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Original article

Bleeding and venous thromboembolism arising in acutely ill hospitalized medical patients. Findings from the Spanish National Discharge Database

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ABSTRACT

Background: There is scarce evidence to identify which acutely ill medical patients might benefit from prophylaxis against venous thromboembolism (VTE).
Methods: The Spanish National Discharge Database was used to identify predictors of bleeding and VTE during hospitalization for an acute medical illness.
Results: Of 1,148,301 patients, 3.10% bled, 1.21% were diagnosed with VTE, and 8.64% died. The case-fatality rate was: 20.8% for bleeding and 19.7% for VTE. Eight clinical variables were independently associated with an increased risk for VTE and bleeding, one with a decreased risk for both events, 4 with an increased risk for VTE and a decreased risk for bleeding, 2 with an increased risk for bleeding but a decreased risk for VTE, and 1 with a decreased risk for bleeding. When all these variables were considered, we composed a risk scoring system, in which we assigned points to each variable according to the ratio between the odds ratio for bleeding and for VTE. Overall, 21% of patients scored less than 0 points and had a bleeding vs. VTE ratio of 1.19; 55% scored 0 to 1.0 points and had a ratio of 2.13; and 24% scored over 1.0 points and had a ratio of 6.10.
Conclusions: A risk score based on variables documented at admission can identify patients with different ratios (near 1.0; about 2.0; and >6.0) between the rate of bleeding and of VTE.

1. Introduction

Pulmonary embolism (PE) is considered the most common preventable cause of death in hospitalized patients [1,2], and most cases of fatal PE in the hospital occur in medical patients [3–5]. Several randomized studies in acutely ill medical patients have shown that the risk of venous thromboembolism (VTE) can be reduced by up to two thirds using adequate pharmacologic VTE prophylaxis [6–10]. Accordingly, evidence-based guidelines on prevention of VTE recommend that at-risk, acutely ill hospitalized medical patients should receive pharmacologic prophylaxis with low-molecular-weight heparin, unfractionated heparin, or fondaparinux [11]. However, pharmacologic VTE prophylaxis is also associated with an increased incidence of bleeding complications compared to placebo [9]. Thus, at hospital admission it would be crucial to identify patient characteristics associated with the risk of bleeding and with the risk of VTE, as to prescribe adequate prophylaxis to those who might benefit most.

Unfortunately, there is limited information on individual risk factors present in hospitalized medical patients at admission, and to what extent they contribute to the risk of bleeding and of VTE. There are some data on the risk for VTE, but most of them were based on expert opinion, or were derived from patients within randomized clinical trials rather than from "real-life" cohorts, [12–16] and there is only one study focused on the risk for bleeding [17]. Furthermore, some of the identified risk factors for VTE (i.e., age, infection, renal failure, cancer) are also strong risk factors for bleeding.

We used data from the administrative Spanish National Discharge Database (SNDD) to assess the frequency of, risk factors for, and clinical impact of bleeding developing during admission, and of VTE during the first three months after admission, in patients hospitalized for an acute medical illness in Spanish centers. We calculated the ratio between the incidence of bleeding and the incidence of VTE, and tried to identify which patients have a low-, medium- or high ratio.

2. Patients and methods

The Spanish Ministry of Health requires its 250 public hospitals to submit information from all inpatients at discharge. The CMBD (Conjunto Mínimo Básico de Datos) database includes information on

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several clinical variables (sex, date of birth), date of admission, date of discharge, destination at discharge, primary diagnosis (the main cause of hospital admission), up to 14 "secondary" diagnoses (co-morbidities that were already present at admission or complications developing during admission), and up to 20 procedures performed during admission. According to the Spanish Health System Organization, physicians must declare all diagnoses and procedures performed during hospital stay (not before admission), using the code of the International Classification of Diseases, 9th revision, as stated in the manuscript. All procedures and diagnoses are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, 4th edition) [18]. Subsequently, all cases are grouped according to Diagnostic Related Groups using the informatic tool AP DRG v 18.

Thus, we considered all patients aged over 14 years with acute DVT (ICD-9-CM, 451.x or 453.x) or PE (ICD-9-CM, 415.x) as secondary diagnosis in medical services (surgical services were excluded), discharged in the period from October 1st, 2005 to September 30th, 2006. All patients admitted for VTE, active bleeding, those who underwent a major surgical procedure for any reason, and those related to pregnancy, childbirth or postpartum were excluded. We also considered bleeding complications: either cerebral (ICD-9-CM: 430, 431, 432.0, 432.1 and 432.9), gastrointestinal (ICD-9-CM: 456.0, 456.20, 459.0, 531.40, 531.41, 532.0, 532.01, 532.4, 532. 533.0, 533.4, 534.0, 534.4, 535.01, 535.11, 535.31, 535.61, 537.83, 537.84, 562.12, 562.13, 569.85, 578.x), or other sites of bleeding (ICD-9-CM: 596.7, 599.7, 626.6, 786.3, 372.72, 459.0, 374.82, 998.1, 998.11). The ICD-9-CM codes for the risk factors considered appear in the Appendix 1. We also considered all VTE events leading to a readmission during the first 90 days after discharge. Unfortunately, the SNDD does not gather information on the use of VTE prophylaxis.

2.1. Statistical analysis

The case-fatality rate (CFR) for bleeding or for VTE was defined as the proportion of patients with these conditions who died. Adjusted odds ratios for bleeding and for VTE were calculated using multiple logistic regression analysis. First, we compared the clinical characteristics, medical conditions and outcome of patients according to the development of VTE or bleeding during hospital stay. Then, the association between a list of baseline variables and the incidence of VTE or bleeding was tested using univariable analysis (chi-square tests for categorical variables and *t*-tests for continuous variables). A logistic regression model was used to examine the individual relationship between each variable and the risk of VTE or bleeding. Variables that were identified by the univariable analyses as potential risk factors and achieving a significance level of $p < 0.05$ were considered for inclusion in the multivariate analysis.

We composed a risk scoring system, in which we assigned points to each risk factor according to the ratio between the OR for bleeding and the OR for VTE. When this ratio was 1.0, no points were assigned. When it was over 1.0, we added as many decimals as decimals exceeded one, rounding to the nearest integer. For instance, when the ratio was 1.68 we assigned +0.7 points. When the ratio was lower than 1.0, we used the ratio between the OR for VTE and the OR for bleeding (the inverse value) to subtract decimals from one. For instance, when the ratio was 0.77 we calculated the ratio between the OR for VTE and the OR for

Table 1
Univariable analysis for venous thromboembolism, bleeding and death in the Spanish National Discharge Database for 1,148,301acutely ill medical patients.

	VTE	No VTE	Bleeding	No bleeding	Death	No death
Patients, N	13,848	1,134,553	35,567	1,112,734	99,163	1,049,138
Clinical characteristics						
Age (mean years ± SD)	69 ± 16‡	66 ± 17	68 ± 16‡	66 ± 17	74 ± 14‡	66 ± 17
Gender (males)	7103 (52%)‡	646,388 (57%)	22,887 (64%)‡	630,604 (57%)	56,939 (57%)†	596,552 (57%)
Hospital stay (mean days ± SD)	19 ± 20‡	9.5 ± 12	15 ± 19‡	9.0 ± 12	13 ± 19‡	9.0 ± 11
Medical conditions						
Obesity	716 (5.2%)	58,059 (5.1%)	1210 (3.4%)‡	57,565 (5.2%)	2578 (2.6%)‡	56,197 (5.4%)
Chronic lung disease	874 (6.4%)	69,292 (6.1%)	2382 (6.7%)‡	67,784 (6.1%)	7385 (7.4%)‡	62,781 (6.0%)
Chronic heart failure	1597 (12%)†	122,757 (11%)	4206 (12%)‡	120,148 (11%)	15,498 (16%)‡	108,856 (10%)
Diabetes	2623 (19%)‡	256,340 (23%)	7333 (21%)‡	251,630 (23%)	22,011 (22%)†	22,011 (22%)
Hypertension	4237 (31%)‡	379,155 (33%)	10,532 (30%)‡	372,860 (33%)	28,758 (29%)‡	354,634 (34%)
Ischemic heart disease	1727 (13%)‡	223,727 (20%)	6433 (18%)‡	219,021 (20%)	16,931 (17%)‡	208,523 (20%)
Ischemic stroke	892 (6.5%)‡	84,666 (7.5%)	2282 (6.4%)‡	83,276 (7.5%)	9424 (9.5%)‡	76,134 (7.3%)
Cancer	4496 (33%)‡	183,033 (16%)	8196 (23%)‡	179,333 (16%)	36,141 (36%)‡	151,388 (14%)
Infection	2860 (21%)‡	148,642 (13%)	6987 (20%)‡	144,515 (13%)	18,308 (18%)‡	133,194 (13%)
Inflammatory bowel disease	153 (1.1%)	10,908 (1.0%)	232 (0.7%)‡	10,829 (1.0%)	248 (0.3%)‡	10,813 (1.0%)
Upper gastrointestinal disease	709 (5.2%)‡	46,585 (4.1%)	4797 (13%)‡	42,497 (3.8%)	3285 (3.3%)‡	44,009 (4.2%)
Liver disease	719 (5.2%)‡	69,499 (6.1%)	6571 (18%)‡	63,647 (5.7%)	8846 (8.9%)‡	61,372 (5.8%)
Coagulation disorders & thrombocytopenia	389 (2.8%)‡	18,646 (1.6%)	1927 (5.4%)‡	17,108 (1.5%)	3803 (3.8%)‡	15,232 (1.5%)
Renal failure	1620 (12%)‡	94,982 (8.4%)	5247 (15%)‡	91,355 (8.2%)	19,992 (20%)‡	76,610 (7.3%)
Anemia	2218 (16%)‡	125,656 (11%)	10,336 (29%)‡	117,538 (11%)	13,474 (14%)‡	114,400 (11%)
Primary diagnosis						
Acute respiratory insufficiency	1190 (8.7%)	99,277 (8.8%)	2190 (6.2%)‡	98,277 (8.8%)	7981 (8.0%)‡	92,486 (8.8%)
Acute heart failure	851 (6.2%)‡	12,900 (1.2%)	1737 (4.9%)‡	78,756 (7.1%)	7629 (7.7%)‡	72,864 (6.9%)
Bleeding complications						
Gastrointestinal	382 (2.8%)‡	16,864 (1.5%)	17,246 (48.5%)	–	4170 (4.2%)‡	13,076 (1.2%)
Cerebral	74 (0.5%)‡	2,220 (0.2%)	2294 (6.4%)	–	866 (0.9%)‡	1428 (0.1%)
Other	410 (3.0%)‡	16,951 (1.5%)	17,361 (49%)	–	2782 (2.8%)‡	14,579 (1.4%)
Any bleeding [a]	798 (5.8%)‡	34,769 (3.1%)	35,567 (100%)	–	7405 (7.5%)‡	28,162 (2.7%)
Venous thromboembolism						
DVT during hospital stay	7800 (57%)	–	431 (1.2%)‡	7369 (0.7%)	1091 (1.1%)‡	6709 (0.6%)
PE during hospital stay	3254 (24%)	–	207 (0.6%)‡	3047 (0.3%)	1260 (1.3%)‡	1994 (0.2%)
DVT during readmission	1289 (9.4%)	–	73 (0.2%)‡	1216 (0.1%)	103 (0.1%)	1186 (0.1%)
PE during readmission	1505 (11%)	–	98 (0.3%)‡	1407 (0.1%)	272 (0.3%)‡	1233 (0.1%)
Any VTE	13,848 (100%)	–	798 (2.2%)‡	12,950 (1.2%)	2710 (2.7%)‡	11,038 (1.1%)

Comparisons between patients with or without the event: *$p < 0.05$; †$p < 0.01$; and ‡$p < 0.001$.
Abbreviations: VTE, venous thromboembolism; SD, standard deviation; DVT, deep vein thrombosis; PE, pulmonary embolism.
[a] 35,465 patients bled during admission and 102 patients bled during readmission.