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CLINICAL RESEARCH STUDY

# Venous Thromboembolism in Patients with Renal Insufficiency: Findings from the RIETE Registry

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## ABSTRACT

**BACKGROUND:** Current guidelines make no specific recommendations for venous thromboembolism (VTE) treatment in patients with renal insufficiency, but some experts recommend some reduction in heparin dose.

**METHODS:** Registro Informatizado de Enfermedad TromboEmbólica (RIETE) is an ongoing, prospective registry of consecutively enrolled patients with objectively confirmed, symptomatic, acute VTE. In this analysis we retrospectively analyzed the effect of renal insufficiency on the incidence of fatal pulmonary embolism (PE) and fatal bleeding within 15 days of diagnosis.

**RESULTS:** Up to March 2005, 10,526 patients with acute VTE were enrolled in RIETE, of whom 9234 (88%) had a creatinine clearance (CrCl) greater than 60 mL/min, 704 (6.7%) had a CrCl 30 to 60 mL/min, and 588 (5.6%) had a CrCl less than 30 mL/min. The incidence of fatal PE during the study period was 1.0%, 2.6%, and 6.6%, respectively. Fatal bleeding occurred in 0.2%, 0.3%, and 1.2% of the patients, respectively. On multivariate analysis, patients with a CrCl less than 30 mL/min were independently associated with an increased risk for fatal PE and fatal bleeding. In addition, initial diagnosis of PE, immobility for 4 days or more, cancer, and initial therapy with unfractionated heparin were independent predictors of fatal PE; whereas immobility for 4 days or more and cancer were independent predictors of fatal bleeding.

**CONCLUSIONS:** Patients with VTE who have renal insufficiency had an increased incidence of both fatal PE and fatal bleeding, but the risk of fatal PE far exceeded that of fatal bleeding. Our data support the use of full-dose anticoagulant therapy, even in patients with a CrCl less than 30 mL/min. 

**KEYWORDS:** Venous thromboembolism; Renal insufficiency; Anticoagulant therapy

Treatment with anticoagulants improves outcomes in patients with venous thromboembolism (VTE).[1-4] Current guidelines from the American College of Chest Physicians, based on evidence from clinical trials, recommend that patients with VTE be treated initially with either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for at least 5 days, followed by long-term treatment with a vitamin K antagonist.[5] However, patients with renal insufficiency are often excluded from clinical trials of anticoagulant therapy, which means that treatment regimens

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based on the results from clinical trials might not be suitable for all patients, such as those with renal insufficiency. Furthermore, the influence of renal insufficiency on the risk of bleeding complications, a factor that can lead physicians to withhold anticoagulant therapy, is not clear.

Registro Informatizado de Enfermedad TromboEmbólica (RIETE) was initiated in March 2001 to record the current clinical management of VTE in Spanish hospitals and has now been expanded to include patients from other countries. It is an ongoing, multicenter, observational registry of consecutively enrolled patients, designed to gather data on treatment patterns and outcomes in patients with symptomatic, objectively confirmed, acute VTE.[6-10] In this retrospective analysis of the registry, we compared the clinical characteristics and 15-day outcomes of patients with VTE with and without renal insufficiency.

**CLINICAL SIGNIFICANCE**

- Patients with venous thromboembolism and severe renal insufficiency have an increased incidence of bleeding complications.
- Their risk of fatal pulmonary embolism clearly exceeds that of fatal bleeding.
- Our data support the use of full-dose heparin therapy, even in patients with severe renal insufficiency.

## PATIENTS AND METHODS

### Inclusion and Exclusion Criteria

Consecutive patients (both outpatients and inpatients) with symptomatic, acute deep vein thrombosis (DVT) or pulmonary embolism (PE) (confirmed by objective tests: contrast venography, ultrasonography, or impedance plethysmography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography scan for suspected PE) are enrolled in RIETE. Patients are excluded if they are participating in a therapeutic clinical trial or if they are not available for follow-up.

### Study Design

Patients were classified according to their estimated creatinine clearance (CrCl) in 3 groups: less than 30 mL/min, 30 to 60 mL/min, and greater than 60 mL/min. CrCl was estimated with the Cockcroft and Gault formula.[11] The first creatinine measured after VTE diagnosis was the one used to calculate the CrCl. The clinical characteristics, treatment details, and clinical outcomes were compared among the 3 groups. The major outcomes were clinically recognized (and objectively confirmed) fatal PE and fatal bleeding during the first 15 days of therapy.

### Study Variables and Definitions

The following parameters were recorded: patient's baseline characteristics; clinical status including any coexisting or underlying conditions, such as chronic heart or lung disease; risk factors for VTE; the type and dose of treatment received on VTE diagnosis; and the outcome during the first 15 days of therapy. Immobilized patients are defined in this analysis as nonsurgical patients who had been immobilized (ie, total bed rest with bathroom privileges) for 4 days or more in the 2-month period before VTE diagnosis. Surgical patients are defined as those who had undergone an operation in the 2 months before VTE diagnosis. Fatal PE, in the absence of autopsy, was defined as death shortly after PE diagnosis in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring shortly after a major bleeding episode. Bleeding complications were classified as "major" if they were overt and associated with a decrease in the hemoglobin level of 2.0 g/dL (20 g/L) or more, required a transfusion of 2 units of blood or more, or were retroperitoneal or intracranial.

### Follow-up

During the study period, special attention was paid to any sign or symptom suggesting either DVT or PE recurrences, or bleeding complications. Each episode of clinically suspected recurrent DVT or PE was documented by repeat ultrasonography, venography, lung scanning, helical-computed tomography scan, or pulmonary angiography.

### Data Collection

All patients provided oral consent for their participation in the registry, in accordance with the requirements of the ethics committee within each hospital. Data are recorded in a computer-based case report form by a RIETE registry coordinator at each participating hospital and submitted to a centralized coordinating center through a secure website. The coordinators also ensure that eligible patients are consecutively enrolled. Patient identities remain confidential because they are identified by a unique number assigned by the study coordinating center, which is responsible for all data management. Study outcomes are adjudicated by the attending physicians. Data quality is regularly monitored and documented electronically to detect inconsistencies or errors, which are resolved by the local coordinators. Data quality is also monitored by periodic visits to participating hospitals by contract research organizations, who compare the medical records with the data on the website. A full data audit is performed at periodic intervals.

### Statistical Analysis

Odds ratios and corresponding 95% confidence intervals were calculated using Confidence Interval Analysis software (version 2.0.0; SPSS Inc., Chicago, Ill), and a $P$ value

less than .05 was considered to be statistically significant. The significance of a number of clinical variables on the risk of death from either PE or bleeding was tested by fitting bivariate proportional hazard models. Candidate variables were selected from clinical variables based on published literature and expert opinion. A logistic regression model was used to examine the individual relationship between each variable and the risk of death due to PE or bleeding. Multivariate analysis was performed with a multivariate logistic regression analysis to determine the independent nature of the variables, while adjusted for other characteristics. Both significance levels of *P* less than .05 and *P* greater than .10 were considered to include and exclude variables in the final multivariate model.

Diagnoses of distal, proximal, and upper extremity DVT in patients were not included in the multivariate analysis because a number of patients with symptomatic PE did not undergo any objective tests to confirm the presence of proximal or distal DVT because they did not have signs of DVT. The long-term treatment received by the patients was not included in the multivariate analysis, because patients dying during initial therapy did not receive long-term therapy.

## RESULTS

As of March 2005, 10,526 patients with symptomatic, acute VTE were consecutively enrolled at 104 participating centers. Of these, 9234 (88%) had a CrCl greater than 60 mL/min; 704 (6.7%) had a CrCl 30 to 60 mL/min; and 588 (5.6%) had a CrCl less than 30 mL/min.

### Baseline Clinical Characteristics

Patients with a CrCl less than 30 mL/min were more often female and older than patients with a CrCl greater than 60 mL/min (Table 1). Recent immobility for 4 days or more and underlying chronic heart failure were also more frequent, whereas recent surgery was less common in patients with a CrCl less than 30 mL/min than in those with a CrCl greater than 60 mL/min.

Patients with a CrCl less than 30 mL/min were more often enrolled with symptomatic PE than patients with a CrCl greater than 60 mL/min (Table 1). Among patients with PE, those with a CrCl less than 30 mL/min more commonly had a severe clinical presentation (ie, arterial $Po_2 < 60$ mm Hg) than corresponding patients with a CrCl greater than 60 mL/min (Table 1). Patients with symptomatic DVT with a CrCl less than 30 mL/min were diagnosed with proximal DVT more often and with distal DVT less often.

### Treatment Details and 15-Day Clinical Outcomes

Most patients in all 3 groups were initially treated for VTE with LMWH, but those with a CrCl less than 30 mL/min received UFH more often (8.8%) than those with a CrCl greater than 60 mL/min (6.1%) (Table 1). Mean initial daily doses of both LMWH and UFH were similar in the 3 patient groups. As for long-term therapy, the use of anti-vitamin K drugs was less common in patients with a CrCl less than 30 mL/min.

The incidence of major bleeding was significantly higher in both subgroups with abnormal CrCl compared with patients with normal renal function, whereas the incidence of VTE recurrences (recurrent DVT or PE) was similar in all three subgroups (Table 1). Moreover, patients with a CrCl less than 30 mL/min had an increased incidence of fatal bleeding, fatal PE, and overall death compared with those with a CrCl greater than 60 mL/min. Patients with a CrCl of 30 to 60 mL/min had an increased rate of fatal PE and overall death, without significant differences in the fatal bleeding rate.

The fatal PE rate was significantly higher in patients with severe renal insufficiency than in those with moderate or normal renal function. PE occurred in 1.0% of patients with a CrCl greater than 60 mL/min, in 2.6% of patients with a CrCl 30 to 60 mL/min, and in 6.6% of patients with a CrCl less than 30 mL/min. In addition, the use of UFH was associated with a significantly higher risk of fatal PE compared with LMWH (Table 2). On multivariate analysis in patients, those with an initial diagnosis of PE, decreasing CrCl, immobility for 4 days or more, cancer, or initial therapy with UFH were independently associated with an increased risk for fatal PE (Table 3).

Fatal bleeding occurred more frequently in patients with severe or moderate renal insufficiency: It occurred in 0.2% of patients with a CrCl greater than 60 mL/min, in 0.3% of patients with a CrCl 30 to 60 mL/min, and in 1.2% of patients with a CrCl less than 30 mL/min. The use of UFH was not associated with significant differences in the rate of fatal bleeding compared with LMWH (Table 4). Multivariate analysis confirmed that decreasing CrCl, cancer, and immobility for 4 days or more were independently associated with an increased risk for fatal bleeding (Table 5).

## DISCUSSION

A number of studies have shown that patients with VTE who have renal insufficiency have an increased incidence of bleeding complications with therapeutic doses of heparin therapy.[12-15] The data in this analysis, obtained from a large prospective series of consecutively enrolled patients in the RIETE registry, confirm this increased incidence of bleeding complications in patients with renal insufficiency. Indeed, the 5.4% incidence of major bleeding clearly outweighs the 1.2% incidence of recurrent VTE in patients with a CrCl less than 30 mL/min. However, their 6.6% incidence of fatal PE also exceeded their 1.2% rate of fatal bleeding. In fact, the fatal PE rate is more than 5-fold higher than that of fatal bleeding in all 3 groups, but patients with a CrCl less than 30 mL/min have a 6 to 7 times greater mortality as the result of PE or bleeding than those with normal function.

Some 39% of patients with VTE who died of PE in our series had some degree of renal insufficiency. The increased

**Table 1** Clinical Characteristics, Treatment Details, and Clinical Outcomes of 10,526 Patients with Venous Thromboembolism, According to Their Creatinine Clearance

| Patients, n (%) | >60 mL/min N = 9234 | 30-60 mL/min N = 704 | <30 mL/min N = 588 | OR (95% CI) 30-60 vs >60 mL/min | OR (95% CI) <30 vs >60 mL/min |
|---|---|---|---|---|---|
| Clinical characteristics | | | | | |
| Gender (males) | 4575 (50%) | 474 (67%) | 208 (35%) | 2.1 (1.8-2.5)‡ | 0.6 (0.5-0.7)‡ |
| Age > 65 y | 5672 (61%) | 615 (87%) | 551 (94%) | 4.3 (3.5-5.4)‡ | 9.4 (6.7-13)‡ |
| Outpatients | 6483 (70%) | 523 (74%) | 403 (69%) | 1.2 (1.0-1.5)* | 0.9 (0.7-1.1) |
| Underlying conditions | | | | | |
| Chronic lung disease | 1016 (11%) | 107 (15%) | 59 (10%) | 1.4 (1.2-1.8)‡ | 0.9 (0.7-1.2) |
| Chronic heart failure | 454 (4.9%) | 79 (11%) | 118 (20%) | 2.4 (1.9-3.1)‡ | 4.8 (3.9-6.1)‡ |
| Risk factors for VTE | | | | | |
| Surgery | 1328 (14%) | 58 (8.2%) | 42 (7.1%) | 0.5 (0.4-0.7)‡ | 0.5 (0.3-0.6)‡ |
| Immobility ≥ 4 d | 2170 (24%) | 198 (28%) | 241 (41%) | 1.3 (1.1-1.5)† | 2.3 (1.9-2.7)‡ |
| Prior VTE | 1478 (16%) | 117 (17%) | 87 (15%) | 1.0 (0.9-1.3) | 0.9 (0.7-1.2) |
| Cancer | 1817 (20%) | 176 (25%) | 131 (22%) | 1.4 (1.1-1.6)† | 1.2 (0.96-1.4) |
| VTE characteristics | | | | | |
| Symptomatic PE | 3896 (42%) | 388 (55%) | 328 (56%) | 1.7 (1.4-2.0)‡ | 1.7 (1.5-2.0)‡ |
| For patients with PE | | | | | |
| Heart rate > 100 beats/min | 3829 (28%) | 125 (32%) | 93 (28%) | 1.3 (1.0-1.6)* | 1.0 (0.8-1.3) |
| Arterial Po2 < 60 mm Hg | 1423 (45%) | 171 (52%) | 151 (56%) | 1.3 (1.0-1.6)* | 1.5 (1.2-2.0)† |
| For patients with DVT | | | | | |
| Proximal DVT | 4937 (82%) | 304 (90%) | 230 (95%) | 2.1 (1.4-3.0)‡ | 4.0 (2.3-7.0)‡ |
| Initial therapy | | | | | |
| LMWH | 8622 (93%) | 637 (91%) | 525 (89%) | 0.7 (0.5-0.9)† | 0.6 (0.5-0.8)‡ |
| Mean daily doses (IU/kg) | 180 ± 36 | 176 ± 41 | 179 ± 42 | $P < .01$ | $P$ = NS |
| LMWH < 175 IU/kg/d | 3010 (33%) | 257 (36%) | 186 (32%) | 1.2 (1.0-1.4)* | 1.0 (0.8-1.2) |
| UFH | 562 (6.1%) | 60 (8.5%) | 52 (8.8%) | 1.4 (1.1-1.9)† | 1.5 (1.1-2.0)† |
| Mean daily doses (IU/kg) | 384 ± 100 | 377 ± 86 | **389 ± 76** | $P$ = NS | $P$ = NS |
| Thrombolytics | 96 (1.0%) | 17 (2.4%) | 10 (1.7%) | 2.4 (1.4-4.0)‡ | 1.6 (0.9-3.2) |
| IVC filter | 172 (1.9%) | 16 (2.3%) | 14 (2.4%) | 1.2 (0.7-2.1) | 1.3 (0.7-2.2) |
| Long-term therapy | | | | | |
| AVK drugs | 6834 (74%) | 509 (72%) | 317 (54%) | 0.9 (0.8-1.1) | 0.4 (0.3-0.5)‡ |
| LMWH | 2028 (22%) | 144 (21%) | 184 (31%) | 0.9 (0.8-1.1) | 1.6 (1.3-1.9)‡ |
| 15-d clinical outcomes | | | | | |
| Major bleeding | 94 (1.0%) | 28 (4.0%) | 32 (5.4%) | 4.0 (2.6-6.2)‡ | 5.6 (3.7-8.4)‡ |
| Fatal bleeding | 17 (0.2%) | 2 (0.3%) | 7 (1.2%) | 1.5 (0.4-6.7) | 6.5 (2.7-16)‡ |
| Recurrent VTE | 90 (1.0%) | 6 (0.9%) | 7 (1.2%) | | |
| Fatal PE | 90 (1.0%) | 18 (2.6%) | 39 (6.6%) | 2.7 (1.6-4.4)‡ | 7.2 (4.9-11)‡ |
| Overall death | 215 (2.3%) | 41 (5.8%) | 93 (16%) | 2.6 (1.8-3.7)‡ | 7.9 (6.1-10)‡ |

VTE = venous thromboembolism; PE = pulmonary embolism; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; IU = international unit; IVC = inferior vena cava; AVK = anti-vitamin K drugs; OR = odds ratio; CI = confidence interval; NS = nonsignificant.

Comparisons between patients with a CrCl < 30 mL/min or 30 to 60 mL/min and patients with a CrCl > 60 mL/min:

*$P < .05$;

†$P < .01$;

‡$P < .001$.

incidence of fatal PE in these patients may be partly attributable to the more severe presentation of VTE compared with patients with normal renal function. However, it is also likely to be partly attributable to the older age, the more frequent occurrence of coexisting underlying conditions (eg, immobility and congestive heart failure), or associated therapies in these patients. Comorbid conditions such as these are predictive of poor survival in patients with VTE.[16-18] Thus, a more severe presentation of VTE, combined with a less favorable prognosis because of concomitant disease, could contribute to the higher fatal PE rate seen in patients with renal insufficiency. More evidence is needed to ascertain whether it is the renal insufficiency rather than the more symptomatic PE or underlying comorbidities that contribute to the greater mortality.

We report that LMWH use is associated with a significantly lower rate of fatal PE when compared with UFH, and that this benefit was found irrespective of renal function. We failed to find any increase in the fatal bleeding rate among patients with VTE and renal insufficiency who were receiving initial therapy with LMWH compared with those receiving UFH. The use of LMWH in patients with renal insufficiency traditionally has been considered hazardous given its impaired metabolism in renal failure, eventually leading to unwanted "overdose" and bleeding complications. Indeed, the current guidelines from the American College of

**Table 2** Univariate Analysis on the Risk of Developing Fatal Pulmonary Embolism

| | Fatal PE N = 149 | No Fatal PE N = 10,449 | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Gender (males) | 61 (41%) | 5237 (50%) | 0.7 (0.5-0.96) | .026 |
| Age > 65 y | 122 (82%) | 6779 (65%) | 2.4 (1.6-3.7) | <.001 |
| Outpatients | 90 (62%) | 7343 (72%) | 0.6 (0.4-0.9) | .005 |
| Underlying conditions | | | | |
| Chronic lung disease | 22 (15%) | 1168 (11%) | 1.4 (0.9-2.2) | .168 |
| Chronic heart failure | 25 (17%) | 638 (6.1%) | 3.1 (2.0-4.8) | <.001 |
| Risk factors for VTE | | | | |
| Surgery | 14 (9.4%) | 1418 (14%) | 0.7 (0.4-1.1) | .139 |
| Immobility ≥ 4 d | 71 (48%) | 2554 (24%) | 2.8 (2.0-3.9) | <.001 |
| Prior VTE | 15 (10%) | 1682 (16%) | 0.6 (0.3-0.997) | .046 |
| Cancer | 42 (28%) | 2103 (20%) | 1.6 (1.1-2.2) | .015 |
| VTE characteristics | | | | |
| Symptomatic PE | 140 (94%) | 4514 (43%) | 20 (10-40) | <.001 |
| Renal function | | | | |
| CrCL > 60 mL/min | 90 (61%) | 9144 (88%) | 0.2 (0.2-0.3) | <.001 |
| CrCl 30-60 mL/min | 18 (12%) | 686 (6.6%) | 2.0 (1.2-3.2) | .007 |
| CrCl < 30 mL/min | 39 (27%) | 549 (5.3%) | 6.5 (4.4-9.4) | <.001 |
| Initial therapy | | | | |
| LMWH | 115 (77%) | 9734 (93%) | 0.2 (0.2-0.4) | <.001 |
| LMWH < 175 IU/kg/d | 34 (30%) | 3443 (35%) | 0.8 (0.5-1.1) | .195 |
| UFH | 26 (17%) | 653 (6.2%) | 3.2 (2.1-4.9) | <.001 |
| Other | 8 (5.4%) | 62 (0.6%) | 9.5 (4.5-20) | <.001 |

VTE = venous thromboembolism; PE = pulmonary embolism; CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; IU = international unit; UFH = unfractionated heparin; CI = confidence interval.

Chest Physicians suggest (grade 2C of evidence) the use of intravenous UFH rather than LMWH in patients with severe renal insufficiency.[1,19] Our findings do not support this recommendation. The benefit of LMWH over UFH in patients with renal insufficiency has been reported in patients with acute coronary syndrome,[20,21] but not thus far in patients with VTE. Unfortunately, there is no information on the anti-Xa levels in the Registry.

Finally, our data confirm that renal insufficiency is an independent predictor of fatal bleeding in patients with acute VTE. This is the reason why many authors suggest that heparin dosing should be reduced for these patients.[14,22] However, because renal insufficiency is consistently used as an exclusion criterion in randomized trials evaluating antithrombotic drugs, there is no clinical evidence to support this view. In our series, patients with renal insufficiency received similar doses of heparin therapy as those with normal function, and the rate of fatal PE in these patients (as in those with normal renal function) remained more than fivefold higher than their fatal bleeding rate. Thus, our findings do not support the use of a change in dosing rate when treating VTE in patients with renal insufficiency.

**Table 3** Multivariate Analysis on the Risk of Developing Fatal Pulmonary Embolism

| Variables | Odds Ratio (95% CI) | *P* Value |
|---|---|---|
| Symptomatic PE | 17 (8.8-34) | <.001 |
| Renal function | | <.001 |
| CrCL > 60 mL/min | Reference | - |
| CrCl 30-60 mL/min | 2.0 (1.2-3.4) | .008 |
| CrCl < 30 mL/min | 5.2 (3.4-7.8) | <.001 |
| Immobility ≥ 4 d | 2.4 (1.7-3.4) | <.001 |
| Cancer | 2.0 (1.4-2.9) | <.001 |
| Initial therapy, UFH | 1.9 (1.2-3.0) | <.001 |
| Inpatients | 1.5 (1.0-2.1) | .027 |

PE = pulmonary embolism; CrCl = creatinine clearance; UFH = unfractionated heparin; CI = confidence interval.

The main limitation of our study lies in its design. In contrast with randomized, controlled trials, no experimental intervention is imposed in RIETE; treatment is determined entirely by the treating physicians. Although this limits the nature of the conclusions that can be drawn, data captured and reported in the registry reflect "real-world" practices and outcomes in the treatment of VTE. In addition, selection bias was avoided by including consecutive patients with objectively confirmed, symptomatic, acute VTE who were referred to study centers. Enrolled patients were treated according to standard practice, and prospective follow-up was completed for all patients. Objective criteria were strictly applied for the diagnosis of initial and recurrent VTE, along with quality control and audit measures.

Another limitation is the likely underestimated incidence rate of fatal PE. Certainly, the deaths of some patients may have been caused by PE, but these would not have been included because the Adjudication Committee accepts only VTE events that have been objectively confirmed. However, because the overall death rate also was significantly higher

**Table 4** Univariate Analysis on the Risk of Developing Fatal Bleeding

| | Fatal Bleeding N = 27 | No Fatal Bleeding N = 10,571 | Odds Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Gender (males) | 12 (44%) | 5286 (50%) | 0.8 (0.4-1.7) | .564 |
| Age > 65 y | 23 (85%) | 6878 (65%) | 3.1 (1.1-8.9) | .028 |
| Outpatients | 15 (56%) | 7418 (72%) | 0.5 (0.2-1.0) | .058 |
| Underlying conditions | | | | |
| Chronic lung disease | 1 (3.7%) | 1189 (11%) | 0.3 (0.04-2.2) | .215 |
| Chronic heart failure | 3 (11%) | 660 (6.2%) | 1.9 (0.6-6.3) | .297 |
| Risk factors for VTE | | | | |
| Surgery | 3 (11%) | 1429 (14%) | 0.8 (0.2-2.7) | .715 |
| Immobility ≥ 4 d | 15 (56%) | 2610 (25%) | 3.8 (1.8-8.2) | <.001 |
| Prior VTE | 2 (7.4%) | 1695 (16%) | 0.4 (0.1-1.8) | .222 |
| Cancer | 10 (37%) | 2135 (20%) | 2.3 (1.1-5.1) | .030 |
| **VTE characteristics** | | | | |
| Symptomatic PE | 13 (48%) | 4641 (44%) | 1.2 (0.6-2.5) | .657 |
| Renal function | | | | |
| CrCL > 60 mL/min | 17 (65%) | 9217 (88%) | 0.3 (0.1-0.6) | .001 |
| CrCl 30-60 mL/min | 2 (7.7%) | 702 (6.7%) | 1.2 (0.3-4.9) | .837 |
| CrCl < 30 mL/min | 7 (27%) | 581 (5.5%) | 6.3 (2.6-15) | <.001 |
| Initial therapy | | | | |
| LMWH | 25 (93%) | 9824 (93%) | 1.0 (0.2-4.0) | .945 |
| LMWH < 175 IU/kg/d | 9 (36%) | 3468 (35%) | 1.0 (0.5-2.3) | .942 |
| UFH | 2 (7.4%) | 677 (6.4%) | 1.2 (0.3-4.9) | .832 |
| Other | 0 (0%) | 70 (0.7%) | - | .671 |

VTE = venous thromboembolism; PE = pulmonary embolism; CrCl = creatinine clearance; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; CI = confidence interval.

in patients with renal insufficiency, it seems unlikely that our findings would have been different if a better knowledge of the cause of death had been obtained. Finally, the Crockcroft Gault calculation overestimates the CrCl in obese patients, rendering some of these patients inappropriately categorized.

## CONCLUSIONS

We confirm that patients with VTE who have severe renal insufficiency demonstrate an increased incidence of bleeding complications, but that their risk of fatal PE clearly exceeds that of fatal bleeding. Thus, our data support the use of full-dose heparin therapy, even in patients with severe renal insufficiency. As for the use of UFH rather than LMWH in this patient population, our data do not confirm any benefit for those receiving UFH. We suggest not avoiding LMWH in these patients, probably with anti-Xa monitoring. We propose to prospectively study this issue.

**Table 5** Multivariate Analysis on the Risk of Developing Fatal Bleeding

| Variables | Odds Ratio (95% CI) | *P* Value |
|---|---|---|
| Immobility ≥ 4 d | 3.3 (1.5-7.3) | .003 |
| Cancer | 2.7 (1.2-6.0) | .015 |
| Renal function, | - | .002 |
| CrCL > 60 mL/min | Reference | - |
| CrCl 30-60 mL/min | 1.4 (0.3-5.9) | .677 |
| CrCl < 30 mL/min | 5.0 (2.0-12) | <.001 |

CrCl = creatinine clearance; CI = confidence interval.

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## APPENDIX

Members of the RIETE Group

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*A full list of RIETE investigators is given in the Appendix.