Effect of the time of diagnosis on outcome in patients with acute venous thromboembolism

Findings from the RIETE Registry

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Summary

The influence of the day of diagnosis (weekends vs. weekdays) on outcome in patients with acute venous thromboembolism (VTE) has not been thoroughly studied. We used the RIETE database to compare the clinical characteristics, treatment details, and mortality rate at 7 and 30 days, of all patients diagnosed with acute VTE on weekends versus those diagnosed on weekdays. Up to January 2010, 30,394 patients were included in RIETE, of whom 5,479 (18%) were diagnosed on weekends. Most clinical characteristics were similar in both groups, but patients diagnosed on weekends had less often cancer (20% vs. 22%; $p=0.004$), and presented more likely with pulmonary embolism (PE) than those diagnosed on weekdays (52% vs. 47%; $p<0.001$). Most patients in both groups received initial therapy with low-molecular-weight heparin (90% and 91%, respectively; $p=0.01$), then switched to vitamin K antagonists (72% and 71%, respectively; $p=0.007$). The

7-day mortality rate in patients presenting with PE was 2.75% in those diagnosed on weekends versus 3.00% in those diagnosed on weekdays ($p=0.49$). At 30 days, the mortality rate was 6.51% versus 6.06%, respectively ($p=0.38$). In patients presenting with deep vein thrombosis alone, the 7-day mortality rate in those diagnosed on weekends was 1.04% versus 0.66% in those diagnosed on weekdays ($p=0.053$). The mortality rate at 30 days was 3.41% versus 2.88% ($p=0.14$), respectively. In RIETE, the clinical characteristics, treatment strategies, and 7- and 30-day mortality rates of patients diagnosed on weekends were similar to those in patients diagnosed on weekdays.

Keywords

Deep venous thrombosis, outcome, pulmonary embolism, weekdays, weekends

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Introduction

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition and a major health problem. Current guidelines from the American College of Chest Physicians recommend that most patients with VTE be treated initially with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), followed by long-term therapy with vitamin K antagonists (1). However, even after adequate anticoagulant treatment some patients suffer VTE recurrences, while others have bleeding complications (2). In most hospitals, availability of experienced staff in the management of VTE may be reduced during weekends, which could lead to a suboptimal care and an increased incidence of early thrombotic and

haemorrhagic complications. Two studies conducted in Canada and the USA found a higher mortality rate in patients with acute PE hospitalised on weekends than in those hospitalised on weekdays, although the treatment used and the cause of mortality were not described (3, 4). Should these results be confirmed, important efforts by national health services would be required to improve medical assistance during weekends, particularly by increasing the rates of on-duty experienced staff.

The RIETE registry is an ongoing, international (Spain, France, Italy, Israel, Brazil), multi-centre, prospective registry of consecutive patients presenting with symptomatic acute VTE. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes (5–8). We analysed the data

from the RIETE registry to evaluate the 7-day and 30-day outcome of patients with acute PE or DVT, according to the day of diagnosis – weekend versus weekday –, focusing also on the influence of the treatments administered, and the causes of death as well.

Patients and methods

Consecutive patients with symptomatic, acute DVT or PE, confirmed by objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography [CT] scan for suspected PE), were enrolled in RIETE. Patients were excluded if they did not receive any anticoagulant therapy or were currently participating in a therapeutic clinical trial with a blinded therapy. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

In the RIETE registry, participating physicians ensure that eligible patients are consecutively enrolled. Data are recorded on to a computer-based case report form at each participating hospital and submitted to a centralised coordinating centre through a secure website. The study coordinating center assigns patients with a unique identification number to maintain patient confidentiality and is responsible for all data management. Data quality is regularly monitored electronically, including checks 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 organisations that compare medical records with the submitted data.

Study endpoints

The major study outcome was overall mortality at 7 and 30 days after diagnosis. Secondary outcomes were fatal PE, fatal bleeding, development of VTE recurrences or major bleeding complications. Fatal PE, in the absence of autopsy, was defined as any death appearing shortly (<10 days) after PE diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring shortly (<10 days) after a major bleeding episode. Bleeding was classified as 'major' if it was fatal, retroperitoneal, spinal or intracranial, or if it required a transfusion of at least two units of blood. Study endpoints were adjudicated by the attending physicians. In case of doubt (i.e. in the absence of objective confirmation of the cause of death) the cause of death was adjudicated by the RIETE Adjudication Committee.

Study variables and definitions

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any co-

existing or underlying conditions; additional risk factors for VTE; diagnostics tools used for diagnosis; laboratory data; the treatment received upon VTE diagnosis; and the outcome during the first 30 days of therapy. Diagnosis on weekends was defined as that obtained during the period from 00:00 hours on Saturday to 24:00 hours on Sunday. Active cancer was defined as newly diagnosed cancer or any cancer receiving anti-neoplastic treatment of any type. Immobilised patients were defined as non-surgical patients who had been immobilised (i.e. total bed rest with bathroom privileges) for ≥ 4 days in the two-month period prior to VTE diagnosis. Surgical patients were defined as those who underwent a surgical intervention in the two months prior to VTE. Recent bleeding was defined as a major bleeding episode <30 days prior to VTE.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e. there was no standardisation of treatment). The type and dose of anticoagulant therapy, as the insertion of an inferior vena cava filter, was recorded. After diagnosis, all patients were followed-up for at least one month. During each visit, any signs or symptoms suggesting either DVT or PE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was investigated by repeat ultrasonography, venography, lung scanning, helical-CT scan or pulmonary angiography as appropriate.

Most outcomes were classified as reported by the clinical centres. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Statistical analysis

Student's t-test and the Mann-Whitney test were used to compare continuous variables. Categorical variables were compared by the Fisher exact test. SPSS software (version 15, SPSS Inc., Chicago, IL, USA) was used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

Results

As of January 2010, 14,472 patients with acute PE and 15,922 with acute DVT had been enrolled in RIETE, and were considered for the study. Of these, 5,479 (18%; 2,608 with DVT and 2,871 with PE) were diagnosed on weekends, and 24,915 (82%; 13,314 with DVT, 11,601 with PE) were diagnosed on weekdays.

Their clinical characteristics at baseline are shown in ► Table 1. There were no differences in age or gender between patients diagnosed on weekends or on weekdays, and the proportion of inpa-

tients at VTE presentation was also similar. VTE patients diagnosed on weekends had more likely recent immobility (25% vs. 23%; $p=0.014$), but less likely cancer (20% vs. 22%; $p=0.004$), and presented more often with PE (52% vs. 47%; $p<0.001$), than those diagnosed on weekdays. Interestingly, though the diagnosis of PE was confirmed in most cases by CT, a lower proportion of patients with PE diagnosed on weekends underwent ventilation/perfusion scintigraphy (37% vs. 29%; $p<0.001$).

Initial and long-term therapy

Most patients (96%) presenting with DVT alone received initial therapy with LMWH, independently of the time of admission (► Table 2), without differences in mean doses between groups. No differences were found either in patients presenting with PE. The use of other therapies (i.e. UFH, thrombolytics or vena cava filter) was uncommon, either in patients diagnosed on weekends or weekdays. However, the proportion of patients with DVT receiving ambulatory treatment was significantly lower during weekends compared to weekdays (24% vs. 30%; $p<0.001$). As for long-term therapy, there were no significant differences between patients with DVT or PE diagnosed on weekends vs. weekdays (► Table 2).

7-day outcome

In patients presenting with PE the rates of overall mortality, recurrent DVT, recurrent PE and major bleeding were 2.95%, 0.03%, 0.40% and 1.06%, respectively. No significant differences were found when comparing patients diagnosed with PE on weekends or weekdays (► Table 2). The causes of death were also similar. In patients presenting with DVT alone, the rates of overall mortality, recurrent DVT, recurrent PE and major bleeding were 0.72%, 0.10%, 0.22% and 0.57%, respectively. Again, the outcome was similar in DVT patients diagnosed on weekends or weekdays (► Table 2).

30-day outcome

In patients presenting with PE, the rates of overall mortality, recurrent DVT, recurrent PE and major bleeding were 6.42%, 0.37%, 0.87% and 2.02% respectively, with no significant differences between those diagnosed on weekends or weekdays (► Table 2). The causes of death were also similar in both groups. In those presenting with DVT alone, the rates of overall mortality, recurrent DVT, recurrent PE and major bleeding after 30 days were 2.96%, 0.64%, 0.48% and 1.30%, respectively.

When considering only patients treated at home, again we found no differences on outcome between patients diagnosed on weekends or weekdays (► Table 3).

Table 1: Clinical characteristics of the patients, according to the day of diagnosis.

	Weekends	Weekdays	P-value
Patients, N	5479	24915	
Clinical characteristics			
Gender (males)	2655 (48%)	12293 (49%)	0.237
Age (years $\pm$ SD)	66 $\pm$ 18	66 $\pm$ 17	0.161
Body weight (kg $\pm$ SD)	74 $\pm$ 15	74 $\pm$ 15	0.872
Inpatients	1442 (27%)	6870 (28%)	0.065
Underlying conditions			
Chronic heart failure	337 (6.2%)	1452 (5.8%)	0.358
Chronic lung disease	584 (11%)	2540 (10%)	0.306
Recent major bleeding	111 (2.0%)	544 (2.2%)	0.467
Abnormal creatinine levels	834 (15%)	3643 (15%)	0.249
Risk factors for VTE			
Surgery	675 (12%)	3065 (12%)	0.971
Immobility $\geq$ 4 days	1367 (25%)	5828 (23%)	0.014
Cancer	1092 (20%)	5403 (22%)	0.004
Pregnancy/puerperium	72 (1.3%)	308 (1.2%)	0.638
None of the above (idiopathic)	2533 (43%)	11579 (47%)	0.744
Prior VTE	807 (15%)	3928 (16%)	0.055
Initial VTE presentation			
Clinically overt PE	2871 (52%)	11601 (47%)	<0.001
For patients with PE			
SBP <100 mm Hg	222 (7.7%)	878 (7.6%)	0.766
If only DVT signs			
Proximal DVT	1978 (83%)	10012 (83%)	0.622
Upper-extremity DVT	161 (6.2%)	828 (6.3%)	0.918
Diagnostic methods			
For patients with PE			
Thorax CT	2193 (77%)	8255 (72%)	<0.001
V/P Scintigraphy	818 (29%)	4176 (37%)	<0.001
Arteriography	76 (2.7%)	188 (1.7%)	<0.001
Echocardiography	859 (37%)	3529 (38%)	0.771
If only DVT signs			
Ultrasonography	2540 (98%)	12813 (96%)	0.007
Venography	104 (4.2%)	610 (4.8%)	0.179

VTE, venous thromboembolism; LMWH, low-molecular-weight heparin; SD, standard deviation; PE, pulmonary embolism; DVT, vein thrombosis.

Discussion

Weekends may be problematic for the diagnosis and management of some acute conditions requiring complex and multidisciplinary care, due to a lower availability of experienced staff and higher workload/staff ratio (9). Increased mortality among patients admitted on weekends has been found in patients with myocardial

Table 2: Therapeutic strategies and 7-day and 30-day outcome.

	DVT patients weekends	DVT patients weekdays	PE patients weekends	PE patients weekdays
Patients, N	2608	13314	2871	11601
Initial therapy				
LMWH	2507 (96%)	12757 (96%)	2414 (84%)	9890 (85%)
Mean LMWH dose (IU/day)	176±39	175±38	183±35	182±37
Unfractionated heparin	69 (2.7%)	386 (2.9%)	351 (12%)	1356 (12%)
Thrombolytics	2 (0.1%)	18 (0.1%)	78 (2.7%)	248 (2.1%)
Inferior vena cava filter	33 (1.3%)	241 (1.8%)	97 (3.4%)	326 (2.8%)
Admission required	1365 (76%) [†]	6318 (70%)	2027 (99%)	7948 (98%)
Long-term therapy				
LMWH	730 (29%)	3889 (30%)	579 (21%)	2461 (22%)
Vitamin K antagonists	1817 (71%)	9092 (69%)	2154 (78%)	8510 (77%)
7-day outcome				
Recurrent DVT	4 (0.15%)	15 (0.11%)	1 (0.03%)	4 (0.03%)
Recurrent PE	4 (0.15%)	32 (0.24%)	14 (0.49%)	44 (0.38%)
Major bleeding	17 (0.65%)	73 (0.55%)	23 (0.80%)	130 (1.12%)
Overall death	27 (1.04%)	88 (0.66%)	79 (2.75%)	348 (3.00%)
Causes of death				
Pulmonary embolism	3 (0.12%)	13 (0.10%)	59 (2.06%)	230 (1.98%)
Bleeding	5 (0.19%)	10 (0.08%)	2 (0.07%)	18 (0.16%)
Disseminated cancer	7 (0.27%)	17 (0.13%)	1 (0.03%)	24 (0.21%)
Sudden, unexpected death	0	2 (0.02%)	1 (0.03%)	2 (0.02%)
Respiratory insufficiency	2 (0.08%)	8 (0.06%)	2 (0.07%)	19 (0.16%)
Heart failure	1 (0.04%)	2 (0.02%)	4 (0.14%)	7 (0.06%)
Infection	2 (0.08%)	17 (0.13%)	2 (0.07%)	18 (0.16%)
Myocardial infarction	0	1 (0.01%)	0	1 (0.01%)
Ischaemic stroke	0	1 (0.01%)	0	2 (0.02%)
Other	0	1 (0.01%)	1 (0.03%)	7 (0.06%)
30-day outcome				
Recurrent DVT	24 (0.92%)	78 (0.59%)	8 (0.28%)	45 (0.39%)
Recurrent PE	14 (0.54%)	63 (0.47%)	27 (0.94%)	99 (0.85%)
Major bleeding	32 (1.23%)	175 (1.31%)	51 (1.78%)	242 (2.09%)
Overall death	89 (3.41%)	383 (2.88%)	174 (6.06%)	755 (6.51%)
Causes of death				
Pulmonary embolism	6 (0.23%)	20 (0.15%)	81 (2.82%)	314 (2.71%)
Bleeding	12 (0.46%)	49 (0.37%)	5 (0.17%)	51 (0.44%)
Disseminated cancer	24 (0.92%)	98 (0.74%)	18 (0.63%)	126 (1.09%)
Sudden, unexpected death	2 (0.08%)	7 (0.05%)	3 (0.10%)	9 (0.08%)
Respiratory insufficiency	6 (0.23%)	25 (0.19%)	12 (0.42%)	65 (0.56%)
Heart failure	3 (0.12%)	13 (0.10%)	6 (0.21%)	19 (0.16%)
Infection	8 (0.31%)	49 (0.37%)	15 (0.52%)	53 (0.46%)
Myocardial infarction	0	1 (0.01%)	1 (0.03%)	5 (0.04%)
Ischaemic stroke	0	7 (0.05%)	0	3 (0.03%)
Other	2 (0.08%)	7 (0.05%)	4 (0.14%)	13 (0.11%)
Comparisons between patients diagnosed on weekdays vs. those diagnosed on weekends: [†] p<0.001. LMWH, low-molecular-weight heparin; IU, international units; DVT, deep vein thrombosis; PE, pulmonary embolism.				

Table 3: Therapeutic strategies and 7-day and 30-day outcome only for patients treated at home.

	DVT patients weekends	DVT patients weekdays	PE patients weekends	PE patients weekdays
Patients, N	436	2771	26	144
Initial therapy				
LMWH	431 (99%)	2729 (98%)	26 (100%)	140 (97%)
Mean LMWH dose (IU/day)	12439 ± 3388	12295 ± 3289	13842 ± 2965	12845 ± 3714
Long term therapy				
Vitamin K antagonists	310 (71%)	1792 (65%)	23 (89%)	103 (72%)
LMWH	125 (29%)	949 (34%)	2 (7.69%)	35 (24%)
7-day outcome				
Recurrent DVT	0	3 (0.11%)	0	0
Recurrent PE	0	7 (0.25%)	0	0
Major bleeding	0	4 (0.14%)	0	0
Overall death	0	4 (0.14%)	1 (3.85%)	1 (0.69%)
30-day outcome				
Recurrent DVT	3 (0.69%)	12 (0.43%)	0	0
Recurrent PE	2 (0.46%)	14 (0.51%)	0	0
Major bleeding	0	15 (0.54%)	0	1 (0.69%)
Overall death	1 (0.23%)	18 (0.65%)	1 (3.85%)	5 (3.47%)
LMWH, low-molecular-weight heparin; IU, international units; DVT, deep vein thrombosis; PE, pulmonary embolism.				

infarction or stroke (10, 11) but not in those with heart failure, acute leukaemia, or admitted to intensive care units (12–17). Our data reveal that patients with a VTE diagnosis established on weekends had similar clinical characteristics (severity of the VTE episode, frequency of underlying diseases) and received the same therapy (drugs, doses) than those in whom the VTE was detected on weekdays. The only difference was the slightly higher proportion of patients with DVT who were treated at home. As a logical consequence, the outcome at 7- and at 30 days was also similar. This similar outcome, including assessment of the cause of death, was consistently found in patients presenting with PE and in those with only DVT signs.

While this is the first report analysing the impact of the time of DVT diagnosis on outcome, our findings disagree from those obtained in two previous studies in patients with acute PE. In one study, there were no data about the clinical characteristics of the patients (3). In the second study, using a database from acute care hospitals in Pennsylvania during the 2000–2002 period, patients admitted on weekends had a higher mortality at 30 days (11.1% vs. 8.8%; $p < 0.001$) than those admitted on weekdays, the differences being particularly significant in the most severely ill patients (4).

One possible explanation for this discrepancy might be the differences in the patients' co-morbidities or the severity of the disease, since the proportion of patients with chronic heart failure or chronic lung disease was higher in the Aujesky et al. population (4). However, the proportion of patients with active cancer or renal failure was lower. Regarding the severity of the PE event, the proportion of patients undergoing fibrinolysis (2.3%) was similar in both studies. In our opinion, these differences in outcome might

partly be justified by differences in therapy. The vast majority of patients in our series (96% of those with DVT, 85% with PE) were initially treated with LMWH. With the exception of patients requiring thrombolysis, the Aujesky et al. report lacks data about initial therapy, but the use of LMWH as initial therapy has been much lower in North America than in Europe. In a recent report, the Worcester VTE study showed that between 1999 and 2003 the proportion of patients with VTE receiving initial LMWH increased from 27% to just 60% (18).

What is known about this topic?

- Two studies conducted in Canada and US found a higher mortality among patients with pulmonary embolism hospitalised on weekends than in those hospitalised on weekdays.
- Should these results be confirmed, important efforts by national health services would be required to improve medical assistance during weekends, particularly by increasing the rates of on-duty experienced staff.

What does this paper add?

- We analysed the data from the RIETE registry to evaluate the 7-day and 30-day mortality rate of patients with acute venous thromboembolism, according to the day of diagnosis – weekends versus weekdays –, and found that they experienced similar outcomes.
- We hypothesise that differences in the prescription of initial therapy (most RIETE patients received low-molecular-weight heparin therapy instead of unfractionated heparin) might partly explain this discrepancy.

A recent meta-analysis concluded that LMWH is more effective than UFH in the initial treatment of VTE, reducing the occurrence of major bleeding and overall mortality (19). Another meta-analysis showed a higher rate of early thrombus regression in patients treated with LMWH compared to UFH. The lack of thrombus regression in venography was correlated with clinical VTE recurrence (20). Due to its simplicity of use (weight-adjusted fixed doses in most patients, no need of laboratory monitoring), initial therapy with LMWH could help to overcome the shortfall of weekend medical care. Thus, we suggest that the higher use of UFH together with a suboptimal treatment monitoring during weekends might partly explain the differences in outcomes observed between weekdays and weekend PE diagnosis in the previous studies and the absence of differences in RIETE.

The RIETE registry provides data on the treatment and outcome of VTE in a real-world situation with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies, providing insights into the natural history of VTE in different settings. The present study has several limitations. First, some patients with severe PE in RIETE may have died before getting an objective confirmation, which is mandatory for inclusion in RIETE. In fact, the 6.4% mortality rate at 30 days in patients with PE is lower than that reported by Aujesky et al. (4), and in the prior Canadian Study (3). This fact may reflect a lower severity of the PE in the RIETE patients, but also could be related to differences in health care policies regarding the organisation of on-duty staff during weekends between sanitary models, as well as in the initial treatment used, UFH or LMWH. In fact, similar mortality rates in patients with PE (ranging from 5.0% to 11.1% at 3 months) have recently been reported in other cohorts, particularly if early anticoagulation was started (21–26). Second, some unmeasured confounders may have contributed to the results. For example, we have not stratified patients according to the severity of disease, particularly in those with PE. Therefore, we can not exclude the possibility of differences in mortality between weekends and weekdays among patients with more severe disease. Third, as an observational study, RIETE is not designed to answer questions regarding the relative efficacy and safety of different modalities of therapy. Data from the registry are hypothesis-generating and provides feedback from real-world clinical situations which may be of help when designing new clinical studies. Finally, since in RIETE only patients with acute, symptomatic, objectively confirmed VTE events are accepted, our study might have underestimated some patients with severe PE.

In summary, patients with DVT or PE in the RIETE registry experienced similar outcomes, independently of the time – weekends or weekdays – when the diagnosis was obtained. These findings were consistently found in patients presenting with PE or DVT alone, and disagree with those in two studies performed in patients with PE in North America. We hypothesise that differences in the prescription of the initial therapy (most RIETE patients received

LMWH therapy instead of UFH) might partly explain the discrepancy.

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Appendix

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References

1. Konstantinides S. Acute pulmonary embolism. *N Engl J Med* 2008; 359: 2804–2813.
2. Baglin T. What happens after venous thromboembolism?. *J Thromb Haemost* 2009; 7 (Suppl 1): 287–290.
3. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med* 2001; 345: 663–668.
4. Aujesky D, Jiménez D, Mor MK, et al. Weekend versus weekday admission and mortality after acute pulmonary embolism. *Circulation* 2009; 119: 962–968.
5. Monreal M, Falgá C, Valle R, et al. Venous thromboembolism in patients with renal insufficiency. Findings from the RIETE Registry. *Am J Med* 2006; 119: 1073–1079.
6. Blanco-Molina A, Trujillo-Santos J, Tirado R, et al.; RIETE Investigators. Venous thromboembolism in women using hormonal contraceptives. Findings from the RIETE Registry. *Thromb Haemost* 2009; 101: 478–482.
7. Vasco B, Villalba JC, López-Jiménez L, et al.; for the RIETE Investigators. Venous thromboembolism in nonagenarians. Findings from the RIETE Registry. *Thromb Haemost* 2009; 1112–1118.
8. Laporte S, Mismetti P, Décousus H, et al. Clinical predictors for fatal pulmonary embolism in 15520 patients with venous thromboembolism: Findings from the Registro Informatizado de la Enfermedad TromboEmbólica venosa (RIETE) Registry. *Circulation* 2008; 117: 1711–1716.
9. Redelmeier DA, Bell CM. Weekend worries. *N Engl J Med* 2007; 356: 1164–1165.
10. Kostis WJ, Demissie K, Marcella SW, et al., for the Myocardial Infarction Data Acquisition System (MIDAS 10) Study Group. Weekend versus weekday admission and mortality from myocardial infarction. *N Engl J Med* 2007; 356: 1099–1109.
11. Saposnik G, Baibergenova A, Bayer N, et al. Weekends: a dangerous time for having a stroke? *Stroke* 2007; 38: 1211–1215.
12. Fonarow GC, Abraham WT, Albert NM, et al. Day of admission and clinical outcomes for patients hospitalized for heart failure: findings from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). *Circ Heart Fail* 2008; 1: 50–57.
13. Wilop S, Galm O, Thompson L, et al. Friday Leukemia: myth or reality? *Blood* 2010; 115: 912.
14. Wunsch H, Mapstone J, Brady T, et al. Hospital mortality associated with day and time of admission to intensive care units. *Intensive Care Med* 2004; 30: 895–901.
15. Dabbagh O, Adams L, Haddadin S, et al. Effect of time of admission on compliance with deep vein thrombosis prophylaxis in a tertiary medical intensive care unit. *J Thromb Haemost* 2009; 7: 950–954.
16. Marco J, Barba R, Plaza S, et al. Analysis of the mortality of patients admitted to Internal Medicine wards over the weekend. *Am J Med Qual* 2010; 25: 312–318.
17. Barba R, Losa JE, Velasco M, et al. Mortality among adult patients admitted to the hospital on weekends. *Eur J Intern Med* 2006; 17: 322–324.
18. Spencer FA, Emery C, Joffe SW, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis* 2009; 28: 401–409.
19. Van Dongen CJ, Van den Belt AG, Prins MH, et al. Fixed dose subcutaneous low molecular weight heparin versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2004; 18: CD001100.
20. Gómez-Outes A, Lecumberri R, Lafuente-Guijosa A, et al. Correlation between thrombus regression and recurrent venous thromboembolism. Examining venographic and clinical effects of low molecular weight heparins: a meta-analysis. *J Thromb Haemost* 2004; 2: 1581–1587.
21. Conget F, Otero R, Jiménez D, et al. Short-term clinical outcome after acute symptomatic pulmonary embolism. *Thromb Haemost* 2008; 100: 937–942.
22. Spencer FA, Goldberg RJ, Lessard D, et al. Factors associated with adverse outcomes in outpatients presenting with pulmonary embolism: the Worcester Venous Thromboembolism Study. *Circ Cardiovasc Qual Outcomes* 2010; 3: 390–394.
23. Sevestre MA, Quashié C, Genty C, et al., for the Optimev Study Investigators. Clinical presentation and mortality in pulmonary embolism: The Optimev study. *J Mal Vasc* 2010; 35: 242–249.
24. Erkens PM, Gandara E, Wells P, et al. Safety of outpatient treatment in acute pulmonary embolism. *J Thromb Haemost* 2010; Epub ahead of print.
25. Park B, Messina L, Dargon P, et al. Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States. Findings from the Nationwide Inpatient Sample. *Chest* 2009; 136: 983–990.
26. Donzé J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index. A clinical prognostic model for pulmonary embolism. *Thromb Haemost* 2008; 100: 943–948.