European Heart Journal Supplements (2023) **25** (Supplement E), E25–E32
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad103

Previous antithrombotic therapy does not have an impact on the in-hospital mortality of patients with upper gastrointestinal bleeding

Marek Hozman[1], Sabri Hassouna[2], Lukas Grochol[3], Petr Waldauf[4], Tomas Hracek[5], Blanka Zborilova Pazdiorova[6], Stanislav Adamec[7], and Pavel Osmancik[2]*

[1]Cardiocenter, Hospital Karlovy Vary, 360 01 Karlovy Vary, Czech Republic; [2]Cardiocenter, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Ruska 87, 100 00 Prague, Czech Republic; [3]2nd Department of Internal Medicine, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady,100 00 Prague, Czech Republic; [4]Department of Anaesthesia and Intensive Care, 3rd Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, 100 00 Prague, Czech Republic; [5]Department of General Surgery, 3rd Faculty of Medicine, Charles University, Faculty Hospital Kralovske Vinohrady, 100 00 Prague, Czech Republic; [6]Department of Gastroenterology, Hospital Karlovy Vary, 360 01 Karlovy Vary, Czech Republic; and [7]Department of Gastroenterology, Hospital Cheb, 350 02 Cheb, Czech Republic

KEYWORDS
Anticoagulants;
Antiplatelet treatment;
Comorbidity;
Gastrointestinal haemorrhage;
Outcome assessment

The association between antithrombotics (ATs) and the risk of gastrointestinal bleeding is well known; however, data regarding the influence of ATs on outcomes are scarce. The goals of this study are: (i) to assess the impact of prior AT therapy on in-hospital and 6-month outcomes and (ii) to determine the re-initiation rate of the ATs after a bleeding event. All patients with upper gastrointestinal bleeding (UGB) who underwent urgent gastroscopy in three centres from 1 January 2019 to 31 December 2019 were retrospectively analysed. Propensity score matching (PSM) was used. Among 333 patients [60% males, mean age 69.2 (±17.3) years], 44% were receiving ATs. In multivariate logistic regression, no association between AT treatment and worse in-hospital outcomes was observed. Development of haemorrhagic shock led to worse survival [odds ratio (OR) 4.4, 95% confidence interval (CI) 1.9–10.2, $P < 0.001$; after PSM: OR 5.3, 95% CI 1.8–15.7, $P = 0.003$]. During 6-months follow-up, higher age (OR 1.0, 95% CI 1.0–1.1, $P = 0.002$), higher comorbidity (OR 1.4, 95% CI 1.2–1.7, $P < 0.001$), a history of cancer (OR 3.6, 95% CI 1.6–8.1, $P < 0.001$) and a history of liver cirrhosis (OR 2.2, 95% CI 1.0–4.4, $P = 0.029$) were associated with higher mortality. After a bleeding episode, ATs were adequately re-initiated in 73.8%. Previous AT therapy does not worsen in-hospital outcomes in after UGB. Development of haemorrhagic shock predicted poor prognosis. Higher 6-month mortality was observed in older patients, patients with more comorbidities, with liver cirrhosis and cancer.

*Corresponding author. Tel: 00420-721544447, Fax: 00420-267162817, Email: pavel.osmancik@gmail.com

Structured Graphical Abstract

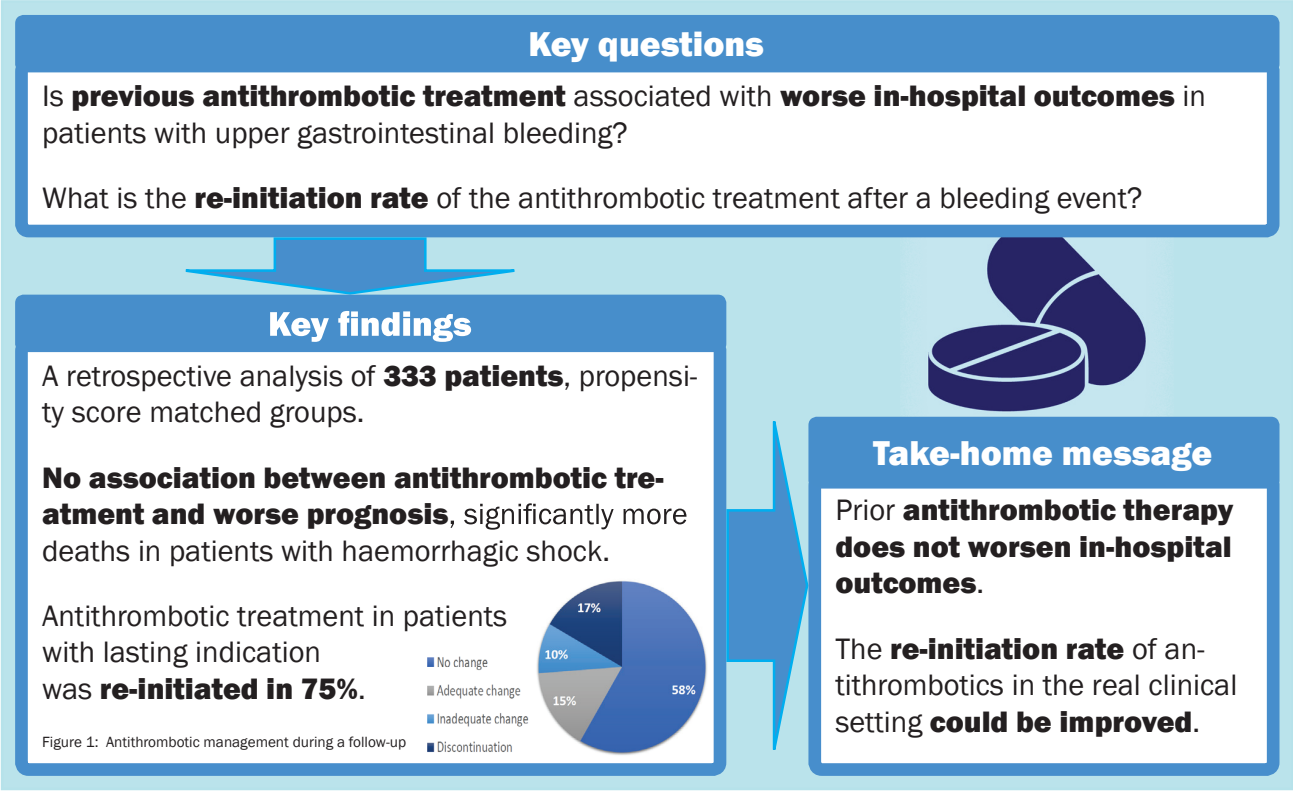

Figure 1: Antithrombotic management during a follow-up

Introduction

Bleeding represents the most frequent adverse event of antithrombotic (AT) treatment with gastrointestinal bleeding being the commonest manifestation. The reported hospitalization rate of upper gastrointestinal bleeding (UGB) based on observational data from the United States in 2012 was 67 per 100 000 inhabitants,[1] with a significant decrease over the last two decades. Nevertheless, it is still a common reason for hospitalization with a short-term all-cause mortality rate of 2–14%.[1,2] UGB can occur spontaneously, without any AT medication. However, the association between AT therapy and UGB was well documented.[3,4]

The most common indications for ATs are cardiovascular disorders, in particular coronary artery disease (CAD), atrial fibrillation (AF), and thromboembolic disease. Coronary artery disease represents the main indication of antiplatelet therapy (single or dual regimen). Both regimens, dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes or after percutaneous coronary interventions, or single antiplatelet therapy in chronic CAD patients have been documented to decrease the risk of acute coronary syndrome and improved prognosis.[5-8] In patients with AF, oral anticoagulation (OAC) with vitamin K antagonist (VKA) or direct oral anticoagulants (DOACs) significantly reduces the risk of ischaemic stroke.[9,10] However, both antiplatelet and anticoagulation treatment increases the risk of gastrointestinal bleeding, and often leads to withdrawal of AT treatment, both in the short term or in the long term. The discontinuation rate in 'real-world clinical settings' can even reach 40% per 1.1 years as reported by Yao *et al.*[11] with the AT drugs withdrawal being associated with a significantly increased risk of ischaemic events. Of note, there are data suggesting that ischaemic strokes after discontinuation of AT therapy are associated with higher mortality.[12] Since most bleeding events can be resolved using pharmacological or non-pharmacological treatments, withdrawal of AT drugs could affect a patient's prognosis more negatively than the bleeding event itself.

In our study, we focused on patients admitted for acute UGB. The goals of the present analysis were (i) to assess the prognostic significance of AT treatment in patients with acute UGB and (ii) to assess the rate of AT treatment re-initiation in patients with persistent indication for ATs after the bleeding event.

Methods

Study design

The study was a retrospective cohort study. It included all patients who underwent acute upper gastrointestinal endoscopy for acute UGB from 1 January 2019 to 31 December 2019 in the Karlovy Vary Region (Karlovy Vary

and Cheb Regional Hospital) and in the University Hospital Kralovske Vinohrady (Prague). All three hospitals provide 24/7 endoscopy cover for the surrounding regions (25 000 and 30 000 inhabitants). The study was approved by the local institutional ethics committee.

Upper gastrointestinal bleeding was defined as clinical signs (i.e. haematemesis/coffee ground vomiting, melena, enterorrhagia) and/or a decrease in haemoglobin levels greater than 10 g/L within 24 h and the presence of a causative lesion confirmed by urgent gastroscopy. Only patients with emergency admission or bleeding events in patients already hospitalised for another reason were included in the analysis; outpatient treatments were excluded. Other excluded patients were those with no signs of bleeding on endoscopy and individuals undergoing endoscopy for anaemia but lacking other signs (either clinical or laboratory) of acute UGB. Patients with lower gastrointestinal bleeding were also not included.

All-cause death (in hospital and within 6 months after the bleed) included deaths due to any cause and not only those related to gastrointestinal bleeding.

Demographic data, data from the bleeding event, concomitant therapy, laboratory findings (blood count, biochemistry, and coagulation parameters), and comorbidities were obtained from the electronic hospital database system. Regarding blood counts, the lowest value of haemoglobin concentration and haematocrit were collected. Regarding other important laboratory findings (such as renal and liver functions, coagulation parameters, and platelet count), the values obtained from the first analysis (usually before the endoscopy procedure) were used. The haemoglobin drop was calculated as the difference between the average haemoglobin concentration within 4 months prior to the index hospitalization (or the value obtained from the first analysis on admission) and the lowest haemoglobin concentration after the bleeding episode.

For the follow-up period (i.e. 6 months after bleeding events), data from the electronic database were used, patients with incomplete database records from the follow-up period were contacted via phone.

Other collected variables that need further explanation are: (i) shock was defined as hypotension (systolic blood pressure < 90 mmHg) requiring fluid resuscitation or the administration of vasoactive agents, (ii) heart failure was defined as heart failure with a reduced ejection fraction < 40%, and symptoms typical for heart failure, (iii) CAD was defined as angiographically documented obstructive coronary atherosclerosis or previous percutaneous coronary intervention, (iv) myocardial infarction was defined as angiographic evidence of coronary thrombus together with the elevation of cardiac troponin or a regional wall motion abnormality on echocardiography with corresponding ECG changes (Q waves), (v) malignancy was defined as cancer without complete remission, and (vi) peripheral arterial disease was defined as documented obstructive atherosclerosis or previous percutaneous transluminal angioplasty of arteries in following regions: carotid, vertebral, mesenterial, renal, upper and lower extremities.

Statistics

The collected data were analysed using SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA) software. The Chi-squared test was used to test differences of dichotomous categorical variables between groups. To assess the normal distribution of continuous variables, the Shapiro–Wilk test of normality was used. To compare continuous variables of two groups, the Whitney–Mann *U* test or the Student's *t*-test was used. The effect of AT treatment and other independent variables on in-hospital and 6-month mortality was assessed using a multivariate logistic regression. Initially, a univariate logistic regression analysis was performed using various clinical variables. All variables showing a value $P < 0.15$ were included in the multivariate stepwise logistic regression. All tests were two-tailed and were performed at the 5% significance level.

To ensure comparable baseline characteristics, a propensity score matching (PSM) was performed (1:1 matching ratio, nearest-neighbour algorithm, caliper 0.2 times the standard deviation of the logit of propensity score[13]). The selected covariates used to calculate the propensity scores were gender, sex, coexisting diseases (diabetes mellitus, heart failure, chronic kidney disease, liver cirrhosis), and Charlson comorbidity index (CCI). Between the matched groups (antiplatelets vs. control, anticoagulants vs. control, antiplatelets vs. anticoagulants), in-hospital mortality and complications were compared.

Study population

Of the 388 screened patients who underwent an urgent gastroscopy, 55 were excluded from the study for reasons mentioned above (mainly for the absence of an endoscopically confirmed causative lesion), and 333 patients entered the analysis.

The study population consisted predominantly of men (200/333, 60.0%). The observed mean age was 69.2 (±17.3) years. Twenty-six (7.8%) patients had a history of gastrointestinal bleeding. In total, 145 (44%) patients were on AT therapy at the time of the gastrointestinal bleeding event. The CCI suggested a relatively high comorbidity burden [median 6, inter-quartile range (IQR): 4–8]. The baseline characteristics are detailed in *Table 1*; comparing patients with and without AT treatment, the latter group was older and, as expected, had higher prevalence of cardiovascular comorbidities. Chronic kidney disease was also more frequent among AT drug users. The higher prevalence of cancer in the group without AT treatment was borderline statistically significant. On the other hand, we observed no difference in diabetes mellitus.

Regarding AT treatment, the observed regimens were as follows: low-dose Aspirin in 61 (42%), VKA in 48 (33.5%), combined treatment (i.e. DAPT or anticoagulant plus antiplatelet) in 19 (13%), DOACs in 16 (11%), and low molecular weight heparin in 1 (0.5%).

Laboratory findings in AT users and non-users are summarised in *Table 2*. A significant difference was observed in coagulation parameters and in creatinine concentration (higher prevalence of chronic renal failure in patients with AT therapy).

Results

Short-term (in-hospital) outcomes and endoscopic findings

The overall hospital-mortality rate was 12.3%. In 12 (29.2%) patients who died during hospitalization, the

bleeding was classified as a cause of death, the other died from different causes with nosocomial infections and multi-organ failure progression being the most prevalent ones.

Comparing the endoscopic findings, the most prevalent causative lesion was a peptic ulcer (46%), with gastric ulcers being more prevalent than duodenal ulcers. There were more variceal bleedings observed among patients without ATs (17.6 vs. 8.3%, $P = 0.014$).

Number of patients requiring blood transfusions did not differ comparing AT drug users and non-users (67.6 v.s. 59.0%, $P = 0.1$). Eleven (3.3%) patients underwent urgent surgery. Haemorrhagic shock requiring the administration of vasoactive agents occurred in 53 (15.9%) patients.

According to the multivariate logistic regression, the only predictor associated with higher risk for in-hospital death, before and after PSM, was the occurrence of haemorrhagic shock [odds ratio (OR) 4.4, 95% confidence interval (CI) 1.9–10.2, $P < 0.001$; after PSM: OR 5.3, 95% CI 1.8–15.7, $P = 0.003$]. Of note, patients receiving AT treatment did not have a significantly higher risk of in-hospital death (OR 2.0, 95% CI 0.8–5.1, $P = 0.1$; after PSM: OR 1.8, 95% CI 0.6–5.7, $P = 0.3$). Higher comorbidities burden showed to be also significant predictor of in-hospital mortality in the analysis performed without PSM (OR 1.3, 95% CI 1.1–1.6, $P = 0.012$); however, it lost statistical significance after PSM (OR 1.4, 95% CI 1.0–1.8, $P = 0.3$) which could have been caused by a reduction of the analysed cohort size during PSM. A history of cancer also narrowly missed statistical significance (after PSM: OR 3.0, 95% CI 0.9–10.4, $P = 0.08$). Interestingly, a history of hypertension was associated with better in-hospital outcomes before and after PSM (OR 0.2, 95% CI 0.1–0.6, $P = 0.001$; after PSM: OR 0.3, 95% CI 0.8–0.9, $P = 0.003$). The impact of other independent variables on in-hospital mortality is shown in *Table 3* (before PSM) and in *Table 4* (after PSM).

To assess the impact of antiplatelet and anticoagulant drugs on in-hospital adverse events (death, shock, administration of blood transfusion, and the magnitude of the haemoglobin drop), we evaluated three pairs of propensity score-matched cohorts: antiplatelet drugs vs. no AT treatment, anticoagulants vs. no AT treatment, and antiplatelet vs. anticoagulants (*Table 5*). Significantly higher number of patients with anticoagulants needed blood transfusion compared with propensity score-matched cohort with antiplatelets (75% vs. 56%, $P = 0.01$), nevertheless this was not observed in comparison with the cohort without AT treatment.

Table 1 Baseline characteristics by antithrombotics

Characteristic	Antithrombotics		*P*-value
	Yes, $n = 145$	No, $n = 188$	
Gender			0.8
Male	88 (60.6%)	112 (59.6%)	
Female	57 (39.4%)	76 (40.4%)	
Age, mean (years)	77.7 (±9.4)	62.6 (±17.3)	<0.001
Body mass index, mean (kg/m^2)	27.8 (±5.5)	25.0 (±5.0)	<0.001
Coexisting disease			
Arterial hypertension	125 (86.2%)	86 (45.7%)	<0.001
Atrial fibrillation	72 (49.7%)	11 (5.9%)	<0.001
Coronary artery disease	56 (38.6%)	6 (3.2%)	<0.001
Peripheral arterial disease	32 (22.0%)	6 (3.2%)	<0.001
Chronic kidney disease	46 (31.7%)	19 (10.1%)	<0.001
Heart failure	29 (20.0%)	9 (4.8%)	<0.001
Diabetes mellitus	46 (31.7%)	45 (23.9%)	0.12
Liver cirrhosis	19 (13.1%)	48 (25.5%)	0.005
Cancer	11 (7.5%)	26 (13.8%)	0.07
History of event			
Myocardial infarction	39 (26.9%)	4 (2.1%)	<0.001
Ischemic stroke	19 (13.1%)	9 (4.8%)	0.03
CCI, mean	5.4 (±2.4)	6.3 (±1.8)	0.01

Pearson Chi-squared test, Student's *t*-test, Mann–Whitney *U* test.
CCI, Charlson comorbidity index.

Six-month outcomes and further antithrombotic management

The 6-month mortality rate was 31.6%. According to the multivariate logistic regression model, the independent predictors of worse outcomes were as follows: older age,

Table 2 Laboratory findings by antithrombotics

Characteristic	Antithrombotics		*P*-value
	Yes, $n = 145$	No, $n = 188$	
Minimal Hb concentration (g/L)	84.72 ± 23.64	88.99 ± 25.69	0.12
Creatinine (μmol/L)	145.05 ± 142.50	112.50 ± 91.79	0.01
ALT (μkat/L)	0.51 ± 0.68	1.09 ± 4.80	0.15
AST (μkat/L)	0.67 ± 0.76	2.29 ± 12.98	0.14
Platelet count (×10^3)	247.93 ± 104.08	255.48 ± 141.35	0.59
INR	2.23 ± 2.60	1.27 ± 0.46	<0.001
aPTT (s)	30.25 ± 18.32	23.81 ± 11.20	<0.001

Student's *t*-test.
ALT, alanine transaminase; aPTT, activated partial thromboplastin time; AST, aspartate transaminase; Hb, haemoglobin; INR, international normalised ratio.

Table 3 In-hospital outcomes (multivariate logistic regression before propensity score matching)

Variable	Death during hospitalization ($n = 41$)	Survived ($n = 292$)	Total ($n = 333$)	Odds ratio (95% CI)	*P*-value
Age, mean (years)	75.0 ± 14.1	68.4 ± 16.3	69.2 ± 16.2	1.0 (1.0-1.1)	0.8
CCI, mean	6.9 ± 2	5.6 ± 2	5.8 ± 2	1.3 (1.1-1.6)	0.012
RBC transfusion	36 (88%)	173 (60%)	209 (63%)	2.9 (1.1-8.6)	0.46
Hypertension	22 (53%)	189 (65%)	211 (64%)	0.2 (0.1-0.6)	0.001
Shock	17 (41%)	36 (12%)	53 (16%)	4.4 (1.9-10.2)	<0.001
Antithrombotics	21 (51%)	124 (42%)	145 (43%)	2.0 (0.8-5.1)	0.1
Cancer	10 (24%)	27 (9%)	37 (11%)	2.1 (0.8-5.8)	0.14

CCI, Charlson comorbidity index; RBC, red blood cell.

Table 4 In-hospital outcomes (multivariate logistic regression, propensity score-matched cohort)

Variable	Death during hospitalization ($n = 24$)	Survived ($n = 164$)	Total ($n = 188$)	Odds ratio (95% CI)	*P*-value
Age, mean (years)	78.0 ± 1.6	74.7 ± 7	75.1 ± 0.7	1.0 (1.0-1.1)	0.1
CCI, mean	7.2 ± 2.0	6.1 ± 1.9	5.8 ± 2.0	1.4 (1.0-1.8)	0.3
RBC transfusion	21 (88%)	97 (59%)	118 (62%)	2.9 (1.1-8.6)	0.46
Hypertension	13 (54%)	119 (73%)	132 (70%)	0.3 (0.8-0.9)	0.03
Shock	11 (45%)	22 (13%)	53 (16%)	5.3 (1.8-15.7)	0.003
Antithrombotics	12 (50%)	82 (50%)	145 (43%)	1.8 (0.6-5.7)	0.3
Cancer	7 (29%)	15 (9%)	37 (11%)	3.0 (0.9-10.4)	0.08

CCI, Charlson comorbidity index; RBC, red blood cell.

Table 5 In-hospital complications and mortality of the study patients (propensity score-matched cohorts)

Outcome			Odds ratio (95% CI)	*P*-value
	Antiplatelet $n = 63$	Control $n = 63$		
Death	9 (14%)	7 (11%)	1.3 (0.5-3.8)	0.6
Shock	9 (14%)	14 (22%)	0.6 (0.2-1.5)	0.2
RBC transfusion	42 (67%)	37 (58%)	1.4 (0.7-2.9)	0.4
Hb drop, mean	27.3 ± 22.6	22.5 ± 19.3	NA	0.2
	Anticoagulant $n = 57$	Control $n = 57$		
Death	5 (9%)	7 (12%)	0.6 (0.2-2.3)	0.5
Shock	7 (12%)	10 (18%)	0.6 (0.2-1.9)	0.4
RBC transfusion	37 (65%)	33 (57%)	1.3 (0.6-2.8)	0.4
Hb drop, mean	30.4 ± 20.5	24.5 ± 20.9	NA	0.1
	Anticoagulant $n = 70$	Antiplatelet $n = 70$		
Death	10 (14%)	7 (10%)	1.5 (0.5-4.1)	0.4
Shock	11 (16%)	11 (16%)	1.0 (0.4-2.4)	1.0
RBC transfusion	53 (75%)	39 (56%)	2.4 (1.2-5.1)	0.01
Hb drop, mean	30.7 ± 22.9	26.7 ± 21.9	NA	0.3

Pearson Chi-squared test, Student's *t*-test.
Hb, haemoglobin; RBC, red blood cell.

Table 6 Six-month outcomes (multivariate logistic regression)

Variable	Death ($n = 100$)	Survived ($n = 216$)	Total ($n = 316$)	Odds ratio (95% CI)	*P*-value
Age, mean	74.1 ± 15.1	66.9 ± 16.3	69.2 ± 16.2	1.0 (1.0-1.1)	0.002
CCI, mean	6.9 ± 1.9	5.4 ± 2.1	5.9 ± 2.2	1.4 (1.2-1.7)	<0.001
BMI, mean (kg/m^2)	25.3 ± 5.2	26.9 ± 5.1	26.4 ± 5.2	0.9 (0.9-1.0)	0.053
Hypertension	62 (62.0%)	141 (65.3%)	203 (60.2%)	0.4 (0.2-0.8)	0.019
Antithrombotics	43 (43.0%)	94 (43.5%)	137 (40.7%)	0.9 (0.5-1.7)	0.8
Cancer	24 (24.0%)	12 (5.6%)	36 (10.7%)	3.6 (1.6-8.1)	0.002
Liver cirrhosis	26 (26.0%)	41 (19.0%)	67 (19.9%)	2.2 (1.0-4.4)	0.029

BMI, body mass index; CCI, Charlson comorbidity index.

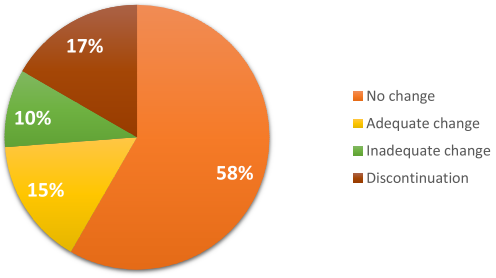

Figure 1 Antithrombotic management after the bleeding event.

higher comorbidity index, a history of cancer, and a history of liver cirrhosis (*Table 6*). A protective effect of hypertension, which was observed in the short-term outcome analysis, was preserved during the follow-up period (OR 0.4, 95% CI 0.2-0.8, $P = 0.02$). Patients with higher body mass index showed a trend towards lower mortality, which did not meet the level of statistical significance (OR 0.9, 95% CI 0.9 1.0, $P = 0.053$).

Long-term data were missing for 17 individuals (these were not further analysed). After the index hospitalization, the indication for AT therapy remained in 84/94 (89.4%) (*Figure 1*). The main reasons for continuation of AT treatment were AF in 39 (46.6%) patients and CAD in 23 (27.4%) patients. Of the 84 patients with persistent indication for AT treatment and complete follow-up data, 49/84 (58.3%) individuals continued the same AT treatment as before the bleeding event; of those, 16 (32.7%) were treated with VKA, 23 (46.9%) were treated with aspirin, 5 (10.2%) were on combined AT therapy, 4 (8.2%) used DOACs, and 1 (2.0%) clopidogrel. In another 13/84 (15.5%) patients, the antithrombotic treatment was adequately changed: in 5 patients, acetylsalicylic acid (ASA) was replaced with clopidogrel, 3 patients were switched to apixaban from another OAC, in another 4 individuals a combined AT therapy was reduced, and in 1 patient rivaroxaban was switched to VKA. In 8/84 (9.5%) individuals, the treatment was inadequately deescalated: in 4 cases, low molecular weight heparin in sub-therapeutic doses was administrated instead of OAC and in 4 cases OAC was replaced by ASA. And 14/84 (16.7%) patients with a persistent indication for AT treatment completely discontinued AT medication (9×AF, 4×CAD, 1×carotid stenosis). Interestingly, only one of the patients with AF requiring anticoagulant therapy was referred for left atrial appendage closure. Of the patients who continued AT therapy after the bleeding event, no re-bleeding was observed. Similarly, no thrombotic events were observed in patients after discontinuation or reduction of AT therapy. One patient on VKA (which was not discontinued after the bleeding event) suffered a fatal ischaemic stroke.

Discussion

In our cohort, previous AT treatment was not associated with worse survival in patients after an acute UGB. The main predictor of poor in-hospital prognosis was the occurrence of haemorrhagic shock. In the long-term perspective, the predictors of poor outcomes were older age, higher comorbidity index, a history of cancer, and a history of liver cirrhosis. Adequate AT treatment was re-initiated in the 73.8% patients within 6 months.

The in-hospital mortality rate in our cohort (12.3%) is comparable to other observational studies (6-14%).[14-17] In the report by Paspatis *et al.*,[18] case fatality during hospitalization was 5.6%; however, in the absence of any comorbidity, no death during hospitalization occurred in patients with UGB. Rockall *et al.*[17] reported 11% mortality in cohort of patients admitted for acute UGB, and similarly, only 0.1% mortality rate was observed in patients under 60 years without any comorbidity. A large observational study by Åhsberg *et al.*[19] showed using a logistic regression model, that a higher number of comorbidities is an independent risk factor of a fatal in-hospital outcome, which is in line with our results. Other factors contributing to the higher mortality are emergency admission, and bleeding in already hospitalised patients (33% mortality in in-patients bleedings reported by Rocall *et al.*).[17] Based on our observations, higher risk of in-hospital death was present in patients who developed shock during hospitalization, which was also in full agreement with previously reported studies.[20,21] Despite being hypothetically in higher risk, patients with previous AT therapy did not have worse in-hospital outcomes. In our view, AT treatment represents a removable precipitating factor. Theoretically, it can lead to earlier manifestation of a bleeding source or to manifestation of otherwise subclinical lesions. Moreover, AT withdrawal plays an important role as a treatment measure. Therefore, it

can be assumed that bleeders without AT medication are more fragile, or the causative lesion could be more severe.

Surprisingly, studies investigating the impact of AT treatment on the prognosis of patients with UGB not only failed to prove worse outcome of these patients but also showed lower short-term mortality in patients on ATs.[15,16,22] Nevertheless, we did not observe a protective effect of AT treatment described by other authors.

The mortality rate during the 6-month follow-up was higher compared with other studies, primarily reflecting higher comorbidities burden in our cohort. Worse outcomes were associated with older age, higher comorbidity index, a history of cancer, and a history of liver cirrhosis. Blatchford *et al.*[23] reported an annual population mortality in patients admitted due to acute UGB as 14%. Factors associated with higher one-year mortality were older age, pre-existing malignancy, and other severe comorbidities such as a history of hepatic or renal failure or a history of heart failure, and hypotension (shock) on admission, but not the use of ATs before the bleeding event, which is fully consistent with our findings.

Of note, in our cohort, antihypertensive drugs were associated with significantly better outcomes during the index hospitalization and during follow-up. The protective effect of previous antihypertensive treatment could be theoretically explained by renin-angiotensin-aldosterone system (RAAS) inhibition, as RAAS blocking agents play the key role in antihypertensive treatment.[24] Afessa[25] has shown that systemic inflammatory response syndrome occurs in approximately one-third of patients admitted for UGB. According to the data from experimental studies, angiotensin II provokes endothelial and microvascular dysfunction and poses pro-inflammatory activity.[26,27] Although little research has been done on this topic, hypothetically RAAS inhibition could prevent haemodynamic adverse events by lowering angiotensin II plasma level concentrations. Nevertheless, in critically ill patients presenting with developed circulatory shock, we could not expect lower mortality after RAAS blockade due to elevated angiotensin I/II ratio as was reported by Bellomo *et al.*[28]

Nearly 75% of patients continued an appropriate AT therapy after the bleeding event; of those, 27.4% were on VKA therapy and 11.3% used DOACs. The reason of more prevalent VKA treatment lies within the reimbursement guidelines, which were in force in 2019. Nevertheless, the rate of gastrointestinal bleeding on VKA and on DOACs seems to be similar, or even higher for rivaroxaban or dabigatran, which was shown in a meta-analysis by Holster *et al.*[29] Interestingly, only one of the AF patients was referred for left atrial appendage closure, which shows the underuse of this treatment modality in real clinical praxis. Antithrombotic treatment was withdrawn and not re-initiated in nearly 17% of patients. As was shown in a study by Broderick *et al.*,[12] withdrawal of ATs within 60 days precedes an ischaemic stroke in 5% of patients. Similarly, in patients with a history of ischaemic heart disease, discontinuation of low-dose ASA leads to a 1.63 times higher risk of non-fatal myocardial infarction.[30] Based on the limited data available in this field, restarting AT medication after a bleeding event probably improves outcomes of patients. A prospective observational trial by Sengupta *et al.*[31] studied 197 patients on OAC with gastrointestinal bleeding (discontinued in 39%) showed a lower risk of thrombotic events after re-initiation of ATs with no significant difference in the rate of bleeding episodes within 90 days. Similarly, Chai-Adisaksopha *et al.*[32] conclude in their meta-analysis of three studies: re-initiation of VKA led to fewer thromboembolic events [hazard ratio (HR) 0.68, 95% CI 0.52–0.88, $P < 0.004$] and lower mortality (HR 0.76, 95% CI 0.66–0.8, $P < 0.001$), but it was nor associated with significantly higher re-bleeding rate. The optimal time to restart AT treatment has been poorly studied. To the best of our knowledge, the only data comes from a study by Qureshi *et al.*[33] In this trial, anticoagulation (VKA) was re-initiated at various intervals after bleeding events [patients were divided into 5 groups: < 7 days ($n = 62$), 7–15 days ($n = 51$), 15–21 days ($n = 58$), 21–30 days ($n = 53$), and >30 days ($n = 429$)]. The mortality rate was lower in each of the first four groups (patients who resumed VKA within 30 days after bleeding) compared with the 5th group (i.e. restarted VKA after 30 days) with $P < 0.05$ for each comparison. Overall re-initiation of VKA was associated with a lower risk of thrombotic events with no difference in bleeding events, which is consistent with the study by Sengupta *et al.* Considering the aforementioned results and the absence of evidence for any relationship between AT treatment before a bleeding episode and short-term mortality, the long-term withdrawal of AT treatment in almost 17% of patients in real clinical settings is an important issue.

Study limitations

Limitations include: (i) a relatively small sample size and missing follow-up data in 17 (5%) individuals, (ii) an absence of lower gastrointestinal bleedings that were not analysed in our study, (iii) a retrospective nature of the study, and (iv) an absence of sufficient medical documentation to analyse the causes of long-term mortality.

The advantages of our study are: (i) a detailed report of comorbidities, which seems to play an important role in the prognosis of patients with gastrointestinal bleeding, (ii) an analysis of AT management during the follow-up period, and (iii) an analysis of complete, non-selected cohort of patients referred to the participating centres from surrounding regions.

Conclusions

In our cohort of patients with UGB neither ATs in general nor anticoagulants were associated with higher short-term mortality. Worse in-hospital outcomes were observed in patients who developed a circulatory shock. Long-term mortality was higher in older patients, patients with more comorbidities, with liver cirrhosis and cancer. A history of hypertension showed to be a protective factor. In 17% of patients, AT treatment was not re-initiated despite it still being indicated. One of the patients with AF was referred for left atrial appendage closure.

Funding

This study was supported by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104), funded by the European Union—Next Generation EU. Partly the manuscript was co-funded also by the Charles University Research Program "Cooperatio Cardiovascular Sciences".

Conflict of interest: None declared.

Data availability

Data can be available on reasonable request from the corresponding author.

References

1. Abougergi MS. Epidemiology of upper gastrointestinal hemorrhage in the USA: is the bleeding slowing down? *Dig Dis Sci* 2018;**63**:1091–1093.
2. Hreinsson JP, Kalaitzakis E, Gudmundsson S, Björnsson ES. Upper gastrointestinal bleeding: incidence, etiology and outcomes in a population-based setting. *Scand J Gastroenterol* 2013;**48**:439–447.
3. Hallas J, Dall M, Andries A, Andersen BS, Aalykke C, Hansen JM *et al*. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. *BMJ* 2006;**333**:726.
4. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunsø J, Gadsbøll N *et al*. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;**170**:1433–1441.
5. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R *et al*. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–1860.
6. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK *et al*. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;**358**:527–533.
7. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
8. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S *et al*. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.
9. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867.
10. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962.
11. Yao X, Abraham NS, Alexander GC, Crown W, Montori VM, Sangaralingham LR *et al*. Effect of adherence to oral anticoagulants on risk of stroke and Major bleeding among patients with atrial fibrillation. *J Am Heart Assoc* 2016;**5**:e003074.
12. Broderick JP, Bonomo JB, Kissela BM, Khoury JC, Moomaw CJ, Alwell K *et al*. Withdrawal of antithrombotic agents and its impact on ischemic stroke occurrence. *Stroke* 2011;**42**:2509–2514.
13. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;**10**:150–161.
14. Bouget J, Viglino D, Yvetot Q, Oger E. Major gastrointestinal bleeding and antithrombotics: characteristics and management. *World J Gastroenterol* 2020;**26**:5463–5473.
15. Marmo R, Occhipinti V, Zullo A, Soncini M; GISED—Gruppo Italiano per lo Studio dell'Emorragia Digestiva. Improved survival for patients with acute upper gastrointestinal bleeding while on antithrombotic therapy: a multicenter prospective cohort study. *J Clin Gastroenterol* 2022;**57**:278–284.
16. Marmo R, Koch M, Cipolletta L, Bianco MA, Grossi E, Rotondano G. *et al*. Predicting mortality in patients with in-hospital nonvariceal upper GI bleeding: a prospective, multicenter database study. *Gastrointest Endosc* 2014;**79**:741–749.e741.
17. Rockall TA, Logan RF, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. *BMJ* 1995;**311**:222–226.
18. Paspatis GA, Matrella E, Kapsoritakis A, Leontithis C, Papanikolaou N, Chlouverakis GJ *et al*. An epidemiological study of acute upper gastrointestinal bleeding in Crete, Greece. *Eur J Gastroenterol Hepatol* 2000;**12**:1215–1220.
19. Åhsberg K, Höglund P, Staël von Holstein C. Mortality from peptic ulcer bleeding: the impact of comorbidity and the use of drugs that promote bleeding. *Aliment Pharmacol Ther* 2010;**32**:801–810.
20. van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol* 2008;**22**:209–224.
21. Barkun A, Sabbah S, Enns R, Armstrong D, Gregor J, Fedorak RN *et al*. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. *Am J Gastroenterol* 2004;**99**:1238–1246.
22. Ashburner JM, Go AS, Reynolds K, Chang Y, Fang MC, Fredman L *et al*. Comparison of frequency and outcome of major gastrointestinal hemorrhage in patients with atrial fibrillation on versus not receiving warfarin therapy (from the ATRIA and ATRIA-CVRN cohorts). *Am J Cardiol* 2015;**115**:40–46.
23. Blatchford O, Davidson LA, Murray WR, Blatchford M, Pell J. Acute upper gastrointestinal haemorrhage in west of Scotland: case ascertainment study. *BMJ* 1997;**315**:510–514.
24. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J* 2018;**39**:3021–3104.
25. Afessa B. Systemic inflammatory response syndrome in patients hospitalized for gastrointestinal bleeding. *Crit Care Med* 1999;**27**:554–557.
26. Hagiwara S, Iwasaka H, Matumoto S, Hidaka S, Noguchi T. Effects of an angiotensin-converting enzyme inhibitor on the inflammatory response in in vivo and in vitro models. *Crit Care Med* 2009;**37**:626–633.
27. Corrêa TD, Jeger V, Pereira AJ, Takala J, Djafarzadeh S, Jakob SM. Angiotensin II in septic shock: effects on tissue perfusion, organ function, and mitochondrial respiration in a porcine model of fecal peritonitis. *Crit Care Med* 2014;**42**:e550–e559.
28. Bellomo R, Wunderink RG, Szerlip H, English SW, Busse LW, Deane AM *et al*. Angiotensin I and angiotensin II concentrations and their ratio in catecholamine-resistant vasodilatory shock. *Crit Care* 2020;**24**:43.
29. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa E. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013;**145**:105–112.e115.
30. Rodríguez LA, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011;**343**:d4094.
31. Sengupta N, Feuerstein JD, Patwardhan VR, Tapper EB, Ketwaroo GA, Thaker AM *et al*. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized in-patients with gastrointestinal bleeding: a prospective study. *Am J Gastroenterol* 2015;**110**:328–335.
32. Chai-Adisaksopha C, Hillis C, Monreal M, Witt DM, Crowther M. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. A meta-analysis. *Thromb Haemost* 2015;**114**:819–825.
33. Qureshi W, Mittal C, Patsias I, Garikapati K, Kuchipudi A, Cheema G *et al*. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. *Am J Cardiol* 2014;**113**:662–668.