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**Mortality from peptic ulcer bleeding: impact of co-morbidity
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Mortality from peptic ulcer bleeding: impact of co-morbidity and use of bleeding promoting drugs

Short title: Mortality from peptic ulcer bleeding

Keywords: peptic ulcer, bleeding, aspirin, NSAID, mortality, warfarin, co-morbidity

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Summary

Background: Use of drugs promoting peptic ulcer bleed (PUB) have increased several fold.

Aim: To make a time-trend analysis of PUB patients and evaluate the impact of age, gender, co-morbidity and use of drugs promoting PUB on outcome.

Methods: Retrospective review of hospitalisations for PUB at Lund University Hospital 1984, 1994 and 2004. Univariate analyses between years and multivariable logistic regression for risk factors of fatal outcome.

Results: Incidence decreased from 62.0 to 32.1 per 100,000 inhabitants between 1984 and 2004. Mortality rates were stable. Median age (70 to 77 years ($p=0.001$)), number of co-morbidities ((mean \pm SD) 0.88 \pm 0.96 to 1.16 \pm 0.77 ($p=0.021$)), use of aspirin (16 to 57% ($p<0.001$)) and warfarin (5 to 17% ($p=0.02$)) increased.

Pharmacological and endoscopic therapy improved. Age above 65 years (OR:1.11, 95%CI:1.02-1.23) and number of co-morbidities (OR:6.00, 95%CI:2.56-17.4) were independent risk factors for in-hospital mortality. **Bleeding promoting drugs did not influence outcome negatively.** Aspirin decreased the risk of fatal outcome (OR:0.12, 95%CI:0.012-0.67).

Conclusion: Incidence of PUB decreased despite higher prescription rates of bleeding promoting drugs. In-hospital mortality was unchanged. The effect of improved therapy against PUB is probably outweighed by older and more co-morbid patients. The decreased risk of fatal outcome in aspirin users warrants further investigations.

Introduction

During several decades we have seen a steady decreasing prevalence of *Helicobacter pylori* (*H. pylori*) infection in the Swedish population, and the introduction of effective antisecretory drugs together with eradication therapies against *H. pylori*, have dramatically improved the possibilities to treat peptic ulcer. Hospitalisation rates for peptic ulcer are therefore declining¹⁻³. During the same period, the prescriptions of low dose aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants (warfarin) as well as selective serotonin reuptake inhibitors (SSRIs) have increased several fold, especially among the elderly⁴. These drugs interfere with the defence mechanisms of the gastric mucosa and/or influence the haemostasis leading to an increased risk of developing upper gastrointestinal (GI) bleeding⁵⁻⁷, of which peptic ulcer bleeding (PUB) constitutes around 50 per cent^{8,9}. Fortunately however, so far, the outcome of PUB has not been shown to be negatively influenced by these drugs¹⁰⁻¹².

The aim of this study was to make a detailed time-trend evaluation of all patients hospitalised for PUB during three distinct time periods, 1984, 1994 and 2004 at the Department of Surgery, Lund University Hospital, Sweden. Special attention was made towards the impact of age, gender, co-morbidity and use of drugs promoting PUB on outcome.

Methods

A retrospective review was done of the medical records for all (in total 766) hospitalisations with a discharge diagnosis of gastrointestinal bleeding according to the International Classification of Diseases, the 8th, 9th and 10th Revisions during three distinct time periods: 1984, 1994 and 2004 at the Department of Surgery (and

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2
3 for 2004 also the Department of Emergency conditions due to re-organisation) at
4
5 Lund University Hospital in Sweden. Two records were missing. Twenty-two cases
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7 were excluded as non bleeders. Additionally 193 hospitalisations for unspecified
8
9 peptic ulcer were evaluated as a Swedish national validation study has shown a
10
11 diagnostic misclassification of PUB in 34-50 % of unspecified ulcer cases¹³. Seven
12
13 of 63 (11.1 per cent) in 1984, four of 41 (9.8 per cent) in 1994 and 24 of 89 (27 per
14
15 cent) in 2004 were found to be misclassified bleeding ulcers and consequently added
16
17 to the PUB group.
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21 In this study we wanted to evaluate only PUB patients. Only patients who had signs
22
23 of GI bleeding and a verified peptic ulcer considered to be the bleeding source were
24
25 eligible. Hospitalisations with incorrect diagnoses were transferred to the correct
26
27 diagnostic group. Only the index hospitalisation was included if a patient had
28
29 recurrent hospitalisations for PUB during the same year. Thus 94
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31 hospitalisations/patients for PUB from 1984, 65 from 1994 and 93 from 2004 were
32
33 included in the study. Hospitalisations of all other causes of GI bleeding during these
34
35 years are presented in another paper.
36
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38
39 Recorded data for every patient included age, gender, history of previous ulcer or GI
40
41 bleed, co-morbidity, drug use, clinical signs of bleeding, haemodynamic instability
42
43 and serum haemoglobin level at admission, in hospital pharmacological treatment,
44
45 endoscopic therapy, surgery and in hospital mortality.
46
47

48
49 Haemodynamic instability was defined as syncope or a systolic blood pressure ≤ 100
50
51 mmHg. Acid reducing therapy in forms of H₂RA and PPIs were analysed together.
52
53 Co-morbidity was analysed as follows; cardiovascular disease included conditions
54
55 like cardiac arrhythmia, ischemic heart disease, chronic heart failure, hypertension
56
57 but also previous history of cerebrovascular insult and cardiac infarction. Pulmonary
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3 disease included both chronic (e.g. bronchitis or chronic obstructive lung disease)
4
5 and acute (e.g. pneumonia) conditions. Kidney failure included both mild forms (e.g.
6
7 having an abnormal serum creatinine value) and severe forms (e.g. regular need of
8
9 dialysis). Liver failure included both mild forms (e.g. having an abnormal serum
10
11 bilirubin value) and severe forms (e.g. end-stage liver failure). For malignant disease
12
13 only diagnosis within one year or end-stage malignancy was included.
14
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16
17 Lund University Hospital provides highly specialised health care for rare conditions in
18
19 the population in the Southern part of Sweden but for common emergency conditions
20
21 like GI bleeding it serves the population in a defined catchment area in the mid-west
22
23 of Skane county. The population in the catchment area grew from 151 711 in 1984,
24
25 to 170 727 in 1994 and 289 560 in 2004.
26
27

28 29 *Statistical analysis*

30
31 Incidence and mortality rates per 100 000 inhabitants were calculated by Poisson
32
33 regression with 95 per cent confidence intervals (CI) and Tukey corrected p-values
34
35 for multiple comparisons. In univariate analyses Kruskal-Wallis or Wilcoxon tests
36
37 were used for continuous variables and Fisher's exact test for categorical variables.
38
39 Logistic regression models were used in the multivariable analyses. The level of
40
41 significance was set at $p < 0.05$. Data were analysed using the Hmisc and Design
42
43 packages of the R software (R Foundation for Statistical Computing, Vienna, Austria),
44
45 version 2.6.2.
46
47

48
49 The study was approved by Lund University Research Ethics Committee.
50
51

52 53 54 55 **Results**

56
57 The hospitalisation rate of peptic ulcer bleeding decreased from 62.0 (CI 50.3 –
58
59 75.3) in 1984 to 38.1 (CI 29.6 – 48.1) in 1994 and 32.1 (CI 26.0 – 39.1) per 100 000
60

1
2
3 inhabitants in 2004. The decrease was significant between 1984 and 1994
4
5 (p=0.0070) but not between 1994 and 2004 (p=0.54). Mortality rates per 100 000
6
7 inhabitants were stable 2.6 (CI 0.82 – 6.1) in 1984, 2.3 (CI 0.73 – 5.4) in 1994 and
8
9 1.7 (CI 0.62 – 3.7) in 2004.
10
11

12 *Gender, age, co-morbidity and medication*

15 Patient characteristics in detail are presented in table 1. The male to female ratio
16
17 decreased from 3.3 to 1.5 between 1984 and 2004. The percentage of patients
18
19 above 75 years of age increased from 26 to 54 per cent (p=0.002). Cardiovascular
20
21 co-morbidity increased to 72 per cent in 2004. The number of co-morbidities
22
23 increased from (mean +/- SD) 0.88 +/- 0.96 to 1.16 +/- 0.77 (p=0.021) between 1984
24
25 and 2004. Accordingly the use of low dose aspirin and warfarin increased, and
26
27 almost 60 per cent were on aspirin and 17 per cent were on warfarin in 2004. The
28
29 use of other NSAIDs was stable at around 10 per cent. In 2004, 75 per cent of
30
31 patients were prescribed at least one and 15 per cent two or more drugs enhancing
32
33 the risk of ulcer bleed - aspirin, warfarin, non-aspirin NSAIDs, steroids or SSRIs.
34
35 (Further on these drugs will be referred to as “risk drugs”). The rate of patients with
36
37 haemodynamic instability was stable but median serum haemoglobin level decreased
38
39 between the years. Clinical presentation in form of haematemesis or blood in
40
41 nasogastric tube (around 55 per cent of patients) and melena (around 75 per cent of
42
43 patients) did not change between years
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50 Co-morbidity was equally frequent among patients with and without a history of
51
52 previous ulcer or GI bleed [any co-morbidity 57/84 (68 per cent) and 115/168 (68 per
53
54 cent)], cardiovascular disease 44/84 [(52 per cent) and 102/168 (61 per cent)
55
56 (p=0.22)] but the use of aspirin was less frequent [20/84 (24 per cent) and 66/168 (40
57
58 per cent) (p=0.016)] and the use of H2RA or PPI was more frequent [19/84 (23 per
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1
2
3 cent) and 8/168 (5 per cent) ($p < 0.001$)] among patients with, compared with those
4
5 without, a history of previous ulcer or GI bleed.
6

7 8 *Therapy and outcome*

9
10 Data of in hospital treatment, discharge status and mortality rates are found in table
11
12 **2.** Intravenous pharmacological treatment with H2RAs/PPIs, tranexamic acid and
13
14 desmopressin (not available in 1984) increased significantly from 1984 to 2004. The
15
16 few patients not subjected to upper GI endoscopy went immediately to surgery (3
17
18 patients 1984 and 3 patients in 1994) or had been hospitalised and diagnosed with
19
20 an ulcer very recently. One ulcer was diagnosed by autopsy. Data of Forrest
21
22 classification was not reliable in this retrospective study. **The indication for**
23
24 **endoscopic intervention nowadays at our department is a bleeding ulcer with Forrest**
25
26 **grade 1 or 2. In 1984, no endoscopic intervention was performed, but the frequency**
27
28 **of endoscopic intervention increased from 8 to 45 per cent among all PUB patients**
29
30 **from 1994 to 2004.** The frequency of a second endoscopy and endoscopic
31
32 intervention also increased between years whereas surgery became less frequent. In
33
34 1984 three gastric resections and five local procedures (gastro/duodenotomy and
35
36 suture ligation) were performed. In six of the eight patients a vagotomy was added. In
37
38 1994 one gastric resection and six local procedures were performed and in two of the
39
40 seven operations a vagotomy was added. In 2004 only one surgical intervention
41
42 (local procedure) was performed. Prescriptions at discharge of H2RA or PPI and
43
44 eradication therapy against *H. pylori* increased. Case fatality rate ranged between 4
45
46 and 8 per cent (not significant). Patients who started to bleed while they were
47
48 hospitalised for another reason had a higher mortality (13, 17, 14 per cent) compared
49
50 with those who started to bleed at home (2, 4, 4 per cent) ($p = 0.004$). **Around 15 per**
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3 cent of patients were transferred to another department at discharge and 85 per cent
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5 could be sent home. These figures did not change between years.
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8 Data by ulcer location in 2004 is shown in table 3. History of previous ulcer or GI
9
10 bleed and endoscopic interventions were more common among duodenal ulcer
11
12 patients whereas use of any “risk drug” was related to gastric ulcer disease.
13

14 Table 4 shows data for PUB patients by mortality. Patients who died during
15
16 hospitalisation were older, had more co-morbidities (mean number of co-morbidities
17
18 (+/-SD) was 2.15 (+/-0.90) compared with 0.94 (+/-0.83)) and had lower serum
19
20 haemoglobin levels at presentation in comparison with those who were alive at
21
22 discharge. Use of “risk drugs” at presentation did not negatively influence the fatality
23
24 rate although they can be seen as surrogate markers of co-morbidities. Patients who
25
26 died had a higher rate of haematemesis at presentation compared with those who
27
28 were alive at discharge, 11/13 (85 per cent) and 127/239 (53 per cent) respectively
29
30 (p=0.042). Melena were equally frequent.
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36 In the multivariable logistic regression model shown in table 5, age above 65 years,
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38 number of co-morbidities and haemodynamic instability were independent risk factors
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40 for in hospital mortality whereas the use of aspirin at start of bleed decreased the risk
41
42 of mortality significantly.
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48 Discussion

49
50 Hospitalisations for PUB per 100 000 inhabitants decreased significantly in this study
51
52 between 1984 and 1994. A decrease in bleeding ulcer during the same period is
53
54 found also by others^{1, 14}, although not agreed on by all^{15, 16}, and is probably due to a
55
56 cohort phenomenon with decreasing prevalence of *H. pylori* in the population. This
57
58 effect was probably enhanced by the introduction of PPIs in the late 1980's and the
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3 spreading knowledge of eradication therapies against *H. pylori*. The hospitalisation
4 rate per 100 000 inhabitants in our study was unchanged between 1994 and 2004
5
6 and the same was found in Danish and Dutch studies from the same time period ¹².
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11 ¹⁷. A potential further decrease was perhaps counterbalanced by the increasing
12 prescription rate of low dose aspirin, other antiplatelet agents and warfarin seen
13 during this period ⁴.
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16
17 In this time trend analysis of PUB over twenty years in Lund, the patients got older
18 and the rate of cardiovascular co-morbidity increased. Consequently the use of
19 aspirin and warfarin increased, both as single drugs and in combination. Four of six
20 patients with concurrent low dose aspirin and warfarin use, also had another
21 antiplatelet agent (clopidogrel) added. The prescriptions of these drugs have
22 naturally increased also in the aging back-ground population during this period ⁴.
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31 However, in comparison with the sales statistics from the Swedish Pharmacy ¹⁸ the
32 use of low dose aspirin in our study was around three times higher in age-groups 45
33 to 74 years and 50 per cent higher in the age-group 75 to 84 years among PUB study
34 patients in 2004. Warfarin use was not higher in age-groups between 45 and 75
35 years but was five times higher in the age-groups over 75 years among study
36 patients. The use of NSAIDs was higher only in the age-group above 85 years while
37 the use of SSRIs was lower and the use of corticosteroids was the same in study
38 patients in comparison with the back-ground population. Aspirin and warfarin are
39 shown in other studies to cause a 2-fold increase as single drugs ¹⁹⁻²¹ and a 5-fold
40 increase in combination ¹⁹, in the risk for PUB.
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55 However, aspirin, non-aspirin NSAIDs and warfarin did not increase the risk of fatal
56 outcome in this study, which is similar to findings reported by others ^{10-12, 22, 23}, though
57 in contrast with two studies ^{24, 25}. Aspirin use at admission was in our study even
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3 found to reduce the risk of in-hospital mortality, which is in line with the results of a
4 recently published randomised trial²⁶ where patients after endoscopic haemostasis
5 of a PUB were given low dose aspirin or placebo for 8 weeks. Aspirin recipients had
6 a higher risk of rebleeding but lower mortality, although some deaths in the placebo
7 group were from causes not normally prevented by aspirin. The international
8 consensus recommendations have recently also concluded that patients with upper
9 GI bleeding who require secondary cardiovascular prophylaxis should resume the
10 low-dose aspirin therapy as soon as the cardiovascular risks outweigh the
11 gastrointestinal risks²⁷.

12
13 The usual regimen in our department, when an aspirin or warfarin recipient is
14 admitted for gastrointestinal haemorrhage, is to discontinue the therapy as long as
15 there is a high risk of rebleeding. The anticoagulative effect of warfarin can be
16 reversed by vitamin K but the antithrombotic effect of aspirin is prolonged for several
17 days after discontinuation, which could have influenced the case fatality rate among
18 aspirin users in our study. We separated aspirin from non-aspirin NSAIDs in our
19 analyses as there is a difference between the drugs in pharmacokinetics and
20 pharmacodynamics. Both drugs impair the capacity of platelets to aggregate by
21 blocking cox-1, but the effect of non-aspirin NSAIDs is reversible while the effect of
22 aspirin is irreversible and consequently persists during the whole life-span of platelets
23^{20, 28}. The separate analyses in our study might explain the difference between our
24 results and others, who did not separate aspirin from other NSAIDs^{10, 12, 23}.

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Desmopressin counteracts the antiplatelet effect of aspirin and NSAIDs on
haemostasis and was given to 7 patients in 2004. All patients were low dose aspirin
recipients and two of them were also taking clopidogrel. One of the patients died.

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3 Causes of mortality after PUB are shown to more often be related to cardiac or
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5 multiorgan failure in these old and co-morbid patients rather than the bleeding itself
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8^{29, 30}. This is reflected in our study, as in others^{10, 31}, by a higher mortality among
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10 patients who start to bleed while hospitalised for another reason than among patients
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12 who start to bleed at home. It may also partly explain why the case fatality rate in our
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14 study was unchanged between 1984 and 2004. The effect of improved therapy
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16 against bleeding with intravenous pharmacological treatment and more frequent
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18 haemostatic endoscopic procedures were probably outweighed by the fact that
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20 patients were older with more co-morbidities.
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23
24 In our study, patients with a history of previous ulcer or GI bleed were taking
25
26 significantly less aspirin and other "risk drugs" although they were equally co-morbid.
27
28 Doctors had prescribed acid reducing therapy to a higher extent (23 per cent) to
29
30 those with, compared to those without (5 per cent), previous ulcer or GI bleed.
31
32 According to the recent international consensus recommendations²⁷, patients with
33
34 indications for secondary cardiovascular prophylaxis with aspirin or warfarin should
35
36 receive these drugs, as the risk to die of cardiovascular events exceeds the risk to
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38 die of PUB. To increase gastrointestinal safety an increase in prophylactic
39
40 prescription of PPIs to risk groups and eradication therapies against *H. pylori* in the
41
42 presence of infection is recommended³².
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48 The strength of this study is the thorough evaluation of the medical records and
49
50 validation of diagnoses. Every record of a gastrointestinal bleeding diagnosis and a
51
52 diagnosis of unspecified ulcer during 1984, 1994 and 2004 at Department of Surgery
53
54 was evaluated giving us a complete data set. All the same the number of patients
55
56 and hospitalisations is small, and this is of course the main weakness of the study.
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59 We analysed in-hospital mortality as we wanted to evaluate outcome undoubtedly
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3 related to the bleeding episode. A longer follow-up of for instance 30 days is also
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5 interesting but then alternative causes of death also have to be considered.
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8 In the multivariable model we have adjusted for factors that we believe increase the
9
10 risk of fatal outcome. Patient characteristics in forms of gender, age, number of co-
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12 morbidities, drug use, ulcer location and previous history of ulcer or GI bleed were
13
14 considered important. The severity of the bleeding was adjusted for in form of
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16 presence of haemodynamic instability. We have tried to control for some changes in
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18 management and standard of care of peptic ulcer bleeding patients that have
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20 occurred during these 20 years by adjusting for year 1994 and 2004 with 1984 as
21
22 reference.
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27 In conclusion we found that PUB incidence decreased despite higher prescription
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29 rates of aspirin, warfarin and other drugs enhancing the risk of PUB between the
30
31 three study periods 1984, 1994 and 2004. This is probably due to a decreasing
32
33 prevalence of *H. pylori* in the population and an increasing awareness among doctors
34
35 of the benefits of *H. pylori* eradication and concurrent use of PPIs to increase GI
36
37 safety. In-hospital mortality was unchanged between years. The effect of improved
38
39 emergency therapy against PUB is to some degree probably outweighed by the fact
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41 that patients have become older with more co-morbidities. Aspirin use on admission
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43 was however found to reduce the risk of fatal outcome. This finding warrants further
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45 investigations.
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		1984 n=94		1994 n=65		2004 n=93		p values
Men/women	N=252	72/22	77/23 %	37/28	57/43 %	56/37	60/40 %	p=0.014 ¹
Ulcer location (GU/DU/other)	N=252	51/41/2	54/44/2%	41/22/2	63/34/3%	41/51/1	44/55/1%	p=0.084 ¹
Median age #	N=252	54	<u>70</u> 76	64	<u>74</u> 79	65	<u>77</u> 84	p=0.001 ²
<65 years	N=252	37	39%	17	26%	22	24%	p=0.049 ¹
65-75 years	N=252	33	35%	21	32%	21	23%	p=0.15 ¹
>75 years	N=252	24	26%	27	42%	50	54%	p<0.001 ¹
Cardiovascular disease	N=252	42	45%	37	57%	67	72%	p<0.001 ¹
Pulmonary disease	N=252	13	14%	5	8%	13	14%	p=0.46 ¹
Kidney failure	N=252	9	10%	3	5%	4	4%	p=0.34 ¹
Liver failure	N=252	7	7%	3	5%	6	6%	p=0.76 ¹
Malignancy	N=252	1	1%	2	3%	2	2%	p=0.75 ¹
Any co-morbidity	N=252	54	57%	42	65%	76	82%	p=0.001 ¹
Median number of co-morbidities #	N=252	0	<u>1</u> 1	0	<u>1</u> 2	1	<u>1</u> 2	p=0.021 ²
Previous GI bleed or Ulcer	N=252	31	33%	36	55%	17	18%	p<0.001 ¹
Aspirin	N=250	15	16%	19	29%	52	57%	p<0.001 ¹
Non-aspirin NSAIDs	N=250	6	6%	8	12%	9	10%	p=0.4 ¹
Steroids	N=250	4	4%	1	2%	3	3%	p=0.75 ¹
Warfarin	N=250	5	5%	4	6%	16	17%	p=0.02 ¹
SSRIs	N=250	0	0%	1	2%	3	3%	p=0.14 ¹
Cox 2 inhibitors	N=250	0	0%	0	0%	1	1%	p=0.63 ¹
Any drug enhancing risk of PUB	N=250	28	30%	29	45%	69	75%	p<0.001 ¹
Any drug enhancing risk of PUB except aspirin	N=250	14	15%	13	20%	29	32%	p=0.027 ¹
Combination of drugs enhancing risk of PUB	N=250	2	2%	4	6%	14	15%	p=0.004 ¹
Acid reducing therapy (H2RA/PPI)	N=250	3	3%	14	22%	10	11%	p=0.001 ¹
Start bleed at home / in hospital	N=247	68/21	76/24%	53/12	82/18%	79/14	85/15%	p=0.33 ¹
Haemodynamic instability at admission *	N=250	16	17%	11	17%	22	24%	p=0.46 ¹
Median serum haemoglobin at admission (g/dL) #	N=252	8.6	<u>11.0</u> 12.3	7.9	<u>9.3</u> 11.1	7.8	<u>9.3</u> 11.7	p=0.005 ²

36 *Tests used:* Fisher's exact test¹ and Kruskal-Wallis test² # (with upper and lower quartile)

37 * =syncope or systolic blood pressure <100 mm Hg

38 *Abbreviations:* GU=gastric ulcer, DU=duodenal ulcer, GI=gastrointestinal, NSAIDs=non-steroidal anti-inflammatory

39 drugs, SSRIs=selective serotonin re-uptake inhibitors, PUB=peptic ulcer bleeding, H2RA=histamin-2 receptor antagonists,

40 PPIs=proton pump inhibitors

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Table 2. Time trend analysis of in hospital treatment and outcome for patients hospitalised for bleeding ulcer 1984, 1994 and 2004.

		1984 n=94	1994 n=65	2004 n=93	p values	
In hospital						
<u>Intravenous pharmacological treatment</u>						
Acid reducing therapy H2RA/PPI	N=250	64 68%	51 78%	82 90%	p=0.001 ¹	
Tranexamic acid	N=250	7 7%	45 69%	69 76%	p<0.001 ¹	
Desmopressin	N=247	0 0%	0 0%	7 8%	p=0.001 ¹	
Median blood transfusion units (upper and lower quartile)	N=227	0 2 7	0 2 4	0 2 4	p=0.39 ²	
Upper GI endoscopy during hospitalisation	N=252	90 96%	60 92%	92 99%	p=0.1 ¹	
Upper GI endoscopy within 24 hours	N=228	73 92%	50 88%	78 85%	p=0.31 ¹	
Second endoscopy during hospitalisation	N=252	15 16%	6 9%	31 33%	p<0.001 ¹	
<u>Endoscopic intervention</u>						
Only adrenaline injection		0 0%	5 8%	15 16%	p<0.001 ¹	
Addition of another modality *		0 0%	0 0%	27 29%		
<u>Second endoscopic intervention</u>						
Only adrenaline injection	N=252	0 0%	1 2%	3 3%		
Addition of another modality *		0 0%	0 0%	11 12%		
Angiography	N=252	2 2%	2 3%	1 1%	p=0.85 ¹	
Surgery	N=252	8 9%	7 11%	1 1%	p=0.015 ¹	
Median hospital stay (days) (with upper and lower quartile)	N=252	2.2 4 7	2 5 7	2 3 6	p=0.55 ²	
After hospitalisation						
<u>Prescriptions</u>						
Acid reducing therapy H2RA/PPI	N=235	78 90%	58 97%	87 99%	p=0.018 ¹	
Eradication of <i>Helicobacter pylori</i>	N=235	1 1%	3 5%	60 71%	p<0.001 ¹	
<u>In hospital mortality total</u>						
Mortality for patients who started to bleed at home	N=247	1 2%	2 4%	3 4%	p=0.67 ¹	
Mortality for patients who started to bleed in hospital	N=247	3 13%	2 17%	2 14%	p=1.0 ¹	

Tests used: Fisher's exact test¹ and Kruskal-Wallis test² for differences between years.

Abbreviations: H2RA=histamin-2 receptor antagonists, PPI=proton pump inhibitors, GI=gastrointestinal. * mostly fibrin glue or vessel clips

Table 3. Bleeding ulcer patients in 2004 by ulcer location								
		Gastric ulcer n=41		Duodenal ulcer n=51		p-value		
Median age (with upper and lower quartile)	N=92	60	77	84	68	78	84	p=0.6 ²
Male gender	N=92	23	56%	32	63%			p=0.53 ¹
Any co-morbidity	N=92	32	78%	44	86%			p=0.41 ¹
Previous GI bleed or ulcer	N=92	3	7%	14	27%			p=0.016 ¹
Aspirin	N=92	28	68%	24	47%			p=0.057 ¹
Non-aspirin NSAIDs	N=92	7	17%	2	4%			p=0.073 ¹
Steroids	N=92	0	0%	3	6%			p=0.25 ¹
Warfarin	N=92	7	17%	9	18%			p=1 ¹
SSRIs	N=92	3	7%	0	0%			p=0.085 ¹
Cox 2 inhibitors	N=92	0	0%	1	2%			p=1 ¹
Any drug enhancing risk of PUB	N=92	36	88%	33	65%			p=0.015 ¹
H2RA/PPI	N=92	6	15%	4	8%			p=0.33 ¹
Upper GI endoscopy within 24 hours	N=91	31	76%	46	92%			p=0.042 ¹
Endoscopic intervention	N=92	11	27%	31	61%			p=0.006 ¹
Second endoscopy	N=92	9	22%	22	43%			p=0.046 ¹
Second endoscopic intervention	N=92	2	5%	12	24%			p=0.034 ¹
Surgery	N=92	1	2%	0	0%			p=0.45 ¹
Mortality	N=92	0	0%	5	10%			p=0.063 ¹

Tests used: Fisher's exact test¹ Wilcoxon test².

Abbreviations: GI=gastrointestinal, NSAIDs=non-steroidal anti-inflammatory drugs, SSRIs=selective serotonin re-uptake inhibitors, PUB=peptic ulcer bleeding, H2RA=histamin-2 receptor antagonists, PPIs=proton pump inhibitors

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Table 4. All bleeding ulcer patients from 1984, 1994, 2004 by in-hospital mortality

		Alive at discharge n=239		Deceased in hospital n=13		p-value
Median age [#]	N=252	60	<u>72</u> 80	77	<u>82</u> 84	p=0.006 ²
Male gender	N=252	157	66%	8	62%	p=0.77 ¹
Ulcer location GU/DU	N=252	129 / 105	54% / 44%	4 / 9	31% / 69%	p=0.21 ¹
Any co-morbidity	N=252	159	67%	13	100%	p=0.011 ¹
Cardiovascular disease	N=252	135	56%	11	85%	p=0.08 ¹
Pulmonary disease	N=252	28	12%	3	23%	p=0.20 ¹
Kidney failure	N=252	13	5%	3	23%	p=0.041 ¹
Liver failure	N=252	11	5%	5	38%	p<0.001 ¹
Malignancy	N=252	3	1%	2	15%	p=0.023 ¹
Median number of co-morbidities [#]	N=252	0	<u>1</u> 1	0	<u>2</u> 3	p<0.001 ²
Combination of two or more co-morbidities	N=252	58	24%	10	77%	p<0.001 ¹
Previous GI bleed or Ulcer	N=252	78	33%	6	46%	p=0.37 ¹
Aspirin	N=250	84	35%	2	15%	p=0.23 ¹
Non-aspirin NSAIDs	N=250	23	10%	0	0%	p=0.62 ¹
Steroids	N=250	8	3%	0	0%	p=1 ¹
Warfarin	N=250	23	10%	2	15%	p=0.63 ¹
SSRIs	N=250	4	2%	0	0%	p=1 ¹
Cox 2 inhibitors	N=250	1	0%	0	0%	p=1 ¹
Any drug enhancing risk of PUB	N=250	122	51%	4	31%	p=0.17 ¹
Any drug enhancing risk of PUB except aspirin	N=250	54	23%	2	15%	p=0.74 ¹
H2RA/PPI	N=250	25	11%	2	15%	p=0.64 ¹
Start bleed at home / in hospital	N=247	194/40	83/17%	6/7	46/54%	p=0.004 ¹
Haemodynamic instability [*]	N=250	44	19%	5	38%	p=0.14 ¹
Median serum haemoglobin at admission (g/dL) [#]	N=252	8.1	<u>9.9</u> 12	7.3	<u>8.4</u> 9.5	p=0.047 ²
Median blood transfusion units [#]	N=227	0	<u>2</u> 4	2	<u>3.5</u> 9	p=0.052 ²
Upper GI endoscopy within 24 hours	N=228	192	88%	9	90%	p=1 ¹
Endoscopic intervention	N=252	43	18%	4	30%	p=0.32 ¹
Angiography	N=252	2	1%	3	23%	p=0.001 ¹
Surgery	N=252	14	6%	2	15%	p=0.20 ¹

Tests used: Fisher's exact test¹ and Kruskal-Wallis test² [#] (with upper and lower quartile) * syncope or systolic blood pressure <100 mmHg

Abbreviations: GU=gastrointestinal, DU=duodenal ulcer, GI=gastrointestinal, NSAIDs=non-steroidal anti-inflammatory drugs,

SSRIs=selective serotonin re-uptake inhibitors, PUB=peptic ulcer bleeding, H2RA=histamin-2 receptor antagonists, PPIs=proton pump inhibitors

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Table 5. Association between variables and in-hospital mortality after bleeding ulcer

Factor	OR	95 % CI	p-value
Year 1994 (1984 reference)	1.9	0.27 - 17	0.52
Year 2004 (1984 reference)	1.9	0.25 - 18	0.54
Male gender	1.9	0.36 - 12	0.48
Age above 65 years (1 year increase)	1.1	1.02 - 1.2	0.040 *
Number of co-morbidities	6.0	2.6 - 17	<0.001 *
Previous ulcer or GI bleed	3.0	0.49 - 20	0.24
Aspirin use	0.12	0.012 - 0.67	0.032 *
Use of drugs enhancing risk of PUB other than Aspirin	0.43	0.049 - 2.4	0.38
Duodenal ulcer location (gastric ulcer reference)	3.4	0.73 - 20	0.14
Haemodynamic instability (syncope or BP<100 mmHg)	5.5	0.99 - 32	0.049 *

Multivariable logistic regression model.

Abbreviations: OR=odds ratio, CI=confidence interval, GI=gastrointestinal, PUB=peptic ulcer bleeding, BP=systolic blood pressure

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