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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; ^{II}CIBERehd, Instituto de Salud Carlos III, Madrid, Spain; ^{II}Epidemiology, Bayer AG, Berlin, Germany

BACKGROUND & AIMS:

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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 sexspecific 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 assess-

ments 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 deffective 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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https://doi.org/10.1016/j.cgh.2018.05.061	116

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117 effects should also be considered-other factors that 118 could potentially shift the benefit-risk profile and influ-119 ence prescribing decisions. GI bleeds (GIBs) vary in 120 severity, and although some may require hospitalization, 121 others may be less severe and be managed on an outpa-122 tient basis. Importantly, discontinuation of low-dose 123 aspirin is not uncommon following an upper GIB 124 (UGIB)⁵ and is associated with an increased risk of cardiovascular events⁶ and death.⁷ Even minor bleeds, in any 125 part of the GI tract, could potentially lead to discontinua-126 127 tion of prophylactic aspirin.

128 There are few studies from observational cohorts of 129 preventative low-dose aspirin users reporting incidence rates for UGIBs,⁸⁻¹² and even fewer for lower GIBs 130 (LGIBs).^{10,11,13} Furthermore, most have reported data only 131 for hospitalized events in individuals without GI ante-132 cedents,¹⁰⁻¹³ and while separate estimates for fatal and 133 nonfatal GIBs are available from clinical trials,¹⁴ there are 134 135 few estimates from observational data.⁸ There is therefore 136 a need to obtain UGIB and LGIB incidence data, including 137 by age and bleed severity, among real-world low-dose 138 aspirin users, including those with previous GIBs or taking 139 concomitant medications known to increase bleeding risk. 140 Using a population-based cohort study in UK primary care, 141 we aimed to estimate the overall and age- and sex-specific 142 incidence of UGIB or LGIB among new users of low-dose 143 aspirin, with subanalyses by level of health care assis-144 tance and case fatality. 145

Methods

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Data Source

150 We used data The Health Improvement Network 151 (THIN), a validated UK population-based primary care 152 database containing anonymized electronic medical re-153 cords (EMRs) of $\sim 6\%$ of the UK population and broadly 154 representative of its demographic.^{15,16} Participating pri-155 mary care practitioners (PCPs) enter clinical information 156 using Read codes¹⁷ and free text; prescriptions are 157 recorded upon issue. Patient-level linkage to the Hospital 158 Episode Statistics (HES) database is possible for in-159 dividuals in linked practices.¹⁸ Although low-dose 160 aspirin available over the counter in the United 161 Kingdom, most chronic aspirin use is via prescriptions 162 (free for individuals aged over 60 years),¹⁸ validation of 163 low-dose aspirin prescription data in THIN shows that 164 exposure misclassification owing to unrecorded over-165 the-counter low-dose aspirin is likely to be minimal.¹⁹ 166 An independent scientific review committee for THIN 167 reviewed and approved the study protocol (reference 168 number 14-088A1). 169

Identification and Follow-Up of the Study Cohort

173A total of 199,079 new users of low-dose aspirin were174identified from THIN source population (N = 1,840,253)

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 lowdose 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

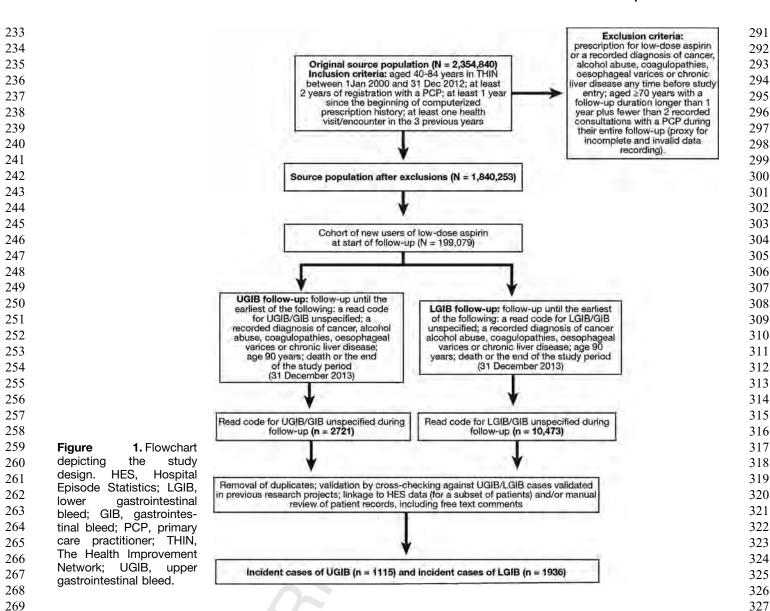
Our findings from an observational study of the burden of UGIB and LGIB could help clinicians balance the benefits and actual risks of low-dose aspirin use.

(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 followup (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







270 a hospitalization in their EMRs within 15 days before 271 and 30 days after the GIB were assigned to the hospi-272 talized group; remaining patients with a record of 273 referral were assigned to the referred group. For cases 274 without a hospitalization or referral, we manually 275 reviewed their EMRs to identify free text comments 276 implying hospitalization or referral. Cases who died on 277 or within 30 days following the index date were deemed 278to be fatal cases irrespective of whether the primary 279 cause of death was due to the bleed itself or to associ-280 ated comorbidities. 281

Covariates

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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. 328

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Statistical Analysis

Crude incidence rates per 1000 person-years with 337 95% confidence interval (CI) were calculated for UGIB 338 and LGIB separately, for all cases, and stratified by age, 339 sex, and GIB history. Incidence rates of UGIB and LGIB 340 were also calculated by the level of health care assistance 341 received (hospitalized or referred) and case fatality. In 342 an additional analysis, we estimated overall incidence 343 rates of UGIB and LGIB separately among a comparison 344 cohort of nonusers of low-dose aspirin. To identify this 345 cohort, each 199,079 new user of low-dose aspirin was 346 matched 1:1 to an individual from the THIN source 347 population (after applying all inclusion or exclusion 348

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Clinical Gastroenterology and Hepatology Vol. ■, No. ■

Table 1. Baseline Characteristics of the Cohort of New Users

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pypertensive agents 108,529 54 ns 48,679 24 29,689 14 5813 2	Insulin	6270	3.1
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Incidence of UGIB and LGIB

467 A total of 3051 individuals in the study cohort (1.5%) 468 suffered a GIB over the follow-up period (median 5.4) 469 years in both the UGIB and LGIB follow-up): 1115 inci-470 dent cases of UGIB and 1936 incident cases of LGIB (4 471 individuals experienced both a UGIB and LGIB). The 472 overall crude incidence rate was lower for UGIB than for 473 LGIB: 0.97 cases per 1000 person-years (95% CI, 474 0.91-1.02) for UGIB and 1.68 cases per 1000 person-475 years (95% CI, 1.60–1.75) for LGIB (Table 2). Incidence 476 rates were higher during the first year of follow-up: 1.31 477 per 1000 person-years (95% CI, 1.16-1.48) for UGIB and 478 1.95 per 1000 person-years (95% CI, 1.76-2.16) for 479 LGIB. Men had a higher incidence of UGIB than women 480 (1.03 vs 0.90 per 1000 person-years) while for LGIB, 481 incidence rates were slightly lower in men than women 482 (1.60 vs 1.76 per 1000 person-years) (Table 2; Figure 2). 483 Incidence rates of UGIB and LGIB increased with age, with LGIB higher than UGIB in all age groups (Table 2, 484 485 Figure 3A; see Supplementary Table 2 for rates by 5-year 486 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% Cl)
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 (0.53–0.6
Referred ^a	452	1,154,032	0.39 (0.36–0.4
Total	1115	1,154,032	0.97 (0.91–1.0)
LGIB			
Male	941	588,281	1.60 (1.50–1.7
Female	995	565,752	1.76 (1.65–1.8
Age 40–64 y	889	632,725	1.41 (1.32–1.5
Age 65–74 y	635	348,673	1.82 (1.68–1.9)
Age 75–89 y	412	174,170	2.39 (2.17-2.6
Fatal cases Nonfatal cases	15 1921	1,154,033 1,154,033	0.01 (0.01–0.02 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 (1.60–1.7
iotai	1000	1,104,000	1.00 (1.00 1.75
NOTE. The number of hosp	italized and r	eferred (but not h	ospitalized) cases o
not sum the total number	of cases for	upper gastrointes	stinal bleed (UGIB)
lower gastrointestinal blee	d (LGIB) bec	ause 6 UGIB ca	ases and three LG

- cases were not referred or hospitalized but died at home.
- 521 Cl, confidence interval.
- 522 ^aReferred but not hospitalized.

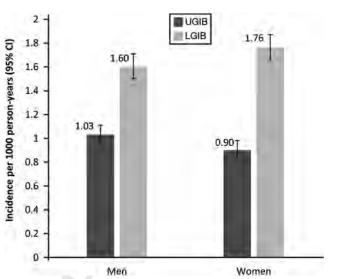
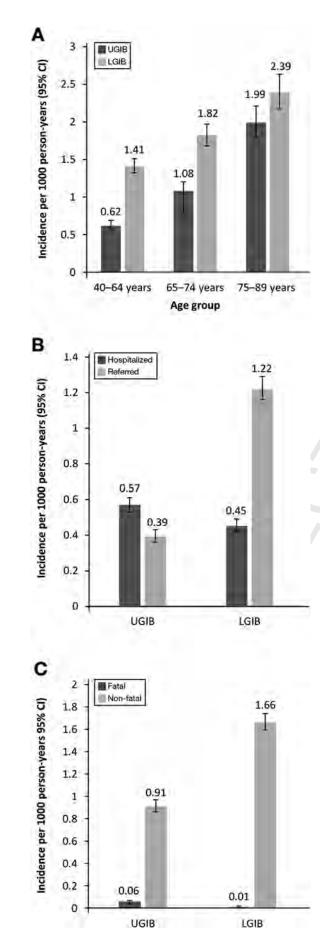


Figure 2. Incidence rate of upper gastrointestinal bleed (UGIB) and lower gastrointestinal bleed (LGIB) per 1000 person-years (with 95% confidence interval [CI]) among new users of low-dose aspirin, by sex.

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 3B). 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 560 and 0.8% (15 of 1936) for LGIB; 3.5% (16 of 452) for 561 referred UGIB, 6.4% (42 of 657) for hospitalized UGIB, 562 0.1% (2 of 1410) for referred LGIB, and 1.9% (10 of 523) 563 for hospitalized LGIB. For UGIB, the mean age of fatal 564 cases was 74.4 years (median 77.0 years) and for 565 nonfatal cases was 67.4 years (median 69 years). For 566 LGIB, the mean age of fatal cases was 78.1 years (median 567 79.0 years), and for nonfatal cases was 65.1 years (me-568 dian 66.0 years). Incidence rates of fatal and nonfatal 569 UGIB per 1000 person-years were 0.06 (95% CI, 570 0.04-0.07) and 0.91 (95% CI, 0.86-0.97), respectively, 571 and for fatal and nonfatal LGIB they were 0.01 (95% CI, 572 0.01-0.02) and 1.66 (95% CI, 1.59-1.74), respectively 573 (Table 2, Figure 3C). Corresponding incidence rates 574 stratified by age group are shown in Supplementary 575 Table 4; incidence rate ratios comparing rates in the 576 75–89 year age group versus the 40–64 age group were 577 15.7 for fatal UGIB, 2.9 for nonfatal UGIB and 1.6 for 578 nonfatal LGIB (note, there were no fatal LGIB cases 579 among the younger age group). 580 

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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 uncom-plicated 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 an-tecedents 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 lowdose 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.

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697 substantial percentage (approximately 40%) were 698 managed as outpatients. Overall, the incidence of LGIB 699 was higher than UGIB in this study, which, based on estimates from previous observational studies²⁵ was 700 701 unexpected. A possible explanation is the use of acid-702 suppressants such as proton pump inhibitors and 703 histamine-2 receptor antagonists (among approximately 704 18% of the cohort at start of follow-up) prescribed to 705 minimize UGIB in preventative aspirin users deemed 706 susceptible to bleeding. Another explanation is that most 707 previous studies addressed only hospitalized bleeds-in 708 terms of hospitalization rates, incidences of UGIB and 709 LGIB were similar in our study. Establishing patterns of 710 low-dose aspirin use among nonserious cases of 711 LGIB—in terms of levels of discontinuation, adherence, 712 treatment interruption, and medication switching-713 would be of interest for study in further research.

714 Incidence of UGIB in this study is in line with that 715 found in a previous study in THIN of individuals using 716 low-dose aspirin for secondary prevention of ischemic 717 vascular disease.9 Incidence rates of hospitalized UGIB 718 and LGIB are slightly lower than those reported in large U.S. observational cohorts of professional males^{10,13} and 719 720 females¹¹ without previous GI bleeding or peptic ulcer disease, who self-reported continuous use of preventa-721 722 tive low-dose aspirin, although differences between UGIB 723 and LGIB incidence were similar. A higher incidence of 724 hospitalized UGIB was reported among low-dose aspirin users in Denmark (3.64 per 1000 person-years) using a 725 726 prescription database and hospital discharge registry 727 records with data collected from 1991 to 1995.¹²

728 As expected by the low case fatality rates, the inci-729 dence of fatal UGIB and LGIB in our study cohort was 730 substantially lower than the incidence of nonfatal events, 731 in line with data from aspirin randomized controlled 732 trials¹⁴ and observational data from secondary prevention aspirin users.⁸ The absolute rate of fatal GIBs in 733 734 Elwood's meta-analysis of randomized controlled trial 735 data was much higher at 0.37 per 1000 person-years 736 than in our study cohort; the incidence of all GIBs was 737 also substantially higher, at 8 cases per 1000 personyears.¹⁴ Difference between individuals in our study 738 739 population and participants in the trials in the meta-740 analysis could at least partly explain this difference; for 741 example, in our study, 63% of the study aspirin cohort 742 did not have recorded antecedents of ischemic vascular 743 disease. Fatal cases of UGIB and LGIB in our study cohort 744 were older than nonfatal cases, and overall incidence 745 rates of both bleeds increased with age, as seen in previous studies.^{8,9} In the Oxford vascular study, conducted 746 over the same time period as our study but among in-747 748 dividuals receiving antiplatelet drugs following an 749 ischemic vascular event (mainly aspirin based), the rate 750 of significant nonmajor UGIB was approximately 2-fold higher among the aged \geq 75-years group vs those aged 751 752 <75 years.⁸ For major nonfatal UGIB, the incidence 753 among the older age group was almost 4-fold higher, and 754 for fatal UGIB it was almost 7-fold higher. We also

observed a higher UGIB incidence among elderly lowdose 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.

760 Our study has several strengths. First, the large size of 761 the study population from a database representative of 762 the UK demographic allowed the calculation of precise 763 and generalizable UGIB and LGIB incidence rates. Second, 764 our study cohort included individuals with prior GI 765 comorbidities and users of comedications that are known 766 to increase GI bleeding risk, as well as those with or 767 768 without ischemic vascular disease, thereby representative of UK patients using preventative low-dose aspirin. 769 Thirdly, survivor bias was removed by the inclusion of 770 only new users of low-dose aspirin. Fourthly, the recor-771 ded UGIB or LGIB diagnoses were validated through a 772 multistep process, including linkage to hospitalization 773 data or through manual review of patient records in 774 775 THIN including the free text comments. Previous validation studies using questionnaires to PCPs as the gold 776 standard have shown UGIB and LGIB Read codes in THIN 777 to have PPVs of 95% and 82%, respectively²¹⁻²⁴ after 778 manual review of medical records incorporating free text 779 comments. A limitation of our study is that misclassifi-780 cation of low-dose aspirin could have occurred from in-781 dividuals discontinuing their preventative treatment 782 during follow-up—in censoring follow-up at 1 year after 783 start of therapy, GI bleeding rates were slightly higher. 784 Another limitation of our study is that we were unable to 785 separate GIB-specific mortality from mortality related to 786 underlying comorbidity because information on cause of 787 death is not available in the THIN. It is also possible that 788 there may have been some overestimation of hospital-789 ized events. While our reasonably wide time window to 790 identify hospitalized bleeds minimized the potential for 791 missing hospitalizations related to the GIB itself, 792 including admissions that may have been related to other 793 conditions will have led to some overestimation of hos-794 pitalized bleeds. However, the level of such misclassifi-795 796 cation is likely to be small because we manually reviewed patient records and it was often clear when a 797 particular hospitalization was related or unrelated to the 798 bleeding event itself. Long-term use of low-dose aspirin 799 is recommended for all patients with established 800 ischemic vascular disease. It is also recommended for 801 certain groups of patients without established ischemic 802 vascular disease but who are considered at high enough 803 risk—predominantly on the basis of age, vascular disease 804 risk score, and risk of bleeding—to warrant prophylactic 805 drug use.^{26–28} Recommendations in this latter group 806 have been informed by the accumulation of evidence 807 regarding the effectiveness of low-dose aspirin in 808 reducing CRC incidence and mortality and probably 809 some other cancers. With possibly increasing numbers of 810 individuals considered eligible to use low-dose aspirin, 811 accurate estimates of benefits and harms are required in 812

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813 general populations. A complete benefit-risk evaluation 814 of low-dose aspirin requires estimates of the absolute 815 excess reduction of ischemic vascular events and CRC 816 and the absolute excess increase of all major bleeds 817 (UGIB, LGIB, and intracranial bleed) in the same real-818 world population that are attributable to the use of 819 low-dose aspirin, together with an appreciation of the 820 severity of these events and potential for long-lasting 821 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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GI Bleed Incidence in Low-Dose Aspirin Users

Reprint requests Address requests for reprints to: Lucía Cea Soriano, Spanish Centre for 93<mark>8</mark>3 Pharmacoepidemiologic Research (CEIFE), Almirante 28; 28004 Madrid, Spain. e-mail: luciaceife@gmail.com.

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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.

Funding

Funding This study was funded by Bayer AG. Medical writing support was provided by 06 EpiMed Communications Ltd (Oxford, UK), funded by 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 1053 or perforation site was required to be the stomach or 1054 duodenum (patients with esophageal bleeding/perfora-1055 tion were excluded); for lower gastrointestinal bleed 1056 (LGIB), bleeding was required to be in the jejunum, 1057 1058 ileum, colon, or rectum (bleeds due to hemorrhoids or anal fissures were excluded). 1059

Step 1: We identified individuals who had been 1060 confirmed as either an incident case of UGIB (n = 599), 1061 LGIB (n = 143), or a noncase (n = 308) during previous 1062 research projects in The Health Improvement Network 1063 (THIN).^{1–4} 1064

Step 2: Among the remaining potential cases who 1065 could not be cross-linked to previous projects (n = 19201066 in the UGIB follow-up, n = 10,224 in the LGIB follow-up), 1067 we identified those belonging to general practices linked 1068 to Hospital Episode Statistics (n = 657 [34.2%]) in the 1069 UGIB follow-up, 3544 [34.7%] in the LGIB follow-up). 1070 Automated computer searches were performed among 1071 these individuals' HES records for International Classifi-1072 cation of Diseases-Tenth Revision ICD-10 codes for a GI 1073 bleed during the study period and up to 90 days after, 1074 and for all hospitalizations within 90 days before and 1075 after the date of the GI bleed Read code in the THIN. 1076 From this process, we identified 332 confirmed UGIB 1077 cases, 544 confirmed LGIB cases and 213 confirmed 1078 cases of a GI bleed with unspecified site (upper/lower; 1079 all hospitalized). To complete the assignment of the site 1080 of the bleed for this latter group (n = 213), we manually 1081 reviewed their medical records in the THIN, including 1082 free text comments while masked to all medication use. 1083

Step 3: Among all remaining unconfirmed cases, we 1084 identified 10,649 individuals who were identified during 1085 both the UGIB and LGIB follow-ups and removed any 1086 duplicates (eg, those with a Read code for an unspecified 1087 GI bleed on the same date in both follow-ups). After this 1088 process, 9753 individuals remained as unconfirmed 1089 cases of UGIB or LGIB. 1090

Step 4: To assign case status to these 9753 in-1091 dividuals, we looked for indicators such as GI pro-1092 cedures, and specific symptoms entered in the 1093 database within the 90 days before and 30 days after 1094 the recorded date of the GI bleed to imply probable, 1095 nonprobable, or still unknown case status. For 1096 example, Read codes indicative of a probable case 1097 included those for relevant GI antecedent, such as 1098 diverticulosis, while codes suggestive of a nonprobable 1099 case included those for digestive malignancies, hem-1100 orrhoids, and anal fissure. From this process, among 1101 the 9753 potential cases there were 2590 probable 1102

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 po-1106 tential incident cases, the medical records in the THIN 1107 with free text comments (already available from previ-1108 ous research studies) of a subset of 767 individuals (190 1109 deemed probable cases, 185 deemed nonprobable cases, 1110 and 392 deemed remaining cases) were manually 1111 reviewed (masked to all information on medication use) 1112 and their case status ascertained. Among this subset of 1113 767 patients, we calculated the positive and negative 1114 predictive value or specific Read codes and applied these 1115 predictive values to the 8986 potential incident cases not 1116 included in this subset (ie, those without free comments 1117 available in their medical records to review). Negative 1118 predictive values for certain Read codes for rectal 1119 bleeding, rectal hemorrhage, and bleeding per rectum 1120 were >90% among the 185 nonprobable cases and 1121 >84% among the 392 remaining patients manually 1122 reviewed, and thus we searched for these codes among 1123 all nonprobable and remaining patients not included in 1124 the manually reviewed sample and excluded those with 1125 these codes. Positive predictive values of various Read 1126 codes were found to be heterogeneous in value and not 1127 sufficiently high or low to help confirm case status. After 1128 this process, there was still a total of 2400 of 2590 1129 probable cases, and 854 of 5524 'remaining' patients 1130 without an assigned case status; all 1062 nonprobable 1131 cases and 4670 patients in the 'remaining' group not 1132 manually reviewed had an assigned case status (ie, all 1133 were deemed noncases and were discarded owing to 1134 having a high NPV Read code). 1135

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 Crohn 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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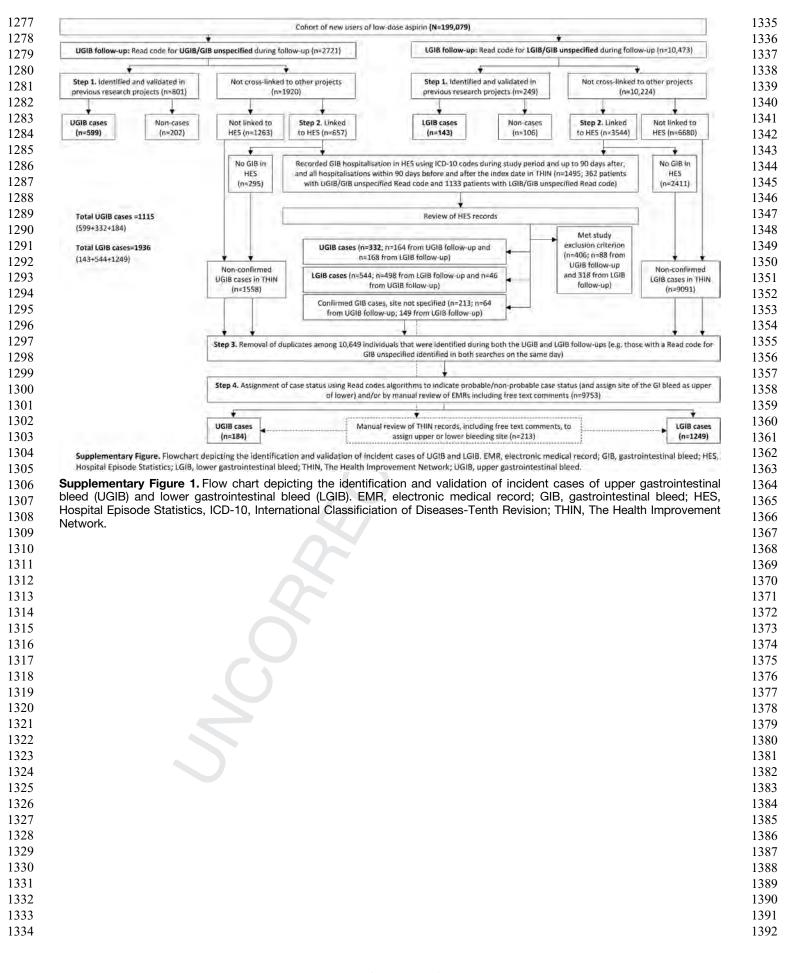
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80–85 y 2.21 (1.87–2.61) 2.52 (2.15–2.94)	

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		Incidence Rate (95% C) per 1000 Person-Years	
	UG	B	LGIB	
Age Group	Hospitalized	Referred Only	Hospitalized	Referred Only
40–64 65–74	0.31 (0.27–0.36) 0.68 (0.60–0.78)	0.31 (0.27–0.36) 0.40 (0.34–0.47)	0.30 (0.26–0.35) 0.50 (0.43–0.58)	1.11 (1.02–1.19) 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)
Cl. confidence interval				
CI, confidence interval	l; LGIB, lower gastrointestinal bleed; U	GIB, upper gastrointestinai bieed.		
Supplementary 1	Table 4. Crude Incidence Rate	s of UGIB and LGIB per 10	00 Person-Years Among Nev	v Users of Low-Dose
		ity and Stratified by Age G		
		Incidence Rate (95% CI)	per 1000 Person-Years	
	UGI	3	LGI	В
Age Group	Fatal ^a	Nonfatal	Fatal ^a	Nonfatal
		0.61 (0.55–0.67)		1.41 (1.32–1.50)
40–64 y 65–74 y	0.014 (0.007–0.027) 0.049 (0.030–0.078)	1.04 (0.93–1.15)	0.012 (0.004-0.031)	1.81 (1.67–1.96)

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