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Clinical Predictors of Poor Outcomes Among Patients with Non-Variceal Upper Gastrointestinal Bleeding in Europe

Angel Lanas, Lars Aabakken, Jorge Fonseca, Zeynel A Mungan, George V. Papatheodoridis, Hubert Piessevaux, Livio Cipolletta, Javier Nuevo, Monica Tafalla

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**Clinical Predictors of Poor Outcomes Among Patients with
Non-Variceal Upper Gastrointestinal Bleeding in Europe**

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2
3 **Manuscript Title: Clinical Predictors of Poor Outcomes Among Patients with Non-Variceal Upper**
4 **Gastrointestinal Bleeding in Europe**
5
6

7 **Point-by-point response to reviewers comments**
8

9 **Reviewer: 1**

10 Comments for Transmission to the Authors

11 Lanas et al present an interesting study of non-variceal upper GI haemorrhage. They found that clinical
12 factors (number of co-morbidities, age, in-hospital bleeding, type of lesion and concomitant medication)
13 explain differences in outcome rather than country, size of hospital, profile of team or endoscopic/
14 pharmacological therapy received.
15

16 **Strengths:**

17 This is a large study (2660) patients and is representative (7 countries, 123 centres).
18 It reflects real-world practice rather than a clinical trial situation.
19

20 **Weaknesses:**
21

22 As acknowledged, it has the weaknesses of all retrospective studies.

23 Only patients undergoing endoscopy have been included. This leads to 2 potential biases. Those patients
24 with such severe bleeding that they die prior to endoscopy will have been excluded and those thought to
25 have insignificant bleeding (e.g. Mallory-Weiss tear) may have been discharged without endoscopy in
26 some cases.

27 The reviewer is right that by including the need for an endoscopic procedure as one of the inclusion
28 criteria of the study we may have lost some patients, potentially those with very mild bleeding
29 attended at the emergency room that did not undergo endoscopy, or those with massive bleeding
30 and death that an endoscopy was not performed. A review of ICD-9 codes with potential bleeding
31 cases in the hospital of the PI has shown that there were no cases hospitalised with NVUGIB and no
32 endoscopy during that period of time. We believe that this is a minor limitation, but have included this
33 aspect in the Discussion. Page 15 On the other hand, by excluding those patients, the study gains in
34 homogeneity and accuracy of diagnosis.
35

36 Some of the clinical predictors are not well described. For example, what constitutes a history of alcohol
37 abuse? This may have been interpreted with a great degree of variability making its inclusion potentially
38 invalid unless it was specifically defined. A reason for the deleterious effect should be postulated.

39 The reviewer is right. We were not able to apply a specific definition to this variable; since the study was
40 retrospective, it was impossible to obtain a clear measure of the exact or the usual amount of alcohol
41 taken by patients. Investigators collected the information as recorded in the chart. Alcohol abuse
42 therefore may represent a wide spectrum of alcohol use, but it is reasonable to assume that patients
43 with no or sporadic use have not been ascribed here. The variable was associated with increased risk of
44 mortality and not with rebleeding, which we believe makes sense, since mortality is linked to morbidity
45 rather than to the bleeding event itself and being an alcohol abuser increases the number of morbidities.
46 We have included this aspect in the discussion.
47

48 How was size of hospital (large v other) defined? How many hospitals fell into each group.

49 The total proportion of centres considered large was 63.18%. We have included this data in the text.

50 **Page:11**
51

52 The definition of low dose aspirin use is slightly unusual. Most clinicians would consider a dose of 75-
53 80mg to be low. We are not told what proportion of patients received each. No mention is then made in
54 the results or discussion of the apparent protective effect of high dose aspirin which seems to be stronger
55 than for low dose.
56

57 Current recommendations for CV prevention with low-dose aspirin is 75-100 mg/day and that's why we
58 have used that dose as the cut-off point to collect either low- or high dose ASA. Of a total of 799
59 patients who have recorded the use of ASA before the bleeding event, 535 (67%) had used ASA at a dose
60 ≤ 100 mg/day. Of the remaining 264 patients, one third (82 – 31 %) had used higher dose for the
indication of ischemic Heart disease. In any case we found the effect of ASA on NVUGIB outcomes to be
very similar for either low or high-dose (in general 325 -1000 mg/day) which may be related to its

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2
3 antiplatelet effect on mortality and agree with the data reported by Sung et al. in Annals of Internal
4 Medicine 2010). We have included a comment in the discussion. Page: 14
5
6

7 Collecting data on presence or absence of co-morbidity means that severity is not taken into account. It
8 would be probable that a NYHA IV heart failure would have a greater impact than NYHA I heart failure
9 although this information would be difficult to gain accurately retrospectively.

10 The referee is right. We have preferred to include this information as 'yes or no' and the number of co-
11 morbidities because of accuracy in retrospective collection of data. We have included this aspect as one
12 of the weaknesses of the study in the discussion. Page:15
13

14 We are given no information on what therapy was delivered (injection, clip, thermal, combination) or to
15 which lesions with which stigmata making it difficult to draw any conclusions from the analysis of
16 patients receiving endoscopic therapy.

17 This information is now provided in the Results text. Page:9
18

19 Was haemodynamic instability not associated with adverse outcome? This is at odds with a body of
20 literature so should be discussed if this is the case.

21 It was indeed. Haemodynamic instability can be shown or expressed in different ways (hypotension,
22 tachycardia, shock , etc.). The inclusion of variables involved in that concept have shown shock as the
23 actual variable associated with poor outcomes.
24

25 Table 3 presents data for a different sub group to that presented in figures 2 and 3. A consistent approach
26 should be made to data presentation. Either figures 2 and 3 should be combined in a table or the data from
27 table 3 should be presented in two figures.

28 Our aim was to provide the relevant primary analysis as Figures 2 and 3 for a better and visual
29 understanding of the primary results. Those of Table 3 were secondary analysis of a subset of patients
30 undergoing therapeutic endoscopy, and we have therefore presented these in a Table. We believe that
31 it is not unusual to present data as a mix of Figures and Tables. We would prefer to avoid inclusion of a
32 third Figure of similar appearance to Figures 2 and 3, as this may not allow easy discrimination of the
33 subset analysis from the primary analysis. We can report all as tables or figures if the referee or editors
34 considered this important.
35

36 It is completely unnecessary to state that AstraZeneca is "the manufacturer of esomeprazole" in the
37 acknowledgements. This is blatant advertising and must be removed.

38 Our intention was to be fully transparent to the reader with respect to the association between the
39 corporate funding for the study, and the marketed product used to manage gastric disorder. This was
40 added in order to comply with the recommended acknowledgement text advised in the GPP2 guidelines.
41 We are sorry this was misunderstood as an attempt to advertise, as this was not the intention. We have
42 removed the sentence.
43
44

45 Reviewer: 2
46

47 Comments for Transmission to the Authors

48 In the past few years, AP&T has published several relevant papers about upper GI bleeding, which could
49 augment the Discussion.
50

51 E.g. Button LA, Roberts SE, Evans PA, Goldacre MJ, Akbari A, Dsilva R, Macey S, Williams JG.
52 Aliment Pharmacol Ther. 2011 Jan;33(1):64-76.

53 Fletcher EH, Johnston DE, Fisher CR, Koerner RJ, Newton JL, Gray CS.
54 Aliment Pharmacol Ther. 2010 Oct;32(7):831-9.
55

56 We have included the first of the references in the discussion, since we believe it has relationship with
57 our paper. Thanks. Page:15
58

59 Reviewer: 3
60

Comments for Transmission to the Authors

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3 The paper retrospectively investigates in a subset of European countries clinical predictors of poor
4 outcomes in pts with NVUGIB
5 The idea to evaluate in "real life" this critical and cost-driven condition is valid and the derived
6 informations are useful.
7

8 However, the methodology of the study is questionable. In fact, there is a geographical unbalance
9 between European included countries i.e. mediterraneans are prevalent, 5 out of 7. These aspects can be
10 reflected on the logistic and routine practice for the patients care. In fact, as stated in mat and meth (page
11 7 lines 3-4) the management of patients was performed according to local routine practice , and these can
12 be greatly different . A criteria to limit this problem should be to included only teaching hospitals or
13 not-teaching hospital or hospitals with GI services or without .

14 There is a predominance of Mediterranean countries included in the study. We did not intend to reflect
15 a picture of the whole of Europe. Since Health Systems in Europe are in general homogeneous in the
16 sense that they are public and universal or highly subsidised by the states, we believe that the
17 homogeneity across countries is much higher than in other regions of the world. However, we wanted
18 to know whether differences in local management of NVUGIB events could impact outcomes. All these
19 potential variables had been included in the multivariate analysis and the results were precisely that
20 within this regional setting, local differences in management did not affect hard outcomes. This was
21 reflected in the Results section (Page: 10) .In any case, we have conducted additional analysis as
22 requested by the reviewer and the conclusions were the same, (please see below the predictors of
23 rebleeding/bleeding continuation and mortality for large teaching hospitals) which seems logical since
24 large hospitals and other factors that may differentiate teaching hospitals (six GI services,) were
25 included in the model. In any case we have included a reference to these analyses in the Result section
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Analysis of predictors of bleeding continuation/re-bleeding and/or mortality in Hospitals ≥ 500 beds (n = 1680)

	Bleeding continuation / rebleeding (n = 219)			Mortality (n = 84)		
	OR	95% CI	p-value	OR	95% CI	p-value
Country						
Greece (vs. Belgium)	0.66	(0.33 - 1.35)	0.27	0.51	(0.16 - 1.55)	0.24
Italy (vs. Belgium)	0.54	(0.28 - 1.06)	0.08	0.86	(0.35 - 2.15)	0.76
Norway (vs. Belgium)	0.52	(0.22 - 1.25)	0.15	1.32	(0.44 - 3.91)	0.62
Portugal (vs. Belgium)	0.75	(0.34 - 1.65)	0.48	0.65	(0.22 - 1.99)	0.46
Spain (vs. Belgium)	0.60	(0.32 - 1.12)	0.12	0.46	(0.18 - 1.16)	0.11
Turkey (vs. Belgium)	0.54	(0.27 - 1.08)	0.09	0.67	(0.25 - 1.85)	0.45
Sex (male vs. female)	1.14	(0.83 - 1.57)	0.43	0.79	(0.51 - 1.23)	0.30
Age (>65 vs. ≤ 65 years)	1.27	(0.91 - 1.78)	0.16	1.53	(0.93 - 2.52)	0.09
History of alcohol abuse	1.16	(0.75 - 1.79)	0.50	2.61	(1.50 - 4.55)	0.001
Comorbidity (per comorbidity)	1.23	(1.07 - 1.41)	0.003	1.74	(1.45 - 2.08)	<0.001
History of NVUGIB	1.36	(0.94 - 1.95)	0.10	1.40	(0.84 - 2.33)	0.21
Admission (acute vs. no)	1.66	(1.11 - 2.48)	0.01	2.16	(1.32 - 3.53)	0.002
Hematemesis	1.45	(1.08 - 1.95)	0.02	1.41	(0.92 - 2.14)	0.12
High-dose ASA (>100 mg/day)	0.86	(0.51 - 1.44)	0.56	0.16	(0.05 - 0.58)	0.005
Low-dose ASA (≤ 100 mg/day)	0.99	(0.69 - 1.44)	0.97	0.26	(0.13 - 0.52)	<0.001
NSAIDS	0.63	(0.41 - 0.98)	0.04	0.45	(0.22 - 0.93)	0.03
Warfarin	1.02	(0.63 - 1.65)	0.93	0.87	(0.45 - 1.68)	0.67
Oesophagitis diagnosis	0.36	(0.19 - 0.67)	0.002	0.68	(0.33 - 1.41)	0.30
Gastric ulcer diagnosis	0.99	(0.70 - 1.40)	0.95	1.38	(0.86 - 2.22)	0.19
Gastritis \ Erosions diagnosis	0.71	(0.44 - 1.15)	0.16	0.95	(0.49 - 1.86)	0.89
Duodenal ulcer diagnosis	1.93	(1.40 - 2.67)	<0.001	1.45	(0.91 - 2.32)	0.12
Erosive duodenitis diagnosis	0.48	(0.20 - 1.19)	0.12	0.63	(0.21 - 1.86)	0.40
Intra-hospital management by GI bleeding team / Gastroenterology	0.79	(0.55 - 1.13)	0.20	0.69	(0.40 - 1.18)	0.17

PPI use before endoscopy was used as adjustment factor.

Comparison of significant predictors of bleeding continuation/re-bleeding and/or mortality, between all patients vs. patients from Hospitals ≥ 500 beds (OR and 95%CI)

	Bleeding continuation / rebleeding		Mortality	
	All patients N=327	Big Hospitals N=219	All patients N=138	Big Hospitals N=84
Country				
Greece (vs. Belgium)				
Italy (vs. Belgium)				
Norway (vs. Belgium)				
Portugal (vs. Belgium)				
Spain (vs. Belgium)				
Turkey (vs. Belgium)				
Sex (male vs. female)				
Age (>65 vs. ≤ 65 years)	1.56 (1.18 - 2.07)		1.75 (1.18 - 2.61)	
History of alcohol abuse			2.69 (1.77 - 4.09)	2.61 (1.50 - 4.55)
Comorbidity (per comorbidity)	1.22 (1.09 - 1.36)	1.23 (1.07 - 1.41)	1.75 (1.52 - 2.00)	1.74 (1.45 - 2.08)
History of NVUGIB	1.47 (1.09 - 1.98)			
Admission (acute vs. no)	1.59 (1.16 - 2.18)	1.66 (1.11 - 2.48)	1.96 (1.34 - 2.86)	2.16 (1.32 - 3.53)
Hematemesis	1.40 (1.10 - 1.78)	1.45 (1.08 - 1.95)	1.60 (1.16 - 2.22)	
High-dose ASA (>100 mg/day)			0.20 (0.09 - 0.45)	0.16 (0.05 - 0.58)
Low-dose ASA (≤ 100 mg/day)			0.39 (0.25 - 0.62)	0.26 (0.13 - 0.52)
NSAIDS	0.66 (0.47 - 0.93)	0.63 (0.41 - 0.98)		0.45 (0.22 - 0.93)
Warfarin	0.65 (0.43 - 0.98)			
Oesophagitis diagnosis	0.43 (0.27 - 0.70)	0.36 (0.19 - 0.67)		
Gastric ulcer diagnosis				
Gastritis \ Erosions diagnosis	0.58 (0.38 - 0.87)			
Duodenal ulcer diagnosis	1.77 (1.36 - 2.31)	1.93 (1.40 - 2.67)	1.53 (1.06 - 2.19)	
Erosive duodenitis diagnosis				
Intra-hospital management by GI bleeding team / Gastroenterology				

PPI use before endoscopy was used as adjustment factor.

Less significant factors in patients from Hospitals ≥ 500 beds, probably due to the reduced sample size.

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3 Another imbalance methodological factor is that three countries are represented with at least 24 centres
4 and the others with half of the centres but with the total patients number overlapping each other except
5 Grece.(i.e Belgium 26 centres total pts =426 vs Portugal 12 centres , pts n= 404). These variability
6 probably means that different Hospitals type are included reflecting expertise, clinical skillness ect
7 I suggest to the authors to revised your data in order to make a more appropriate comparison at least
8 between similar Hospital

9 We agree that some countries participated with less centres than others although the number of
10 patients was the same and that this could have induced an imbalance. As commented above, this
11 potential bias has been controlled in the logistic regression model since country, and size of hospital
12 variables, among other potential confounders have been introduced in the models. We have conducted
13 analysis according to size of centres and found no differences. This potential bias has been included in
14 the discussion (Page 15), but we do not present these data in the Ms core text since subgroup analyses
15 reduce dramatically the estimated sample size, and post-hoc analysis could be mislead the main goal of
16 the study and be misinterpreted.
17

18
19 Finally the lack of generalisation of the study conclusion (page 15, conclusion last para) weakens the
20 study

21 We had a very conservative approach in our conclusion due to the retrospective nature of the study. We
22 do believe however that the extension of the study allows us to expand the scope of the conclusions and
23 have modified this accordingly.
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**Title: Clinical Predictors of Poor Outcomes Among Patients with
Non-Variceal Upper Gastrointestinal Bleeding in Europe**

Running head: Clinical predictors of NVUGIB outcomes in Europe

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SUMMARY

Background: Non-variceal upper gastrointestinal bleeding (NVUGIB) is a common medical emergency associated with substantial morbidity and mortality. Despite advances in endoscopic and pharmacological treatment during the past two decades, the incidence of mortality associated with NVUGIB has remained relatively constant.

Aim: To report outcomes and predictive factors for bleeding continuation/re-bleeding and mortality of NVUGIB in clinical practice in different European countries.

Methods: This observational, retrospective cohort study (NCT00797641; **ENERGIB**) was conducted in Belgium, Greece, Italy, Norway, Portugal, Spain and Turkey. Eligible patients were hospitalised (new admissions or inpatients), presenting with overt NVUGIB with endoscopy from 1 October to 30 November, 2008. Patients were managed according to routine care, and data regarding bleeding continuation/re-bleeding, pharmacological treatment, surgery and mortality during 30-days after the initial bleed were collected. A multivariate analysis of clinical factors predictive of poor outcomes was conducted.

Results: Overall, 2660 patients (64.7% men; mean age 67.7 years) were evaluable. Significant differences across countries in bleeding continuation/re-bleeding (range: 9–15.8%) or death (2.5–8%) at 30 days were explained by clinical factors (number of comorbidities, age >65 years, history of bleeding ulcers, in-hospital bleeding, type of lesion or type of concomitant medication). Other factors (country, size of hospital, profile of team managing the event, or endoscopic/pharmacological therapy received) did not affect these outcomes. Similar predictors were observed in patients with high-risk stigmata.

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3 **Conclusions:** Differences in the outcomes of NVUGIB in clinical practice across
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5 **some** European countries are explained mainly by patient-related factors, and not
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8 management factors.
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11 [Word limit 250: Current word count 239 excluding section headings]
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18 **Keywords:** non-variceal upper gastrointestinal bleeding, predictors, rebleeding,
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20 mortality
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For Peer Review

Introduction

Acute upper gastrointestinal (GI) bleeding is a common cause of emergency hospitalisation worldwide.¹⁻³ While considerable advances in the prevention of peptic ulcer complications have meant that the incidence of acute non-variceal upper GI bleeding (NVUGIB) has decreased substantially in the past decade,^{4,5} NVUGIB is still associated with considerable morbidity and mortality. Studies from North America, Europe and Asia most commonly place the incidence of continued and/or re-bleeding and mortality following acute NVUGIB between 2–17%.⁶⁻¹² Recent data from randomised, controlled trials and meta-analyses have shown that appropriate endoscopic and pharmacological treatments can reduce the incidence of re-bleeding^{6, 11, 13, 14} and surgery,¹⁴ duration of hospitalisation^{13, 15} and number of blood units transfused.^{13, 15} However, mortality associated with the bleeding event seems to be much more difficult to improve.^{13, 14} For example, in a population-based study of patients hospitalised due to GI complications in Spain, the age- and sex-adjusted mortality rate associated with upper GI bleeding events decreased between 1996 and 2005, but the case fatality rate has remained unchanged over this time period.¹⁶ The reasons for this are unclear, but progressive population aging and increased frequency of comorbidities may be relevant. Furthermore, the outcomes of NVUGIB, and factors associated with these outcomes in clinical practice, may be very different from those reported in randomised clinical trials. Also, factors unrelated to endoscopic and pharmacological treatments, such as organisational factors, early endoscopy, specialty-based management, and the use of predetermined care protocols may have a major impact on clinical outcomes. In order to further improve the management of NVUGIB, precise information regarding these issues is needed in clinical practice.

1
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3 The aim of the European Survey of Non-variceal Upper Gastrointestinal Bleeding
4
5 (ENERGIB) was to report on outcomes across different countries and evaluate a
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7
8 number of variables possibly associated with outcomes of acute NVUGIB including
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10 clinical predictors, management strategies and healthcare resource utilisation in a
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12 'real-world', European, clinical practice setting. This report focuses on the predictors
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14 of poor outcomes of NVUGIB in terms of bleeding continuation/re-bleeding and
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16 mortality.
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For Peer Review

Patients and Methods

Study design and patients

ENERGIB (ClinicalTrials.gov Identifier: NCT00797641; study code: NIS-GEU-DUM-2008/2) was an observational, retrospective cohort study carried out across multiple centres in seven countries (Belgium, Greece, Italy, Norway, Portugal, Spain and Turkey). Eligible patients were adult (aged 18 years or older) men and women who underwent endoscopy due to overt NVUGIB at participating hospitals. Both patients admitted to the hospital because of NVUGIB and those admitted for another reason who developed NVUGIB during hospitalisation were eligible. Overt NVUGIB was defined as haematemesis/coffee ground vomiting, melaena, haematochezia and other clinical or laboratory evidence of acute blood loss from the upper GI tract confirmed by upper GI endoscopy. Patients with incomplete medical records were excluded from the study.

The initial enrolment period was between October 1 and November 30, 2008. In order to avoid bias in patient selection, all consecutive patients admitted to hospital with NVUGIB were identified by hospital computer records based on ICD-9 codes¹⁷. Based on a previous internal survey and in order to have a representative sample from each country, we estimated that 20 consecutive patients per centre matching the required diagnosis would require around 20 centres per country and around 2 months for large general hospitals. Data were extracted by specialists from participating centres. If the number of patients identified during the initial recruitment period was lower than the recruitment target for each centre, further selection windows were used to ensure adequate enrolment of patients. If the number of patients was greater than the recruitment target, study participants were selected at random among eligible

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3 patients. The study was designed in line with the ethical principles described in the
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5 Declaration of Helsinki, and the final study protocol was approved by local ethics
6
7 committees in each participating country. As this was a non-interventional study, the
8
9 management of patients was according to routine practice at each centre. Data were
10
11 collected retrospectively from patient medical records in relation to the initial
12
13 NVUGIB episode and up to 30 days afterwards.
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19 **Outcome definition**

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21 The main outcome variables were continued bleeding following therapeutic
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23 endoscopy, re-bleeding, need for surgical procedures to control bleeding (other than
24
25 endoscopic treatment) and in-hospital and 30-day all-cause mortality. Bleeding
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27 continuation was defined as one of the following: spurting from an artery at the initial
28
29 endoscopic examination, which did not respond to endoscopic therapy or persisted
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31 following initial endoscopy; red bloody nasogastric aspirate; shock with pulse >100
32
33 beats/min, systolic blood pressure <100 mmHg, or both; or need for substantial
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35 replacement of blood and fluid volume (transfusion of >3 units of blood within
36
37 4 hours) following endoscopy. Re-bleeding was defined as recurrent vomiting of fresh
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39 blood, melaena, or both with either shock or a decrease in haemoglobin level of ≥ 20
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41 g/L following initial successful treatment.
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49 This report focuses on clinical factors predictive of a poor outcome of an initial
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51 NVUGIB episode, defined as bleeding continuation/re-bleeding or all-cause mortality
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53 within 30 days.
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Statistical analysis

Multivariable analyses were performed using random-intercept mixed-model logistic regression to account for clustering by study centre. Model creation and selection was based on *a priori* clinical and biological considerations. PPI use before endoscopy was used as an adjustment factor in every model. Raw (univariate) and multivariable adjusted odds ratios and 95% confidence intervals (CIs) were calculated from the logistic regression coefficients and standard errors. The significance level was 5% for keeping independent predictors in the models.

Sample size calculation

A target sample size of 400 patients per country was established in order to obtain country-specific estimates of the incidence of 30-day bleeding continuation/re-bleeding with 95% CIs of width $\pm 3.5\%$, based on an expected combined endpoint incidence of 14.1%.¹¹

Results

Patients and initial management of NVUGIB

A total of 123 centres participated in the study, with the following distribution per country: Belgium (26 centres), Greece (10), Italy (11), Norway (16), Portugal (12), Spain (24) and Turkey (24). A total of 2664 patients were included in the study, and 2660 patients were eligible for the statistical analyses (4 patients were excluded because of missing data); patients had a mean age of 66.7 years and 64.7% of patients were men. The majority of patients (85.3%) were admitted due to NVUGIB; however, the proportion of inpatients was substantially higher in Belgium (29.7%) than in other

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3 European countries (3.8–19.8%). Patients' demographics and clinical characteristics,
4 by country of origin, are summarised in Table 1.
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9 Overall, 33.0% of patients were haemodynamically unstable (most commonly
10 presenting with tachycardia [18.3%]). The most common symptoms of NVUGIB
11 were melaena (67.9% of patients), haematemesis (fresh blood and coffee ground
12 vomiting; 42.7%) and shock/syncope (9.0%). The endoscopic diagnoses most
13 commonly underlying NVUGIB were duodenal ulcer (34.6% of patients) and gastric
14 ulcer(s) (28.7%). Patients were most commonly managed in general medical wards
15 (37.0%); emergency observation was required for 14.3% of patients. The descriptions
16 of bleeding episode characteristics and hospital management strategies are
17 summarised in Table 2. A gastroenterology team managed the event in 46.7% of cases
18 with great variability across countries (19.4% in Portugal vs 64.8% in Turkey), as was
19 the case for PPI before endoscopy (66.0% overall, but 32.6% in Belgium vs. 87.7% in
20 Turkey). Endoscopic therapy was applied in 35.8% of cases (24.9% in Greece to
21 47.6% in Spain). Therapeutic procedures applied during endoscopy were epinephrine
22 injection (24.6%), ulcer base injection sclerotherapy (11.5%), endoclip (s) applied
23 (8.3%), BICAP / heater probe (3.6%), argon plasma coagulation (5.0%), variceal
24 banding (0.3%), variceal injection / sclerotherapy (0.2%), glue injection (0.2%), and
25 others (0.8%). Among the 1548 (58.3%) patients with stigmata of recent
26 haemorrhage, 571 (21.5%) patients had blood in upper GI tract, 343 (12.9%) had
27 visible vessel, 325 (12.3%) had oozing bleeding, 323 (12.2%) had adherent clot, 218
28 (8.2%) had dark spot in ulcer base, 107 (4.0%) had red spot / wheal markings, 101
29 (3.8%) had spurting vessel and 12 (0.5%) had nipple sign.
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Outcomes of NVUGIB

Overall, 12.3% of patients experienced bleeding continuation/re-bleeding within 30 days of the initial NVUGIB episode. Continued bleeding was observed in 7.3% of patients, while 10.5% of patients experienced re-bleeding within 30 days. A second-look endoscopy was performed in 28.6% of patients, but in most cases no therapeutic endoscopy was performed. The proportion of patients undergoing surgery (other than endoscopy) to control bleeding was low at 3.3%. The mortality rate within 30 days of the bleeding event was 5.2%. There were significant unadjusted differences across countries in these outcomes ($p=0.017$ for bleeding continuation/re-bleeding and $p=0.005$ for any death) (Figure 1).

Clinical predictors of poor outcomes

Predictors for bleeding continuation and re-bleeding were very similar (data not shown) and therefore, since these two outcomes imply a failure to control bleeding, here we report the combined outcome. The determinants for bleeding continuation/re-bleeding are summarised in Figure 2. The multivariate analysis did not detect differences across countries in this outcome. No differences were also observed concerning the type of team managing the bleeding event or size of hospital (defined as those with ≥ 500 beds). However, the number of comorbidities, bleeding during hospitalisation for other non-GI bleeding reasons, age >65 years and a history of NVUGIB were associated with an increased risk of bleeding continuation/re-bleeding. Bleeding from a gastric or duodenal ulcer was associated with a worst outcome; however, bleeding from acute mucosal lesions, or associated with anticoagulants or use of non-steroidal anti-inflammatory drugs (NSAIDs) had a lower risk.

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3 The multivariate analysis for predictors of death showed no differences by country
4 and only Spain was close to significance for a lower risk with Belgium as a reference
5 group. Also, the size of the hospital, the type of team managing the bleeding event,
6 the type of lesion causing the bleeding event or therapy were not linked to this
7 outcome. Only the number of comorbidities, age >65 years, alcohol abuse, presence
8 of haematemesis at admission, duodenal ulcer as the cause of bleeding, and bleeding
9 during hospitalisation for other non-GI bleeding reasons were associated with
10 increased risk of death. On the contrary, use of low-dose acetylsalicylic acid (ASA;
11 aspirin) was associated with decreased risk of death (Figure 3). When data were
12 analysed to identify the determinants of poor outcomes in large teaching hospitals
13 (which represented 63.2% of all hospitals of the study) similar results were found
14 (data not shown).

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33 When the analysis was restricted to patients undergoing therapeutic endoscopy
34 (patients with high-risk stigmata for rebleeding) the rate of bleeding continuation/re-
35 bleeding was 18.8% ($n = 178$) and surgery to control bleeding was carried out in 5.6%
36 ($n = 49$) of cases; 6.0% of patients ($n = 57$) died. Table 3 summarises the predictors of
37 bleeding continuation/re-bleeding in this subset of patients. Country differences,
38 teams who managed the episode of bleeding or PPI treatment were not identified as
39 independent predictors. Unlike the whole patient cohort, hospital size was associated
40 with an increased risk of re-bleeding.
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Discussion

In this 'real-life' study, the overall rate of the combined endpoint of bleeding continuation/re-bleeding, need of surgery to control bleeding and mortality rates were found to be within the lower range of previously reported findings.^{6, 8, 9, 11, 12, 18, 19} The **ENERGIB** study therefore confirms that mortality associated with NVUGIB has not decreased substantially in recent years, despite advances in endoscopic and pharmacological therapies. We have reported bleeding continuation and rebleeding as a single outcome due to several reasons. First, both outcomes represent a similar concept which is a failure to control bleeding with medical and endoscopy therapy; second, the retrospective collection of data may not always distinguish clearly between these two events; third, by doing so, we avoid double counting, and finally the analysis of the determinants for each event report very similar results.

To our knowledge, this is the first study to characterise the outcomes of NVUGIB, and factors predictive of poor outcomes, in a 'real-world', **within a** European setting. By recruiting a significant number of centres from each participating country, and including all consecutive patients with NVUGIB within a limited period of time, we have made a picture of patient characteristics, type of management and outcomes in the participating countries that probably reflects outcomes of bleeding events in clinical practice. By doing so, we have detected important differences in the main outcomes, including death, of NVUGIB events across countries. The hypothesis was that these differences could be attributed to differences in patient management and teams dealing with bleeding patients between countries, or even within the same country depending of the size of the hospital, for example. However, further analysis of the data, in a multivariate context, has shown that these differences are basically dependent on patients' characteristics rather than differences in the clinical

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3 management of the bleeding event. One explanation for this may be the fact that the
4 two major factors affecting outcome-related bleeding – use of therapeutic endoscopy
5 for peptic ulcer bleeding and use of parenteral PPI after endoscopy – were high in the
6 whole cohort and differences between countries were minor. The analysis carried out
7 in the subgroup of patients at the highest risk for re-bleeding or death (i.e. those with
8 high-risk stigmata undergoing therapeutic endoscopy) have shown that country or
9 management factors were not associated with these outcomes. There were some
10 countries (e.g Belgium) which showed clearly a higher mortality rate when compared
11 to others, but this difference disappeared when adjusted for other important variables
12 such as comorbidities or in-hospital vs extra-hospital bleeding. The size of the
13 hospital (> 500 beds) was linked to a higher risk of re-bleeding when the analysis was
14 restricted to patients with high-risk stigmata, which may be confounded by the fact
15 that these hospitals may receive complex referral patients.
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35 Risk factors that have been previously identified to be predictive of bleeding
36 continuation and re-bleeding include: presence of comorbidities;⁶ endoscopy-observed
37 high-risk stigmata of bleeding;^{1, 6, 11} worse health status at admission;^{6, 11} bleeding
38 from a peptic ulcer;²⁰ a finding of bright blood during rectal examination and in
39 nasogastric tube aspirate;¹¹ smoking;¹¹ failure to use PPIs post-endoscopy;²⁰ post-
40 endoscopy use of intravenous or low molecular-weight heparins;²⁰ and low
41 endoscopist experience.²¹ A number of these previously identified predictive factors
42 were confirmed in ENERGIT (i.e. presence of comorbidities, bleeding from a
43 duodenal ulcer), and a number of new predictors of bleeding continuation/re-bleeding
44 were characterised: older age (>65 years), presentation with haematemesis and a
45 history of NVUGIB at baseline. A diagnosis of reflux esophagitis and admission as an
46 outpatient (vs. patients who developed acute NVUGIB whilst hospitalised for other
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3 reasons) were associated with a significantly lower risk of poor outcomes. The latter
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5 may be explained by a potentially worse health status and the presence of
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8 comorbidities among patients who were already hospitalised.
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11 Previously characterised predictors of mortality include: older age;¹¹ presence of, and
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13 increasing number of, comorbidities;^{6, 11} continued bleeding and/or re-bleeding;^{1, 6} and
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15 a finding of bright blood in the nasogastric tube aspirate.⁶ The predictive validity of
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17 older age and the presence of comorbidities were confirmed in **ENERGIB**; in fact, the
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19 presence of comorbidities was by far the strongest predictor of mortality in this patient
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21 population. Other factors identified to be significantly predictive of mortality in this
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23 study were presentation with clinical symptoms of acute upper GI bleeding
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25 (haematemesis) and alcohol abuse. Patients' use of either low- (≤ 100 mg/day) or
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28 higher dose of ASA (33% of ASA use was ≥ 100 mg/day and one third of that for
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31 ischaemic heart disease) was found to be protective against mortality, which could be
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33 related to the findings of Sung et al. that almost 80% of deaths following acute peptic
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35 ulcer bleeding were non-bleeding related.¹² Unfortunately, we do not have data on the
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37 prescription of low-dose ASA after the bleeding event in terms of whether this could
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39 have contributed to the finding of decreased mortality.
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46 The strength of this study is its observational nature and the finding that differences in
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48 outcomes of NVUGIB reported across countries does not seem to be due to
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50 differences in clinical management or health organisations attending these GI
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52 complications, at least within a European setting. While data obtained through high-
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54 quality, randomised controlled trials are very valuable; there is a difference between
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56 outcomes in such studies and outcomes that can be observed in everyday clinical
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58 practice in the general population. As all patients included in the **ENERGIB** study
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3 were treated according to the standard clinical care protocol at each participating
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5 study site, the results of this study are able to represent a 'real-world' scenario of the
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7 outcomes of NVUGIB in the community. The observational, pan-European nature of
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10 **ENERGIB** means important information based on a large and diverse group of
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12 patients is accessible.

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16 However, the methodological limitations inherent in the design of all observational,
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18 retrospective studies must also be considered. In this way, the variable described as
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20 alcohol abuse is not well defined and may represent a wide spectrum of alcohol use.
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23 However, it is reasonable to assume that patients with no or sporadic use have not
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25 been ascribed here. The variable was associated with increased risk of mortality and
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27 not with rebleeding, which we believe makes sense, since mortality is linked to
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29 morbidity rather than to the bleeding event in most cases¹². Also, the severity of the
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31 comorbidities has not been taken into account, which could have determined a more
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33 specific profile for poor outcomes, but the retrospective collection of data does not
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35 allow this. Other factors that have been linked to fatality rates in upper GI bleeding
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37 such as social deprivation, day of the week of hospitalisation etc²² have not been
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39 considered. Another limitation is that some countries are represented with less number
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41 of centres, but with the total patient number overlapping each other, which may
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43 impact the results by over-representing different clinical expertise. The inclusion of
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45 these variables in the logistic regression model limit this impact but may not
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47 overcome all potential bias. Finally, we need to point out that we may have missed
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49 bleeding events with no endoscopy study. Although we believe these to be very few,
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51 they may represent either very severe or very mild events. The potential for large
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53 differences in medical record keeping across the sites and European studies included
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55 in **ENERGIB** may also have impacted the results. As this study design is not
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3 experimental, any new predictive factors for bleeding continuation/re-bleeding and
4 mortality need to be reassessed in an independent, prospective setting. In any case we
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6 believe that the sample size of the data collected and the results obtained represent
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8 those of each country and probably they can be expanded to, at least, part of Europe,
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10 since although there was a predominance of Southern European Mediterranean
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12 countries, there were 2 others such as Belgium and Norway that can be considered
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14 North European countries.
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27
28 the first and subsequent drafts.
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33 34 Disclosures of Interest

35
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37
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46 employee of AstraZeneca
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Table 1. Summary of patient baseline characteristics, by country^a

	Overall (<i>n</i> = 2659)	Belgium (<i>n</i> = 426)	Greece (<i>n</i> = 201)	Italy (<i>n</i> = 402)	Norway (<i>n</i> = 400)	Portugal (<i>n</i> = 404)	Spain (<i>n</i> = 403)	Turkey (<i>n</i> = 423)
Age, years (SD)	66.7 (17.2)	69.0 (15.5)	66.3 (15.1)	68.1 (16.5)	72.0 (14.7)	68.5 (17.0)	65.4 (18.0)	57.8 (18.9)
Men, %	64.7	58.7	68.7	66.2	55.8	66.8	71.7	67.4
History of alcohol abuse, %	13.7	18.5	13.9	8.5	12.8	16.6	20.6	5.4
Current smoker, %	17.8	16.4	22.4	13.7	24.0	9.4	20.6	20.3
Comorbidities (≥1), %	68.3	76.3	60.7	64.7	77.0	72.0	62.5	60.8
Comorbidities, number (SD)	1.17 (1.11)	1.47 (1.23)	1.05 (1.13)	1.14 (1.13)	1.39 (1.14)	1.07 (0.90)	1.11 (1.16)	0.91 (0.92)
Ischaemic heart disease, %	21.8	28.6	31.8	19.9	32.0	14.1	10.7	20.1
Congestive heart failure, %	11.8	15.0	11.9	8.7	14.8	10.9	13.6	7.6
Respiratory disease, %	10.9	15.0	7.0	10.4	13.5	9.4	13.2	5.7
Cancer, %	9.7	16.0	5.5	9.7	13.0	6.4	9.4	5.4
Stroke, %	8.5	9.9	6.5	7.5	12.0	8.4	9.9	4.7
Dementia, %	4.3	4.2	4.0	5.7	5.3	6.2	3.7	1.0
Cirrhosis, %	4.2	6.3	1.0	7.0	2.5	6.2	4.0	1.0
Renal disease, %	9.0	12.2	7.5	10.9	9.8	7.7	7.2	6.6
Other significant disease, %	37.3	39.4	30.3	34.6	36.5	37.6	39.5	39.2

Table 1. Contd

	Overall (n = 2659)	Belgium (n = 426)	Greece (n = 201)	Italy (n = 402)	Norway (n = 400)	Portugal (n = 404)	Spain (n = 403)	Turkey (n = 423)
History of NVUGIB, %	16.1	10.1	14.4	16.9	15.5	16.3	20.1	18.4

^aDemographic characteristics were missing for one patient.

NVUGIB, non-variceal upper gastrointestinal bleeding; SD, standard deviation.

For Peer Review

Table 2. Summary of bleeding episode characteristics and management strategies

	Overall (n = 2655)
Bleeding episode characteristics	
Bleeding episode occurring outside of hospital, %	85.3
Haemodynamically stable (systolic blood pressure > 100 mm Hg and pulse < 100), %	62.4
Haematemesis, %	42.6
<i>Helicobacter pylori</i> test, % performed	32.4
Esophagitis, %	11.0
Stomach gastritis/erosion(s), %	15.7
Gastric ulcer, %	28.7
Erosive duodenitis, %	6.4
Duodenal ulcer, %	34.6
Management strategy (n = 2644)	
General medical ward, %	37.0
Emergency observation, %	14.3
Gastroenterology team, %	46.7
Mean duration of hospitalisation in days (SD)*	6.9 (5.9)
Therapeutic procedure during endoscopy, %	35.8
Pre-endoscopy PPI treatment, %	66.0
Post-endoscopy PPI treatment, %	92.6

*Overall (n = 2444).

SD, standard deviation; PPI, proton pump inhibitor.

Table 3. Significant predictors of bleeding continuation/re-bleeding and/or mortality among patients undergoing therapeutic endoscopy (n = 951)

	Bleeding continuation/ re-bleeding (n = 178)		Mortality (n = 57)	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (>65 vs ≤65 years)	1.81 (1.21–2.70)	0.004	2.66 (1.46–4.83)	0.002
Hospital size (large vs other)	1.59 (1.02–2.47)	0.04	0.74 (0.33–1.67)	0.48
Admission (inpatient vs outpatient)	1.55 (0.97–2.47)	0.07	2.92 (1.69–5.06)	<0.001
Duodenal ulcer diagnosis	1.48 (1.01–2.18)	0.05	1.17 (0.68–2.00)	0.58
History of alcohol abuse	1.36 (0.83–2.25)	0.23	4.32 (2.38–7.85)	<0.001
Comorbidities (per comorbidity)	1.13 (0.96–1.33)	0.14	1.72 (1.40–2.12)	<0.001
Low-dose ASA (≤100 mg/day)	0.89 (0.57–1.38)	0.61	0.39 (0.21–0.73)	0.004
High-dose ASA (>100 mg/day)	0.83 (0.47–1.46)	0.52	0.13 (0.04–0.41)	0.001

ASA, acetylsalicylic acid (aspirin); CI, confidence interval; OR, odds ratio.

Other non-significant factors included in the models: Country, Sex (male vs. female), History of alcohol abuse, History of NVUGIB, Hematemesis, NSAIDS, Warfarin, Oesophagitis diagnosis, Gastric ulcer diagnosis, Gastritis \ Erosions diagnosis, Erosive duodenitis diagnosis, Intra-hospital management by GI bleeding team / Gastroenterology. PPI use before endoscopy was used as adjustment factor in these models.

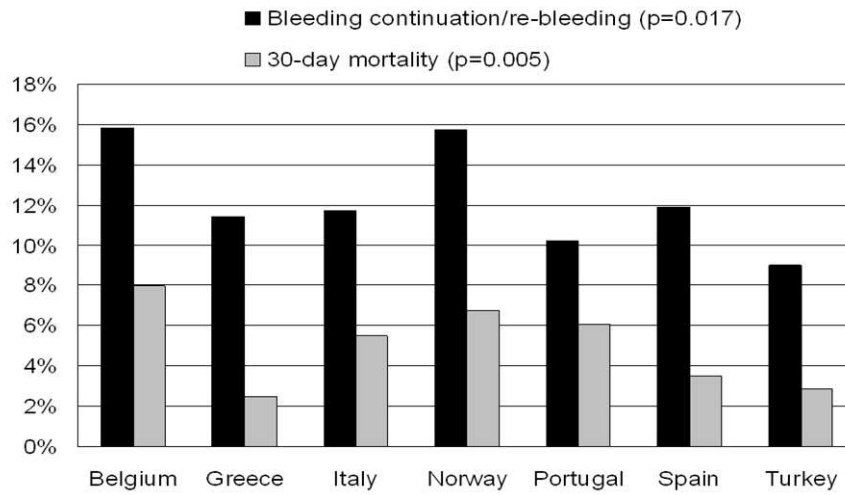
Figure Legends

Figure 1. Inter-country differences in rates of bleeding continuation/re-bleeding and 30-day mortality among patients with non-variceal upper gastrointestinal bleeding (unadjusted chi-squared test p-values).

Figure 2. Factors significantly predictive of the combined endpoint of bleeding continuation/re-bleeding within 30 days of the initial non-variceal upper gastrointestinal bleeding (NVUGIB) episode.

Figure 3. Factors significantly predictive of mortality within 30 days of the initial non-variceal upper gastrointestinal bleeding (NVUGIB) episode.

FIGURE 1

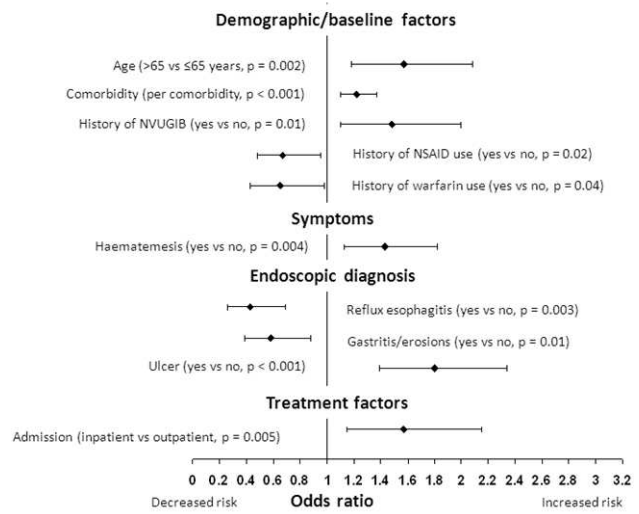


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FIGURE 2

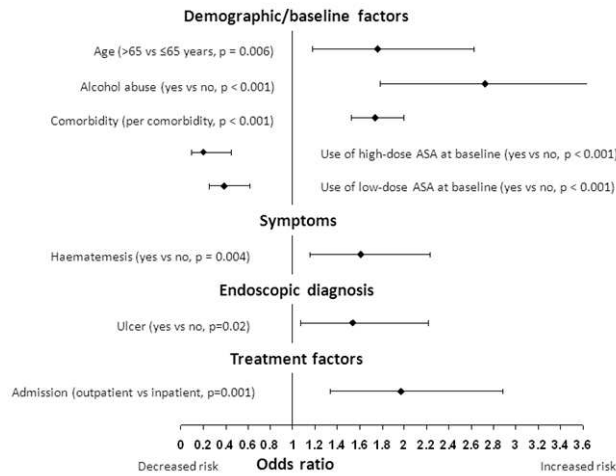


Footnote:
 Other non-significant factors included in the model: Country, Hospital size (large vs. small), Sex (male vs. female), History of alcohol abuse, Aspirin high dose, Aspirin low dose, Erosive duodenitis diagnosis and Intra-hospital management by GI bleeding team / Gastroenterology, PPI use before endoscopy was used as adjustment factor in this model.

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FIGURE 3



Footnote

Other non-significant factors included in the model: Country, Hospital size (large vs. small), Sex (male vs. female), History of NVUGIB, NSAIDs, Warfarin, Oesophagitis diagnosis, Gastritis / Erosions diagnosis, Erosive duodenitis diagnosis and Intra-hospital management by GI bleeding team / Gastroenterology. PPI use before endoscopy was used as adjustment factor in this model.

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