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Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE)

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Aims There have been no large observational studies attempting to identify predictors of major bleeding in patients with acute coronary syndromes (ACS), particularly from a multinational perspective. The objective of our study was thus to develop a prediction rule for the identification of patients with ACS at higher risk of major bleeding.

Methods and results Data from 24 045 patients from the Global Registry of Acute Coronary Events (GRACE) were analysed. Factors associated with major bleeding were identified using logistic regression analysis. Predictive models were developed for the overall patient population and for subgroups of patients with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina. The overall incidence of major bleeding was 3.9% (4.8% in patients with STEMI, 4.7% in patients with NSTEMI and 2.3% in patients with unstable angina). Advanced age, female sex, history of bleeding, and renal insufficiency were independently associated with a higher risk of bleeding ($P<0.01$). The association remained after adjustment for hospital therapies and performance of invasive procedures. After adjustment for a variety of potential confounders, major bleeding was significantly associated with an increased risk of hospital death (adjusted odds ratio 1.64, 95% confidence interval 1.18, 2.28).

Conclusions In routine clinical practice, major bleeding is a relatively frequent non-cardiac complication of contemporary therapy for ACS and it is associated with a poor hospital prognosis. Simple baseline demographic and clinical characteristics identify patients at increased risk of major bleeding.

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Introduction

Recent advances in antithrombotic and mechanical therapy have resulted in significant improvements in the outcome of patients with acute coronary syndromes (ACS).[1,2] Unfortunately, the reduced risk of fatal and non-fatal cardiac complications associated with advancements in technology has also been paralleled by an increase in the incidence of bleeding complications.[3–6] Major bleeding is currently the most common non-cardiac complication of therapy for patients with ACS.

Data that are currently available about the magnitude and predictors of bleeding complications in patients with ACS have been obtained from patients enrolled in randomized clinical trials. Patients perceived to be at higher risk of complications, including those of advanced age or with renal insufficiency, are often excluded from these trials but constitute a significant percentage of patients treated for ACS. There are no contemporary data available describing the incidence, risk factors, and outcomes of bleeding complications in patients with ACS in routine clinical practice and outside the more controlled environment of randomized clinical trials. The identification of demographic, clinical, and treatment characteristics associated with an increased risk of bleeding could foster changes in the care process aimed at decreasing the frequency of major bleeding in patients at higher risk.

The objective of this study was to develop a prediction rule for the identification of patients at higher risk of major bleeding in the large, prospective, multicentre Global Registry of Acute Coronary Events (GRACE)[7,8] A secondary goal of this descriptive study was to examine whether the predictors of major bleeding differ in the different manifestations of ACS, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina.

Methods

Study patients

The study sample consisted of 24 045 patients with ACS enrolled in the Global Registry of Acute Coronary Events (GRACE) between April 1999 and September 2002 with bleeding status known. Full details of the GRACE rationale and methodology have been published elsewhere[7,8]and are briefly summarized. GRACE is designed to reflect an unbiased and generalizable sample of patients with ACS within 18 geographic locations. Currently, 94 hospitals located in 14 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, United Kingdom, United States) are participating in this observational study. These 18 geographic regions were chosen to represent care received by patients with ACS in populations that varied by demographic, clinical and treatment characteristics. Utilizing a similar approach to that adopted in the MONICA study,[9] all acute-care hospitals in a well-defined geographic area are recruited to participate in the study.

Data collection

Data were collected at each site by a trained coordinator using a standardized six-page case report form. Demographic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected. Standardized definitions of all patient-related variables and clinical diagnoses were used. All cases of confirmed acute coronary disease were assigned to one of the following categories – ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), unstable angina, and other cardiac/non-cardiac diagnoses that have been previously described.[7,8] Standardized definitions were also used for selected hospital complications and outcomes.[7,8] Major bleeding was defined as life-threatening bleeding requiring transfusion of ≥2 units of packed red blood cells, or resulting in an absolute decrease in haematocrit of ≥10% or death, or haemorrhagic/subdural haematoma. This information was obtained from the review of hospital medical records by trained nurse and physician data abstractors. Renal insufficiency was defined as any documented history of renal compromise.

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables are expressed as medians. Continuous variables were analysed using the Wilcoxon rank sum test and categorical variables were analysed using the chi-square test. Factors associated with occurrence of major bleeding episodes were identified using stepwise, multivariate, logistic regression analysis. Variables included in the initial model were those factors associated with major bleeding at a significance level of $P<0.25$. Criteria for entry and for removal of candidate variables in the stepwise analysis were assigned a significance level of $P<0.05$. Adjusted odds ratios and 95% Wald confidence intervals were computed. The linearity of the continuous variables with the log (odds) of bleeding was also assessed. A total of eight regression models were developed. The first model was developed on the entire data set and separate models were developed for our three primary diagnostic categories including unstable angina, STEMI and NSTEMI. Four additional models were developed by limiting the analysis to: (1) patients who underwent invasive diagnostic and therapeutic procedures, (2) patients who received thrombolytic therapy, (3) patients who did not receive thrombolytic therapy, (4) and to patients who did not undergo invasive diagnostic and therapeutic procedures. Model discrimination was assessed using C statistics, and goodness of fit was assessed using the Hosmer–Lemeshow statistics.[10]

Results

Baseline characteristics and frequency of major bleeding

The study sample consisted of 24 045 patients hospitalized with ACS over the period under study. A total of 933 (3.9%) patients developed major bleeding during hospitalization for ACS. Patients who developed major bleeding were significantly older, had lower mean arterial pressure and lower body mass index (Table 1). Additional baseline clinical characteristics associated with an increased risk of major bleeding were female sex,

Table 1 Baseline clinical characteristics and frequency of major bleeding

	Major bleed *n*=933 (3.0%)	No major bleed *n*=23 112 (96.1%)	*P*-value
Region			
Australia/NZ/Canada	98 (2.8%)	3440 (97.2%)	<0.001
Europe	328 (3.2%)	9826 (96.8%)	
Argentina/Brazil	121 (2.5%)	4653 (97.5%)	
USA	386 (6.9%)	5193 (93.1%)	
Age category			
Median age, years (IQR)	71.1 (61.5, 79.5)	66.2 (55.7, 75.1)	<0.001
<60	212 (2.6%)	7956 (97.4%)	<0.001
60–69	216 (3.5%)	5946 (96.5%)	
70–79	277 (4.4%)	6065 (95.6%)	
≥80	221 (6.8%)	3011 (93.2%)	
Male	530 (3.3%)	15399 (96.7%)	<0.001
Female	400 (5.0%)	7563 (95.0%)	
Medical history			
Angina (+)	543 (3.6%)	14527 (96.4%)	<0.05
Angina (−)	384 (4.4%)	8425 (95.6%)	
Myocardial infarction (+)	283 (3.8%)	7089 (96.2%)	0.97
Myocardial infarction (−)	636 (3.9%)	15892 (96.2%)	
Diabetes (+)	254 (4.4%)	5591 (95.7%)	0.03
Diabetes (−)	669 (3.7%)	17378 (96.3%)	
Hyperlipidaemia (+)	409 (3.8%)	10236 (96.2%)	0.81
Hyperlipidaemia (−)	513 (3.9%)	12640 (96.1%)	
Stroke (+)	92 (4.6%)	1931 (95.5%)	0.09
Stroke (−)	824 (3.8%)	20965 (96.2%)	
Peripheral vascular disease (+)	134 (5.5%)	2314 (94.5%)	<0.001
Peripheral vascular disease (−)	783 (3.7%)	20544 (96.3%)	
Renal insufficiency (+)	125 (6.5%)	1801 (93.5%)	<0.001
Renal insufficiency (−)	802 (3.6%)	21234 (96.4%)	
Bleeding (+)	39 (11.5%)	299 (88.5%)	<0.001
Bleeding (−)	892 (3.8%)	22729 (96.2%)	
Weight, median (kg)	73.3 (63.0, 85.0)	77.0 (67.0, 87.0)	<0.001
Height, median (m)	1.7 (1.6, 1.7)	1.7 (1.6, 1.8)	<0.001
BMI, median (kg/m$^{2)}$	26.2 (23.5, 29.8)	26.9 (24.2, 30.1)	<0.001
Systolic arterial pressure, median (mmHg)	137 (114, 160)	140 (120, 160)	<0.001
Diastolic arterial pressure, median (mmHg)	77 (62, 90)	80 (70, 90)	<0.001
Mean arterial pressure, median (mmHg)	97 (83, 110)	100 (88, 113)	<0.001
Killip class I	662 (3.5%)	18333 (96.5%)	<0.001
Killip class II	141 (4.4%)	3045 (95.6%)	
Killip class III	69 (7.1%)	904 (92.9%)	
Killip class IV	36 (13.1%)	238 (86.9%)	
ST-segment elevation myocardial infarction	387 (4.8%)	7764 (95.3%)	<0.001
Non-ST segment elevation myocardial infarction	352 (4.7%)	7088 (95.3%)	
Unstable angina	194 (2.3%)	8260 (97.7%)	

peripheral vascular disease, renal insufficiency, and history of bleeding. The development of major bleeding was more frequent in patients with STEMI or NSTEMI than in patients with unstable angina (Fig. 1).

Therapeutic interventions

Pharmacological interventions associated with an increased frequency of bleeding included diuretics, vasopressors, thrombolytic agents, platelet glycoprotein (GP) IIb/IIIa receptor blockers and unfractionated heparin (Table 2). Analysis of the potential interaction between thrombolytic therapy and GP IIb/IIIa receptor blockers and bleeding risk revealed a 3.6% incidence of major bleeding in patients who had received thrombolytic

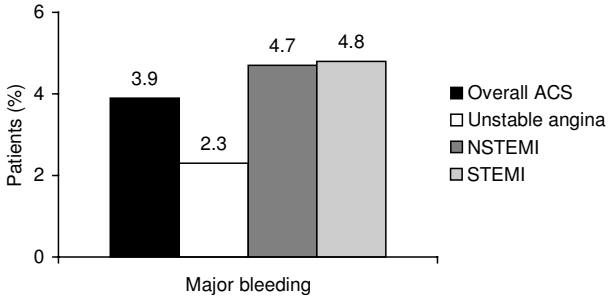

Fig. 1 Frequency of major bleeding in the overall patient population, in the group of patients with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina.

Table 2 Therapies, interventional procedures and frequency of major bleeding

	Major bleed	No major bleed	*P*-value
Aspirin, prehospital acute (+)	192 (3.6%)	5219 (96.5%)	0.15
Aspirin, prehospital acute (−)	739 (4.0%)	17849 (96.0%)	
Hospital therapies			
Aspirin (+)	828 (3.7%)	21471 (96.3%)	<0.001
Aspirin (−)	103 (6.1%)	1597 (93.9%)	
ACE inhibitors (+)	556 (3.9%)	13706 (96.1%)	0.84
ACE inhibitors (−)	368 (3.9%)	9196 (96.2%)	
Beta-blockers (+)	710 (3.7%)	18393 (96.3%)	0.03
Beta-blockers (−)	210 (4.4%)	4569 (95.6%)	
Diuretic (+)	548 (6.4%)	8022 (93.6%)	<0.001
Diuretic (−)	370 (2.4%)	14845 (97.6%)	
Calcium channel blockers (+)	267 (4.2%)	6028 (95.8%)	0.06
Calcium channel blockers (−)	646 (3.7%)	16719 (96.3%)	
Thrombolytics (+)	180 (4.3%)	3988 (95.7%)	0.1
Thrombolytics (−)	746 (3.8%)	18982 (96.2%)	
Glycoprotein IIb/IIIA receptor blockers (+)	339 (6.7%)	4734 (93.3%)	<0.001
Glycoprotein IIb/IIIA receptor blockers (−)	581 (3.1%)	18127 (96.9%)	
Thrombolytics only (+)	121 (3.6%)	3230 (96.4%)	<0.001
Glycoprotein IIb/IIIA receptor blockers only (+)	279 (6.5%)	4010 (93.5%)	
Both thrombolytics and glycoprotein IIb/IIIA receptor blockers	56 (7.6%)	685 (92.4%)	
Neither thrombolytics and glycoprotein IIb/IIIA receptor blockers	459 (3.0%)	14815 (97.0%)	
Unfractionated heparin (+)	605 (4.6%)	12447 (95.4%)	<0.001
Unfractionated heparin (−)	316 (3.0%)	10338 (97.0%)	
Low molecular weight heparin (+)	390 (3.3%)	11570 (96.7%)	<0.001
Low molecular weight heparin (−)	528 (4.5%)	11157 (95.5%)	
Unfractionated heparin only (+)	389 (4.8%)	7714 (95.2%)	<0.001
Low molecular weight heparin only (+)	178 (2.5%)	6892 (97.5%)	
Both unfractionated heparin and low molecular weight heparin	208 (4.5%)	4454 (95.5%)	
Neither unfractionated heparin or low molecular weight heparin	137 (3.8%)	3431 (96.2%)	
Vasopressors/inotropic (+)	270 (11.8%)	2028 (88.3%)	<0.001
Vasopressors/inotropic (−)	639 (3.0%)	20672 (97.0%)	
Intravenous nitrates (+)	524 (4.2%)	12027 (95.8%)	0.01
Intravenous nitrates (−)	393 (3.5%)	10720 (96.5%)	
Other vasodilator (+)	117 (6.1%)	1805 (93.9%)	<0.001
Other vasodilator (−)	790 (3.7%)	20826 (96.4%)	
Interventional procedures			
Right heart catheterization (+)	190 (14.5%)	1119 (85.5%)	<0.001
Right heart catheterization (−)	734 (3.3%)	21817 (96.8%)	
Cardiac catheterization (+)	572 (4.6%)	11989 (95.5%)	<0.001
Cardiac catheterization (−)	352 (3.1%)	10895 (96.9%)	
Percutaneous coronary intervention (+)	404 (5.5%)	6984 (94.5%)	<0.001
Percutaneous coronary intervention (−)	519 (3.2%)	15841 (96.8%)	
Coronary artery bypass grafting (+)	92 (6.0%)	1449 (94.0%)	<0.001
Coronary artery bypass grafting (−)	825 (3.7%)	21292 (96.3%)	
Intra-aortic balloon pump (+)	114 (18.2%)	512 (81.8%)	<0.001
Intra-aortic balloon pump (−)	803 (3.5%)	22243 (96.5%)	

therapy, a 6.5% incidence of major bleeding in patients who had received GP IIb/IIIa receptor blockers, and a 7.6% incidence in 741 patients who had received both. In addition, any type of invasive diagnostic or therapeutic procedure including right-heart catheterization, pacemaker placement, cardiac catheterization, percutaneous coronary intervention (PCI), coronary artery bypass surgery and intra-aortic balloon pump placement was associated with an increased risk of bleeding (Table 2).

Predictors of major bleeding

Advanced age, female sex, history of bleeding, and renal insufficiency were significantly associated with a higher risk of bleeding (Table 3), even after controlling for the influence of other variables, including hospital therapies and performance of invasive procedures. Pharmacological interventions independently associated with an increased risk of bleeding included diuretics, inotropic agents, thrombolytic agents and GP IIb/IIIa receptor blockers, and vasodilators. In addition, use of right heart catheterization and PCI were independently associated with an increased risk of bleeding (Table 3). Administration of low-molecular-weight heparin (LMWH) was associated with a lower risk of bleeding. The model C statistic was 0.75, indicating good model discrimination.

Table 3 Factors significantly associated with major bleeding in all ACS patients

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10-year increase)	1.28	1.21,1.37	<0.0001
Female sex	1.43	1.23,1.66	<0.0001
History of renal insufficiency	1.48	1.19,1.84	0.0004
History of bleeding	2.83	1.94,4.13	<0.0001
Mean arterial pressure (per 20 mmHg decrease)	1.11	1.04,1.19	0.0016
Diuretics	1.69	1.44,1.99	<0.0001
LMWH only[a]	0.70	0.57,0.85	0.0003
Thrombolytics only	1.43	1.14,1.78	0.0017
GP IIb/IIIa blockers only	1.93	1.59,2.35	<0.0001
Thrombolytics and GP IIb/IIIa blockers	2.38	1.69,3.35	<0.0001
IV inotropic agents	2.05	1.68,2.50	<0.0001
Other vasodilators	1.35	1.09,1.68	0.0068
Right-heart catheterization	2.48	1.98,3.11	<0.0001
Percutaneous coronary intervention	1.63	1.36,1.94	<0.0001

[a] Referent groups: male gender; UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor GP IIb/IIIa blockers for thrombolytics only, GP IIb/IIIa blockers only, and both thrombolytics and GP IIb/IIIa blockers; no for other variables. Hosmer–Lemeshow goodness-of-fit Test P-value=0.59; C-statistic=0.75. GP=glycoprotein; LMWH=low-molecular-weight heparin; OR=odds ratio; UFH=unfractionated heparin.

Table 4 Factors significantly associated with major bleeding in patients with ST-segment-elevation myocardial infarction

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10-year increase)	1.25	1.14,1.38	<0.0001
Female sex	1.71	1.35,2.17	<0.0001
History of bleeding	2.37	1.18,4.77	0.015
Killip class IV	1.73	1.05,2.86	0.03
Diuretics	1.45	1.12,1.87	0.005
LMWH only[a]	0.60	0.42,0.85	0.004
Thrombolytics only	1.45	1.07,1.97	0.017
GP IIb/IIIa blockers only	1.95	1.40,2.70	<0.0001
Thrombolytics and GP IIb/IIIa blockers	2.09	1.35,3.23	0.0009
IV inotropic agents	1.85	1.38,2.49	<0.0001
Other vasodilators	1.50	1.04,2.15	0.030
Right-heart catheterization	2.79	2.01,3.89	<0.0001
Percutaneous coronary intervention	1.63	1.24,2.15	0.0005

[a] Referent groups: male gender; UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor GP IIb/IIIa blockers for thrombolytics only, GP IIb/IIIa blockers only, and both thrombolytics and GP IIb/IIIa blockers; no for other variables. Hosmer–Lemeshow goodness-of-fit test *P*-value=0.99; C-statistic=0.74. GP=glycoprotein; LMWH=low-molecular-weight heparin; OR=odds ratio; STEMI=ST-segment elevation myocardial infarction; UFH=unfractionated heparin.

The multivariate regression models of factors associated with increased risk of major bleeding in patients with STEMI, NSTEMI and unstable angina are shown in Table 4, Table 5 and Table 6, respectively. In patients with STEMI, presentation in cardiogenic shock, advanced age and female sex were associated with an increased risk of major bleeding, while use of pulmonary artery catheters, PCI and GP IIb/IIIa receptors blockers were therapeutic interventions associated with an increase in risk.

Relatively similar factors were associated with the occurrence of major bleeding when the analysis was restricted to patients presenting with NSTEMI or unstable angina. In these patients, additional predictors of major bleeding were history of renal insufficiency, lower mean arterial pressure, and administration of diuretics during hospital admission (Table 5).

In patients with unstable angina, advanced age, renal insufficiency and history of bleeding were important baseline clinical characteristics associated with an increased risk of bleeding (Table 6). Administration of GP IIb/IIIa receptor blockers, and performance of invasive diagnostic or therapeutic procedures were also associated with an increased risk of bleeding in these patients.

Predictors of major bleeding in the PCI and thrombolytic groups

Several additional analyses were carried out that were limited to patients who received or did not receive thrombolytic therapy, and to patients who did or who did not undergo invasive diagnostic and therapeutic procedures. In these subgroups, relatively similar predictors of major bleeding were identified. Female sex, advanced

Table 5 Multivariate model for major bleeding in patients with non-ST-segment elevation myocardial infarction

Variable	Adjusted OR	95% CI	*P*-value
Age (per 10-year increase)	1.22	1.10,1.35	0.0002
Female sex	1.36	1.07,1.73	0.0116
History of renal insufficiency	1.53	1.13,2.08	0.0062
History of bleeding	2.18	1.17,4.08	0.014
Mean arterial pressure (per 20 mmHg decrease)	1.14	1.02,1.27	0.019
Diuretics	1.91	1.46,2.49	<0.0001
LMWH only	0.68	0.50,0.92	0.012
LMWH and UFH[a]	0.72	0.52,0.98	0.035
GP IIb/IIIa blockers only	1.86	1.43,2.43	<0.0001
Thrombolytics and GP IIb/IIIa blockers	4.19	1.68,10.4	0.002
IV inotropic agents	1.88	1.35,2.62	0.0002
Right-heart catheterization	2.01	1.38,2.91	0.0003

[a]Referent groups: male gender; UFH for LMWH only, both LMWH and UFH, and neither LMWH nor UFH; neither thrombolytics nor GP IIb/IIIa blockers for thrombolytics only, GP IIb/IIIa blockers only, and both thrombolytics and GP IIb/IIIa blockers; no for other variables. Hosmer–Lemeshow goodness-of-fit test *P*-value=0.70; C-statistic=0.73. GP=glycoprotein; LMWH=low-molecular-weight heparin; MAP=mean arterial pressure; OR=odds ratio; UFH=unfractionated heparin.

Table 6 Multivariate model for major bleeding in patients with unstable angina

Variable	Adjusted OR	95% CI	p-value
Age (per 10-year increase)	1.32	1.15,1.52	0.0001
History of renal insufficiency	1.90	1.22,2.96	0.0045
History of bleeding	3.92	2.01,7.66	<0.0001
Diuretics	1.54	1.10,2.15	0.011
GP IIb/IIIa blockers[a]	1.95	1.23,3.09	0.0042
IV inotropic agents	2.86	1.78,4.59	<0.0001
Right-heart catheterization	2.32	1.34,4.03	0.0027
Percutaneous coronary intervention	2.24	1.53,3.27	<0.0001

[a]Referent groups: male gender; neither thrombolytics nor GP IIb/IIIa blockers for thrombolytics only, GP IIb/IIIa blockers only, and both thrombolytics and GP IIb/IIIa blockers; no for other variables. Hosmer–Lemeshow goodness-of-fit test *P*-value=0.12; C-statistic=0.72. GP=glycoprotein; OR=odds ratio.

age and renal insufficiency were consistently associated with an increased risk of bleeding even when the analysis was limited to different subgroups. In addition, in the group of patients who did not undergo invasive procedures, and in patients who did not receive thrombolytic therapy, administration of LMWH was associated with a significantly lower risk of bleeding ($P<0.05$). In patients who did not receive either thrombolytic therapy or GP IIb/IIIa receptor blockers, the incidence of major bleeding was 3.4% with unfractionated heparin and 2.2% with LMWH.

Bleeding sites

The most common bleeding complications were gastrointestinal bleeding (31.5%) and vascular access site bleeds (23.8%). Retroperitoneal bleeding accounted for 6.0% of bleeding episodes, while genitourinary bleeding was observed in 4.8%. A large proportion of patients developed bleeding from only one site (90.5%). The distribution of bleeding complications was similar in patients undergoing central venous catheterization as in the overall patient population. In patients undergoing PCI, the most common bleeding complication was bleeding at the vascular access site. This was followed in order of decreasing frequency by gastrointestinal bleeding, bleeding at other unspecified sites, and retroperitoneal bleeding.

Relation between major bleeding and hospital death

The hospital case fatality rate was significantly higher in patients with major bleeding than in patients without major bleeding (18.6% vs 5.1%, $P<0.001$). Regardless of clinical presentation, development of major bleeding was associated with a higher hospital death rate (Fig. 2). After adjustment for comorbidities, clinical presentation and hospital therapies, major bleeding was independently associated with an increased risk of hospital death (adjusted odds ratio 1.64, 95% confidence interval 1.18, 2.28).

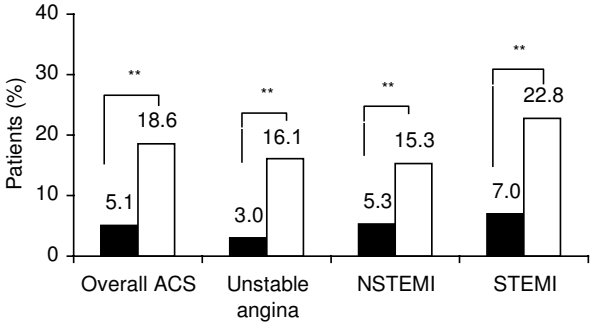

Fig. 2 In-hospital death rates in patients who developed (open bars) or did not develop major bleeding (closed bars) (STEMI=ST-segment elevation myocardial infarction; NSTEMI=non-ST-segment elevation myocardial infarction). **P< 0.001 for differences in unadjusted death rates.

Discussion

In this large, clinical-practice-based, multinational registry of patients with ACS, the overall incidence of major bleeding was 3.9%. Not surprisingly, major bleeding was more frequent in patients presenting with STEMI. This latest finding likely reflects the use of thrombolytic therapy and more frequent use of invasive procedures in these patients than in patients with unstable angina.

The incidence of major bleeding in patients with ACS reported from randomized clinical trials has varied, depending on clinical presentation and treatment. An incidence as high as 15% was reported in the TIMI I trial,[11] while an incidence of major bleeding of 4.1% was observed in the TIMI II trial.[5] In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial,[12] investigating the use of the GP IIb/IIIa receptor blocker tirofiban in patients with unstable angina and non-Q-wave myocardial infarction, the incidence of major bleeding was 4% in patients treated with tirofiban and 3% in patients treated with unfractionated heparin. Overall, our findings are consistent with a high frequency of major bleeding in patients with ACS.

Predictors of major bleeding

In our study, female sex, advanced age, renal insufficiency and history of bleeding were associated with an increased risk of bleeding. The importance of age cannot be overemphasized. Several studies have identified age as an important predictor of fatal and non-fatal complications following percutaneous or surgical coronary revascularization procedures. In particular, advanced age has been found to be associated with an increased risk of death,[13–15] vascular complications and transfusion requirement following PCI,[16,17] with an increased risk of intracranial bleeding after administration of thrombolytic therapy,[18] and with an overall increased risk of bleeding following thrombolytic[19] or antithrombotic therapy.[3] The presence of local vascular changes, or of more advanced vascular disease, has been postulated as a potential explanation for the increased incidence of bleeding complications in elderly patients. The relationship noted between female sex and bleeding risk is more difficult to interpret but confirms the findings of prior studies that have shown a higher incidence of complications in women than in men even after adjustment for other demographic variables and comorbidities.[13,15,20–22] An increased propensity for the development of vascular complications following PCI,[16,23] older average age than men, and a different threshold for transfusion as a result of a lower baseline haemoglobin are all possible explanations for the increased risk of major bleeding in women.

Similarly to advanced age, renal dysfunction has been identified as an important correlate of adverse outcomes following percutaneous and surgical cardiac procedures.[13,14,20,21,24,25] Platelet dysfunction,[26,27] impaired clearance of unfractionated heparin and of LMWH,[27–32] and additional abnormalities in the coagulation cascade are all plausible explanations for the increased bleeding risk observed in renally impaired patients.[33]

Not surprisingly, pharmacological and mechanical therapeutic interventions, and in particular the use of thrombolytic agents, GP IIb/IIIa receptor blockers, and invasive procedures, were identified as independent factors associated with major bleeding. Interestingly, the incidence of bleeding in this group of patients, and particularly in those receiving GP IIb/IIIa receptor blockers, is higher than the incidence reported in randomized clinical trials. In the Chimeric c7E3 AntiPlatelet Therapy in Unstable angina Refractory (capture) trial to investigate the use of abciximab in patients with refractory unstable angina, major bleeding occurred in 3.8% of patients randomized to abciximab and 1.9% of patients randomized to placebo .[34] Similarly, in the PRISM-PLUS trial, where patients with unstable angina and non-Q-wave myocardial infarction were randomized to tirofiban, tirofiban and heparin, or heparin alone, the occurrence of major bleeding was 4% in patients randomized to tirofiban and 3% in patients receiving heparin alone.[12] We believe that the higher incidence observed in this study may be due to the unselected patient populations that constitute this multinational registry, and that it might be more reflective of the true incidence of major bleeding in general clinical practice. A review of exclusion criteria and of baseline clinical characteristics in the two cited clinical trials and in the GRACE registry supports this hypothesis, although comparisons across different clinical trials and registry studies are always difficult to make, and, in the absence of the proper methodology, are subject to significant bias.

The fact that right-heart catheterization and the use of PCI were associated with an increased risk of bleeding is also not surprising. Prior studies have shown that most of the bleeding complications associated with the administration of thrombolytic therapy occur at arterial or venous puncture sites.[11,35] In the TIMI II trial, major and minor haemorrhagic events were significantly more common in patients assigned to an invasive strategy than in patients assigned a non-invasive strategy.[5] Thus, careful weighing of the risks and benefits of right-heart catheterization and avoidance of potentially unnecessary

procedures might be an important approach for improving outcomes in patients with ACS.

In this study, administration of LMWH appeared to be associated with a decreased risk of major bleeding. This effect was consistent across different subgroups, and particularly in the groups undergoing no thrombolysis and no invasive procedures. Reported data on bleeding risk with LMWH have differed depending on the indication. A meta-analysis of randomized trials in the initial treatment of deep venous thrombosis showed a trend toward a lower incidence of major bleeding with LMWH compared with unfractionated heparin.[36] On the other hand, randomized clinical trials in ACS have shown no significant differences in the incidence of major bleeding, and an increase in minor bleeding in patients treated with LMWH.[37] More recently, in the ASSENT-3 trial, the combination treatment of LMWH enoxaparin and tenecteplase was found to be associated with a non-significant trend toward a higher incidence of major bleeding when compared with the combination of unfractionated heparin and tenecteplase, and a lower incidence of major bleeding when compared with the combination of abciximab and tenecteplase.[38] One possible explanation of our finding might be the differences between clinical trials and general practice. Clinical trials have traditionally used careful weight-adjusted dosing of unfractionated heparin and close monitoring of anticoagulation. In addition, both in the TIMI 11B[39] and in the ASSENT-3 trial,[38] duration of therapy was longer with the LMWH enoxaparin than with unfractionated heparin (7 days versus 48 h in the ASSENT-3 trial), possibly contributing to the higher incidence of bleeding observed with LMWH. Information on weight-adjusted dosing of unfractionated heparin, use of heparin nomograms, monitoring of anticoagulation, and duration of therapy were not available in this registry, but it is possible that dosing and adjustment might not have been as strict and uniform as in clinical trials. Thus, it is also possible that the more predictable effect of LMWH might have resulted in more stable anticoagulation, a lower frequency of excessive anticoagulation, and a lower incidence of bleeding complications. However, this is speculative and will need to be further assessed in other studies.

Major bleeding and mortality risk

Higher mortality rates were observed in the group of patients with major bleeding in each diagnostic category, and were three to four times higher than the mortality rates of the groups of patients who did not develop major bleeding. Importantly, after adjusting for baseline comorbidities, clinical presentation and hospital therapies, major bleeding was still an independent predictor of hospital death.

Study strengths and limitations

Several studies have shown a relationship between excessive anticoagulation and increased risk of bleeding. Measurements of the degree of anticoagulation were not obtained in the present study and we could not therefore determine the influence of excessive anticoagulation on bleeding risk. However, we believe that excessive anticoagulation may have played an important role, particularly in the high-risk patients, and every step should be taken to prevent its occurrence. In addition, due to differences in definitions of major bleeding across different clinical trials and registries, a direct comparison between the bleeding rates observed in our study and those of other studies is not possible. Finally, although a significantly higher mortality rate was observed in patients with major bleeding, the true contribution of the bleeding episode itself to the fatal event is unknown.

Conclusions

In routine clinical practice, major bleeding is a frequent non-cardiac complication of contemporary therapy for ACS, and it is associated with a poor prognosis. Simple baseline clinical characteristics identify patients at increased risk of major bleeding.

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Appendix A

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