 (0.35–0.94)
≥42	10	1.5	94	0.9	1.50 (0.76–2.99)	1.39 (0.69–2.81)
Unknown	91	13.8	1276	12.8	0.96 (0.73–1.26)	0.79 (0.58–1.07)
PCP visits						
0–4	65	9.8	1415	14.1	1 (–)	1 (–)
5–9	108	16.4	2320	23.2	1.00 (0.73–1.37)	1.01 (0.73–1.41)
10–15	127	19.2	2285	22.9	1.20 (0.88–1.63)	1.16 (0.84–1.61)
15–19	109	16.5	1584	15.8	1.50 (1.09–2.06)	1.37 (0.98–1.93)
≥20	251	38.0	2396	24.0	2.31 (1.74–3.08)	1.89 (1.38–2.59)
Referrals						
0–4	248	37.6	4669	46.7	1 (–)	1 (–)
5–9	190	28.8	2836	28.4	1.15 (0.93–1.41)	1.17 (0.95–1.45)
10–19	135	20.5	1781	17.8	1.16 (0.91–1.48)	1.16 (0.91–1.49)
≥20	87	13.2	714	7.1	1.62 (1.20–2.19)	1.61 (1.18–2.20)
Hospitalizations						
None	446	67.6	8376	83.8	1 (–)	1 (–)
1	122	18.5	969	9.7	2.04 (1.64–2.54)	1.93 (1.54–2.42)
2	52	7.9	387	3.9	2.03 (1.48–2.78)	1.79 (1.29–2.48)
≥3	40	6.1	268	2.7	2.17 (1.51–3.10)	1.79 (1.23–2.61)
Townsend score						
Deprived 1 (least deprived)	149	22.6	2634	26.3	1 (–)	1 (–)
Deprived 2	162	24.5	2369	23.7	1.16 (0.92–1.47)	1.20 (0.95–1.52)
Deprived 3	130	19.7	2039	20.4	1.09 (0.86–1.39)	1.09 (0.85–1.40)
Deprived 4	107	16.2	1628	16.3	1.09 (0.84–1.41)	1.08 (0.83–1.41)
Deprived 5 (most deprived)	95	14.4	1036	10.4	1.52 (1.16–2.00)	1.56 (1.18–2.06)
Unknown	17	2.6	294	2.9	1.00 (0.59–1.67)	1.05 (0.62–1.78)
Urban/rural						
Urban	431	65.3	6238	62.4	1 (–)	1 (–)
Town	84	12.7	1247	12.5	0.93 (0.73–1.19)	0.90 (0.70–1.15)
Rural	38	5.8	781	7.8	0.70 (0.50–0.99)	0.70 (0.49–0.99)
Unknown	107	16.2	1734	17.3	0.90 (0.72–1.12)	0.89 (0.71–1.11)

[*]Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 20. The frequency of comorbidities among non-traumatic ICH cases and controls, and their association with non-traumatic ICH.

Comorbidities	**Non-traumatic ICH cases N=660**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
MI	52	7.9	748	7.5	0.97 (0.72–1.30)	1.03 (0.74–1.43)
IS/TIA	139	21.1	884	8.8	2.44 (1.99–3.00)	2.13 (1.71–2.64)
IS	93	14.1	532	5.3	2.57 (2.02–3.27)	1.93 (1.48–2.51)
TIA	76	11.5	518	5.2	2.11 (1.63–2.73)	1.57 (1.18–2.08)
IHD‡	71	10.8	1448	14.5	0.63 (0.49–0.81)	0.65 (0.49–0.85)
Prior ICB	27	4.1	46	0.5	8.24 (5.04–13.47)	7.96 (4.79–13.21)
COPD	58	8.8	746	7.5	0.99 (0.75–1.31)	0.92 (0.69–1.25)
Asthma	81	12.3	1544	15.4	0.67 (0.52–0.85)	0.69 (0.53–0.88)
Hypertension	411	62.3	5795	58.0	1.05 (0.89–1.25)	1.07 (0.89–1.27)
Hyperlipidemia	161	24.4	2495	24.9	0.92 (0.76–1.10)	0.93 (0.77–1.13)
Diabetes	124	18.8	1829	18.3	0.86 (0.70–1.07)	0.98 (0.79–1.22)
DVT	63	9.5	789	7.9	1.08 (0.82–1.42)	1.02 (0.76–1.36)
Anaemia§	19	2.9	175	1.8	1.17 (0.72–1.91)	1.07 (0.64–1.77)
Atrial fibrillation	137	20.8	1014	10.1	1.93 (1.56–2.38)	1.43 (1.07–1.90)
Heart failure	50	7.6	491	4.9	1.25 (0.92–1.71)	1.00 (0.72–1.39)
PU, uncomplicated/ complicated	60	9.1	702	7.0	1.17 (0.89–1.55)	1.09 (0.82–1.46)
PU, uncomplicated	40	6.1	479	4.8	1.17 (0.83–1.63)	1.09 (0.77–1.54)
PU, complicated	34	5.2	302	3.0	1.51 (1.04–2.18)	1.36 (0.93–2.00)
IBD	15	2.3	142	1.4	1.45 (0.84–2.50)	1.57 (0.91–2.72)
Dyspepsia	190	28.2	2429	24.3	1.12 (0.94–1.34)	1.17 (0.97–1.40)
Gout	58	8.8	710	7.1	1.16 (0.87–1.54)	1.13 (0.84–1.52)
Osteoporosis	69	10.5	775	7.8	1.21 (0.92–1.59)	1.13 (0.85–1.50)
GERD	125	18.9	1724	17.2	1.02 (0.83–1.25)	1.09 (0.88–1.34)
Anxiety	120	18.2	1622	16.2	1.07 (0.87–1.32)	1.07 (0.86–1.33)
Depression	169	25.1	2061	20.6	1.23 (1.02–1.48)	1.22 (1.00–1.48)
Migraine	45	6.8	570	5.7	1.22 (0.89–1.68)	1.19 (0.86–1.65)
Epilepsy	18	2.7	156	1.6	1.64 (1.00–2.70)	1.33 (0.79–2.24)
Dementia	34	5.2	248	2.5	1.81 (1.25–2.64)	1.53 (1.03–2.27)
Falls§	37	5.6	270	2.7	1.66 (1.16–2.39)	1.64 (1.13–2.38)
Osteoarthritis	267	40.5	3991	39.9	0.89 (0.75–1.05)	0.95 (0.80–1.13)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin

‡Excluding MI.

§In the year before the index date.

Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 21. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among SDH cases and controls, and their association with SDH.

	SDH cases N=483		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	298	61.7	5164	51.6	NA	NA
Female	185	38.3	4836	48.4	NA	NA
Age (years)						
40–59	40	8.3	1174	11.7	NA	NA
60–69	74	15.3	2231	22.3	NA	NA
70–79	205	42.4	3708	37.1	NA	NA
80–89	164	34.0	2887	28.9	NA	NA
Calendar year						
2000–2004	46	9.5	1669	16.7	NA	NA
2005–2010	184	38.1	3988	39.9	NA	NA
2010 and beyond	253	52.4	4343	43.4	NA	NA
Cohort type						
Comparison	200	41.4	4790	47.9	1 (–)	1 (–)
Low-dose ASA	283	58.6	5210	52.1	1.07 (0.88–1.29)	0.99 (0.76–1.28)
Smoking						
Non-smoker	197	40.8	4403	44.0	1 (–)	1 (–)
Current	46	9.5	1193	11.9	0.93 (0.67–1.31)	0.89 (0.63–1.25)
Former	236	48.9	4215	42.1	0.98 (0.80–1.20)	0.96 (0.78–1.18)
Unknown	4	0.8	189	1.9	0.98 (0.35–2.75)	1.02 (0.34–3.01)
BMI (kg/m^2)						
15–19	19	3.9	355	3.5	0.88 (0.53–1.44)	0.89 (0.54–1.46)
20–24	171	35.4	2774	27.7	1 (–)	1 (–)
25–29	183	37.9	3712	37.1	0.77 (0.62–0.96)	0.75 (0.60–0.93)
≥30	84	17.4	2328	23.3	0.53 (0.40–0.69)	0.51 (0.38–0.67)
Unknown	26	5.4	831	8.3	0.72 (0.47–1.11)	0.67 (0.42–1.06)
Polypharmacy (in month before the index date)						
0–1 drug	158	32.7	3658	36.6	1 (–)	1 (–)
2–4 drugs	115	23.8	3039	30.4	0.64 (0.49–0.82)	0.60 (0.46–0.78)
≥5	210	43.5	3303	33.0	0.80 (0.63–1.00)	0.72 (0.57–0.93)
Polypharmacy (in month before the start date)						
0–1 drug	239	49.5	5572	55.7	1 (–)	1 (–)
2–4 drugs	156	32.3	3231	32.3	0.93 (0.76–1.15)	0.96 (0.77–1.19)
≥5	88	18.2	1197	12.0	1.22 (0.94–1.59)	1.32 (1.00–1.73)

	SDH cases N=483		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Alcohol (u/w)						
None	94	19.5	1955	19.6	1 (–)	1 (–)
1–9	221	45.8	4867	48.7	0.96 (0.74–1.23)	1.00 (0.77–1.29)
10–20	84	17.4	1365	13.7	1.30 (0.95–1.79)	1.36 (0.98–1.89)
21–41	27	5.6	443	4.4	1.23 (0.78–1.95)	1.26 (0.79–2.02)
≥42	4	0.8	94	0.9	0.99 (0.35–2.80)	1.13 (0.40–3.25)
Unknown	53	11.0	1276	12.8	1.05 (0.74–1.50)	1.08 (0.74–1.57)
PCP visits						
0–4	18	3.7	1415	14.1	1 (–)	1 (–)
5–9	66	13.7	2320	23.2	2.15 (1.27–3.64)	2.07 (1.21–3.53)
10–15	80	16.6	2285	22.9	2.58 (1.54–4.34)	2.37 (1.39–4.04)
15–19	87	18.0	1584	15.8	4.01 (2.40–6.71)	3.52 (2.07–6.00)
≥20	232	48.0	2396	24.0	7.05 (4.32–11.49)	5.41 (3.24–9.06)
Referrals						
0–4	132	27.3	4669	46.7	1 (–)	1 (–)
5–9	119	24.6	2836	28.4	1.09 (0.84–1.42)	1.08 (0.82–1.41)
10–19	138	28.6	1781	17.8	1.61 (1.22–2.12)	1.58 (1.20–2.09)
≥20	94	19.5	714	7.1	2.17 (1.57–3.00)	2.06 (1.48–2.87)
Hospitalizations						
None	281	58.2	8376	83.8	1 (–)	1 (–)
1	89	18.4	969	9.7	2.07 (1.60–2.67)	1.98 (1.52–2.57)
2	65	13.5	387	3.9	3.33 (2.46–4.50)	3.08 (2.25–4.21)
≥3	48	9.9	268	2.7	3.21 (2.27–4.53)	2.91 (2.03–4.17)
Townsend score						
Deprived 1 (least deprived)	131	27.1	2634	26.3	1 (–)	1 (–)
Deprived 2	111	23.0	2369	23.7	0.88 (0.68–1.14)	0.94 (0.72–1.23)
Deprived 3	89	18.4	2039	20.4	0.84 (0.64–1.11)	0.91 (0.68–1.21)
Deprived 4	75	15.5	1628	16.3	0.87 (0.65–1.16)	0.92 (0.68–1.24)
Deprived 5 (most deprived)	68	14.1	1036	10.4	1.28 (0.94–1.74)	1.45 (1.06–2.00)
Unknown	9	1.9	294	2.9	0.69 (0.34–1.38)	0.70 (0.35–1.41)
Urban/rural						
Urban	300	62.1	6238	62.4	1 (–)	1 (–)
Town	60	12.4	1247	12.5	0.96 (0.72–1.28)	0.93 (0.69–1.25)
Rural	37	7.7	781	7.8	1.01 (0.71–1.44)	1.00 (0.70–1.43)
Unknown	86	17.8	1734	17.3	1.03 (0.80–1.32)	1.02 (0.79–1.32)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 22. The frequency of comorbidities among SDH cases and controls, and their association with SDH.

Comorbidities	**Cases SDH N=483**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
MI	45	9.3	748	7.5	0.97 (0.70–1.33)	0.85 (0.59–1.22)
IS/TIA	95	19.7	884	8.8	1.96 (1.54–2.49)	1.67 (1.30–2.15)
IS	58	12.0	532	5.3	1.83 (1.36–2.46)	1.34 (0.97–1.85)
TIA	56	11.6	518	5.2	1.88 (1.39–2.53)	1.57 (1.14–2.16)
IHD‡	74	15.3	1448	14.5	0.84 (0.65–1.08)	0.76 (0.57–1.01)
Prior ICB	16	3.3	46	0.5	6.64 (3.65–12.08)	6.84 (3.68–12.71)
COPD	42	8.7	746	7.5	0.80 (0.57–1.11)	0.82 (0.58–1.16)
Asthma	71	14.7	1544	15.4	0.72 (0.56–0.94)	0.78 (0.60–1.02)
Hypertension	300	62.1	5795	58.0	0.92 (0.76–1.12)	0.92 (0.75–1.13)
Hyperlipidemia	137	28.4	2495	24.9	1.03 (0.84–1.27)	1.05 (0.85–1.29)
Diabetes	112	23.2	1829	18.3	0.93 (0.74–1.16)	1.15 (0.90–1.45)
DVT	57	11.8	789	7.9	1.29 (0.96–1.73)	1.12 (0.81–1.54)
Anaemia§	21	4.3	175	1.8	1.55 (0.97–2.49)	1.59 (0.98–2.59)
Atrial fibrillation	112	23.2	1014	10.1	1.76 (1.40–2.23)	1.00 (0.72–1.40)
Heart failure	45	9.3	491	4.9	1.33 (0.96–1.85)	1.07 (0.76–1.52)
Haemodialysis (all)	2	0.4	12	0.1	2.60 (0.56–12.12)	2.80 (0.54–12.12)
Haemodialysis extracorporeal	2	0.4	8	0.1	3.89 (0.79–19.22)	4.06 (0.72–22..83)
eGFR (mL/min/1.73 m^2)						
0–14	3	0.6	25	0.2	1.58 0.47–5.38)	1.46 (0.42–5.16)
15–29	20	4.1	126	1.3	2.23 (1.35–3.69)	2.44 (1.45–4.09)
30–44	38	7.9	670	6.7	0.84 (0.59–1.21)	0.84 (0.58–1.22)
45–59	90	18.6	1881	18.8	0.85 (0.66–1.10)	0.85 (0.66–1.10)
≥60	292	60.5	5960	59.6	1 (–)	1 (–)
Unknown	40	8.3	1338	13.4	1.34 (0.93–1.95)	1.36 (0.93–2.00)
PU, uncomplicated/ complicated	38	7.9	702	7.0	0.88 (0.62–1.24)	0.84 (0.59–1.20)
PU, uncomplicated	25	5.2	479	4.8	0.86 (0.56–1.30)	0.81 (0.53–1.25)
PU, complicated	20	4.1	302	3.0	1.03 (0.65–1.65)	0.95 (0.59–1.54)
IBD	7	1.4	142	1.4	0.84 (0.39–1.81)	0.85 (0.39–1.85)
Dyspepsia	134	27.7	2406	24.1	0.97 (0.78–1.19)	1.00 (0.81–1.24)
Gout	48	9.9	710	7.1	1.04 (0.76–1.43)	0.99 (0.71–1.37)
Osteoporosis	47	9.7	775	7.8	1.13 (0.81–1.57)	1.02 (0.73–1.43)
GERD	86	17.8	1724	17.2	0.84 (0.66–1.07)	0.88 (0.68–1.13)
Anxiety	82	17.0	1622	16.2	0.98 (0.76–1.26)	1.00 (0.77–1.29)
Depression	113	23.4	2061	20.6	1.10 (0.88–1.38)	1.12 (0.89–1.41)
Migraine	30	6.2	570	5.7	1.17 (0.79–1.72)	1.12 (0.75–1.66)
Epilepsy	31	6.4	156	1.6	3.56 (2.37–5.35)	3.25 (2.12–4.97)
Dementia	42	8.7	248	2.5	2.76 (1.93–3.94)	2.61 (1.80–3.78)
Falls§	72	14.9	270	2.7	4.81 (3.59–6.46)	4.82 (3.54–6.56)
Osteoarthritis	206	42.7	3991	39.9	0.91 (0.75–1.10)	0.94 (0.77–1.15)

[*]Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

[‡]Excluding MI.

[§]In the year before the index date.

Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 23. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic SDH cases and controls, and their association with non-traumatic SDH.

	Non-traumatic SDH cases N=205		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	140	68.3	5164	51.6	NA	NA
Female	65	31.7	4836	48.4	NA	NA
Age (years)						
40–59	14	6.8	1174	11.7	NA	NA
60–69	34	16.6	2231	22.3	NA	NA
70–79	95	46.3	3708	37.1	NA	NA
80–89	62	30.2	2887	28.9	NA	NA
Calendar year						
2000–2004	21	10.2	1669	16.7	NA	NA
2005–2010	82	40.0	3988	39.9	NA	NA
2010 and beyond	102	49.8	4343	43.4	NA	NA
Cohort type						
Comparison	91	44.4	4790	47.9	1 (–)	1 (–)
Low-dose ASA	114	55.6	5210	52.1	0.92 (0.69–1.22)	0.85 (0.58–1.25)
Smoking						
Non-smoker	77	37.6	4403	44.0	1 (–)	1 (–)
Current	18	8.8	1193	11.9	0.90 (0.53–1.52)	0.87 (0.51–1.49)
Former	108	52.7	4215	42.1	1.05 (0.77–1.42)	1.06 (0.77–1.45)
Unknown	2	1.0	189	1.9	1.15 (0.27–4.93)	1.19 (0.25–5.61)
BMI (kg/m^2)						
15–19	5	2.4	355	3.5	0.56 (0.22–1.40)	0.54 (0.21–1.38)
20–24	76	37.1	2774	27.7	1 (–)	1 (–)
25–29	75	36.6	3712	37.1	0.70 (0.50–0.97)	0.67 (0.48–0.93)
≥30	39	19.0	2328	23.3	0.54 (0.36–0.81)	0.53 (0.35–0.80)
Unknown	10	4.9	831	8.3	0.64 (0.32–1.25)	0.56 (0.27–1.17)
Polypharmacy (in month before the index date)						
0–1 drug	62	30.2	3658	36.6	1 (–)	1 (–)
2–4 drugs	50	24.4	3039	30.4	0.69 (0.47–1.01)	0.66 (0.44–0.98)
≥5	93	45.4	3303	33.0	0.85 (0.60–1.21)	0.80 (0.55–1.17)
Polypharmacy (in month before the start date)						
0–1 drug	90	43.9	5572	55.7	1 (–)	1 (–)
2–4 drugs	71	34.6	3231	32.3	1.13 (0.82–1.56)	1.16 (0.84–1.61)
≥5	44	21.5	1197	12.0	1.60 (1.09–2.33)	1.72 (1.15–2.55)

	Non-traumatic SDH cases N=205		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Alcohol (u/w)						
None	40	19.5	1955	19.6	1 (–)	1 (–)
1–9	96	46.8	4867	48.7	0.93 (0.64–1.36)	0.98 (0.66–1.45)
10–20	35	17.1	1365	13.7	1.13 (0.70–1.82)	1.21 (0.73–1.98)
21–41	10	4.9	443	4.4	0.90 (0.44–1.86)	0.94 (0.45–1.97)
≥42	0	0.0	94	0.9	–	–
Unknown	24	11.71	1276	12.8	1.08 (0.64–1.81))	1.06 (0.61–1.85)
PCP visits	8	3.9	1415	14.1		
0–4	23	11.2	2320	23.2	1 (–)	1 (–)
5–9	30	14.6	2285	22.9	1.72 (0.76–3.87)	1.70 (0.75–3.85)
10–15	31	15.1	1584	15.8	2.25 (1.02–4.95)	2.10 (0.94–4.71)
15–19	113	55.1	2396	24.0	3.36 (1.53–7.39)	2.88 (1.28–6.48)
≥20	8	3.9	1415	14.1	8.34 (4.01–17.36)	5.89 (2.73–12.71)
Referrals						
0–4	57	27.8	4669	46.7	1 (–)	1 (–)
5–9	41	20.0	2836	28.4	0.85 (0.56–1.30)	0.83 (0.54–1.28)
10–19	63	30.7	1781	17.8	1.58 (1.05–2.38)	1.59 (1.05–2.42)
≥20	44	21.5	714	7.1	2.02 (1.26–3.24)	1.85 (1.14–3.01)
Hospitalizations						
None	125	61.0	8376	83.8	1 (–)	1 (–)
1	34	16.6	969	9.7	1.62 (1.09–2.41)	1.58 (1.05–2.37)
2	24	11.7	387	3.9	2.42 (1.52–3.86)	2.16 (1.32–3.52)
≥3	22	10.7	268	2.7	2.78 (1.70–4.55)	2.58 (1.53–4.34)
Townsend score						
Deprived 1 (least deprived)	53	25.9	2634	26.3	1 (–)	1 (–)
Deprived 2	58	28.3	2369	23.7	1.12 (0.77–1.64)	1.20 (0.81–1.77)
Deprived 3	33	16.1	2039	20.4	0.78 (0.50–1.21)	0.83 (0.53–1.30)
Deprived 4	30	14.6	1628	16.3	0.86 (0.55–1.36)	0.88 (0.55–1.42)
Deprived 5 (most deprived)	26	12.7	1036	10.4	1.22 (0.75–1.98)	1.35 (0.82–2.23)
Unknown	5	2.4	294	2.9	0.92 (0.36–2.35)	0.96 (0.37–2.48)
Urban/rural						
Urban	120	58.5	6238	62.4	1 (–)	1 (–)
Town	27	13.2	1247	12.5	1.06 (0.70–1.63)	1.07 (0.69–1.65)
Rural	17	8.3	781	7.8	1.13 (0.67–1.90)	1.13 (0.67–1.92)
Unknown	41	20.0	1734	17.3	1.22 (0.85–1.75)	1.19 (0.82–1.73)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications

Appendix Table 24. The frequency of comorbidities among non-traumatic SDH cases and controls, and their association with non-traumatic SDH.

Comorbidities	**Non-traumatic SDH cases N=205**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
MI	22	10.7	748	7.5	1.06 (0.67–1.67)	0.88 (0.52–1.48)
IS/TIA	47	22.9	884	8.8	2.32 (1.65–3.27)	2.11 (1.47–3.03)
IS	28	13.7	532	5.3	2.07 (1.36–3.14)	1.47 (0.93–2.34)
TIA	30	14.6	518	5.2	2.38 (1.59–3.58)	2.04 (1.30–3.19)
IHD‡	29	14.1	1448	14.5	0.71 (0.47–1.06)	0.59 (0.37–0.92)
Prior ICB	8	3.9	46	0.5	7.80 (3.51–17.35)	8.05 (3.47–18.71)
COPD	17	8.3	746	7.5	0.70 (0.42–1.17)	0.71 (0.42–1.21)
Asthma	31	15.1	1544	15.4	0.72 (0.49–1.07)	0.77 (0.57–1.04)
Hypertension	120	58.5	5795	58.0	0.78 (0.59–1.04)	0.88 (0.52–1.48)
Hyperlipidemia	53	25.9	2495	24.9	0.90 (0.65–1.24)	0.92 (0.66–1.28)
Diabetes	44	21.5	1829	18.3	0.77 (0.54–1.09)	1.02 (0.70–1.47)
DVT	30	14.6	789	7.9	1.67 (1.12–2.51)	1.34 (0.85–2.11)
Anaemia§	7	3.4	175	1.8	1.10 (0.50–2.40)	1.16 (0.52–2.59)
Atrial fibrillation	52	25.4	1014	10.1	1.82 (1.29–2.55)	0.66 (0.40–1.10)
Heart failure	18	8.8	491	4.9	1.15 (0.69–1.90)	0.83 (0.48–1.41)
PU, uncomplicated/ complicated	15	7.3	702	7.0	0.76 (0.44–1.29)	0.68 (0.39–1.19)
PU, uncomplicated	11	5.4	479	4.8	0.84 (0.45–1.56)	0.76 (0.40–1.45)
PU, complicated	7	3.4	302	3.0	0.78 (0.36–1.70)	0.66 (0.30–1.45)
IBD	4	2.0	142	1.4	1.09 (0.40–3.01)	1.17 (0.42–3.27)
Dyspepsia	62	29.5	2429	24.3	1.06 (0.78–1.45)	1.12 (0.82–1.54)
Gout	27	13.2	710	7.1	1.34 (0.88–2.04)	1.32 (0.85–2.05)
Osteoporosis	18	8.8	775	7.8	1.11 (0.66–1.87)	0.99 (0.58–1.68)
GERD	35	17.1	1724	17.2	0.79 (0.55–1.15)	0.79 (0.54–1.17)
Anxiety	32	15.6	1622	16.2	0.93 (0.63–1.38)	0.99 (0.66–1.47)
Depression	43	21.0	2061	20.6	0.98 (0.69–1.39)	1.03 (0.72–1.47)
Migraine	13	6.3	570	5.7	1.28 (0.72–2.28)	1.18 (0.65–2.14)
Epilepsy	13	6.3	156	1.6	3.44 (1.89–6.24)	3.14 (1.68–5.86)
Dementia	13	6.3	248	2.5	1.96 (1.08–3.55)	1.91 (1.03–3.56)
Falls§	14	6.8	270	2.7	1.91 (1.07–3.39)	1.78 (0.97–3.28)
Osteoarthritis	78	38.0	3991	39.9	0.74 (0.55–0.99)	0.76 (0.56–1.03)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin

‡Excluding MI.

§In the year before the index date.

Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 25. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among traumatic SDH cases and controls, and their association with traumatic SDH.

	Traumatic SDH cases N=278		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	158	56.8	5164	51.6	NA	NA
Female	120	43.2	4836	48.4	NA	NA
Age (years)						
40–59	26	9.4	1174	11.7	NA	NA
60–69	40	14.4	2231	22.3	NA	NA
70–79	110	39.6	3708	37.1	NA	NA
80–89	102	36.7	2887	28.9	NA	NA
Calendar year						
2000–2004	25	9.0	1669	16.7	NA	NA
2005–2010	102	36.7	3988	39.9	NA	NA
2010 and beyond	151	54.3	4343	43.4	NA	NA
Cohort type						
Comparison	109	39.2	4790	47.9	1 (–)	1 (–)
Low-dose ASA	169	60.8	5210	52.1	1.20 (0.93–1.53)	1.10 (0.78–1.54)
Smoking						
Non-smoker	120	43.2	4403	44.0	1 (–)	1 (–)
Current	28	10.1	1193	11.9	0.96 (0.63–1.47)	0.91 (0.59–1.40)
Former	128	46.0	4215	42.1	0.92 (0.71–1.20)	0.90 (0.69–1.17)
Unknown	2	0.7	189	1.9	0.86 (0.20–3.60)	0.89 (0.20–3.99)
BMI (kg/m^2)						
15–19	14	5.0	355	3.5	1.10 (0.62–1.97)	1.12 (0.62–2.01)
20–24	95	34.2	2774	27.7	1 (–)	1 (–)
25–29	108	38.8	3712	37.1	0.83 (0.63–1.10)	0.81 (0.61–1.08)
≥30	45	16.2	2328	23.3	0.51 (0.36–0.74)	0.48 (0.33–0.70)
Unknown	16	5.8	831	8.3	0.79 (0.46–1.36)	0.77 (0.43–1.38)
Polypharmacy (in month before the index date)						
0–1	96	34.5	3658	36.6	1 (–)	1 (–)
2–4	65	23.4	3039	30.4	0.61 (0.44–0.84)	0.57 (0.41–0.79)
≥5	117	42.1	3303	33.0	0.77 (0.57–1.03)	0.67 (0.49–0.92)

	Traumatic SDH cases N=278		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Polypharmacy (in month before the start date)						
0–1	149	53.6	5572	55.7	1 (–)	1 (–)
2–4	85	30.6	3231	32.3	0.82 (0.62–1.08)	0.84 (0.63–1.10)
≥5	44	15.8	1197	12.0	0.99 (0.70–1.42)	1.06 (0.74–1.52)
Alcohol (u/w)						
None	54	19.4	1955	19.6	1 (–)	1 (–)
1–9	125	45.0	4867	48.7	0.97 (0.70–1.35)	1.04 (0.74–1.45)
10–20	49	17.6	1365	13.7	1.43 (0.95–2.16)	1.52 (1.00–2.32)
21–41	17	6.1	443	4.4	1.52 (0.85–2.72)	1.61 (0.90–2.90)
≥42	4	1.4	94	0.9	1.94 (0.67–5.60)	2.23 (0.76–6.51)
Unknown	29	10.4	1276	12.8	1.03 (0.65–1.64)	1.10 (0.67–1.78)
PCP visits						
0–4	10	3.6	1415	14.1	1 (–)	1 (–)
5–9	43	15.5	2320	23.2	2.51 (1.26–5.02)	2.36 (1.17–4.77)
10–15	50	18.0	2285	22.9	2.89 (1.45–5.72)	2.58 (1.28–5.21)
15–19	56	20.1	1584	15.8	4.58 (2.32–9.05)	4.04 (2.01–8.15)
≥20	119	42.8	2396	24.0	6.26 (3.25-12.05)	5.12 (2.58–10.15)
Referrals						
0–4	75	27.0	4669	46.7	1 (–)	1 (–)
5–9	78	28.1	2836	28.4	1.28 (0.91–1.79)	1.27 (0.90–1.78)
10–19	75	27.0	1781	17.8	1.62 (1.13–2.32)	1.57 (1.09–2.26)
≥20	50	18.0	714	7.1	2.27 (1.48–3.49)	2.18 (1.41–3.37)
Hospitalizations						
None	156	56.1	8376	83.8	1 (–)	1 (–)
1	55	19.8	969	9.7	2.46 (1.78–3.40)	2.31 (1.66–3.22)
2	41	14.7	387	3.9	4.18 (2.87–6.09)	3.95 (2.68–5.81)
≥3	26	9.4	268	2.7	3.57 (2.27–5.63)	3.25 (2.04–5.20)

	Traumatic SDH cases N=278		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Townsend score						
Deprived 1 (least deprived)	78	28.1	2634	26.3	1 (–)	1 (–)
Deprived 2	53	19.1	2369	23.7	0.71 (0.50–1.02)	0.76 (0.53–1.09)
Deprived 3	56	20.1	2039	20.4	0.89 (0.62–1.26)	0.95 (0.66–1.36)
Deprived 4	45	16.2	1628	16.3	0.87 (0.60–1.26)	0.92 (0.63–1.36)
Deprived 5 (most deprived)	42	15.1	1036	10.4	1.31 (0.89–1.92)	1.50 (1.01–2.22)
Unknown	4	1.4	294	2.9	0.52 (0.19–1.43)	0.52 (0.19–1.44)
Urban/rural						
Urban	180	64.7	6238	62.4	1 (–)	1 (–)
Town	33	11.9	1247	12.5	0.90 (0.61–1.31)	0.85 (0.58–1.24)
Rural	20	7.2	781	7.8	0.92 (0.58–1.48)	0.90 (0.56–1.45)
Unknown	45	16.2	1734	17.3	0.90 (0.64–1.25)	0.90 (0.64–1.26)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 26. The frequency of comorbidities among traumatic SDH cases and controls, and their association with traumatic SDH.

Comorbidity	Traumatic SDH cases N=280		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
MI	23	8.3	748	7.5	0.90 (0.58–1.39)	0.80 (0.49–1.32)
IS/TIA	48	17.3	884	8.8	1.69 (1.22–2.34)	1.39 (0.99–1.96)
IS	30	10.8	532	5.3	1.65 (1.11–2.45)	1.23 (0.80–1.88)
TIA	26	9.4	518	5.2	1.69 (1.22–2.34)	1.27 (0.81–1.97)
IHD‡	45	16.2	1448	14.5	0.94 (0.68–1.30)	0.89 (0.62–1.27)
Prior ICB	8	2.9	46	0.5	5.70 (2.63–12.36)	5.70 (2.56–12.70)
COPD	25	9.0	746	7.5	0.88 (0.58–1.35)	0.91 (0.59–1.42)
Asthma	40	14.4	1544	15.4	0.73 (0.52–1.03)	0.79 (0.55–1.12)
Hypertension	180	64.7	5795	58.0	1.04 (0.81–1.35)	1.04 (0.80–1.35)
Hyperlipidemia	84	30.2	2495	24.9	1.14 (0.87–1.48)	1.13 (0.87–1.49)
Diabetes	68	24.5	1829	18.3	1.06 (0.80–1.42)	1.24 (0.92–1.67)
DVT	27	9.7	789	7.9	1.04 (0.69–1.57)	0.95 (0.61–1.47)
Anaemia§	14	5.0	175	1.8	1.96 (1.11–3.47)	1.97 (1.10–3.52)
Atrial fibrillation	60	21.6	1014	10.1	1.71 (1.25–2.32)	1.35 (0.89–2.05)
Heart failure	27	9.7	491	4.9	1.49 (0.98–2.25)	1.28 (0.83–1.99)
PU, uncomplicated/ complicated	23	8.3	702	7.0	0.97 (0.63–1.51)	0.96 (0.61–1.51)
PU, uncomplicated	14	5.0	479	4.8	0.88 (0.51–1.53)	0.86 (0.49–1.50)
PU, complicated	13	4.7	302	3.0	1.23 (0.69–2.19)	1.18 (0.66–2.12)
IBD	3	1.1	142	1.4	0.63 (0.20–2.00)	0.65 (0.20–2.07)
Dyspepsia	72	25.9	2406	24.1	0.90 (0.68–1.18)	0.93 (0.70–1.23)
Gout	21	7.6	710	7.1	0.82 (0.52–1.29)	0.76 (0.47–1.21)
Osteoporosis	29	10.4	775	7.8	1.14 (0.76–1.73)	1.03 (0.68–1.57)
GERD	51	18.3	1724	17.2	0.88 (0.64–1.20)	0.93 (0.68–1.28)
Anxiety	50	18.0	1622	16.2	1.03 (0.75–1.41)	1.02 (0.74–1.41)
Depression	70	25.2	2061	20.6	1.20 (0.91–1.60)	1.20 (0.90–1.60)
Migraine	17	6.1	570	5.7	1.10 (0.66–1.82)	1.09 (0.66–1.82)
Epilepsy	18	6.5	156	1.6	3.70 (2.22–6.16)	3.49 (2.06–5.92)
Dementia	29	10.4	248	2.5	3.38 (2.21–5.16)	3.05 (1.97–4.72)
Falls§	58	20.9	270	2.7	7.57 (5.43–10.57)	7.45 (5.27–10.55)
Osteoarthritis	128	46.0	3991	39.9	1.05 (0.82–1.34)	1.10 (0.85–1.41)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin. [‡]Excluding MI.
[§]In the year before the index date.
Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 27. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among SAH cases and controls, and their association with SAH.

	SAH cases N=385		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	155	40.3	5164	51.6	NA	NA
Female	230	59.7	4836	48.4	NA	NA
Age (years)						
40–59	93	24.2	1174	11.7	NA	NA
60–69	122	31.7	2231	22.3	NA	NA
70–79	109	28.3	3708	37.1	NA	NA
80–89	61	15.8	2887	28.9	NA	NA
Calendar year						
2000–2004	81	21.0	1669	16.7	NA	NA
2005–2010	153	39.7	3988	39.9	NA	NA
2010 and beyond	151	39.2	4343	43.4	NA	NA
Cohort type					NA	
Comparison	194	50.4	4790	47.9	1 (–)	1 (–)
Low-dose ASA	191	49.6	5210	52.1	0.89 (0.72–1.10)	0.93 (0.66–1.29)
Smoking						
Non-smoker	129	33.5	4403	44.0	1 (–)	1 (–)
Current	111	28.8	1193	11.9	2.78 (2.13–3.64)	2.54 (1.93–3.36)
Former	140	36.4	4215	42.1	1.31 (1.02–1.68)	1.28 (1.00–1.66)
Unknown	5	1.3	189	1.9	0.94 (0.37–2.38)	0.87 (0.33–2.31)
BMI (kg/m^2)						
15–19	27	7.0	355	3.5	2.18 (1.39–3.41)	2.08 (1.32–3.29)
20–24	100	26.0	2774	27.7	1 (–)	1 (–)
25–29	139	36.1	3712	37.1	1.03 (0.79–1.34)	1.07 (0.81–1.40)
≥30	82	21.3	2328	23.3	0.80 (0.59–1.08)	0.84 (0.61–1.15)
Unknown	37	9.6	831	8.3	1.20 (0.81–1.78)	1.32 (0.85–2.03)
Polypharmacy (in month before the index date)						
0–1 drug	163	42.3	3658	36.6	1 (–)	1 (–)
2–4 drugs	123	31.9	3039	30.4	0.96 (0.75–1.24)	0.92 (0.72–1.17)
≥5	99	25.7	3303	33.0	0.73 (0.55–0.96)	0.96 (0.68–1.36)

	SAH cases N=385		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Polypharmacy (in month before the start date)						
0–1 drug	223	57.9	5572	55.7	1 (–)	1 (–)
2–4 drugs	115	29.9	3231	32.3	0.92 (0.73–1.17)	0.93 (0.72–1.21)
≥5	47	12.2	1197	12.0	0.99 (0.71–1.39)	0.69 (0.51–0.94)
Alcohol (u/w)						
None	69	17.9	1955	19.6	1 (–)	1 (–)
1–9	186	48.3	4867	48.7	1.08 (0.81–1.44)	1.15 (0.86–1.54)
10–20	56	14.5	1365	13.7	1.17 (0.81–1.70)	1.22 (0.83–1.79)
21–41	18	4.7	443	4.4	1.29 (0.74–2.24)	1.17 (0.67–2.07)
≥42	8	2.1	94	0.9	2.61 (1.19–5.71)	2.09 (0.93–4.68)
Unknown	48	12.5	1276	12.8	1.08 (0.74–1.58)	1.04 (0.69–1.57)
PCP visits						
0–4	55	14.3	1415	14.1	1 (–)	1 (–)
5–9	90	23.4	2320	23.2	1.14 (0.81–1.62)	1.15 (0.80–1.65)
10–15	88	22.9	2285	22.9	1.18 (0.84–1.68)	1.21 (0.83–1.75)
15–19	49	12.7	1584	15.8	0.96 (0.65–1.43)	1.00 (0.66–1.52)
≥20	103	26.8	2396	24.0	1.40 (1.00–1.98)	1.42 (0.97–2.08)
Referrals						
0–4	159	41.3	4669	46.7	1 (–)	1 (–)
5–9	108	28.1	2836	28.4	1.27 (0.97–1.66)	1.21 (0.92–1.59)
10–19	82	21.3	1781	17.8	1.59 (1.16–2.18)	1.56 (1.13–2.16)
≥20	36	9.4	714	7.1	1.76 (1.13–2.72)	1.80 (1.15–2.81)
Hospitalizations						
None	278	72.2	8376	83.8	1 (–)	1 (–)
1	64	16.6	969	9.7	2.13 (1.59–2.86)	2.12 (1.57–2.87)
2	22	5.7	387	3.9	2.01 (1.27–3.20)	1.77 (1.10–2.86)
≥3	21	5.5	268	2.7	2.94 (1.80–4.78)	2.92 (1.75–4.85)
Townsend score						
Deprived 1 (least deprived)	91	23.6	2634	26.3	1 (–)	1 (–)
Deprived 2	80	20.8	2369	23.7	0.99 (0.73–1.35)	0.96 (0.70–1.31)
Deprived 3	76	19.7	2039	20.4	1.08 (0.79–1.47)	0.96 (0.70–1.33)
Deprived 4	62	16.1	1628	16.3	1.08 (0.77–1.50)	0.97 (0.69–1.37)
Deprived 5 (most deprived)	67	17.4	1036	10.4	1.76 (1.27–2.44)	1.47 (1.04–2.08)
Unknown	9	2.3	294	2.9	0.80 (0.40–1.62)	0.74 (0.36–1.51)

	SAH cases N=385		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Urban/rural						
Urban	236	61.3	6238	62.4	1 (–)	1 (–)
Town	39	10.1	1247	12.5	0.84 (0.59–1.19)	0.82 (0.57–1.16)
Rural	30	7.8	781	7.8	1.07 (0.72–1.58)	1.14 (0.77–1.70)
Unknown	80	20.8	1734	17.3	1.15 (0.88–1.49)	1.12 (0.85–1.46)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 28. The frequency of comorbidities among SAH cases and controls, and their association with SAH.

Comorbidity	Cases SAH N=385		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	%	n	%		
MI	17	4.4	748	7.5	0.69 (0.34–1.38)	0.54 (0.31–0.94)
IS/TIA	45	11.7	884	8.8	1.69 (1.22–2.34)	1.52 (1.07–2.16)
IS	27	7.0	532	5.3	1.62 (1.08–2.44)	1.15 (0.73–1.82)
TIA	28	7.3	518	5.2	1.71 (1.23–2.37)	1.66 (1.07–2.57)
IHD‡	41	10.6	1448	14.5	0.76 (0.54–1.06)	0.74 (0.51–1.07)
Prior ICB	20	5.2	46	0.5	12.81 (7.34–22.35)	11.84 (6.56–21.36)
COPD	35	9.1	746	7.5	1.43 (0.99–2.06)	1.10 (0.75–1.62)
Asthma	68	17.7	1544	15.4	1.43 (0.99–2.06)	1.08 (0.81–1.43)
Hypertension	216	56.1	5795	58.0	1.13 (0.86–1.49)	1.19 (0.95–1.50)
Hyperlipidemia	87	22.6	2495	24.9	1.08 (0.87–1.34)	0.90 (0.70–1.16)
Diabetes	52	13.5	1829	18.3	0.86 (0.67–1.10)	0.76 (0.55–1.05)
DVT	30	7.8	789	7.9	1.03 (0.70–1.52)	1.02 (0.67–1.56)
Anaemia§	9	2.3	175	1.8	1.34 (0.67–2.67)	1.38 (0.68–2.80)
Atrial fibrillation	24	6.2	1014	10.1	0.75 (0.49–1.16)	0.59 (0.34–1.03)
Heart failure	10	2.6	491	4.9	0.65 (0.34–1.24)	0.66 (0.34–1.28)
PU, uncomplicated/ complicated	29	7.5	702	7.0	1.33 (0.90–1.97)	1.14 (0.76–1.71)
PU, uncomplicated	24	6.2	479	4.8	1.62 (1.06–2.49)	1.39 (0.89–2.16)
PU, complicated	6	1.6	302	3.0	0.64 (0.28–1.45)	0.53 (0.23–1.23)
IBD	4	1.0	142	1.4	0.72 (0.26–1.96)	0.77 (0.28–2.12)
Dyspepsia	97	25.2	2406	24.1	1.04 (0.82–1.33)	0.99 (0.78–1.27)
Gout	16	4.2	710	7.1	0.72 (0.43–1.20)	0.71 (0.42–1.19)
Osteoporosis	24	6.2	775	7.8	0.87 (0.56–1.35)	0.79 (0.50–1.23)
GERD	60	15.6	1724	17.2	0.86 (0.65–1.15)	0.85 (0.64–1.14)
Anxiety	92	23.9	1622	16.2	1.36 (1.06–1.74)	1.25 (0.97–1.62)
Depression	132	34.3	2061	20.6	1.64 (1.31–2.06)	1.49 (1.18–1.88)
Migraine	34	8.8	570	5.7	1.20 (0.83–1.74)	1.21 (0.82–1.77)
Epilepsy	10	2.6	156	1.6	1.66 (0.86–3.21)	1.45 (0.73–2.87)
Dementia	112	28.9	1842	18.4	2.76 (1.63–4.65)	2.52 (1.46–4.33)
Falls§	17	4.4	270	2.7	2.01 (1.20–3.38)	2.09 (1.23–3.55)
Osteoarthritis	133	34.5	3991	39.9	0.75 (0.49–1.16)	0.90 (0.72–1.13)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

[†]Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.[‡]Excluding MI.
[§]In the year before the index date.
Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 29. The frequency of demographics, lifestyle factors, healthcare use and levels of polypharmacy among non-traumatic SAH cases and controls, and their association with non-traumatic SAH.

	Non-traumatic SAH cases N=311		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
Sex						
Male	115	37.0	5164	51.6	NA	NA
Female	196	63.0	4836	48.4	NA	NA
Age (years)						
40–59	82	26.4	1174	11.7	NA	NA
60–69	103	33.1	2231	22.3	NA	NA
70–79	86	27.7	3708	37.1	NA	NA
80–89	40	12.9	2887	28.9	NA	NA
Calendar year						
2000–2004	74	23.8	1669	16.7	NA	NA
2005–2010	132	42.4	3988	39.9	NA	NA
2010 and beyond	105	33.8	4343	43.4	NA	NA
Cohort type					NA	
Comparison	153	49.2	4790	47.9	1 (–)	1 (–)
Low-dose ASA	158	50.8	5210	52.1	0.96 (0.76–1.22)	1.18 (0.79–1.76)
Smoking						
Non-smoker	100	32.2	4403	44.0	1 (–)	1 (–)
Current	98	31.5	1193	11.9	3.07 (2.29–4.12)	2.76 (2.03–3.74)
Former	109	35.0	4215	42.1	1.39 (1.05–1.84)	1.37 (1.03–1.83)
Unknown	4	1.3	189	1.9	0.88 (0.32–2.47)	0.77 (0.26–2.31)
BMI (kg/m^2)						
15–19	21	6.8	355	3.5	2.09 (1.27–3.46)	2.04 (1.22–3.42)
20–24	83	26.7	2774	27.7	1 (–)	1 (–)
25–29	105	33.8	3712	37.1	0.95 (0.70–1.27)	0.99 (0.73–1.35)
≥30	68	21.9	2328	23.3	0.80 (0.57–1.12)	0.86 (0.61–1.22)
Unknown	34	10.9	831	8.3	1.28 (0.84–1.94)	1.49 (0.94–2.37)
Polypharmacy (in month before the index date)						
0–1 drug	140	45.0	3658	36.6	1 (–)	1 (–)
2–4 drugs	101	32.5	3039	30.4	0.94 (0.71–1.24)	0.92 (0.69–1.22)
≥5	70	22.5	3303	33.0	0.64 (0.46–0.88)	0.63 (0.44–0.89)

	Non-traumatic SAH cases N=311		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Polypharmacy (in month before the start date)						
0–1 drug	188	60.5	5572	55.7	1 (–)	1 (–)
2–4 drugs	87	28.0	3231	32.3	0.84 (0.65–1.10)	0.83 (0.63–1.09)
≥5	36	11.6	1197	12.0	0.93 (0.64–1.36)	0.90 (0.61–1.34)
Alcohol (u/w)						
None	58	18.6	1955	19.6	1 (–)	1 (–)
1–9	151	48.6	4867	48.7	1.03 (0.75–1.41)	1.10 (0.80–1.52)
10–20	44	14.1	1365	13.7	1.09 (0.72–1.66)	1.13 (0.74–1.73)
21–41	12	3.9	443	4.4	1.06 (0.55–2.03)	0.91 (0.46–1.79)
≥42	8	2.6	94	0.9	3.22 (1.45–7.16)	2.36 (1.03–5.41)
Unknown	38	12.2	1276	12.8	0.99 (0.65–1.50)	0.90 (0.57–1.43)
PCP visits						
0–4	49	15.8	1415	14.1	1 (–)	1 (–)
5–9	76	24.4	2320	23.2	1.11 (0.76–1.60)	1.10 (0.75–1.62)
10–15	74	23.8	2285	22.9	1.15 (0.79–1.67)	1.17 (0.78–1.75)
15–19	35	11.3	1584	15.8	0.80 (0.51–1.25)	0.81 (0.51–1.31)
≥20	77	24.8	2396	24.0	1.24 (0.85–1.80)	1.22 (0.80–1.85)
Referrals						
0–4	136	43.7	4669	46.7	1 (–)	1 (–)
5–9	85	27.3	2836	28.4	1.25 (0.93–1.68)	1.18 (0.87–1.60)
10–19	63	20.3	1781	17.8	1.60 (1.13–2.27)	1.57 (1.10–2.25)
≥20	27	8.7	714	7.1	1.81 (1.10–2.97)	1.85 (1.12–3.07)
Hospitalizations						
None	225	72.3	8376	83.8	1 (–)	1 (–)
1	54	17.4	969	9.7	2.36 (1.71–3.24)	2.35 (1.69–3.27)
2	20	6.4	387	3.9	2.48 (1.51–4.05)	2.16 (1.30–3.60)
≥3	12	3.9	268	2.7	2.38 (1.27–4.43)	2.38 (1.25–4.56)

	Non-traumatic SAH cases N=311		Controls N=10,000		RR (95% CI)*	RR (95% CI)†
	n	**%**	**n**	**%**		
Townsend score						
Deprived 1 (least deprived)	70	22.5	2634	26.3	1 (–)	1 (–)
Deprived 2	69	22.2	2369	23.7	1.12 (0.80–1.58)	1.08 (0.76–1.52)
Deprived 3	60	19.3	2039	20.4	1.12 (0.79–1.60)	0.97 (0.68–1.40)
Deprived 4	50	16.1	1628	16.3	1.14 (0.79–1.66)	0.99 (0.67–1.45)
Deprived 5 (most deprived)	55	17.7	1036	10.4	1.87 (1.30–2.70)	1.50 (1.02–2.20)
Unknown	7	2.3	294	2.9	0.78 (0.35–1.72)	0.70 (0.31–1.58)
Urban/rural						
Urban	187	60.1	6238	62.4	1 (–)	1 (–)
Town	31	10.0	1247	12.5	0.85 (0.57–1.25)	0.82 (0.55–1.22)
Rural	23	7.4	781	7.8	1.03 (0.66–1.61)	1.12 (0.72–1.76)
Unknown	70	22.5	1734	17.3	1.27 (0.95–1.68)	1.24 (0.92–1.66)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

PCP visits, referrals and hospitalizations were ascertained in the year before the index date. BMI, smoking and alcohol were ascertained any time before the index date using the most recent status/value as appropriate. Polypharmacy refers to the number of different medications.

Appendix Table 30. The frequency of comorbidities among non-traumatic SAH cases and controls, and their association with non-traumatic SAH.

Comorbidities	**Non-traumatic SAH cases N=311**		**Controls N=10,000**		**RR (95% CI)***	**RR (95% CI)†**
	n	**%**	**n**	**%**		
MI	11	3.5	748	7.5	0.53 (0.29–0.98)	0.47 (0.24–0.92)
IS/TIA	38	12.2	884	8.8	1.95 (1.37–2.80)	1.80 (1.22–2.65)
IS	23	7.4	532	5.3	1.87 (1.20–2.92)	1.26 (0.76–2.08)
TIA	25	8.0	518	5.2	2.17 (1.41–3.34)	2.05 (1.27–3.29)
IHD‡	26	8.4	1448	14.5	0.60 (0.40–0.91)	0.59 (0.38–0.93)
Prior ICB	18	5.8	46	0.5	14.96 (8.29–26.99)	13.52 (7.17–25.48)
COPD	28	9.0	746	7.5	1.51 (1.00–2.27)	1.13 (0.74–1.74)
Asthma	55	17.7	1544	15.4	1.16 (0.86–1.58)	1.10 (0.80–1.50)
Hypertension	172	55.3	5795	58.0	1.11 (0.87–1.41)	1.25 (0.97–1.62)
Hyperlipidemia	66	21.2	2495	24.9	0.81 (0.61–1.08)	0.85 (0.64–1.14)
Diabetes	36	11.6	1829	18.3	0.55 (0.38–0.79)	0.68 (0.46–0.99)
DVT	25	8.0	789	7.9	1.10 (0.72–1.67)	1.11 (0.70–1.76)
Anaemia§	5	1.6	175	1.8	0.96 (0.39–2.40)	0.99 (0.39–2.49)
AF	18	5.8	1014	10.1	0.78 (0.48–1.28)	0.57 (0.30–1.08)
Heart failure	5	1.6	491	4.9	0.44 (0.18–1.09)	0.44 (0.17–1.09)
PU, uncomplicated/ complicated	27	8.7	702	7.0	1.67 (1.11–2.52)	1.40 (0.92–2.15)
PU, uncomplicated	23	7.4	479	4.8	2.08 (1.34–3.25)	0.56 (0.22–1.40)
PU, complicated	5	1.6	302	3.0	0.72 (0.29–1.76)	1.77 (1.12–2.80)
IBD	3	1.0	142	1.4	0.70 (0.22–2.22)	0.75 (0.23–2.41)
Dyspepsia	80	25.7	2406	24.1	1.11 (0.85–1.45)	1.05 (0.80–1.39)
Gout	10	3.2	710	7.1	0.61 (0.32–1.16)	0.60 (0.31–1.16)
Osteoporosis	105	33.8	3991	39.9	0.70 (0.41–1.20)	0.62 (0.36–1.08)
GERD	49	15.8	1724	17.2	0.91 (0.66–1.25)	0.89 (0.64–1.23)
Anxiety	76	24.4	1622	16.2	1.40 (1.06–1.84)	1.26 (0.95–1.68)
Depression	110	35.4	2061	20.6	1.69 (1.31–2.17)	1.49 (1.15–1.94)
Migraine	26	8.4	570	5.7	1.07 (0.70–1.63)	1.08 (0.70–1.68)
Epilepsy	5	1.6	156	1.6	1.04 (0.42–2.58)	0.88 (0.34–2.26)
Dementia	9	2.9	248	2.5	2.01 (1.00–4.04)	1.75 (0.85–3.62)
Falls§	6	1.9	270	2.7	0.91 (0.39–2.08)	0.91 (0.39–2.13)
Osteoarthritis	105	33.8	3991	39.9	0.89 (0.70–1.15)	0.91 (0.70–1.17)

*Adjusted by age, sex, calendar year and number of PCP visits in the year prior to the index date.

†Adjusted by age, sex, calendar year, number of PCP visits in the year prior to the index date, smoking, BMI, alcohol consumption, atrial fibrillation, hypertension and history of ischemic stroke, TIA and intracerebral bleeding, clopidogrel, low-dose ASA and warfarin.

‡Excluding MI.

§In the year before the index date.

Comorbidities were ascertained any time before the index date, unless otherwise specified.

Appendix Table 31. Distribution of follow-up time (time between start date and index date) among UGIB cases and controls, and association between follow-up time and UGIB.

Follow-up time	UGIB cases N= 1,843 n (%)	Controls N= 5,000 n (%)	RR (95% CI)*	RR (95%CI)†
<6 months	213 (11.6)	485 (9.7)	1 (−)	1 (−)
6 months–<1year	173 (9.4)	435 (8.7)	0.84 (0.66–1.08)	0.84 (0.65–1.09)
1–<2 years	279 (15.1)	795 (15.9)	0.82 (0.66–1.02)	0.81 (0.65–1.02)
2–<3 years	229 (12.4)	229 (13.2)	0.80 (0.63–1.00)	0.78 (0.61–0.99)
3–<5 years	406 (22.0)	1143 (22.9)	0.80 (0.64–0.98)	0.80 (0.64–1.00)
><5 years	543 (29.5)	1484 (29.7)	0.77 (0.62–0.95)	0.76 (0.60–0.96)

*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date

†Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, BMI, history of polyps, history of LGIB, history of unspecified GIB, peptic ulcer diseases (complicated and uncomplicated), GORD, IBD, IBS, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

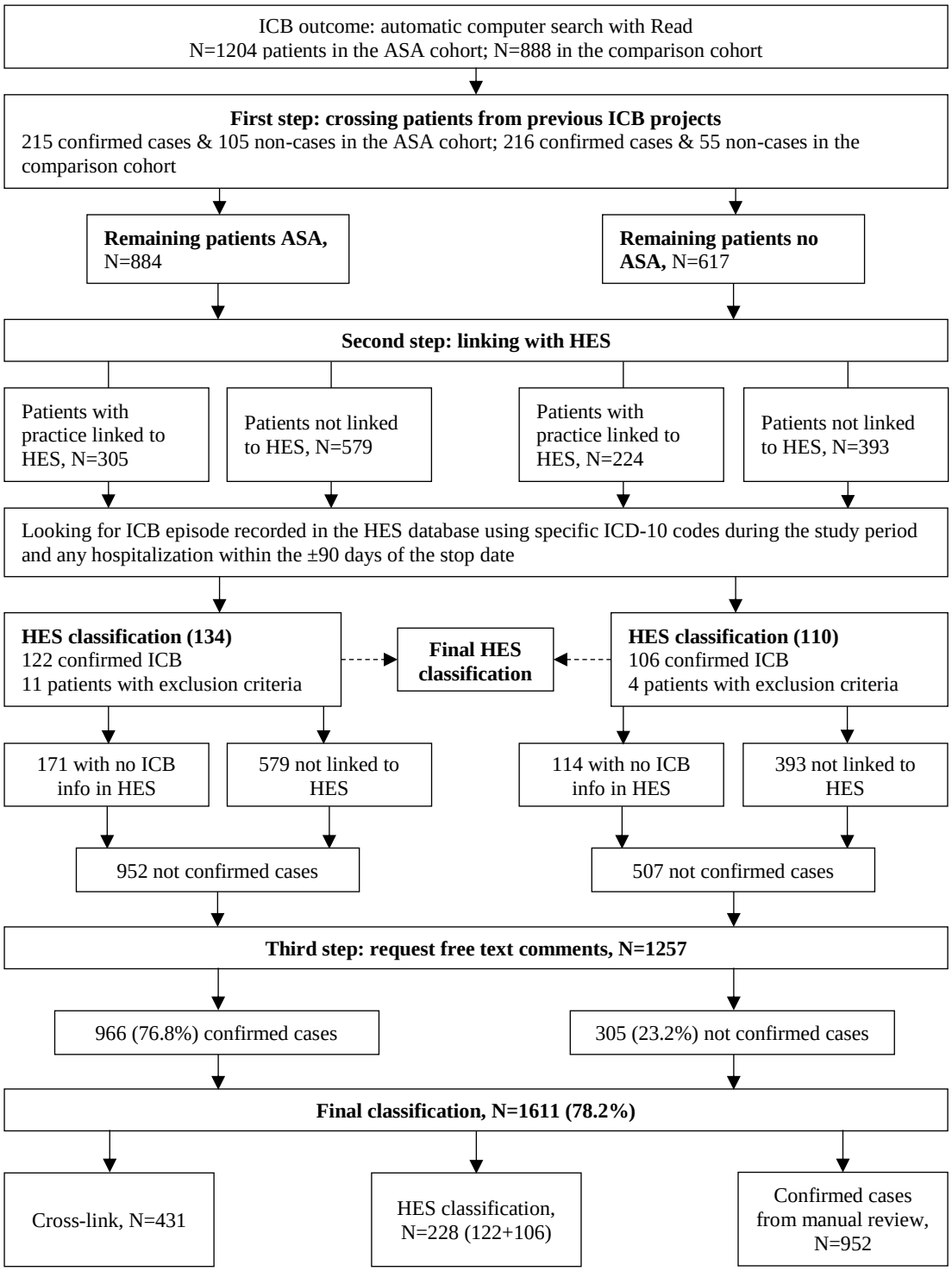
Appendix Table 32. Distribution of follow-up time (time between start date and index date) among LGIB cases and controls, and association between follow-up time and LGIB.

Follow-up time	LGIB cases N=2763 n (%)	Controls N=10,000 n (%)	RR (95% CI)*	RR (95%CI)†
<6 months	266 (9.6)	923 (9.2)	1 (−)	1 (−)
6 months–<1year	264 (9.6)	865 (8.6)	1.06 (0.87−1.29)	1.06 (0.86−1.30)
1–<2 years	430 (15.6)	1603 (16.0)	1.00 (0.84−1.19)	0.95 (0.79−1.14)
2–<3 years	364 (13.2)	1379 (13.8)	0.99 (0.82−1.19)	0.92 (0.76−1.11)
3–<5 years	610 (22.1)	2260 (22.6)	0.98 (0.83−1.17)	0.87 (0.73−1.04)
><5 years	829 (30.0)	2970 (29.7)	0.98 (0.83−1.17)	0.83 (0.69−0.99)

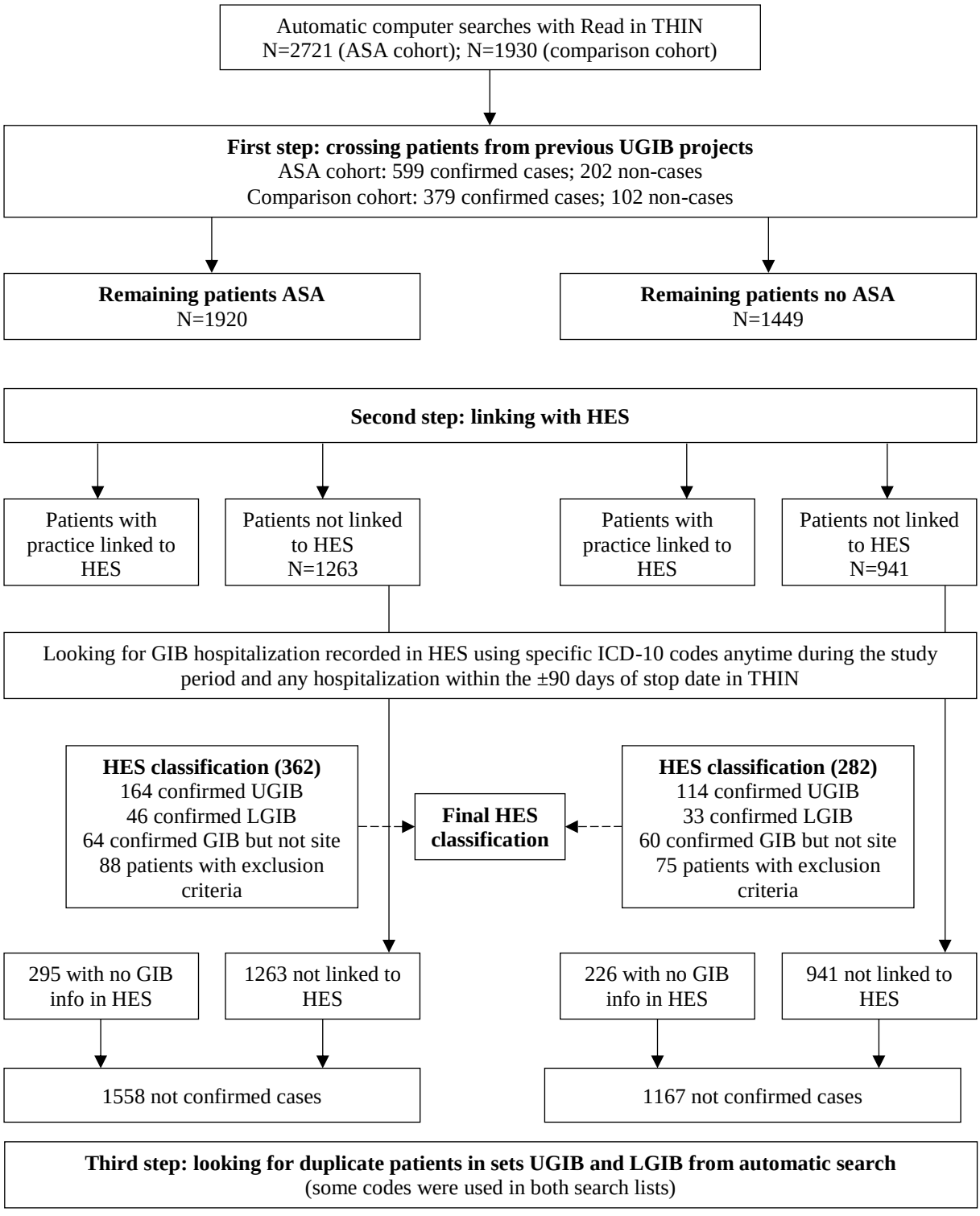
*Adjusted by age, sex, calendar year and number of PCP visits in the year before the index date

†Adjusted by age, sex, calendar year, number of PCP visits in the year before the index date, smoking, alcohol consumption, BMI, history of polyps, history of LGIB, history of unspecified GIB, peptic ulcer diseases (complicated and uncomplicated), GORD, IBD, IBS, use of NSAIDs, PPIs, clopidogrel, warfarin and low-dose ASA.

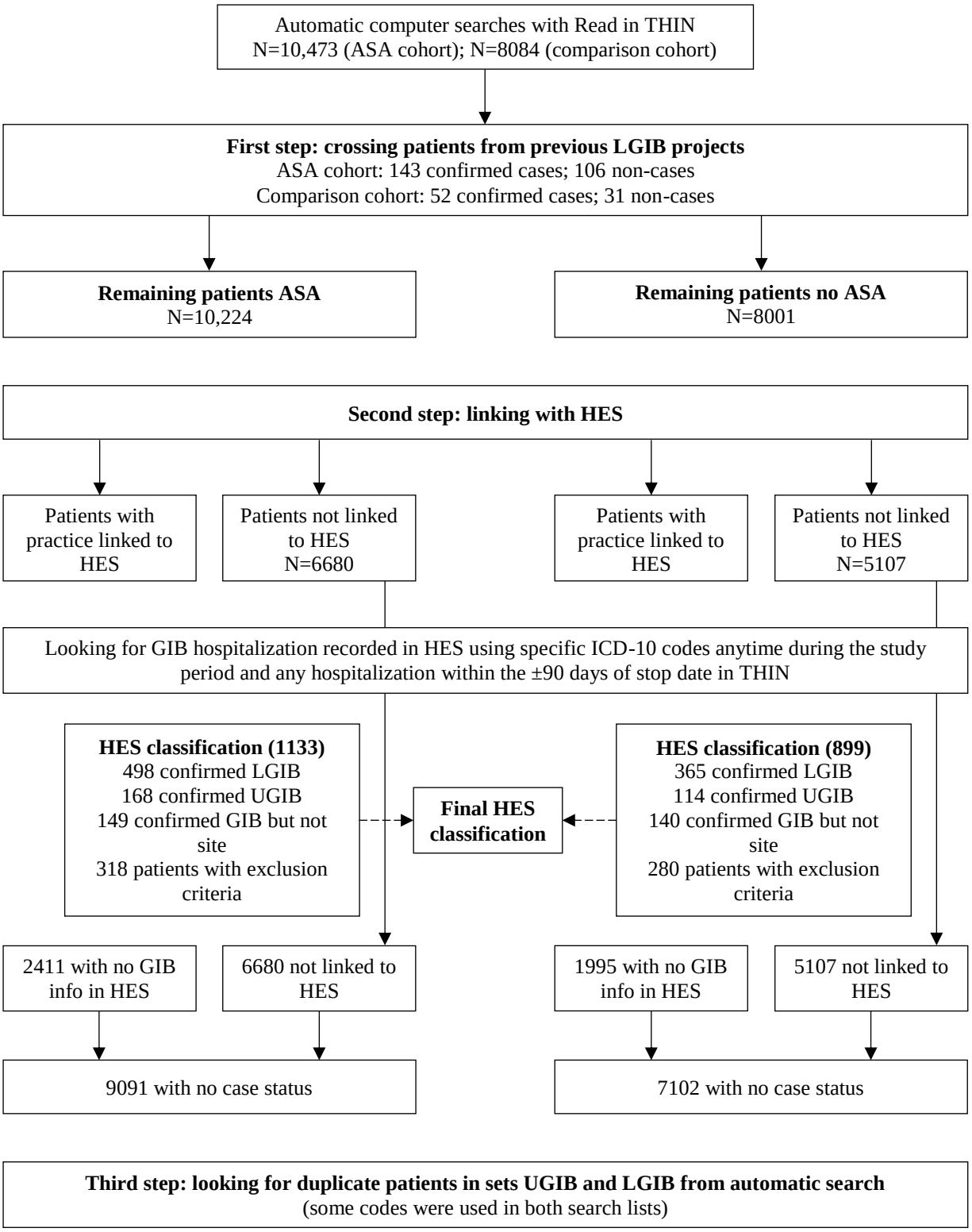
15.2 Appendix figures



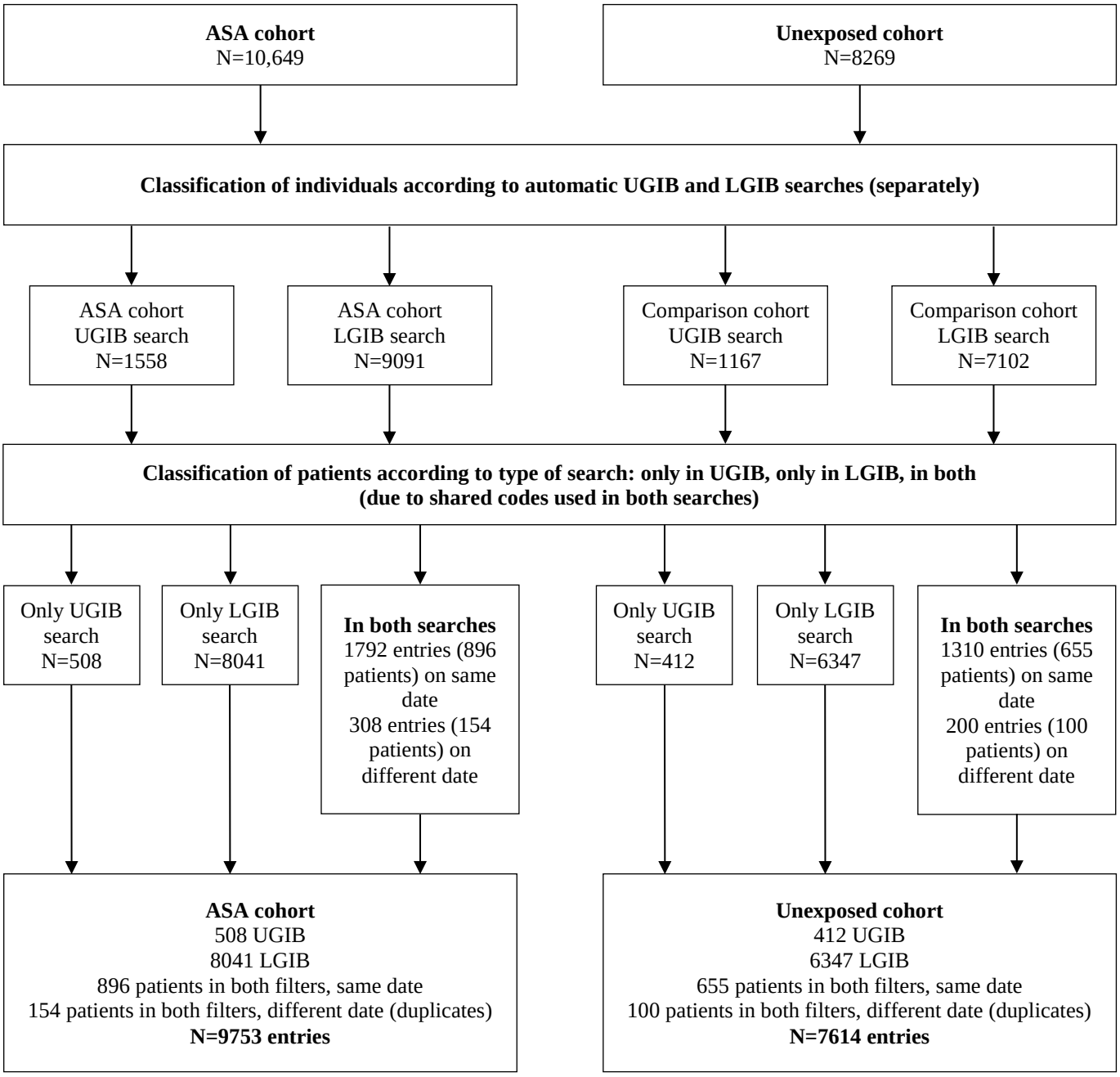
Appendix Figure 1. Flowchart depicting the identification and validation of incident cases of ICB, by study cohort.



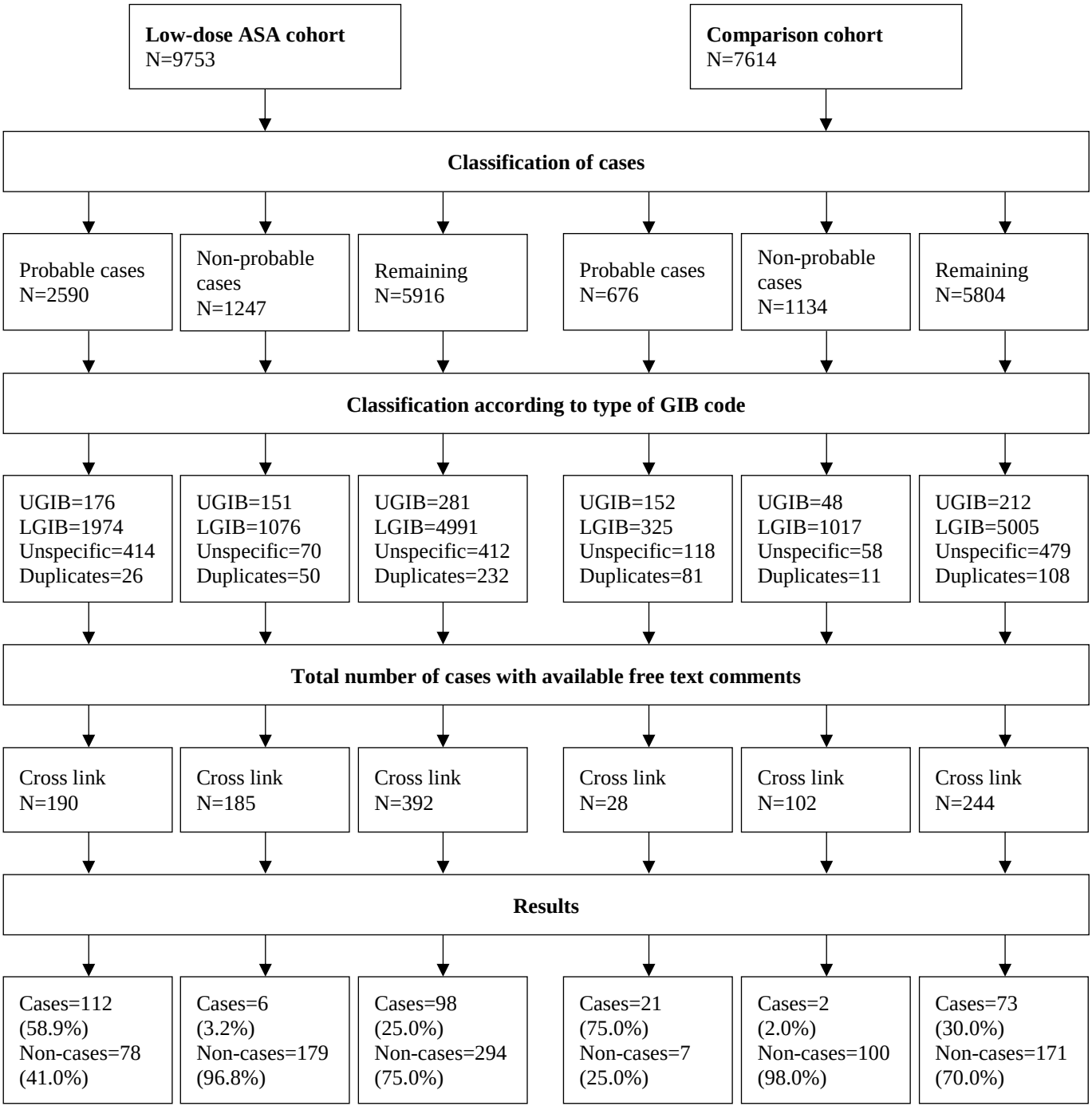
Appendix Figure 2. Flowchart depicting preliminary UGIB case ascertainment phase (cross-linking with previous studies) and case ascertainment Phase 1 (cross-linking with HES) for UGIB, by study cohort.



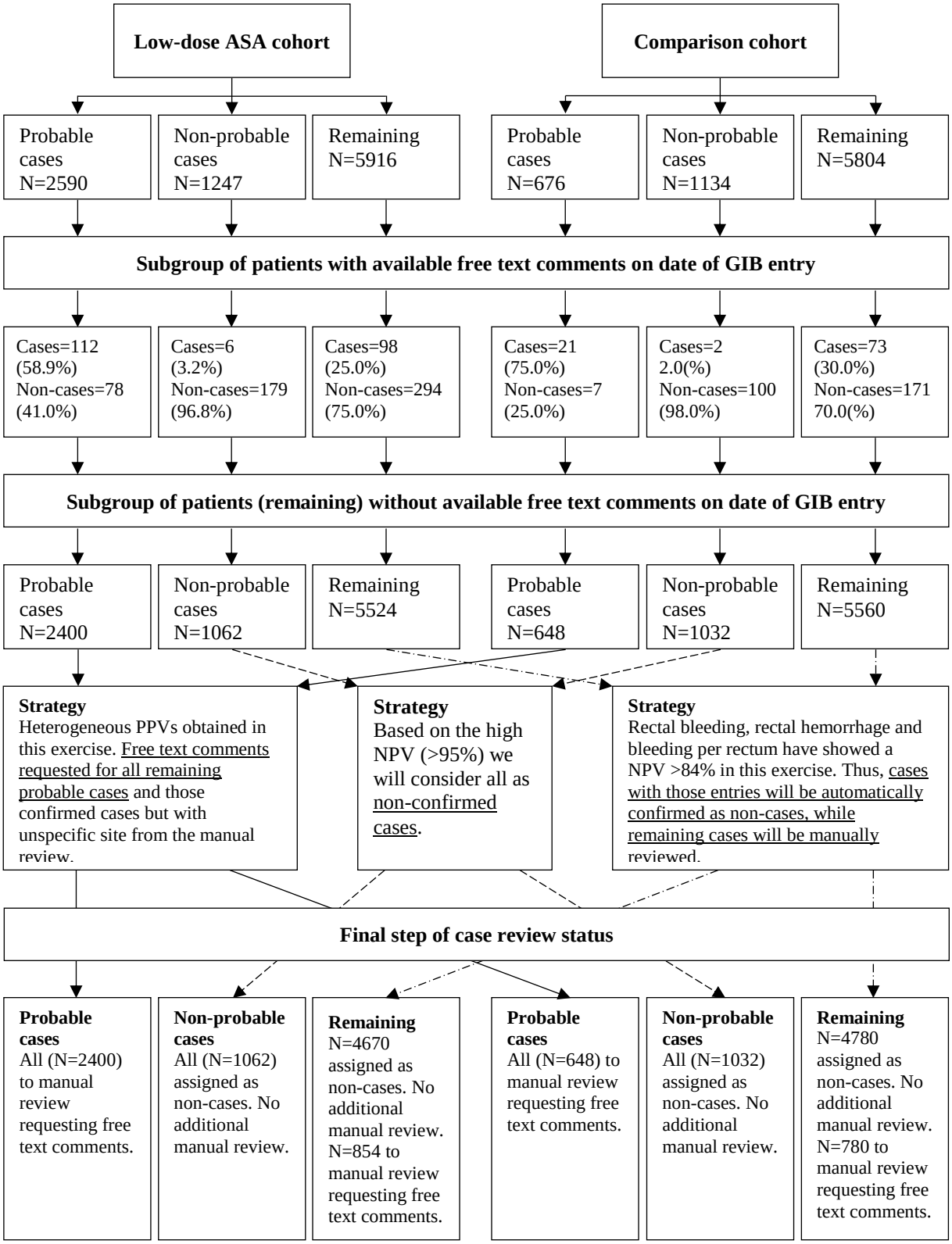
Appendix Figure 3. Flowchart depicting preliminary LGIB case ascertainment phase (cross-linking with previous studies) and case ascertainment Phase 1 (cross-linking with HES) for LGIB, by study cohort.



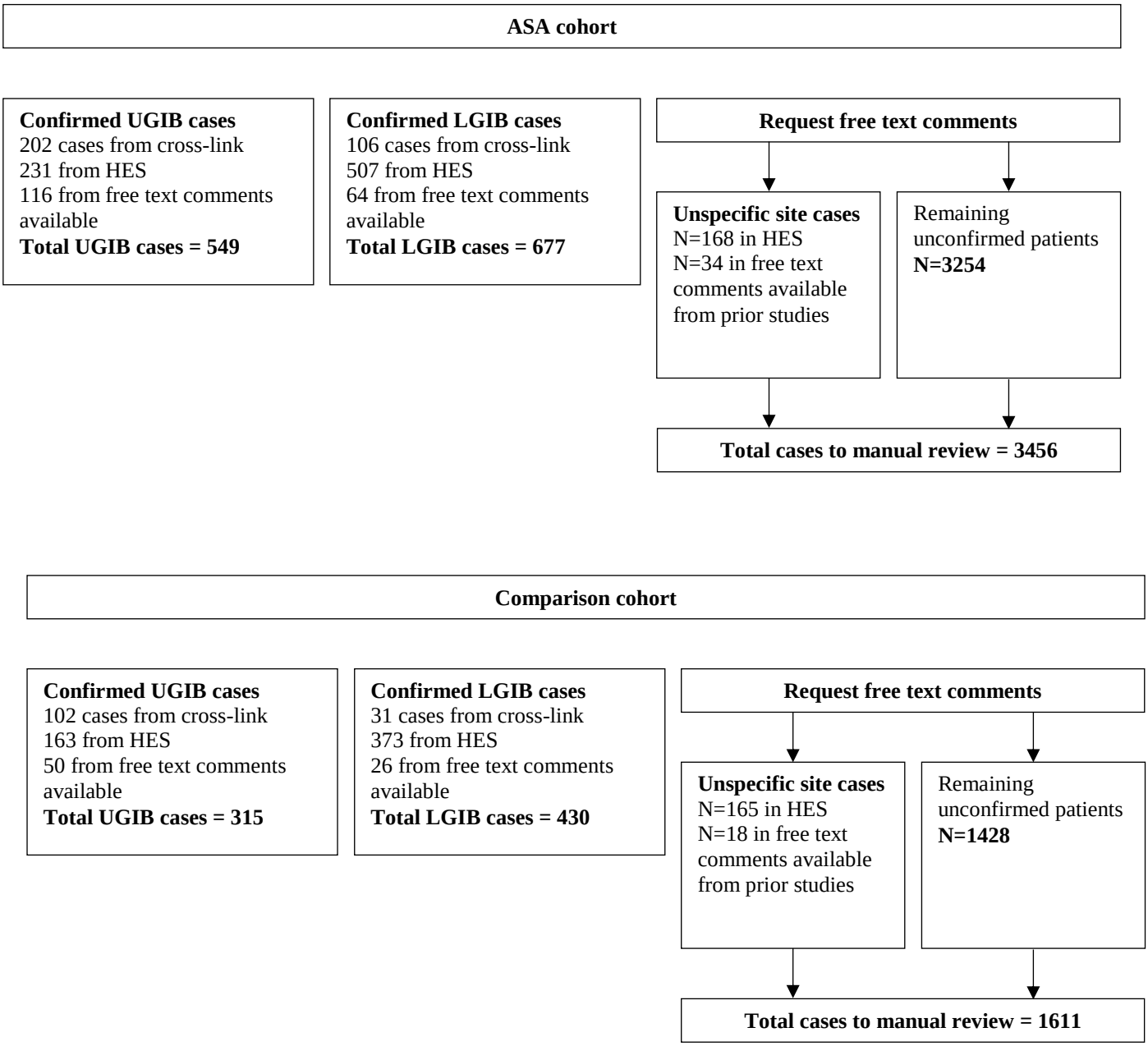
Appendix Figure 4. Flowchart depicting case ascertainment phase II: identifying duplicate patients occurring from the two separate GIB follow-ups (UGIB and LGIB), by study cohort.



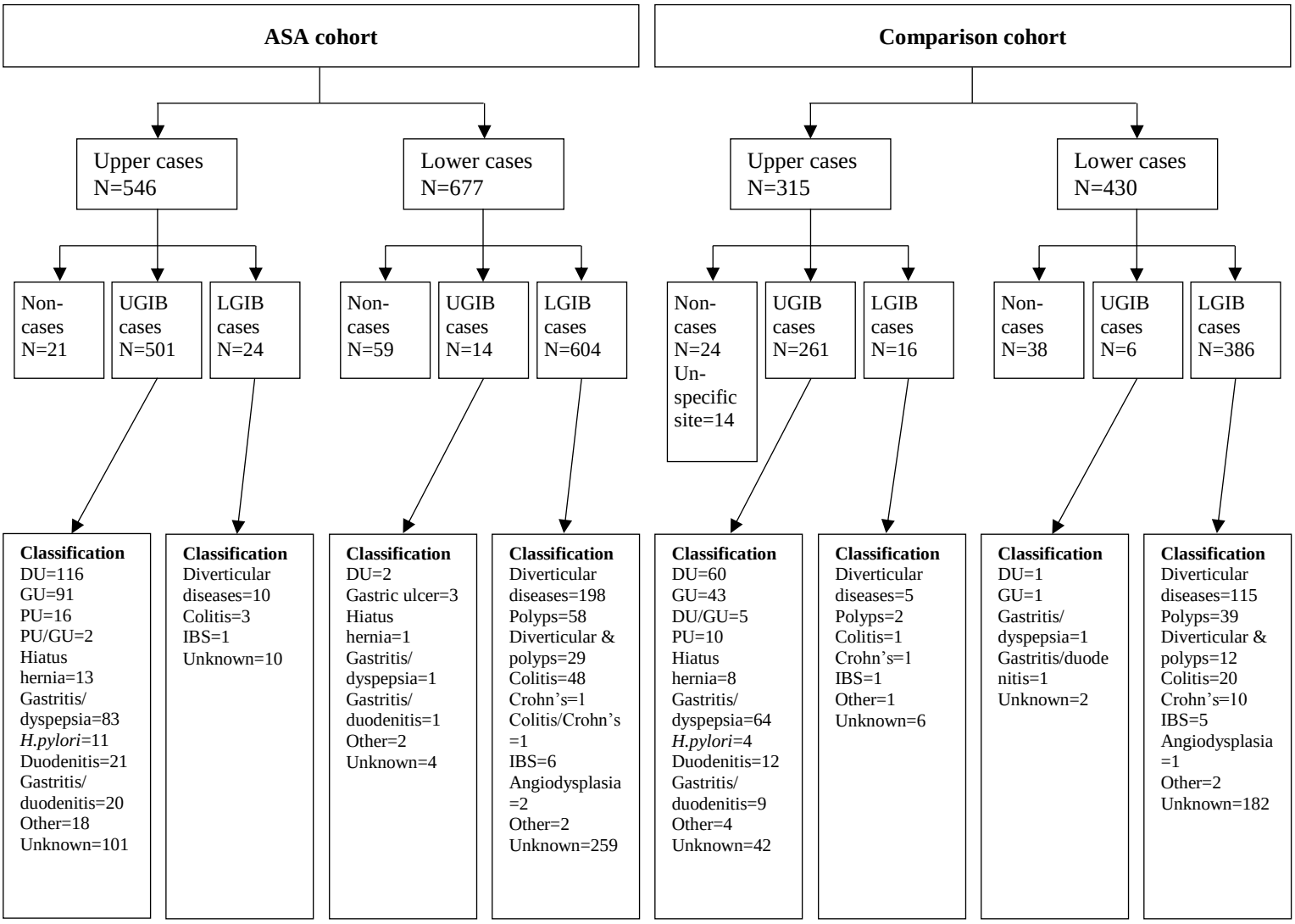
Appendix Figure 5. Flowchart depicting UGIB/LGIB case ascertainment phase III: looking for indicators in THIN and manual review, by study cohort.



Appendix Figure 6. Flowchart depicting case ascertainment phase IV, by study cohort.



Appendix Figure 7. Summary of case ascertainment phases I to IV, by study cohort.



Appendix Figure 8. Flowchart depicting case ascertainment phase VII, by study cohort.

15.3 Annex. Signature Pages

Signatures are found on the following pages.

Reference Number: RD-OI-0216
Best Practice Document Version: 3

Signature Page – Study Conduct Responsible

Study Title:	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Product:	Aspirin, BAY e 4465
IMPACT Study Number:	18116
Study Type:	PASS
EU PAS Register Number:	EUPAS 10837
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG 51368 Leverkusen Germany
Function:	Study Conduct Responsible
Name:	
Title:	
Address:	

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature

Confidentiality statement:

Reference Number: RD-OI-0216
Best Practice Document Version: 3

Signature Page – Study Epidemiologist

Study Title:	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Product:	Aspirin, BAY e 4465
IMPACT Study Number:	18116
Study Type:	PASS
EU PAS Register Number:	EUPAS 10837
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG 51368 Leverkusen Germany
Function:	Study Epidemiologist
Name:	
Title:	
Address:	

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature: _

Confidentiality statement:

Reference Number: RD-OI-0216
Best Practice Document Version: 3

Signature Page – Study Medical Expert

Study Title:	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Product:	Aspirin, BAY e 4465
IMPACT Study Number:	18116
Study Type:	PASS
EU PAS Register Number:	EUPAS 10837
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG 51368 Leverkusen Germany
Function:	Study Medical Expert
Name:	
Title:	
Address:	

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature:

Confidentiality statement:

Reference Number: RD-OI-0216
Best Practice Document Version: 3

Signature Page – Study Safety Leader

Study Title:	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Product:	Aspirin, BAY e 4465
IMPACT Study Number:	18116
Study Type:	PASS
EU PAS Register Number:	EUPAS 10837
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG 51368 Leverkusen Germany
Function:	Study Safety Leader
Name:	
Title:	
Address:	

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature:

Confidentiality statement:

Reference Number: RD-OI-0216
Best Practice Document Version: 3

Signature Page – Study Statistician

Study Title:	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Product:	Aspirin, BAY e 4465
IMPACT Study Number:	18116
Study Type:	PASS
EU PAS Register Number:	EUPAS 10837
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG 51368 Leverkusen Germany
Function:	Study Statistician
Name:	
Title:	
Address:	

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature:

Confidentiality statement:

Reference Number: RD-OI-0216
Best Practice Document Version: 3

Signature Page – Study Clinical Development

Study Title:	A pharmacoepidemiological study on the risk of bleeding in new users of low-dose aspirin (ASA) in The Health Improvement Network (THIN), UK (EPIdemiological Study on the Safety of Aspirin in THIN – EPISAT)
Product:	Aspirin, BAY e 4465
IMPACT Study Number:	18116
Study Type:	PASS
EU PAS Register Number:	EUPAS 10837
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG 51368 Leverkusen Germany
Function:	Study Clinical Development
Name:	
Title:	
Address:	

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature:

Confidentiality statement: