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**The changing face of hospitalization due to gastrointestinal
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The changing face of hospitalization due to gastrointestinal bleeding and perforation

Authors:

Angel Lanás,^{1,2,3} Luis A. García-Rodríguez,⁴ Mónica Polo-Tomás², Marta Ponce^{5,2}, Enrique Quintero,⁶ Maria Angeles Perez-Aisa⁷, Javier P. Gisbert^{8,2} Luis Bujanda^{9,2}, Manuel Castro^{10,2}, Maria Muñoz¹, Dolores Del-Pino¹², Santiago Garcia¹³, Xavier Calvet^{14,2}

Affiliations

¹Servicio de Aparato Digestivo, Hospital Clínico. Universidad de Zaragoza. Spain

² Centro de Investigación Biomédica en Red de enfermedades hepáticas y digestivas (CIBERehd). Spain

³ Instituto Aragonés de Ciencias de la Salud (IACS)

⁴ Centro Español de Investigación Farmacoepidemiológica. Madrid. Spain

⁵Servicio de Aparato Digestivo. Hospital La Fe. Valencia

⁶Servicio de Aparato Digestivo. Hospital Universitario de Canarias. La Laguna. Tenerife. Spain.

⁷. Servicio de Aparato Digestivo. Hospital Costa del Sol. Marbella. Spain.

⁸. Servicio de Aparato Digestivo. Hospital de la Princesa. Madrid. Spain.

⁹ Servicio de Aparato Digestivo. Hospital Donostia Universidad del País Vasco. San Sebastián. Spain.

¹⁰ Servicio de Aparato Digestivo. Hospital de Valme.- Sevilla. Spain.

¹¹. Servicio de Aparato Digestivo. Hospital de Asturias. Oviedo. Spain.

¹². Servicio de Codificación. Hospital Clínico Universitario. Zaragoza. Spain

¹³ Servicio de Aparato Digestivo. Hospital Universitario Miguel Servet. Zaragoza. Spain

¹⁴ Servicio de Aparato Digestivo. Hospital de Sabadell. Barcelona. Spain

Short title: Trends in GI hospitalizations

To whom correspondence should be addressed:

Angel Lanás. Servicio de Aparato Digestivo. Hospital Clínico Universitario. C/ San Juan Bosco 15. 50009 Zaragoza. Spain. Phone: 34 976765786; Fax: 34 976765787).

Email: alanas@unizar.es

Abstract:

Background: Temporal changes in the incidence of cause-specific gastrointestinal (GI) complications may be one of the factors underlying changing medical practice patterns. **Aim:** To report temporal changes in the incidence of five major causes of specific gastrointestinal (GI) complication events. **Methodology:** Population-based study of patients hospitalized due to GI bleeding and perforation from 1996–2005 in Spain. We report crude rates, and estimate regression coefficients of temporal trends, severity, and recorded drug use for 5 frequent GI events. GI hospitalization charts were validated by independent review of large random samples. **Results:** The incidence per 100,000 person-years of hospitalizations due to upper GI ulcer bleeding and perforation decreased over time (from 54.6 and 3.9 in 1996 [$R^2=0.944$] to 25.8 and 2.9 in 2005 [$R^2=0.410$], respectively). On the contrary, the incidence per 100,000 person-years of colonic diverticular and angiodysplasia bleeding increased over time (3.3 and 0.9 in 1996 [$R^2=0.443$] and 8.0 and 2.6 in 2005 [$R^2=0.715$], respectively). A small increasing trend was observed for the incidence per 100,000 person-years of intestinal perforations (from 1.5 to 2.3 events). Based on data extracted from the validation process, recent recorded drug intake showed an increased frequency of anticoagulants with colonic diverticular and angiodysplasia bleeding, whereas NSAID and low-dose aspirin use were more prevalent in peptic ulcer bleeding and colonic diverticular bleeding respectively. **Conclusions:** From 1996–2005, hospitalizations due to peptic ulcer bleeding and perforation have decreased significantly, whereas the number of cases of colonic diverticular and angiodysplasia bleeding have increased.

Key words: peptic ulcer, bleeding, perforation, angiodysplasia, diverticulum

Background

Gastrointestinal (GI) complications are major causes of hospitalization. Major therapeutic advances in the treatment and prevention of peptic ulcer diseases have been implemented in the past decade, which should contribute to a significant decrease in the incidence and mortality due to peptic ulcer diseases. Opposing trends in peptic ulcer complications such as bleeding or perforation have been reported in different countries, and no decrease or increase in hospitalizations due to peptic ulcer bleeding complications have been observed (1-6). More recently, two studies from different geographical areas suggested that there has been a marked decrease in the incidence of upper GI complications and a slight increase in the incidence of lower GI complications (7,8); however, the specific lesions leading to these changes have not been analyzed. Furthermore, the time trends for bleeding and perforation may not be parallel, since the underlying pathogenic mechanisms and risk factors could diverge (9,10). Additionally, the exact source of lower GI complications are often more difficult to identify than upper GI complications because of the anatomic complexity of the lower gut and available diagnostic tests. Among the causes of lower GI bleeding, colonic diverticuli and angiodysplasia are two lesions which could explain, at least in part, the recent trends, since age was found to be one of the main risk factors for hospitalizations (7). However, the time trends and clinical characteristics of hospitalizations owing to these two lesions have not been reported.

Prevention strategies and optimization of hospital resources require a clear understanding of the type of pathology causing hospitalization. In a previous report, we presented the overall time trends of hospitalizations due to GI complications, (7) which were obtained from a data-base including information provided by 10 Spanish general hospitals representative of the entire country (11). Now, as part of the pre-specified analysis plan, we aim to characterize and analyze in detail the time trends for hospitalizations due to five specific major causes of GI complications; namely, peptic ulcer bleeding, peptic ulcer perforation, intestinal perforation, colonic diverticular bleeding, and bleeding caused by angiodysplasia. We believe that these data are needed since, as discussed above, the available literature for some of these causes and

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3 the comparative trends among them are sparse or absent. Additionally, we also
4 describe the severity characteristics and recorded drug use for each of these
5 entities.
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10 **Methods:**

13 **Setting and data collection**

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15 The study (7) was approved by the Institutional Review Board of Aragón
16 and was carried out in 10 Spanish general hospitals distributed across the
17 entire country, serving a population of 3,281,973 people in 1996 and 3,681,822
18 in 2005. Based on previous reports (11), the population covered by these
19 hospitals was representative of the whole country, where the majority (80%) of
20 the population uses the Spanish NHS, which provides open access free-to-all
21 healthcare services including hospitals, drugs, and diagnostic and therapeutic
22 procedures.
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30 The methodology of data collection was described in our first report of
31 this study (7). Each hospital provided data from January 1, 1996 to December
32 31, 2005 on patients identified with a primary discharge diagnosis, coded
33 according to the International Classification of Diseases (9th revision, Clinical
34 Modification [ICD9]), for the 5 specific diagnoses investigated in this study (1).
35 The codes used were as follows: (1) upper GI Bleeding, gastric ulcer with
36 bleeding, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, and 531.61;
37 duodenal ulcer with bleeding, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41,
38 532.60, and 532.61; peptic ulcer with bleeding, 533.00, 533.01, 533.21, 533.40,
39 533.41, 533.60, and 533.61; gastrojejunal ulcer with bleeding, 534.00, 534.01,
40 534.20, 534.21, 534.40, 534.41, 534.60, and 534.61; gastric ulcer with
41 perforation, 531.10, 531.11, 531.20, 531.21, 531.50, 531.51, 531.60, and
42 531.61. For (2) upper GI perforation, duodenal ulcer with perforation, codes
43 532.10, 532.11, 532.20, 532.21, 532.50, 532.51, 532.60, and 532.61; peptic
44 ulcer with perforation, 533.10, 533.11, 533.21, 533.50, 533.51, 533.60, and
45 533.61; gastrojejunal ulcer with perforation, 534.10, 534.11, 534.20, 534.21,
46 534.50, 534.51, 534.60, and 534.61; and for (3) GI perforation, intestinal
47 perforation, 569.83; and for (4) diverticuli, diverticulosis with bleeding, 562.02
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3 and 562.12; diverticulitis with bleeding, 562.03 and 562.13; and finally, for (5)
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and 562.12; diverticulitis with bleeding, 562.03 and 562.13; and finally, for (5) angiodyplasia, 569.85.

The primary discharge diagnosis was considered to be the cause leading to hospitalization based on the clinical judgment of the physician who managed the patient. In this way, each hospitalization event is unequivocally classified according to the main diagnosis together with other variables (7). We only included bleeding or perforation events that occurred in the community and excluded those that developed after hospitalization, since they probably represent a group different from our target population. The type and number of variables provided by each hospital were the same and were introduced in a common database specifically designed for this study.

Validation process

In brief and as described previously (7), we validated around 10% of events with specific codes. However, since there was no experience or previous report on the accuracy of some undefined events from the lower GI tract codes, we undertook a more extensive validation process for intestinal perforation to study the exact location of the perforation event (e.g. small vs. large bowel). The selection of episodes available in each centre was carried out using the "SAMPLE" procedure available in the SPSS program (SPSS, Chicago, IL USA). This information was introduced into a second database along with other variables which included the original diagnosis code (ICD9) undergoing validation and the final diagnosis after the validation process. Data were coded anonymously. The process of validating the codes and chart review was carried out by gastroenterologists or trained GI residents with experience in these types of studies (7,11). These investigators ensure the appropriate interpretation of data and tests carried out during the hospitalization event. In addition to validation of the diagnostic codes, this process allowed us to collect additional information including death outcome, number of days of hospitalizations, number of comorbidities, lowest Hb level detected, number of units of blood transfusions, and recorded drug use. The severity and burden of the events for this report were based on the following variables: (a) death rate, (b) days of

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3 hospitalization, (c) number of diagnostic procedures, (d) weight of **diagnosis-**
4 **related groups** (DRG), (e) number of comorbidities, (f) lowest Hb level recorded
5 during hospitalization, and (g) number of blood units transfused as described
6 elsewhere (12).
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12 We considered only recent use of drugs when they were taken by
13 patients within 7 days before the date of hospitalization. The data entry was
14 carried out by **staff** trained and experienced in managing databases, which was
15 designed to minimize the data entry errors. One in five questionnaires was
16 completely checked, and virtually no data entry errors were found.
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22 **Management and analysis of data**

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26 The data obtained from each hospital was entered in the two databases; one
27 included the information gathered from the Minimum Basic Data Set (MBDS)
28 and the other contained the information collected **during** the validation process.
29 Time trends were reported based on the first database (MBDS), whereas data
30 reported for severity of events and drug use was based on the database
31 obtained from the validation and chart review process. A data analysis plan
32 was pre-determined in advance for each database. Estimates of the actual
33 frequencies were based on the validation process. Outcome variables are
34 reported as rates, mean (SD), and 95% **confidence interval** (CI) depending on
35 the type of variable. Rates were calculated overall, by year, and by source of
36 the event. We estimated both crude and age- and sex-adjusted incidence rates
37 with 95% CI **for the** five GI events. However, since the number of events was
38 not large enough in 4 of the 5 codes to provide accurate age- and sex-adjusted
39 rates, we report only crude rates. Wherever it may apply, data from different
40 years (mean \pm SD) were analyzed by one-way **analysis of** variance followed by
41 unpaired Student's t-test. **Additionally**, we estimated regression coefficients of
42 the incidence trend line from 1996 to 2005 with the ordinary least squares
43 method. Categorical data were analyzed by Chi-square, and logistic regression
44 analysis was performed to estimate the effect of a number of risk factors
45 comparing upper versus lower GI events. **Because of** the multiple comparisons
46 made for some of the analyses, values were considered statistically significant
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3 when p-values were < 0.01. All statistics were carried out with Excel (Microsoft
4 Office 2000), SPSS (Chicago, IL USA), and STATA (StataCorp, 2005, TX USA).
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10 Results

11 Time trends of events

12 Data obtained from the database collecting the MBDS information
13 provided by the participant hospitals showed a statistically significant decrease
14 in the incidence rate of peptic ulcer bleeding as well as ulcer perforation from
15 1996 to 2005 (Figures 1 and 2). These decreasing trends were seen for both
16 gastric and duodenal ulcer bleeding and perforations (data not shown). On the
17 contrary, the trends for both colonic diverticular and bleeding due to colonic
18 angiodysplasia showed a statistically significant increase over the same time
19 period (Figures 1 and 2). Intestinal (lower GI) perforations showed a non-
20 significant increase over the same time period. Validation of codes showed >
21 90% accuracy for the 5 GI complications (Table 1). Incidence rates were
22 adjusted according to the confirmation obtained with the manual chart review.
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33 Based on the validation process of the 5 diagnostic codes identified in
34 2082 cases, 53.7% of intestinal perforations were located in the large bowel and
35 39% in the small bowel, whereas the remaining 7.2% were ascribed to the lower
36 GI tract without further site specification. Validation of codes for peptic ulcer
37 perforation showed that 6.5% of cases were indeed intestinal perforations.
38 Among cases coded as diverticular bleeding, the validation process showed
39 that 1% of cases were actually upper GI bleeding events, and another 1% were
40 unconfirmed events. Among those with angiodysplasia, 2.9% were upper GI
41 bleeding events and in 1.4% of cases the source could not be ascribed to any
42 cause. Finally, among peptic ulcer bleeds, only 1.5% were lower GI bleeding
43 events and in 0.3% of cases the source could not be identified.
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53 The age and gender distribution was markedly different across the 5
54 causes of hospitalization (Table 2). Patients with bleeding from the colonic
55 diverticuli or angiodysplasia were older than those with other causes for
56 hospitalization, whereas males were predominant among those with peptic ulcer
57 perforation and bleeding. Very similar results were found in the validation
58 random sample (data not shown).
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3 Overall, **the** case fatality rates were higher for perforation than for
4 bleeding events (intestinal perforation > peptic ulcer perforation > bleeding
5 angiodysplasia > peptic ulcer bleeding > diverticular bleeding). Overall mortality
6 trends did not change over time during the period studied for intestinal or peptic
7 ulcer perforation or angiodysplasia or diverticular bleeding (**specific information**
8 **concerning these mortality trends can be seen on-line in “Supporting**
9 **Information Table 1”).**

18 19 **Severity of events and drug use**

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22 The review of charts provided an opportunity to collect a number of
23 variables **that** described the severity of the different types of events. The case
24 fatality rate was similar to that reported above in the overall sample. **The** length
25 of hospitalization **was longer** in patients with perforation than **for** those with
26 bleeding events, and **the** weight of DRG (an indirect measure of **hospitalization**
27 costs for each type of event) was higher **for** complications in the lower GI tract
28 when compared **with** those from the upper GI tract. The number of co-
29 morbidities was greater in patients with colonic diverticular bleeding and
30 angiodysplasia bleeding compared **with** the other type of lesions studied. As
31 expected, hemoglobin **decline** and **the** number of blood units transfused were
32 higher in patients with bleeding events than in those with perforations (**specific**
33 **information concerning the severity of events based on chart validation can be**
34 **seen on-line in “Supporting Information Table 2”).**

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37 **Detailed** recorded drug use concerning nonsteroidal anti-inflammatory
38 drugs (NSAIDs), proton pump inhibitors (PPI), and anti-platelet agents **can be**
39 **seen on-line in “Supporting Information Table 3”).** Peptic ulcer and diverticular
40 colonic bleeding had the highest NSAID/aspirin drug use compared **with** cases
41 of perforation and even bleeding from GI angiodysplasia. PPI use was more
42 frequently recorded in patients **with colonic and angiodysplasia** bleeding events.
43 **Recorded anticoagulant** use was high in patients with diverticular bleeding and
44 in patients with angiodysplasia.

Discussion

This study shows that hospitalizations due to both peptic ulcer bleeding and perforations progressively and importantly decreased from 1996 to 2005. These trends were not observed for other types of bleeding or perforation events from the lower GI tract. In fact, we found that the incidences of colonic diverticular bleeding or angiodysplasia are increasing, whereas the rate of intestinal perforation remains virtually stable with a slight increase over the study period.

There is wide agreement that hospitalizations due to uncomplicated peptic ulcer are decreasing over time (1,2), but there were discrepancies between hospitalizations on rates due to complicated peptic ulcers. Our results agree with data from Sweden (14,15) and the USA (8) showing that hospitalizations due to peptic ulcer bleeding are decreasing. However, these data are not in agreement with reports from other European countries (3, 4, 5, 6,16), which show either no decrease or even an increase in hospitalizations for this type of event. The reasons for these discrepancies are unclear, since a decrease of *H. pylori* infection among the population, increasing *H. pylori* eradication therapy, and increasing PPI use across Europe should be accompanied by a progressive decrease in peptic ulcer complications (14, 15, 17). The variability in the use of low-dose aspirin (ASA) and gastro-protective treatments between countries may partly explain these differences (18,19), but our study and those reporting decreasing peptic ulcer bleeding rates collected data from more recent years and were population-based (7, 8).

Our data also show very low rates of mortality due to peptic ulcer bleeding, which is consistent with other studies (8, 14, 15). The lack of improvement in case fatality rates is usually linked to a progressively aging population with increasing numbers of co-morbidities, despite data that show better bleeding management strategies associated with reduction in the risk of rebleeding and a reduced need for surgery (20). In any case, our data agree with a recent USA report (8) that shows an overall decrease (absolute numbers)

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3 in in-hospital deaths linked to GI bleeding diagnoses between 1998 and 2006,
4 owing to a decrease in the number of hospitalizations.
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9 Time trends on peptic ulcer perforation are rarely reported and those
10 available show no change or small changes overtime (9, 10, 21). Here we
11 report a clearly decreasing trend (~ 50%) in peptic ulcer perforation from 1996
12 to 2005, which is consistent with a decrease in the overall incidence of peptic
13 ulcer and peptic ulcer complications. The decrease in incidence of
14 hospitalizations owing to peptic ulcer perforation was not associated with a
15 decrease in case fatality rates over this time.
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23 Other studies have reported time trends for peptic ulcer bleeding or
24 perforation, but not other sources of GI bleeding or perforation. In our first
25 overall report of this study (7), we pointed out that the ratio of hospitalizations
26 for upper vs. lower GI complications has changed from a 4:1 to 1.4:1. Here we
27 report that two common reasons for hospitalizations, colonic diverticular and
28 angiodysplasia bleeding, are more frequent today than 10 years ago. A
29 progressively aging population and the increasing use of NSAIDs and low-dose
30 ASA may explain, at least in part, these results. (22). PPI use was more
31 frequently recorded in patients hospitalized with diverticular bleeding and
32 bleeding due to angiodysplasia than in those with peptic ulcer bleeding. This
33 could support the concept that PPI use is associated with the prevention of
34 upper GI but not lower GI complications, but age and its accompanying greater
35 number of co-morbidities could also explain the observed higher prevalence of
36 PPI use. Eventually, it must be noted that anticoagulant use, a growing clinical
37 practice, is especially associated with bleeding events and overall with
38 diverticular and angiodysplasia bleeding.
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53 Trends on intestinal perforation are rarely reported. Here we report
54 overall intestinal (small and large bowel) perforation rates and found that these
55 rates remained stable over time, although with a numerical tendency to increase
56 in agreement with the data reported from the UK on diverticular perforation (23).
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3 Our study has strengths and limitations. A strength is that we carried out
4 an extensive validation of events. This is especially important for intestinal
5 perforation, and diverticular and bleeding from angiodysplasia lesions. Contrary
6 to peptic ulcer bleeding and perforation, these have rarely been reported in the
7 literature. Therefore, these ICD-9 codes have rarely been validated in
8 observational studies. This is of major importance since the diagnostic process
9 of diseases from the lower GI tract is more complex than those used in the
10 upper GI tract.
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19 The study also has limitations. First, undefined codes such as “GI
20 bleeding” may include patients with both peptic ulcer bleeding and bleeding
21 from diverticular disease and angiodysplasia lesions. This means that the
22 reported incidence and trends reflect minimum rates, since it is possible that a
23 proportion of patients with the events studied here may not be counted because
24 of misclassification under undefined codes. In our previous report, we observed
25 that this proportion was constant over time (7). Another limitation refers to data
26 on drug use, which relies on data recorded in charts and are subject to reporting
27 bias in the clinical history. Ascertainment of NSAID, ASA, and PPI use may be
28 more frequently searched in patients with peptic ulcer complications than in
29 diverticular or angiodysplasia bleeding events. Finally, our mortality rates refer
30 to in-hospital mortality, as we could not provide 30-day mortality, since most
31 patients were discharged from hospital before this window of time.
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44 In summary, our study shows that, over the past decade, there has been
45 a significant decrease in hospitalization rates for peptic ulcer bleeding and
46 perforation, but an increase for colonic diverticular and angiodysplasia bleeding,
47 with virtually no change in intestinal perforation. These data show a clear
48 change in the incidence of hospitalizations due to GI complications over time,
49 with upper GI events decreasing and lower GI events increasing. Since the
50 severity of these events are very different, these data should be of interest for
51 improving clinical practice in terms of preventive strategies and to better
52 address the increasing prevalence of lower GI events, specifically the increase
53 in colonic diverticular and angiodysplasia bleeding.
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Table 1: Accuracy of codes for the final diagnosis after validation of clinical history for five major causes of specific gastrointestinal complication events.

Recorded discharge diagnosis code before validation	Number of patients	Cases validated n (%)	Actual diagnosis after validation n (%)
Peptic ulcer Bleeding	13616	1241 (9.1%)	1218 (98.1%) = peptic ulcer bleeding 23 (1.8%) = Other
Peptic Ulcer Perforation	1655	138 (8.3%)	129 (93.5%) = peptic ulcer perforation 9 (6.5%) = Other
Diverticulosis or Diverticulitis with bleeding	2130	193 (9.1%)	189 (97.9%) = colonic diverticular bleeding 4 (2%) = Other
Angiodysplasia Bleeding	597	69 (11.6%)	66 (95.7%) = intestinal (lower GI) angiodysplasia 3 (4.3%) = Other
Intestinal perforation	759	441 (58.1%)	422 (95.7%) = intestinal perforation 26 (5.9%) = Other
Total (5 causes)	18757	2082 (11.1%)	2024 (97.2%) = Accurate 58 (2.85%) = Other

Table 2: Age and gender distribution by lesion type.

a)

	n	Age (Mean, SD)	Male Gender (n, %)
Peptic ulcer bleeding	13616	63.50 (16.7)	9615 (70.6%)
Peptic ulcer perforation	1655	55.13 (19.1)	1050 (69.5%)
Diverticulosis or Diverticulitis with bleeding	2130	75.91 (10.2)	950 (44.6%)
Angiodysplasia Bleeding	597	73.32 (11.6)	333 (55.9%)
Intestinal perforation	759	63.37 (18.6)	414 (54.5%)

Mean comparison among categories: p-value < 0.001

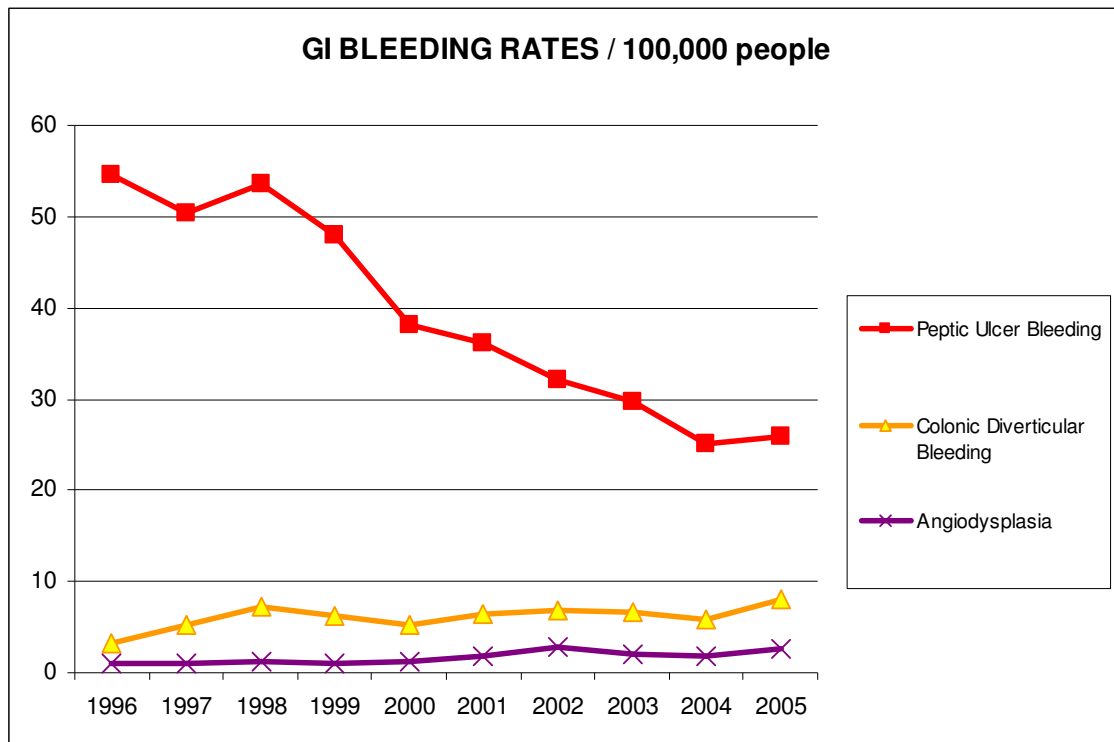
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Figure Legends

Figure 1: Estimated number of peptic ulcer, colonic diverticular, and angiodysplasia bleeding events per 100,000 person-years based on the adjudication of events in the validation process. Regression coefficients of temporal trends were: $R^2 = 0.944$ ($p < 0.0001$) for peptic ulcer bleeding rates; $R^2 = 0.443$ ($p = 0.03$) for colonic diverticular bleeding rates; $R^2 = 0.715$ ($p = 0.002$) for angiodysplasia bleeding rates.

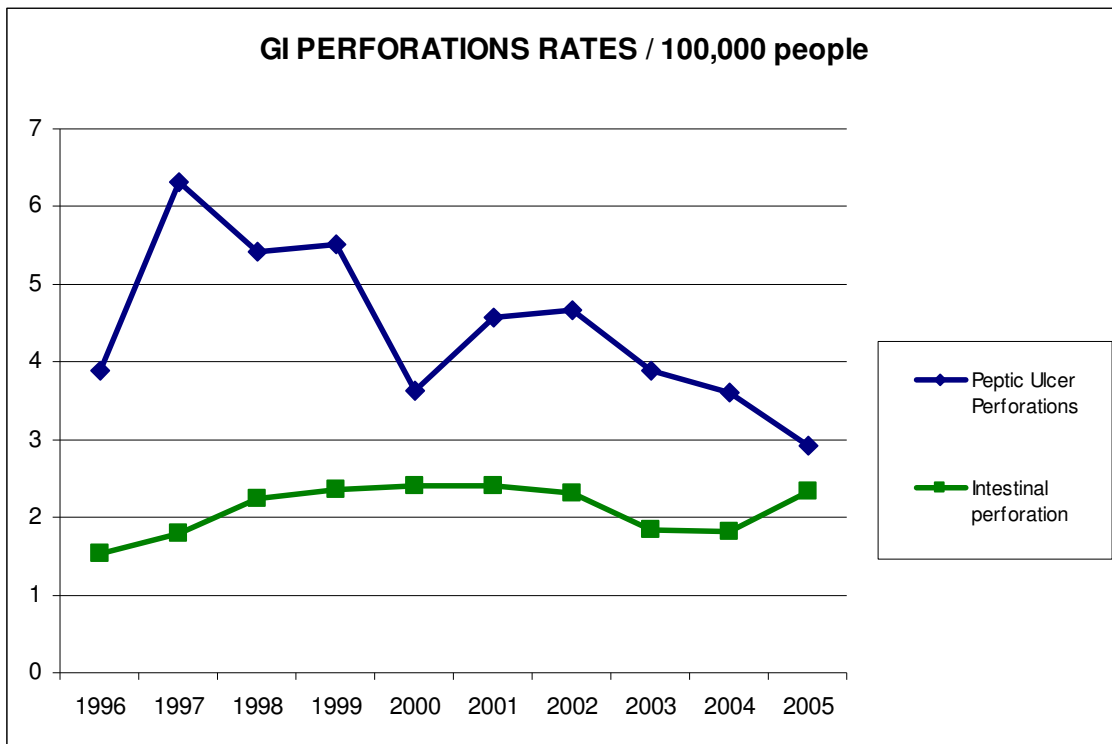
Figure 2: Estimated number of perforations per 100,000 person-years based on the adjudication of events in the validation process. Regression coefficients of temporal trends were: $R^2 = 0.410$ ($p = 0.04$) for peptic ulcer perforation; $R^2 = 0.091$ ($p = 0.395$) for intestinal perforation rates.

Figure 1:



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Figure 2:



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Statements of interest:

Acknowledgements: The study was supported by Pfizer Inc. Pfizer had no role in the conduct of the study, **or the** analysis or interpretation of the data.

Information concerning the role of authors in the study

Dr. Lanás and Dr Garcia Rodriguez designed the study. Dr. Lanás drafted the manuscript with major contributions from Mónica Polo-Tomás and Dr Luis Garcia Rodriguez. All the authors contributed to the collection of data and had full access to the raw data set **from** the study, the results, the manuscript, and made their own comments and contributions. Dr. Dolores Del-Pino designed the data extraction process for the ICD-9 codes. Mónica Polo-Tomás introduced the data in the database and, with Luis Alberto Garcia Rodriguez and Dr Lanás, checked the quality of the data base. Mónica Polo-Tomás produced the outputs and **ran the statistical analysis** with Dr. Garcia Rodriguez. Dr. Lanás acted as guarantor of the submission.

Conflict of interest:

Angel Lanás is member of the adjudication Committee of the international multicenter CONDOR trial, sponsored by Pfizer, and has received honoraria for lecturing at Pfizer- and AstraZeneca-sponsored symposiums.

Xavier Calvet has received honoraria for participating in advisory boards and for lecturing at AstraZeneca-sponsored **symposiums**. Javier P. Gisbert has received honoraria for lecturing at AstraZeneca- and Pfizer-sponsored symposiums. Luis Bujanda has received small honoraria for lecturing at Pfizer-**sponsored** symposiums.

The other **study** authors have no conflicts of interest **to report**.

Supporting Information Table 1: Time trends of case fatality by lesion type (n =18757). No statistical differences were found for any of the 5 types of lesions over time.

Mortality		Year										Total
		1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	
Peptic Ulcer Bleeding	n	46	59	57	53	41	29	45	40	39	18	427/13616
	%	2.5	3.5	3.2	3.2	3.1	2.2	4.0	3.7	4.2	1.9	3.1
Peptic ulcer perforation	n	19	19	16	21	21	16	17	15	10	10	164/1655
	%	9.5	8.2	8.9	11.4	13.5	10.0	10.3	10.6	7.6	9.2	9.9
Diverticular Bleeding	n	0	3	6	5	5	6	5	4	5	4	43/2130
	%	.0	1.8	2.5	2.5	2.8	2.7	2.1	1.6	2.3	1.3	2.0
Angiodysplasia Bleeding	n	2	2	1	4	2	3	9	1	2	4	30/597
	%	6.7	5.7	2.4	11.1	4.5	4.6	9.1	1.3	2.8	4.0	5.0
Intestinal perforation	n	11	22	29	24	28	24	22	20	22	30	232/759
	%	21.2	36.1	36.3	30.8	30.1	28.2	25.9	30.3	31.0	34.1	30.6

Supporting Information Table 2. Severity of events using several measures, by type of lesion based on the chart validation.

Lesion	N		Mortality	Hospital Stay (days)	Number of diagnostic tests performed	DRG Weight	Number of Comorbidities	Lowest Hemoglobin level	Blood units transfused
Peptic Ulcer Bleeding	1218	Mean (%)	1.69	6.93	1.04	1.13	1.55	9.18	1.51
		95% CI	[0.96, 2.43]	[6.54, 7.32]	[1.03, 1.06]	[1.09, 1.18]	[1.50, 1.60]	[9.05, 9.30]	[1.40, 1.63]
Peptic Ulcer Perforation	129	Mean (%)	4.40	11.56	1.20	3.06	1.40	12.25	1.16
		95% CI	[0.10, 8.69]	[8.74, 14.38]	[1.04, 1.36]	[2.52, 3.61]	[1.23, 1.56]	[11.65, 12.85]	[0.25, 2.08]
Diverticular Bleeding	189	Mean (%)	2.84	9.34	1.31	1.28	2.07	10.14	1.28
		95% CI	[0.36, 5.32]	[8.32, 10.36]	[1.20, 1.41]	[1.15, 1.41]	[1.92, 2.22]	[9.76, 10.53]	[0.95, 1.61]
Angiodysplasia	66	Mean (%)	1.56	8.84	1.34	1.17	2.70	8.31	2.02
		95% CI	[0, 4.68]	[6.58, 11.10]	[1.04, 1.64]	[1.06, 1.29]	[2.41, 3.00]	[7.78, 8.85]	[1.54, 2.50]
Intestinal perforation	422	Mean (%)	28.66	21.78	0.99	4.04	1.85	10.96	0.91
		95% CI	[23.58, 33.75]	[19.21, 24.35]	[0.92, 1.05]	[3.64, 4.43]	[1.73, 1.97]	[10.66, 11.27]	[0.59, 1.24]

Comparisons among categories:

- Mortality:
 - Intestinal perforation vs. Any other lesion: $p < 0.001$
 - Peptic Ulcer Bleeding vs. Peptic Ulcer Perforation: $p = 0.363$ (NS)
- Hospital stay: Peptic Ulcer Bleeding vs. Peptic Ulcer Perforation: $p < 0.001$
- Number of diagnostic tests performed:
 - Angiodysplasia vs. Peptic Ulcer Bleeding: $p < 0.001$
 - Angiodysplasia vs. Peptic Ulcer Perforation: $p = 0.019$ (NS)
 - Angiodysplasia vs. Diverticular Bleeding: $p = 0.905$ (NS)
 - Angiodysplasia vs. Intestinal perforation: $p < 0.001$
 - Diverticular Bleeding vs. Peptic Ulcer Bleeding: $p < 0.001$
 - Diverticular Bleeding vs. Peptic Ulcer Perforation: $p = 0.012$ (NS)
 - Diverticular Bleeding vs. Intestinal perforation: $p < 0.001$
- Number of Comorbidities:

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- Angiodysplasia vs. Any other lesion: $p < 0.001$
 - Diverticular Bleeding vs. Any other lesion: $p < 0.001$
 - Lowest Hemoglobin level:
 - Angiodysplasia vs. Peptic Ulcer Bleeding: $p = 0.012$ (NS)
 - Angiodysplasia vs. Peptic Ulcer Perforation: $p < 0.001$
 - Angiodysplasia vs. Diverticular Bleeding: $p < 0.001$
 - Angiodysplasia vs. Intestinal perforation: $p < 0.001$
 - Peptic Ulcer Bleeding vs. Peptic Ulcer Perforation: $p < 0.001$
 - Blood units transfused:
 - Angiodysplasia vs. Peptic Ulcer Bleeding: $p = 0.226$ (NS)
 - Angiodysplasia vs. Peptic Ulcer Perforation: $p = 0.035$
 - Angiodysplasia vs. Diverticular Bleeding: $p = 0.087$ (NS)
 - Angiodysplasia vs. Intestinal perforation: $p = 0.002$
 - Peptic Ulcer Bleeding vs. Peptic Ulcer Perforation: $p = 0.252$ (NS)

Supporting Information Table 3: NSAID, Low-Dose Aspirin, PPI use recorded in the charts by lesion type

Recorded Drug Use		Cause					Total (N=2024)
		Peptic Ulcer Bleeding (N=1218)	Peptic Ulcer Perforation (N=129)	Diverticular Bleeding (N=189)	Angiodysplasia (N=66)	Intestinal perforation (N=422)	
Any NSAID or Low- ASA	n	533	22	65	15	40	675
	%	44.2%	17.1%	34.4%	22.7%	9.5%	33.5%
NSAID	n	371	20	28	11	12	442
	%	30.7%	15.5%	14.8%	16.7%	2.8%	22.0%
LOW DOSE ASA	n	191	3	41	4	28	267
	%	15.8%	2.3%	21.7%	6.1%	6.6%	13.3%
PPI	n	92	7	48	19	30	196
	%	7.6%	5.4%	25.4%	28.8%	7.1%	9.7%
NSAID + PPI	n	27	1	7	5	2	42
	%	2.2%	0.8%	3.7%	7.6%	0.5%	2.1%
Low-Dose ASA + PPI	n	20	0	14	2	11	47
	%	1.7%	0.0%	7.4%	3.0%	2.6%	2.3%
Anticoagulant	n	69	1	27	18	15	130
	%	5.7%	0.8%	14.3%	27.3%	3.6%	6.5%

* p-value < 0.001 among categories

- Any NSAID or Low- ASA:
 - Peptic Ulcer Bleeding vs. Peptic Ulcer Perforation: $p < 0.001$
 - Peptic Ulcer Bleeding vs. Diverticular Bleeding: $p = 0.022$ (NS)
 - Peptic Ulcer Bleeding vs. Angiodysplasia: $p = 0.001$

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- Peptic Ulcer Bleeding vs. Intestinal perforation: $p < 0.001$
 - NSAID:
 - Peptic Ulcer Bleeding vs. Peptic Ulcer Perforation: $p < 0.001$
 - Peptic Ulcer Bleeding vs. Diverticular Bleeding: $p < 0.001$
 - Peptic Ulcer Bleeding vs. Angiodysplasia: $p = 0.021$ (NS)
 - Peptic Ulcer Bleeding vs. Intestinal perforation: $p < 0.001$
 - Low- ASA:
 - Diverticular Bleeding vs. Peptic Ulcer Bleeding: $p = 0.080$ (NS)
 - Diverticular Bleeding vs. Peptic Ulcer Perforation: $p < 0.001$
 - Diverticular Bleeding vs. Angiodysplasia: $p = 0.004$
 - Diverticular Bleeding vs. Intestinal perforation: $p < 0.001$
 - PPI:
 - Diverticular Bleeding vs. Peptic Ulcer Bleeding: $p < 0.001$
 - Diverticular Bleeding vs. Peptic Ulcer Perforation: $p < 0.001$
 - Diverticular Bleeding vs. Angiodysplasia: $p = 0.813$ (NS)
 - Diverticular Bleeding vs. Intestinal perforation: $p < 0.001$
 - NSAID + PPI:
 - Angiodysplasia vs. Peptic Ulcer Bleeding: $p = 0.008$
 - Angiodysplasia vs. Peptic Ulcer Perforation: $p = 0.005$
 - Angiodysplasia vs. Diverticular Bleeding: $p = 0.128$ (NS)
 - Angiodysplasia vs. Intestinal perforation: $p = 0.001$
 - Low- ASA + PPI:
 - Diverticular Bleeding vs. Peptic Ulcer Bleeding: $p < 0.001$
 - Diverticular Bleeding vs. Peptic Ulcer Perforation: $p < 0.001$
 - Diverticular Bleeding vs. Angiodysplasia: $p = 0.127$ (NS)
 - Diverticular Bleeding vs. Intestinal perforation: $p = 0.001$
 - Anticoagulants

- Peptic Ulcer Bleeding vs. Peptic Ulcer Perforation: $p = 0.103$ (NS)
- Peptic Ulcer Bleeding vs. Diverticular Bleeding: $p < 0.001$
- Peptic Ulcer Bleeding vs. Angiodysplasia: $p < 0.001$
- Peptic Ulcer Bleeding vs. Intestinal perforation: $p = 0.376$ (NS)

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Reply to comments from the Editor and Referees

1. EDITOR'S COMMENTS TO AUTHOR:

a) *Please can you work on the standard of English - it is sub-optimal.*

Reply: The manuscript was submitted to a professional English medical editing service for correction and revision of the English language (www.sanfranciscoedit.com).

b) *Please would you make Table 3 to be Supporting Information Table 1, and label the two duplicate Tables 4 & 5 as Supporting Information Tables 2 and 3. [Supporting Information is available to readers on-line. The important / significant results should be mentioned in the text, and the supporting information referred to in the text. This is explained in the Author Guidelines at www.APandT.org or at <http://authorservices.wiley.com/bauthor/suppmat.asp>].*

Reply: We made this change and incorporated the main data from Tables 3, 4, and 5 into the text. These Tables have been converted to Supporting Information Tables 1, 2 and 3.

c) *Can you really look at your paper, and make it clear what's new - in addition to your already well-cited earlier paper?*

Reply: We reworked the introduction and discussion to clarify what it is new in this manuscript. Below is the list of the new information provided:

- a) time trends for hospitalizations due to peptic (gastric and duodenal) ulcer bleeding and its contrast with peptic ulcer perforation
- b) time trends for intestinal perforation
- c) time trends for colonic diverticular bleeding
- d) time trends for bleeding due to angiodysplasia
- e) mortality rates of these events
- f) description of severity characteristics of these lesions
- g) recorded drug use for each of these entities. We outlined the association between anticoagulant use with both diverticular bleeding and angiodysplasia, which we believe is of utmost importance.

Reviewer: 1

We thank referee 1 for saying that we adequately addressed the prior comments. Concerning the new comments:

a) *Abstract*

The aim does not make sense: "To report temporal changes in the incidence of five major cause-specific gastrointestinal (GI) bleeding and perforation." Do the authors mean the incidence of five major cause-specific gastrointestinal (GI) events?

Reply: We revised the sentence accordingly.

Introduction

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3 1. The first sentence is vague, and could mean anything: "Gastrointestinal complications are
4 major causes of GI hospitalization." In any case, they need to make it clear that GI is an
5 abbreviation of gastrointestinal in this sentence.
6

7 **Reply:** We revised the sentence accordingly, and defined the abbreviation. We believe the
8 sentence specifies a clear and important fact, which is essential to our paper.
9

10 2. The statement on two occasions in the Introduction that "...no cause specific analyses were
11 performed" as part of their previous study (reference 7), and that "...trends for the specific
12 cause of lower GI complications were not reported" as part of their previous study again leaves
13 me with the feeling that this is a post hoc analysis of data in an attempt to obtain another
14 publication from the same piece of work. Why weren't these analyses performed in the prior
15 publication if, as the authors presumably believe, this is important information?
16
17

18 **Reply:** We now make clear that this piece of information was not reported. As we responded to
19 the editor, the data presented are new and it well know that databases with extensive data can
20 provide important information that cannot always be included in a single publication.
21

22 *Methods*

23
24 1. Page 6, line 42/43. I think the authors mean that "...gastroenterologists or trained GI
25 residents with experience of these types of studies." rather than "...on this type of studies."
26

27 2. Page 6, line 56/57. There is now no mention whatsoever of what DRG is an abbreviation of.
28 This needs to be added.
29

30 **Reply:** We changed the text in accordance with these suggestions.
31

32 *Results*

33
34 1. Page 8, lines 7 to 10 don't make sense: "...information provided by the participant hospitals
35 showed and statistically significant decrease..." The authors mean "...a statistically
36 significant..."
37

38 2. Page 9, lines 19/20: "...length of hospitalization were higher..." should be "...was higher..."
39

40 3. Page 9, lines 24/25: "...from the lower GI tract when compared those..." should be "...when
41 compared with those..."
42

43 **Reply:** The text was corrected by a professional editing service to improve the readability of the
44 manuscript.
45

46 *Discussion*

47
48 The authors state on page 11, lines 8 to 11 that: "Time trends on peptic ulcer perforation are rarely
49 reported and those available show no change or small changes overtime." They reference their previous
50 study here. This makes it seem as though the results of the current study are at odds with those of the
51 previous study, yet how can this be the case, as they are derived from the same dataset?!

52 **Reply:** The referee is right. We included this reference because it reported overall trends, but
53 clearly it should not be there. We have removed reference 7.
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55 *Reviewer: 2*

56 *Comments for Transmission to the Authors*

57 *None*
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3 **Reply:** We thank reviewer 2 for being comfortable with our previous reply.
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