Incidence of Upper and Lower Gastrointestinal Bleeding in New Users of Low-Dose Aspirin

Lucía Cea Soriano,[*,‡] Angel Lanas,[§,‖] Montse Soriano-Gabarró,[¶] and Luis A. García Rodríguez[*]

*Spanish Centre for Pharmacoepidemiologic Research, Madrid, Spain; ‡Department of Public Health and Maternal and Child Health, Faculty of Medicine, Complutense University of Madrid, Madrid, Spain; §Servicio de Aparato Digestivo, Hospital Clínico, University of Zaragoza, IIS Aragón, Zaragoza, Spain; ‖CIBERehd, Instituto de Salud Carlos III, Madrid, Spain; ¶Epidemiology, Bayer AG, Berlin, Germany

BACKGROUND & AIMS: **There are few data on the incidence of upper and lower gastrointestinal bleeding (UGIB and LGIB) from observational studies of low-dose aspirin users. We aimed to estimate incidence rates of UGIB and LGIB in a large cohort of new users of low-dose aspirin in the United Kingdom, with subanalyses of hospitalization status and fatalities.**

METHODS: **We performed a population-based study of 199,079 new users of low-dose aspirin (median age, 64.0 years) identified from the Health Improvement Network primary care database (2000–2012). Individuals were followed for a median 5.4 years (maximum, 14 years) to identify new cases of UGIB and LGIB. Following multistep validation, we calculated overall and age- and sex-specific incidence rates; we performed subanalyses for health care use and death within 30 days of GIB. We also estimated rates within a matched (1:1) cohort of nonusers of low-dose aspirin at the start of the follow-up period.**

RESULTS: **The low-dose aspirin users had 1115 UGIB events and 1936 LGIB events; most subjects with UGIB events (58.9%) were hospitalized, whereas most subjects with LGIB events were referred to secondary care (72.8%). Crude incidence rates of GIB per 1000 person-years were 0.97 for subjects with UGIB (95% CI, 0.91–1.02) and 1.68 for subjects with LGIB (95% CI, 1.60–1.75). Incidence rates per 1000 person-years for hospitalized patients with GIB were 0.57 for UGIB (95% CI, 0.53–0.61) and 0.45 for LGIB (95% CI, 0.42–0.49); for referred (but not hospitalized) cases, these values were 0.39 for UGIB (95% CI, 0.36–0.43) and 1.22 for LGIB (1.16–1.29). Incidence rates per 1000 person-years were 0.06 for fatal UGIB (95% CI, 0.04–0.07), 0.01 for fatal LGIB (95% CI, 0.01–0.02), 0.91 for nonfatal UGIB (95% CI, 0.86–0.97), and 1.66 for nonfatal LGIB (95% CI, 1.59–1.74). Among nonusers of low-dose aspirin, incidence rates per 1000 person-years were 0.67 (95% CI, 0.63–0.75) for UGIB and 0.76 (95% CI, 0.72–0.82) for LGIB.**

CONCLUSION: **In a population-based study of low-dose aspirin users, the incidence of LGIB was higher than the incidence of UGIB. However, patients with LGIB had higher rates of hospitalization or death within 30 days than patients with UGIB. These estimates are valuable for benefit–risk assessments of low-dose aspirin for cardiovascular and colorectal cancer prevention.**

Keywords: Observational Study; Ischemic Vascular Disease Prophylaxis; Major Bleeding; UK.

Low-dose aspirin is widely acknowledged to be effective for ischemic vascular disease prophylaxis,[1] and evidence also suggests a potential role in chemoprevention, in particular for colorectal cancer (CRC),[2,3] possibly mediated by platelet inhibition.[4] Decisions to prescribe prophylactic low-dose aspirin are based on whether the clinical benefits are deemed to outweigh the risk of major bleeding events, one of the most clinically important being those of the gastrointestinal (GI) tract. The balance of benefits and risks may vary with age and other factors such as history of major bleeding. While evaluation of low-dose aspirin should thereby consider age-specific frequencies of clinical events attributable to aspirin and patients' clinical history, the severity of these events and the potential for long-lasting disabling

Abbreviations used in this paper: CI, confidence interval; CRC, colorectal cancer; GI, gastrointestinal; EMR, electronic medical record; GIB, gastrointestinal bleed; HES, Hospital Episode Statistics; LGIB, lower gastrointestinal bleed; PCP, primary care practitioner; THIN, The Health Improvement Network; UGIB, upper gastrointestinal bleed.

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effects should also be considered—other factors that could potentially shift the benefit–risk profile and influence prescribing decisions. GI bleeds (GIBs) vary in severity, and although some may require hospitalization, others may be less severe and be managed on an outpatient basis. Importantly, discontinuation of low-dose aspirin is not uncommon following an upper GIB (UGIB)[5] and is associated with an increased risk of cardiovascular events[6] and death.[7] Even minor bleeds, in any part of the GI tract, could potentially lead to discontinuation of prophylactic aspirin.

There are few studies from observational cohorts of preventative low-dose aspirin users reporting incidence rates for UGIBs,[8–12] and even fewer for lower GIBs (LGIBs).[10,11,13] Furthermore, most have reported data only for hospitalized events in individuals without GI antecedents,[10–13] and while separate estimates for fatal and nonfatal GIBs are available from clinical trials,[14] there are few estimates from observational data.[8] There is therefore a need to obtain UGIB and LGIB incidence data, including by age and bleed severity, among real-world low-dose aspirin users, including those with previous GIBs or taking concomitant medications known to increase bleeding risk. Using a population-based cohort study in UK primary care, we aimed to estimate the overall and age- and sex-specific incidence of UGIB or LGIB among new users of low-dose aspirin, with subanalyses by level of health care assistance and case fatality.

What You Need to Know

Background

There are few data on the incidence of upper gastrointestinal bleed (UGIB) and lower gastrointestinal bleed (LGIB) in the same population-based cohort of low-dose aspirin users.

Findings

Among approximately 200,000 new users of low-dose aspirin in primary care in the United Kingdom, there were 3051 cases of GIB: 1115 UGIBs and 1936 LGIBs. Incidence rates of UGIB and LGIB per 1000 person-years were 0.97 and 1.68 among users of low-dose aspirin and 0.67 and 0.76 among matched nonusers of low-dose aspirin, respectively.

Implications for Patient Care

Our findings from an observational study of the burden of UGIB and LGIB could help clinicians balance the benefits and actual risks of low-dose aspirin use.

Methods

Data Source

We used data The Health Improvement Network (THIN), a validated UK population-based primary care database containing anonymized electronic medical records (EMRs) of ~6% of the UK population and broadly representative of its demographic.[15,16] Participating primary care practitioners (PCPs) enter clinical information using Read codes[17] and free text; prescriptions are recorded upon issue. Patient-level linkage to the Hospital Episode Statistics (HES) database is possible for individuals in linked practices.[18] Although low-dose aspirin available over the counter in the United Kingdom, most chronic aspirin use is via prescriptions (free for individuals aged over 60 years),[18] validation of low-dose aspirin prescription data in THIN shows that exposure misclassification owing to unrecorded over-the-counter low-dose aspirin is likely to be minimal.[19] An independent scientific review committee for THIN reviewed and approved the study protocol (reference number 14-088A1).

Identification and Follow-Up of the Study Cohort

A total of 199,079 new users of low-dose aspirin were identified from THIN source population (N = 1,840,253) (Figure 1) after applying inclusion and exclusion criteria as described previously.[20] The date of the first low-dose aspirin prescription was designated the start date. Two separate follow-ups of the cohort were undertaken: the first to identify incident UGIB cases, the second to identify incident LGIB cases. Follow-up ended at the earliest of the following: a Read code for UGIB or unspecified GIB (UGIB follow-up) or Read code for LGIB or unspecified GIB (LGIB follow-up), esophageal varices, coagulopathies, chronic liver disease, alcohol abuse, cancer, age 90 years, death, or December 31. 2013. Individuals with a Read code for UGIB or unspecified GIB during the UGIB follow-up (n = 2721) and those with a Read code for LGIB or unspecified GIB during the LGIB follow-up (n = 10,473) were identified as potential incident cases of UGIB or LGIB. The index date was the date of the diagnostic Read code.

Validation of UGIB and LGIB Cases

As summarized in Supplementary Figure 1, a multistage process was undertaken to confirm the recorded diagnosis of UGIB or LGIB or unspecified GIB, involving at least 1 of the following validation processes: cross-checking with cases validated in previous studies,[21–24] linkage to HES data, and manual review of patient EMRs including free-text comments and data mining using text strings (see Supplementary Methods). Potential incident UGIB or LGIB cases were considered confirmed if there was evidence or referral to a consultant or hospitalization. Cases of UGIB or LGIB were subsequently classified by type of health care assistance received either hospitalization or specialist referral only (referred but not hospitalized). Cases with

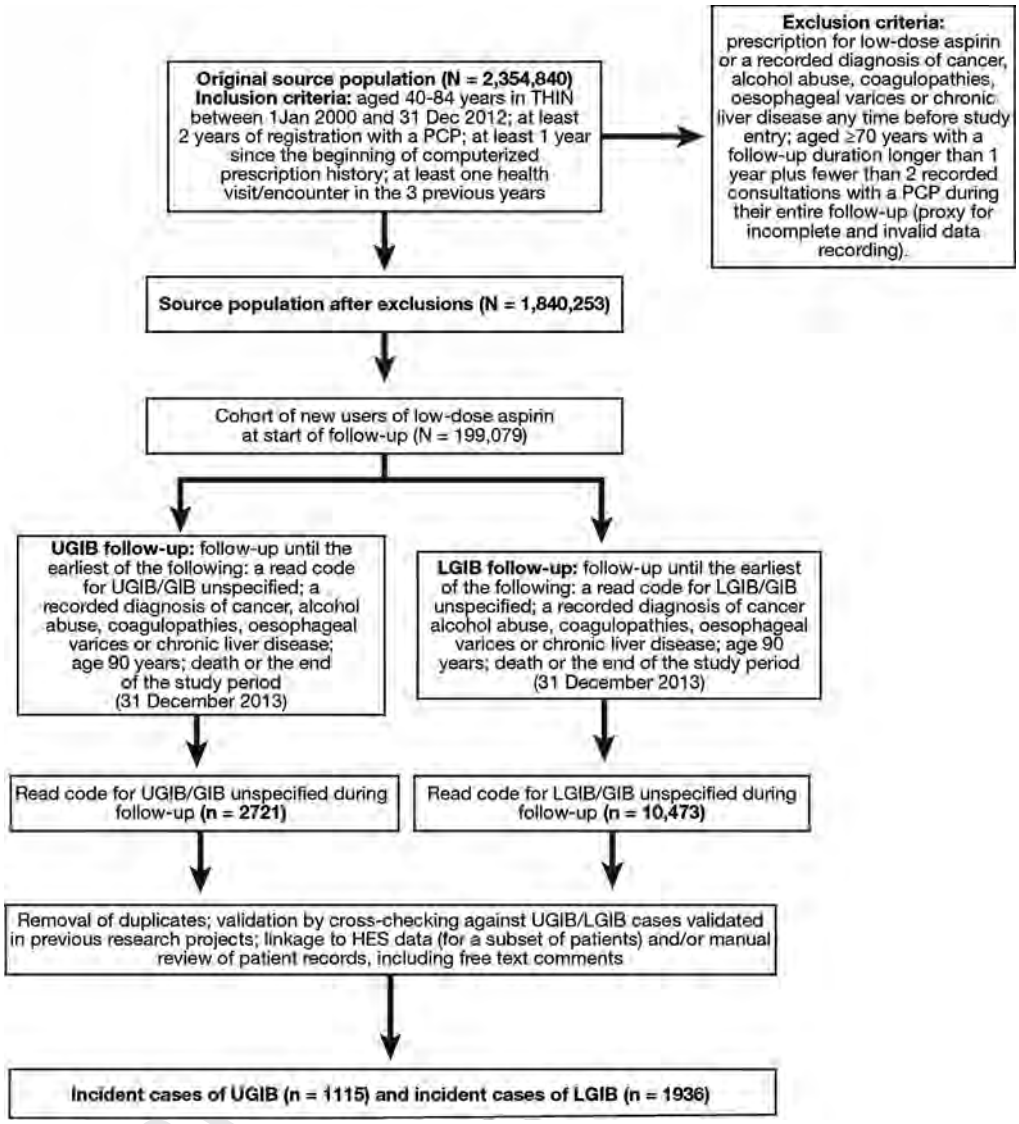


Figure 1. Flowchart depicting the study design. HES, Hospital Episode Statistics; LGIB, lower gastrointestinal bleed; GIB, gastrointestinal bleed; PCP, primary care practitioner; THIN, The Health Improvement Network; UGIB, upper gastrointestinal bleed.

a hospitalization in their EMRs within 15 days before and 30 days after the GIB were assigned to the hospitalized group; remaining patients with a record of referral were assigned to the referred group. For cases without a hospitalization or referral, we manually reviewed their EMRs to identify free text comments implying hospitalization or referral. Cases who died on or within 30 days following the index date were deemed to be fatal cases irrespective of whether the primary cause of death was due to the bleed itself or to associated comorbidities.

Covariates

Patient characteristics were ascertained at the start of follow-up. In addition to demographics, we collected information on lifestyle variables (smoking status, alcohol consumption and body mass index), comorbidities, and health care use (number of PCP visits, referrals, and hospitalizations). Lifestyle variables and comorbidities were ascertained any time before the start date, while health care use was ascertained in the year before the start date, using the most recent value or status. Medication use was ascertained on the start date or in the prior 90 days.

Statistical Analysis

Crude incidence rates per 1000 person-years with 95% confidence interval (CI) were calculated for UGIB and LGIB separately, for all cases, and stratified by age, sex, and GIB history. Incidence rates of UGIB and LGIB were also calculated by the level of health care assistance received (hospitalized or referred) and case fatality. In an additional analysis, we estimated overall incidence rates of UGIB and LGIB separately among a comparison cohort of nonusers of low-dose aspirin. To identify this cohort, each 199,079 new user of low-dose aspirin was matched 1:1 to an individual from the THIN source population (after applying all inclusion or exclusion

Table 1. Baseline Characteristics of the Cohort of New Users of Low-Dose Aspirin (N = 199,049)

Characteristics	n	%
Sex		
Male	102,432	51.5
Female	96,617	48.5
Age		
40–59 y	21,933	11.0
60–69 y	45,482	22.8
70–79 y	66,560	33.4
80–89 y	49,366	24.8
Smoking[a]		
Nonsmoker	84,223	42.3
Current	41,137	20.7
Former	64,780	32.5
Unknown	8909	4.5
BMI[a]		
15–19 kg/m^2	5449	2.7
20–24 kg/m^2	45,443	22.8
25–29 kg/m^2	70,216	35.3
≥30 kg/m^2	54,538	27.4
Unknown	23,403	11.8
Alcohol[a]		
None	34,578	17.4
1–9 u/w	88,133	44.3
10–20 u/w	30,222	15.2
21–41 u/w	10,521	5.3
≥42 u/w	2795	1.4
Unknown	32,800	16.5
Polypharmacy[b]		
0–1	111,232	55.9
2–4	62,085	31.2
≥5	25,732	12.9
PCP visits[c]		
0–4	32,534	16.3
5–9	57,102	28.7
10–19	76,021	38.2
≥20	33,392	16.8
Referrals[c]		
0–4	159,856	80.3
5–9	29,312	14.7
10–19	9036	4.5
≥20	845	0.4
Hospitalizations[c]		
None	154,871	77.8
1	27,058	13.6
2	10,773	5.4
≥3	6347	3.2
Comorbidities[d]		
Intracranial bleed	1189	0.7
Ischemic stroke	9790	4.9
MI	17,023	8.6
IS	9790	4.9
TIA	7025	3.5
IHD (excluding MI)	19,768	9.9
Hypertension	95,934	48.2
Hypercholesterolemia	26,833	13.5
Diabetes	36,608	18.4
Atrial fibrillation	11,248	5.7
Heart failure	5367	2.7
PU, uncomplicated/complicated	10,092	5.1
Dyspepsia	38,584	19.4
Comedications[e]		
Warfarin	3794	1.9
Clopidogrel	2855	1.4
NSAIDs	30,754	15.5
Insulin	6270	3.1
Oral antidiabetics	20,772	10.4
Antihypertensive agents	108,529	54.5
Statins	48,679	24.5
PPI	29,689	14.9
H_2RA	5813	2.9

BMI, body mass index; H_2RA, histamine-2 receptor antagonist; IHD, ischemic heart disease; IS, ischemic stroke; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PCP, primary care practitioner; PPI, proton pump inhibitor; PU, peptic ulcer; TIA, transient ischemic attack; u/w, units per week.
[a]Alcohol, BMI, and smoking were ascertained any time before the start date the most recent status/value as appropriate.
[b]Polypharmacy was taken as the number of different medications in the month before the start date.
[c]PCP visits, referrals and hospitalizations were ascertained in the year before the start date.
[d]Recorded any time before the start of follow-up.
[e]Use on the start date or in the previous 90 days.

criteria) free of low-dose aspirin on the aspirin user's start date.

Results

Characteristics of the Study Cohort

Baseline characteristics of the low-dose aspirin study cohort have been published previously.[20] Briefly, the median age of cohort members was 64.0 years (mean 63.9 ± 10.8 years) and just over half were men (51.5%). GI comorbidities recorded before the start of follow-up were as follows: UGIB (0.9%), LGIB (5.6%), any GIB (7.0%), uncomplicated peptic ulcer (3.8%), complicated peptic ulcer (1.8%), dyspepsia (19.4%), and irritable bowel disease (6.3%) (Supplementary Table 1). The most common non-GI comorbidity was hypertension, affecting 48.2% of the cohort. Use of medication among cohort members (on the start date or in the previous 90 days) was as follows: nonsteroidal anti-inflammatory drugs (16%), warfarin (1.9%), proton pump inhibitors (14.9%), histamine-2 receptor antagonists (2.9%), and clopidogrel (1.4%), while 7 patients were using direct oral anticoagulants. Based on the computer algorithm,[20] 37% of the cohort had recorded cardiovascular antecedents and were assumed to have received low-dose aspirin for secondary prevention of ischemic vascular disease. The remaining cohort members were assumed to have received low-dose aspirin for primary prevention purposes.

Incidence of UGIB and LGIB

A total of 3051 individuals in the study cohort (1.5%) suffered a GIB over the follow-up period (median 5.4 years in both the UGIB and LGIB follow-up): 1115 incident cases of UGIB and 1936 incident cases of LGIB (4 individuals experienced both a UGIB and LGIB). The overall crude incidence rate was lower for UGIB than for LGIB: 0.97 cases per 1000 person-years (95% CI, 0.91–1.02) for UGIB and 1.68 cases per 1000 person-years (95% CI, 1.60–1.75) for LGIB (Table 2). Incidence rates were higher during the first year of follow-up: 1.31 per 1000 person-years (95% CI, 1.16–1.48) for UGIB and 1.95 per 1000 person-years (95% CI, 1.76–2.16) for LGIB. Men had a higher incidence of UGIB than women (1.03 vs 0.90 per 1000 person-years) while for LGIB, incidence rates were slightly lower in men than women (1.60 vs 1.76 per 1000 person-years) (Table 2; Figure 2). Incidence rates of UGIB and LGIB increased with age, with LGIB higher than UGIB in all age groups (Table 2, Figure 3*A*; see Supplementary Table 2 for rates by 5-year age stratification).

Table 2. Incidence Rates of UGIB and LGIB per 1000 Person-Years Among a Cohort of New Users of Low-Dose Aspirin, Overall and by Sex, Age Group, Case Fatality, and Level of Health Care Assistance

	Cases	Person-Years	Incidence per 1000 Person-Years (95% CI)
UGIB			
Male	605	588,279	1.03 (0.95–1.11)
Female	510	566,971	0.90 (0.83–0.98)
Age 40–64 y	393	632,725	0.62 (0.56–0.69)
Age 65–74 y	378	348,673	1.08 (0.80–1.20)
Age 75–89 y	344	172,634	1.99 (1.79–2.21)
Fatal cases	64	1,154,032	0.06 (0.04–0.07)
Nonfatal cases	1051	1,154,032	0.91 (0.86–0.97)
Hospitalized cases	657	1,154,032	0.57 (0.53–0.61)
Referred[a]	452	1,154,032	0.39 (0.36–0.43)
Total	1115	1,154,032	0.97 (0.91–1.02)
LGIB			
Male	941	588,281	1.60 (1.50–1.71)
Female	995	565,752	1.76 (1.65–1.87)
Age 40–64 y	889	632,725	1.41 (1.32–1.51)
Age 65–74 y	635	348,673	1.82 (1.68–1.97)
Age 75–89 y	412	174,170	2.39 (2.17–2.63)
Fatal cases	15	1,154,033	0.01 (0.01–0.02)
Nonfatal cases	1921	1,154,033	1.66 (1.59–1.74)
Hospitalized cases	523	1,154,033	0.45 (0.42–0.49)
Referred[a]	1410	1,154,033	1.22 (1.16–1.29)
Total	1936	1,154,033	1.68 (1.60–1.75)

NOTE. The number of hospitalized and referred (but not hospitalized) cases do not sum the total number of cases for upper gastrointestinal bleed (UGIB) or lower gastrointestinal bleed (LGIB) because 6 UGIB cases and three LGIB cases were not referred or hospitalized but died at home.
CI, confidence interval.
[a]Referred but not hospitalized.

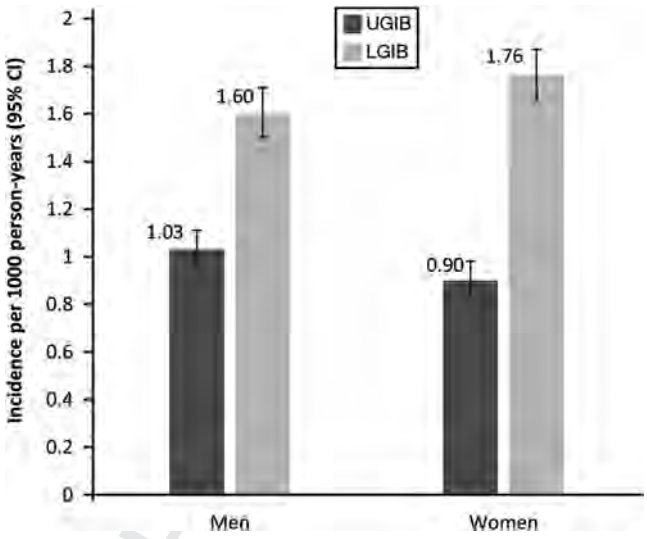
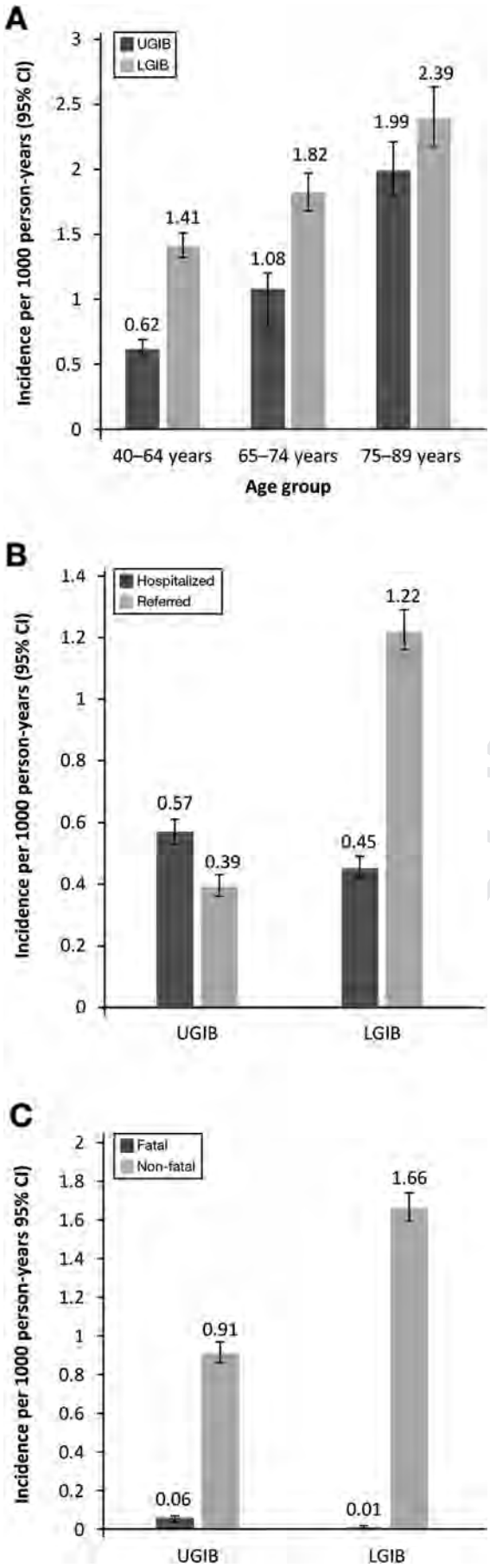


Figure 2. Incidence rate of upper gastrointestinal bleed (UGIB) and lower gastrointestinal bleed (LGIB) per 1000 person-years (with 95% confidence interval [CI]) among new users of low-dose aspirin, by sex.

The majority of UGIB cases (58.9%) were hospitalized whereas the majority of LGIB cases (72.8%) were referred but not hospitalized. The incidence of hospitalized bleeds per 1000 person-years was 0.57 (95% CI, 0.53–0.61) for UGIB and 0.45 (95% CI, 0.42–0.49) for LGIB, while the incidence of referred only bleeds per 1000 person-years was 0.39 (95% CI, 0.36–0.43) for UGIB and 1.22 (95% CI, 1.16–1.29) for LGIB (Table 2, Figure 3*B*). Corresponding incidence rates stratified by age group are shown in Supplementary Table 3; incidence rate ratios comparing rates in the 75–89-year age group versus the 40–64-years age group were 1.3 for hospitalized UGIB, 2.2 for referred only UGIB, 3.0 for hospitalized LGIB, and 1.3 for referred-only LGIB.

Case-fatality rates were 5.7% (64 of 1115) for UGIB and 0.8% (15 of 1936) for LGIB; 3.5% (16 of 452) for referred UGIB, 6.4% (42 of 657) for hospitalized UGIB, 0.1% (2 of 1410) for referred LGIB, and 1.9% (10 of 523) for hospitalized LGIB. For UGIB, the mean age of fatal cases was 74.4 years (median 77.0 years) and for nonfatal cases was 67.4 years (median 69 years). For LGIB, the mean age of fatal cases was 78.1 years (median 79.0 years), and for nonfatal cases was 65.1 years (median 66.0 years). Incidence rates of fatal and nonfatal UGIB per 1000 person-years were 0.06 (95% CI, 0.04–0.07) and 0.91 (95% CI, 0.86–0.97), respectively, and for fatal and nonfatal LGIB they were 0.01 (95% CI, 0.01–0.02) and 1.66 (95% CI, 1.59–1.74), respectively (Table 2, Figure 3*C*). Corresponding incidence rates stratified by age group are shown in Supplementary Table 4; incidence rate ratios comparing rates in the 75–89 year age group versus the 40–64 age group were 15.7 for fatal UGIB, 2.9 for nonfatal UGIB and 1.6 for nonfatal LGIB (note, there were no fatal LGIB cases among the younger age group).



The most frequent recorded GI antecedent among UGIB cases was gastroduodenal mucosal lesions (29.3%), followed by duodenal ulcer (20.1%) and gastric ulcer (17.1%), with 26.7 of UGIB cases not having a reason for their bleed recorded. For cases of LGIB, 43.4% of cases previously presented with diverticular diseases, 12.1% had polyps, and 8.0% had colitis, with 28.6% having no recorded GI antecedent. The incidence of UGIB was 3.15 per 1000 person-years (95% CI, 2.22–4.48) for those with a previous UGIB, was 1.68 per 1000 person-years (95% CI, 1.33–2.11) for those with a previous uncomplicated peptic ulcer, and was 3.00 per 1000 person-years (95% CI, 2.30–3.91) for those with a previous complicated peptic ulcer. Among members of the study cohort with a previous LGIB, the incidence of LGIB was 5.32 (95% CI, 4.77–5.94). For cohort members with antecedents of ischemic vascular disease, incidence rates were 1.20 (95% CI, 1.09–1.31) for UGIB and 1.80 (95% CI, 1.68–1.94) for LGIB. Lower incidence rates were among individuals without antecedents of ischemic vascular disease: 0.84 (95% CI, 0.78–0.91) for UGIB and 1.61 (95% CI, 1.52–1.70) for LGIB.

Among the comparison cohort of nonusers of low-dose aspirin at start of follow-up, the overall incidence rates were 0.67 (95% CI, 0.63–0.75) for UGIB and 0.76 (95% CI, 0.72–0.82) for LGIB. The incidence rate ratio for the aspirin vs comparison cohort was 1.42 (95% CI, 1.29–1.56) for UGIB and 2.17 (95% CI, 2.00–2.35) after adjustment for age, sex, and number of PCP visits in the year before the start date (Supplementary Table 5).

Discussion

In this large population-based study we have estimated incidence rates of UGIB and LGIB among nearly 200,000 new users of preventative low-dose aspirin in the United Kingdom after follow-up of up to 14 years. By estimating incidence rates of both serious (hospitalized) and nonserious (referred-only) UGIB and LGIB as well as fatal and nonfatal cases in the same cohort, ours is the first observational study to report on the actual burden of all types of bleeding in the GI tract, and is thereby helpful in appropriately balancing benefits and actual risks of low-dose aspirin.

Case-fatality rates were low for both UGIB (6%) and LGIB (<1%). Low case-fatality rates for GIBs have also been shown among individuals randomized to low-dose aspirin in clinical trials, especially among those without ischemic vascular disease.[14] Almost three-quarters of LGIBs in our study did not require hospitalization, and while the majority of UGIBs were hospitalized, a

Figure 3. Incidence rate of upper gastrointestinal bleed (UGIB) and lower gastrointestinal bleed (LGIB) per 1000 person-years (with 95% confidence interval [CI]) among new users of low-dose aspirin, by (*A*) age group, (*B*) level of health care assistance, and (*C*) case fatality.

substantial percentage (approximately 40%) were managed as outpatients. Overall, the incidence of LGIB was higher than UGIB in this study, which, based on estimates from previous observational studies[25] was unexpected. A possible explanation is the use of acid-suppressants such as proton pump inhibitors and histamine-2 receptor antagonists (among approximately 18% of the cohort at start of follow-up) prescribed to minimize UGIB in preventative aspirin users deemed susceptible to bleeding. Another explanation is that most previous studies addressed only hospitalized bleeds—in terms of hospitalization rates, incidences of UGIB and LGIB were similar in our study. Establishing patterns of low-dose aspirin use among nonserious cases of LGIB—in terms of levels of discontinuation, adherence, treatment interruption, and medication switching—would be of interest for study in further research.

Incidence of UGIB in this study is in line with that found in a previous study in THIN of individuals using low-dose aspirin for secondary prevention of ischemic vascular disease.[9] Incidence rates of hospitalized UGIB and LGIB are slightly lower than those reported in large U.S. observational cohorts of professional males[10,13] and females[11] without previous GI bleeding or peptic ulcer disease, who self-reported continuous use of preventative low-dose aspirin, although differences between UGIB and LGIB incidence were similar. A higher incidence of hospitalized UGIB was reported among low-dose aspirin users in Denmark (3.64 per 1000 person-years) using a prescription database and hospital discharge registry records with data collected from 1991 to 1995.[12]

As expected by the low case fatality rates, the incidence of fatal UGIB and LGIB in our study cohort was substantially lower than the incidence of nonfatal events, in line with data from aspirin randomized controlled trials[14] and observational data from secondary prevention aspirin users.[8] The absolute rate of fatal GIBs in Elwood's meta-analysis of randomized controlled trial data was much higher at 0.37 per 1000 person-years than in our study cohort; the incidence of all GIBs was also substantially higher, at 8 cases per 1000 person-years.[14] Difference between individuals in our study population and participants in the trials in the meta-analysis could at least partly explain this difference; for example, in our study, 63% of the study aspirin cohort did not have recorded antecedents of ischemic vascular disease. Fatal cases of UGIB and LGIB in our study cohort were older than nonfatal cases, and overall incidence rates of both bleeds increased with age, as seen in previous studies.[8,9] In the Oxford vascular study, conducted over the same time period as our study but among individuals receiving antiplatelet drugs following an ischemic vascular event (mainly aspirin based), the rate of significant nonmajor UGIB was approximately 2-fold higher among the aged ≥75-years group vs those aged <75 years.[8] For major nonfatal UGIB, the incidence among the older age group was almost 4-fold higher, and for fatal UGIB it was almost 7-fold higher. We also observed a higher UGIB incidence among elderly low-dose aspirin users in our study compared with those in the youngest age group (aged 40–64 years); a 16-fold increase for fatal UGIB and a 3-fold increase for nonfatal UGIB; however, age-related differences for LGIB were much lower.

Our study has several strengths. First, the large size of the study population from a database representative of the UK demographic allowed the calculation of precise and generalizable UGIB and LGIB incidence rates. Second, our study cohort included individuals with prior GI comorbidities and users of comedications that are known to increase GI bleeding risk, as well as those with or without ischemic vascular disease, thereby representative of UK patients using preventative low-dose aspirin. Thirdly, survivor bias was removed by the inclusion of only new users of low-dose aspirin. Fourthly, the recorded UGIB or LGIB diagnoses were validated through a multistep process, including linkage to hospitalization data or through manual review of patient records in THIN including the free text comments. Previous validation studies using questionnaires to PCPs as the gold standard have shown UGIB and LGIB Read codes in THIN to have PPVs of 95% and 82%, respectively[21–24] after manual review of medical records incorporating free text comments. A limitation of our study is that misclassification of low-dose aspirin could have occurred from individuals discontinuing their preventative treatment during follow-up—in censoring follow-up at 1 year after start of therapy, GI bleeding rates were slightly higher. Another limitation of our study is that we were unable to separate GIB-specific mortality from mortality related to underlying comorbidity because information on cause of death is not available in the THIN. It is also possible that there may have been some overestimation of hospitalized events. While our reasonably wide time window to identify hospitalized bleeds minimized the potential for missing hospitalizations related to the GIB itself, including admissions that may have been related to other conditions will have led to some overestimation of hospitalized bleeds. However, the level of such misclassification is likely to be small because we manually reviewed patient records and it was often clear when a particular hospitalization was related or unrelated to the bleeding event itself. Long-term use of low-dose aspirin is recommended for all patients with established ischemic vascular disease. It is also recommended for certain groups of patients without established ischemic vascular disease but who are considered at high enough risk—predominantly on the basis of age, vascular disease risk score, and risk of bleeding—to warrant prophylactic drug use.[26–28] Recommendations in this latter group have been informed by the accumulation of evidence regarding the effectiveness of low-dose aspirin in reducing CRC incidence and mortality and probably some other cancers. With possibly increasing numbers of individuals considered eligible to use low-dose aspirin, accurate estimates of benefits and harms are required in

general populations. A complete benefit–risk evaluation of low-dose aspirin requires estimates of the absolute excess reduction of ischemic vascular events and CRC and the absolute excess increase of all major bleeds (UGIB, LGIB, and intracranial bleed) in the same real-world population that are attributable to the use of low-dose aspirin, together with an appreciation of the severity of these events and potential for long-lasting disability.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.05.061.

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Reprint requests
Address requests for reprints to: Lucía Cea Soriano, Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Almirante 28; 28004 Madrid, Spain. e-mail: luciaceife@gmail.com.

Conflicts of interest
These authors disclose the following: Lucía Cea Soriano and Luis A. García Rodríguez work for CEIFE, which has received research funding from Bayer AG. Luis A. García Rodríguez has received honoraria for serving on advisory boards for Bayer AG. Angel Lanas has previously received a research grant from Bayer AG and has served as an advisory board member for Bayer AG and Bayer HealthCare. Montse Soriano-Gabarró is a full-time employee of Bayer AG.

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Supplementary Methods

Upper and Lower Gastrointestinal Bleed Case Identification and Validation.

Case Inclusion Criteria

For upper gastrointestinal bleed (UGIB), the bleeding or perforation site was required to be the stomach or duodenum (patients with esophageal bleeding/perforation were excluded); for lower gastrointestinal bleed (LGIB), bleeding was required to be in the jejunum, ileum, colon, or rectum (bleeds due to hemorrhoids or anal fissures were excluded).

Step 1: We identified individuals who had been confirmed as either an incident case of UGIB (n = 599), LGIB (n = 143), or a noncase (n = 308) during previous research projects in The Health Improvement Network (THIN).[1–4]

Step 2: Among the remaining potential cases who could not be cross-linked to previous projects (n = 1920 in the UGIB follow-up, n = 10,224 in the LGIB follow-up), we identified those belonging to general practices linked to Hospital Episode Statistics (n = 657 [34.2%] in the UGIB follow-up, 3544 [34.7%] in the LGIB follow-up). Automated computer searches were performed among these individuals' HES records for International Classification of Diseases-Tenth Revision ICD-10 codes for a GI bleed during the study period and up to 90 days after, and for all hospitalizations within 90 days before and after the date of the GI bleed Read code in the THIN. From this process, we identified 332 confirmed UGIB cases, 544 confirmed LGIB cases and 213 confirmed cases of a GI bleed with unspecified site (upper/lower; all hospitalized). To complete the assignment of the site of the bleed for this latter group (n = 213), we manually reviewed their medical records in the THIN, including free text comments while masked to all medication use.

Step 3: Among all remaining unconfirmed cases, we identified 10,649 individuals who were identified during both the UGIB and LGIB follow-ups and removed any duplicates (eg, those with a Read code for an unspecified GI bleed on the same date in both follow-ups). After this process, 9753 individuals remained as unconfirmed cases of UGIB or LGIB.

Step 4: To assign case status to these 9753 individuals, we looked for indicators such as GI procedures, and specific symptoms entered in the database within the 90 days before and 30 days after the recorded date of the GI bleed to imply probable, nonprobable, or still unknown case status. For example, Read codes indicative of a probable case included those for relevant GI antecedent, such as diverticulosis, while codes suggestive of a nonprobable case included those for digestive malignancies, hemorrhoids, and anal fissure. From this process, among the 9753 potential cases there were 2590 probable cases, 1247 nonprobable, and 5916 remaining (no information from Read codes in their medical records to help assign case status).

Manual Review of a Subset. Among these 9753 potential incident cases, the medical records in the THIN with free text comments (already available from previous research studies) of a subset of 767 individuals (190 deemed probable cases, 185 deemed nonprobable cases, and 392 deemed remaining cases) were manually reviewed (masked to all information on medication use) and their case status ascertained. Among this subset of 767 patients, we calculated the positive and negative predictive value or specific Read codes and applied these predictive values to the 8986 potential incident cases not included in this subset (ie, those without free comments available in their medical records to review). Negative predictive values for certain Read codes for rectal bleeding, rectal hemorrhage, and bleeding per rectum were >90% among the 185 nonprobable cases and >84% among the 392 remaining patients manually reviewed, and thus we searched for these codes among all nonprobable and remaining patients not included in the manually reviewed sample and excluded those with these codes. Positive predictive values of various Read codes were found to be heterogeneous in value and not sufficiently high or low to help confirm case status. After this process, there was still a total of 2400 of 2590 probable cases, and 854 of 5524 'remaining' patients without an assigned case status; all 1062 nonprobable cases and 4670 patients in the 'remaining' group not manually reviewed had an assigned case status (ie, all were deemed noncases and were discarded owing to having a high NPV Read code).

Use of Specific Read codes or Free Text Strings. Last, for all individuals with a case status still unconfirmed (n = 3254), we applied a manual review process of their THIN medical records, including free text comments (while masked to medication exposure), to assign case status and identify the site of the bleed (UGIB or LGIB). To do this, we used the presence of specific Read codes or text strings within the free text comments, within 1 year either side of the index date. For example, individuals with a code for hematemesis were classed as having UGIB, as were those with a Read code for gastrointestinal bleeding together with text involving *duodenal*, *hematemesis*, *gastritis*, and *coffee ground* detected in the free text comments. Similarly, individuals with a Read code for gastrointestinal bleeding together with text involving *divert*, *colitis*, or C*rohn* detected in the free text comments, were assigned as having LGIB.

After this process, there were a total of 1115 confirmed UGIB cases and 1936 confirmed LGIB cases).

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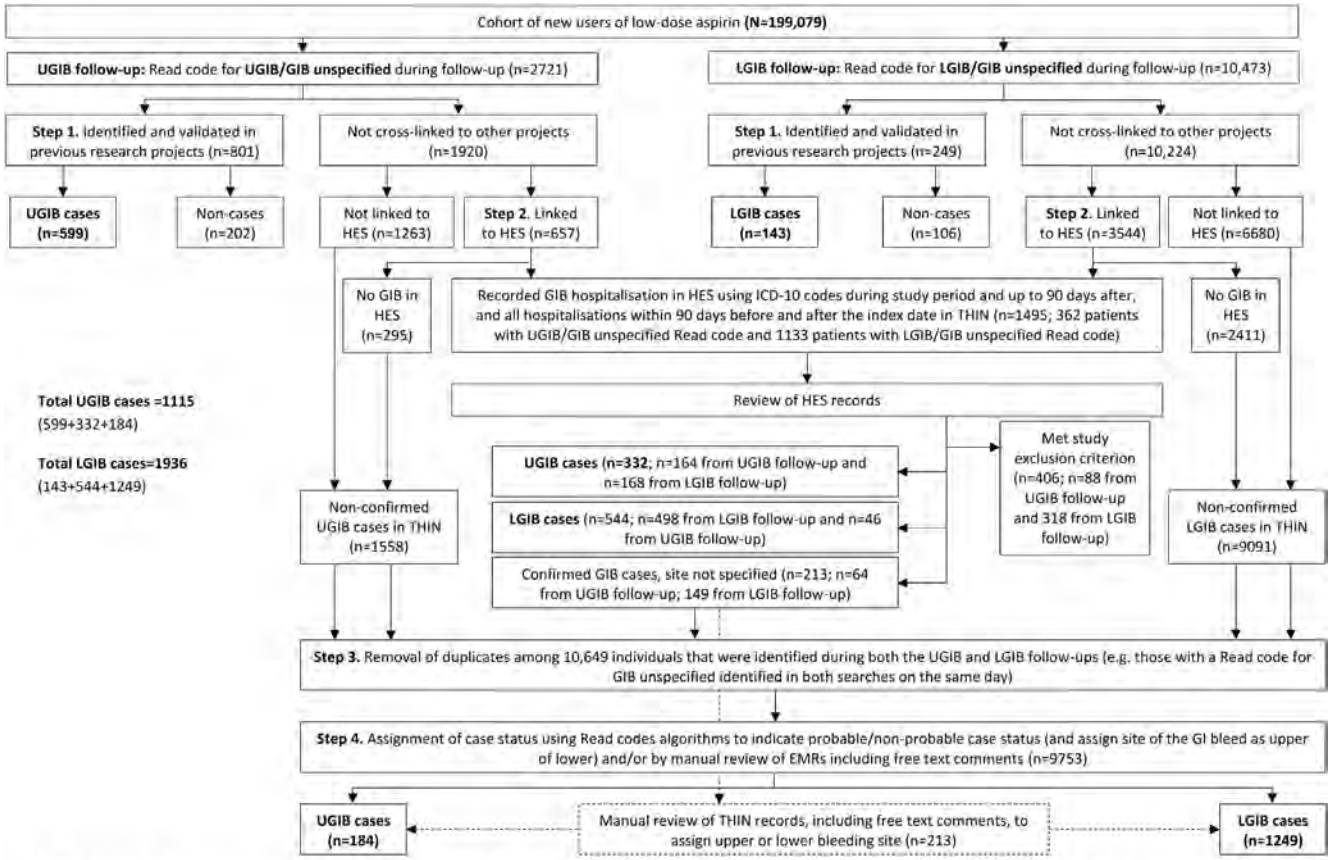

Supplementary Figure. Flowchart depicting the identification and validation of incident cases of UGIB and LGIB. EMR, electronic medical record; GIB, gastrointestinal bleed; HES, Hospital Episode Statistics; LGIB, lower gastrointestinal bleed; THIN, The Health Improvement Network; UGIB, upper gastrointestinal bleed.

Supplementary Figure 1. Flow chart depicting the identification and validation of incident cases of upper gastrointestinal bleed (UGIB) and lower gastrointestinal bleed (LGIB). EMR, electronic medical record; GIB, gastrointestinal bleed; HES, Hospital Episode Statistics, ICD-10, International Classificiation of Diseases-Tenth Revision; THIN, The Health Improvement Network.

Supplementary Table 1. Gastrointestinal Comorbidities of the Study Cohort (New Users of Low-Dose Aspirin) at the Start of Follow-Up

Characteristic	Primary Prevention Users (n = 126,072, 63.3%)	Secondary Prevention Users (n = 72,977, 36.7%)	All New Users of low-Dose Aspirin (N = 199,049)
Any GI bleed[a]	8511 (6.8)	5403 (7.4)	13,914 (7.0)
UGIB	983 (0.8)	903 (1.2)	1886 (0.9)
LGIB	7136 (5.7)	4096 (5.6)	11,232 (5.6)
Complicated peptic ulcer[b]	1834 (1.5)	1674 (2.3)	3508 (1.8%)
Uncomplicated peptic ulcer[b]	3892 (3.1)	3704 (5.1)	7596 (3.8)
IBD	1368 (1.1)	950 (1.3)	2318 (1.2)
Dyspepsia	23,012 (18.3)	15,572 (21.3)	38,584 (19.4)

GI, gastrointestinal; IBD, irritable bowel disease; LGIB, lower gastrointestinal bleed; UGIB, upper gastrointestinal bleed.
[a]Includes patients that had at least one episode of a previous GIB Any time before the start date taking the most recent value or status.
[b]Complicated peptic ulcers were events that presented with hematemesis or perforation, unlike uncomplicated peptic ulcer events.

Supplementary Table 2. Crude Incidence Rates of UGIB and LGIB per 1000 Person-Years Among New Users of Low-Dose Aspirin Stratified by 5-Year Age Group

	Incidence Rate (95% CI) per 1000 Person-Years	
Age Group	UGIB	LGIB
40–44 y	0.42 (0.27–0.63)	1.14 (0.88–1.46)
45–49 y	0.53 (0.40–0.72)	1.20 (0.98–1.47)
50–59 y	0.65 (0.52–0.82)	1.32 (1.13–1.54)
55–59 y	0.59 (0.48–0.72)	1.43 (1.26–1.63)
60–64 y	0.71 (0.61–0.84)	1.58 (1.42–1.75)
65–69 y	0.93 (0.80–1.08)	1.77 (1.59–1.98)
70–74 y	1.26 (1.10–1.45)	1.88 (1.68–2.10)
75–79 y	1.87 (1.63–2.14)	2.31 (2.05–2.62)
80–85 y	2.21 (1.87–2.61)	2.52 (2.15–2.94)

CI, confidence interval; LGIB, lower gastrointestinal bleed; UGIB, upper gastrointestinal bleed.

Supplementary Table 3. Crude Incidence Rates of UGIB and LGIB per 1000 Person-Years Among New Users of Low-Dose Aspirin by Level of Health Care Use and Stratified by Age Group

	Incidence Rate (95% CI) per 1000 Person-Years			
	UGIB		LGIB	
Age Group	Hospitalized	Referred Only	Hospitalized	Referred Only
40–64	0.31 (0.27–0.36)	0.31 (0.27–0.36)	0.30 (0.26–0.35)	1.11 (1.02–1.19)
65–74	0.68 (0.60–0.78)	0.40 (0.34–0.47)	0.50 (0.43–0.58)	1.32 (1.21–1.45)
75–89	1.29 (1.13–1.47)	0.67 (0.59–0.81)	0.91 (0.78–1.06)	1.46 (1.29–1.65)

CI, confidence interval; LGIB, lower gastrointestinal bleed; UGIB, upper gastrointestinal bleed.

Supplementary Table 4. Crude Incidence Rates of UGIB and LGIB per 1000 Person-Years Among New Users of Low-Dose Aspirin by Case Fatality and Stratified by Age Group

	Incidence Rate (95% CI) per 1000 Person-Years			
	UGIB		LGIB	
Age Group	Fatal[a]	Nonfatal	Fatal[a]	Nonfatal
40–64 y	0.014 (0.007–0.027)	0.61 (0.55–0.67)	—	1.41 (1.32–1.50)
65–74 y	0.049 (0.030–0.078)	1.04 (0.93–1.15)	0.012 (0.004-0.031)	1.81 (1.67–1.96)
75–89 y	0.22 (0.160–0.30)	1.77 (1.58–1.98)	0.064 (0.035-0.115)	2.32 (2.11–2.56)

CI, confidence interval; LGIB, lower gastrointestinal bleed; UGIB, upper gastrointestinal bleed.
[a]Fatal = death within 30 days.

Supplementary Table 5. Crude Incidence Rates of UGIB and LGIB per 1000 Person-Years in the Comparison Cohort of Nonusers of Low-Dose Aspirin at Start of Follow-Up

	UGIB	LGIB
Cases	728	827
Median person-years	5.20	5.20
Total person-years	1,079,283	1,079,302
Incidence rate (95% CI) per 1000 person-years	0.67 (0.63–0.75)	0.76 (0.72–0.82)
IRR (95% CI) of low-dose aspirin vs comparison cohort[a]	1.42 (1.29–1.56)	2.17 (2.00–2.35)

CI, confidence interval; IRR, incidence rate ratio; LGIB, lower gastrointestinal bleed; UGIB, upper gastrointestinal bleed.

[a]Adjusted by age, sex, and number of primary care practitioner visits in the year before the start date.