Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **32** (8): 1205-11 (2013)

Regular article
Received: March 21, 2013
Revised version: August 1, 2013
Accepted: August 8, 2013

Adequacy of Thromboembolic Prophylaxis Prescribed in an Emergency Department

Ana de LORENZO-PINTO *[1], Lucía CORTEJOSO [1], Antonio MUIÑO-MÍGUEZ [2], María GÓMEZ-ANTÚNEZ [2], Esther DURÁN-GARCÍA [1], ANA HERRANZ-ALONSO [1], Raquel GARCÍA-SÁNCHEZ [1] & María SANJURJO-SÁEZ [1]

[1] *Pharmacy Department &* [2] *Internal Medicine Department, Gregorio Marañón University General Hospital, Madrid, Spain*

SUMMARY. **An observational, longitudinal and prospective study was carried out from October 2011 to March 2012 in order to evaluate the adequacy of thromboembolic prophylaxis prescribed in an Emergency Department according to the PRETEMED (Prevention of thromboembolic venous disease in medical patients) guide. For each patient an adjusted risk of venous thromboembolism (VTE) was calculated and the clinical pharmacist compared the prescribed prophylaxis to the recommended by the PRETEMED guide and assessed concordance. A total of 73 patients were included in the study and in 34.2% of them, the recommendation of prophylaxis did not match with the prophylaxis prescribed at admission: omission of prophylaxis (16.4%), no indication of mechanical or pharmacological prophylaxis (5.5%), indication of mechanical prophylaxis, but not pharmacological prophylaxis (11.0%) and overdosage (1.4%). In a high proportion of patients the thromboprophylaxis prescribed was not consistent with PRETEMED recommendations. The existence of discrepancies in both directions (underestimation and overestimation of VTE risk and both in similar percentages) could suggest that the individual risk is not valued enough.**

INTRODUCTION

Venous thromboembolism (VTE) which includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) is considered the leading preventable cause of death in hospitalized patients and an important health problem due to its high morbidity, mortality and resource consumption [1].

Risk factors for VTE are usually related to any component of the Virchow's triad [2] (stasis, vascular damage and hypercoagulability) and hospitalized patients often have two or more risk factors, that cumulatively, may increase the risk of VTE [3].

Several studies, as the published by Goldhaber *et al.* [4], have shown that VTE remains a common complication in hospitalized patients. An estimated 5-10% of inpatient deaths are due to PTE. In most cases, VTE occurs abruptly or within 2 h before effective treatments can be applied, in other cases VTE follows silently or presents with non-specific symptoms that make it difficult or impossible for an early diagnosis, therefore prevention is of paramount importance [1,4].

Prophylaxis reduces morbidity and mortality associated with VTE, both in patients with medical and surgical conditions. Preventive methods that have proven efficacy in controlled clinical trials can be mechanical (graduated compression stockings, intermittent pneumatic compression) or pharmacological (heparin, hirudin, fondaparinux, oral anticoagulants). Furthermore, early ambulation is recommended [3].

Clinical practice guidelines (CPGs) as those published by the National Institute for Health and Clinical Excellence have been available for the last 15 years, with the objective of health quality improvement [5-8]. Most of them classify patients into three groups: low, medium and high risk for the development of VTE based on risk factors present in the patient. However, these factors are not usually weighed up and quantified, a fact that may lead to an under/

KEY WORDS: Anticoagulants, Emergency medical services, venous thrombosis

* Author to whom correspondence should be addressed. *E-mail:* ana.lorenzo@salud.madrid.org

overestimation of the risk of VTE by physicians and a variability in the prescription of thromboprophylaxis. In this sense, the 2007 PRETEMED (Prevention of thromboembolic venous disease in medical patients) guide [9] is considered one of the first international clinical practice guidelines whose aims are to provide recommendations on the prophylaxis of VTE in patients with acute or chronic medical conditions when combining several risk factors.

The PRETEMED guideline is highly recognized as being important in our hospital and therefore it has been chosen to be included in the official protocol about prevention of thromboembolism which is now being updated and whose last recommendations come from the 2004 ACCP guideline [10]. Although many of our professionals evaluate VTE risk using the PRETEMED guide, its use cannot be mandatory as long as the protocol is not completely finished and officially approved by the Pharmacy and Therapeutics Committee.

On the other hand, the Emergency Department (ED) is a fast paced work environment prone to medication errors and adverse drug events. According to the EVADUR study, 23% of adverse events occurring in the ED were related to drug use and 70% of them were preventable [11].

The main objective of this study was to evaluate the adequacy of thromboembolic prophylaxis prescribed in an ED according to the PRETEMED guide.

MATERIAL AND METHODS

An observational, descriptive, longitudinal and prospective study was carried out from October 2011 to March 2012 in an Internal Medicine Section belonging to a general university hospital.

Patients included in the study were adults admitted to the Internal Medicine Section transferred from the ED. Patients in whom one of these drugs was prescribed for therapeutic purposes were excluded. Patients with contraindications for the prescription of thromboprophylaxis (hypersensitivity to the drug, background or suspected heparin-induced thrombocytopenia, active bleeding or increased risk of bleeding due to impaired haemostasis and/or terminally ill patients) were not excluded from the study and the omission of pharmacological prophylaxis was considered a correct measure regardless of risk factors present in the patient.

The PRETEMED guide was first published at <www.guidelines.gov> [12] in 2003 but this version was updated four years later in order to assign a weight (adjusted for the presence of precipitating/associated processes, drugs and other processes) to each variable and the final score classifies the patient into one of four risk categories using the RAND/UCLA appropriateness method: no risk (AR = 0), low (AR = 1-3), moderate (AR = 4) or high (AR > 4) (Table 1) [9]. In patients with moderate risk, the guideline suggests low molecular weight heparin prophylaxis, but it is mandatory in patients at high risk. The scale was validated by a consensus of well known Spanish experts and it is widely used by physicians and hospital pharmacists in our country.

The clinical pharmacist located in the inpatient unit assessed the risk for VTE and collected the following information in a database: 1) demographic data (age, gender, date of birth and body weight), 2) Risk factors for the development of VTE according to the PRETEMED guide (Table 1); severe infection was considered an episode that led to the admission of the patient, 3) date of admission and discharge, 4) prior use of antithrombotic therapy, 5) admission diagnosis, 6) laboratory findings at the moment of admission (glomerular filtration rate (ml / min), INR, prothrombin time and number of platelets/μL), 7) antithrombotic prophylaxis prescribed in the ED, 8) complications during hospitalization (deep vein thrombosis, thrombocytopenia, pulmonary embolism, bleeding events and death); thrombocytopenia was defined as platelet count less than 100/μL, pulmonary embolism as a positive pulmonary computed tomographic angiogram and bleeding events were classified according to the definition published by the International Society on Thrombosis and Haemostasis [13], 9) adjusted risk (AR) according to the PRETEMED guide; for each patient AR was calculated using the following formula: *AR = Sum of weights of the different precipitating processes + sum of weights of other risk circumstances*. This formula was applied only if the patient had at least one precipitating process or a process with adjusted weight ≥ 2. *(i.e.,* if a 80-year-old patient has been on bed rest for 5 days, the AR will be 3, because bed rest has an adjusted weight of 2 although it is not a precipitating process).

If a patient had several admissions during the study period, each of these was considered a different episode. The recommendation of thromboprophylaxis varied according to the individual AR (Table 1).

	Adjusted weights		
	1	**2**	**3**
Precipitating processes	Pregnancy / postpartum a Air travel > 6 h	Active inflammatory bowel disease Severe infection Class III CHF Neoplasia	Stroke with lower limb paralysis COPD with severe decompensation AMI Class IV CHF Myeloma with chemotherapyd Lower limb injury without surgery
Associated processes	Diabetes mellitus Hyperhomocysteinemia HIV Paralysis of lower limbs Prior SVT	Nephrotic sindrome Thrombophilia b Previous DVT c Vasculitis (Beçhet/Wegener)	
Drugs	Hormonal contraceptives Antidepressants Antipsychotics Aromatase inhibitors Tamoxifen / Raloxifene Hormone replacement therapy	Chemotherapy	
Others	Central venous catheter Age> 60 years Obesity (BMI> 28 Kg/m^2) Smoking> 35 cigarettes/day	Bed rest > 4 days	

Table 1. Table for calculating the risk of VTE in medical patients according to the 2007 PRETEMED guide and VTE prophylaxis recommendations AMI: acute myocardial infarction; BMI: body mass index; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; HIV: human immunodeficiency virus; SVT: superficial vein thrombosis. (a) Weight 3 if: pregnancy and thrombophilia; Weight 4 if: pregnancy and previous DVT. (b) Weight 2 if: factor V Leiden in> 60 years, deficit of protein S or C deficiency combined antithrombin deficiency, antiphospholipid antibodies. Weight 1 if: factor VIII> 150% or factor V Leiden in <60 years. (c) Weight 3 if: prior spontaneous DVT. Weight 5 if: previous DVT and thrombophilia. (d) Weight 4 if: myeloma treated with thalidomide and chemotherapy.

The drugs included in the formulary for the prevention of VTE are unfractionated heparin, enoxaparin and bemiparin. As regards mechanical measures, the official protocol in our institution does not contemplate their use for the prophylaxis of VTE in patients considered low to moderate risk due to their high cost.

The PRETEMED guide includes the dose of antithrombotic prophylaxis, but does not include the optimal dose of every antithrombotic drug according to patient risk factors. For this reason, the degree of correlation between the prescribed prophylaxis in the ED and the suggested by the PRETEMED guide was assessed in regard to an appropriate indication and not to the dosage prescribed. However, patients with indication for only pharmacological prophylaxis could be classified as overdosed if they were treated with therapeutic doses.

According to the AR calculated, the medical team and the clinical pharmacist agreed on the need for an adjustment of the antithrombotic regimen prescribed in the ED during the daily ward round. This intervention was performed within 24 h of admission in the Internal Medicine Section, except in patients who had been hospitalized at the weekend, in which case the intervention took place on the following Monday.

After the detection of a medication error, physicians were notified immediately. No additional risk was observed and the hospital considered unnecessary the approval by the hospital Research Ethics Committee as well as the requirement to obtain informed consent from patients included in the study.

Statistical analysis

This was a descriptive study that utilized descriptive statistics only. Continuous, normally distributed variables are expressed as mean (± standard deviation) and non-normally distributed variables are expressed as median with interquartile range. Proportions are expressed as per-

cents with inter-quartile range. All statistical analysis mentioned were performed using the statistical analysis package SPSS 15.0.

RESULTS

A total of 153 patients were examined and 80 of them were excluded as they do not meet inclusion criteria, then 73 patients were finally included in the study, 54.8% were men and the median age was 81.6 years (minimum 25, maximum 105 years). The average length of stay was 11.5 days and the most common diagnosis of admission was respiratory disease (36.4%) (Table 2). Body weight was not registered in the Emergency medical record of any patient and 37.0% of patients had antithrombotic treatment before admission (87.1% with antiplatelet therapy and 12.9% with anticoagulants).

Regarding the frequency of risk factors (Table 2), age was the most prevalent factor (87.7%), followed by diabetes mellitus (34.2%) and admission for severe infection (30.1%).

After stratifying patients according to the risk of developing VTE, most of them (45.2%) were classified as high risk (AR greater than 4) (Table 3).

After analyzing the adequacy of the prophylaxis prescribed in the ED, it was observed that in 34.2% of patients (25 patients), the recommendation of prophylaxis according to the PRETEMED guide did not match the prophylaxis prescribed at admission (Table 4). Reasons for non concordance were: a) omission of prophylaxis: 16.4% (12 patients and 7 of them were at high risk of VTE), b) no indication of mechanical or pharmacological prophylaxis: 5.5% (4 patients), c) indication of mechanical prophylaxis, but not pharmacological prophylaxis: 11.0% (8 patients), and d) overdosage: 1.4% (1 patient). Considering that patients in the two previous sections were also overdosed, then this percentage increases to 17.8%.

As regards patients with antithrombotic therapy prior to admission, omission of thromboprophylaxis was detected in a 29.6% (8 patients).

Regarding the distribution of prescriptions at the time of admission, no patient was anticoagulated with unfractionated heparin, and bemiparin was used only in two patients at doses of 2,500 U/24h s.q. The anticoagulant most commonly used was enoxaparin (45 patients) and the principal treatment regimen was 40 mg/24 h s.q. (33 patients). The dose of 20 mg/24h s.q. was prescribed in those patients with renal function below 30 mL/min (4 patients), in 1 pa-

Characteristic	
No	73
Median age (years)	81.6
Gender N (%)	40 (54.8) men, 33 (45.2) women
Average length of stay ± SD (days)	11.5 ± 11.0
MDRD (ml/min) at admission ± SD	50.6 ± 15.9
Number of platelets at admission/µl ± SD	229.9 ± 112.6
INR at admission ± SD	1.3 ± 1.7
Prothrombin time at admission ± SD	18.9 ± 26.7
Admission diagnosis	**N (%)**
Respiratory disease	26 (35.6)
Genitourinary disease	15 (20.5)
Signs and symptoms not associated with a clear disease	12 (16.4)
Cardiovascular disease	9 (12.3)
Gastrointestinal disease	4 (5.5)
Others	7 (9.6)
Frequency of risk factors	**N (%)**
Age over 60 years	64 (87.7)
Diabetes mellitus	25 (34.2)
Severe infection	22 (30.1)
Obesity	17 (23.3)
Antidepressant	15 (20.5)
Neoplasia	13 (17.8)
Bed rest > 4 days	12 (16.4)
Superficial vein thrombosis	11 (15.1)
COPD with severe decompensation	9 (12.3)
Acute myocardial infarction	8 (11.0)
Class III CHF	8 (11.0)
Class IV CHF	4 (5.5)
Paralysis of lower limbs	4 (5.5)
Previous DVT	4 (5.5)
Antipsychotics	3 (4.1)
Smoking> 35 cigarettes / day	3 (4.1)
Hormonal contraceptives	1 (1.4)
Stroke with lower limb paralysis	1 (1.4)
Central venous catheter	1 (1.4)
Raloxifene	1 (1.4)

Table 2. Demographic and Baseline Characteristics of Study Subjects AMI: acute myocardial infarction; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; MDRD: modification of diet in renal disease; SD: standard deviation; SVT: superficial vein thrombosis.

Adjusted Risk	**N (%)**
0	10 (13.7)
1-3	11 (15.1)
4	19 (26.0)
>4	33 (45.2)

Table 3. Distribution of patients included in the study according to the degree of VTE risk.

Adjusted Risk	Total (Nº patients with an incorrect prescription)	Reasons for non concordance			
		Omission	No indication MP or PP	No indication PP	Overdosage
0	4	0	4	0	0
3	8	0	0	8	0
4	5	5	0	0	0
5	5	5	0	0	0
6	1	0	0	0	1
7	1	1	0	0	0
8	1	1	0	0	0
TOTAL	25	12	4	8	1

Table 4. Classification of mismatch prescriptions according to the adjusted risk of patients. MP: mechanical prophylaxis; PP: pharmacological prophylaxis.

tient with a suspected bleeding event and those whom the clinician considered of low risk for developing VTE (6 patients). In 1 patient, the initial prescription was enoxaparin at therapeutic doses (60 mg/12h s.q.), but once transferred to the Internal Medicine Section, this regimen was modified to 40 mg/24 h s.q. as there was no justification for a higher dose.

Complications

There were no episodes of thrombocytopenia or deep vein thrombosis. One patient, who had not been prescribed thromboprophylaxis in the ED, although presenting an AR of 4: age over 60 years, diabetes mellitus and active neoplasia, was diagnosed with a possible pulmonary embolism during hospitalization and 7 patients developed a bleeding event. In 71.4% of them (5 patients) bleeding was classified as minor. Bleeding events in the 2 remaining patients were classified as major bleeding: 1) anaemia, possibly secondary to upper gastrointestinal bleeding in a patient who was prescribed enoxaparin at admission despite having post-traumatic subdural hematoma and an AR of 3; 2) rectal bleeding in a patient with chronic kidney disease (CrCl = 26.2 mL/min) and an AR of 3, who also was prescribed thromboprophylaxis in the ED. In both cases the prescription of enoxaparin was suspended in the Internal Medicine Section. There were 3 deaths (neither of them was related to the use or omission of thromboprophylaxis, 2 deaths were caused by sepsis and 1 was related to cancer hypercalcemia).

DISCUSSION

Our study shows that in a high proportion of patients the thromboprophylaxis prescribed was not consistent with PRETEMED recommendations (drug and type of treatment). Although the scale is not officially approved in our institution, it is widely used by physicians and the existence of discrepancies in both directions (underestimation and overestimation of VTE risk and both in similar percentages) could suggest that the individual risk is not valued enough.

In 2008, the ENDORSE study was published and is considered the largest study that has addressed this issue. This study assessed the risk of VTE and the appropriateness of thromboprophylaxis in 68,183 patients from 358 hospitals in 32 different countries [14]. It showed that, while the percentage of hospitalized patients at risk of developing VTE, according to the ACCP guideline [10], varied between 35.6 and 72.6%, the percentage of patients who received thromboprophylaxis varied between 1.6 and 84.2%, being more frequent the use of preventive measures in surgical patients (58.5%) than in those with medical conditions (39.5%). This fact can be explained by the scientific information available on the risk of VTE and the potential for prevention is much higher in surgical patients than in those with medical conditions. Our results are consistent with those of the ENDORSE study and 16.4% of patients did not receive any kind of thromboprophylaxis despite being at high risk of VTE and most of them treated with antithrombotic therapy prior to admission. However, one of the main findings of our study which the ENDORSE did not show has been that the percentage of patients overdosed had been surprisingly higher (17.8%), a fact that could indicate the first changes in patterns of use of VTE prophylaxis.

Although the CPGs have attracted increasing interest in recent years as tools that can improve

clinical practice, the VTE is a clear example that, despite the existence of good guides and their increasing popularity and proliferation, often their advice is not adopted by clinicians. The reasons why clinicians did not appropriately assess the thromboembolic risk in their patients remain unclear. This reluctance to assess VTE risk could be explained by a combination of factors such as lack of knowledge, physicians under pressure in the ED, the fear of bleeding events caused by the use of heparins and the fact that, in many cases, DVT may remain subclinical or episodes of PE can occur after hospital discharge of patients, so they go unnoticed by clinicians [15]. All these situations have led to a variability in the thromboprophylaxis prescription as shown in the study. Moreover, the use of thromboprophylaxis in routine clinical practice in the medical field may be complicated by the fact that stratifying the risk of developing VTE is more complex in patients who usually present, concomitantly, several risk factors as it occured in the study (most of the patients were elderly with multiple health problems).

To improve the quality of health, models have been developed to assess individual risk of VTE by stratification and weighing of the different risk factors and a subsequent quantification of the individual patient risk, in order to identify patients who should receive thromboprophylaxis. The PRETEMED guide is a useful tool that facilitates risk stratification of VTE in patients with medical conditions due to the existence of a table of well-defined risk calculation. However, the model has not yet been officially approved in our institution and, the fact that there is such a high number of physicians working at the hospital -approximately 1,500 and 500 of them are residents- makes difficult to follow the same criteria.

It is important to note that there are discrepancies in the recommendations proposed by the different CPGs. Thus, the PRETEMED guide includes mechanical prophylaxis as the optimal method for prevention of VTE in patients with an AR of 1-3, while the ACCP guideline [16], only recommends this method in patients with a contraindication to pharmacologic prophylaxis. For this reason, it is imperative that treatment protocols approved by each hospital should be the result of the selection of those recommendations that best suit their environment and should have been agreed upon by a broad panel of experts.

In order to improve the adequacy of thromboembolic prophylaxis prescribed in our institution, some measures will be implemented:

1. In the hospital, mechanical prophylaxis is mostly used in surgical patients but not in medical patients due to their high cost. However, as has been mentioned before, the current protocol is being updated using PRETEMED recommendations and it has been decided that despite this limitation, mechanical prophylaxis will also be included for medical patients with moderate risk or patients at high risk but with contraindications for pharmacologic prophylaxis. This measure will certainly help to reduce the percentage of patients found in the study to be treated with pharmacological prophylaxis but with an indication of only mechanical prophylaxis.

2. Besides, tools associated with the electronic prescription program will be developed in order to alert the doctor on the individual risk of VTE and, thus, preventing that an error committed on admission should last for the whole hospitalization. This measure will guide physicians to choose the best treatment depending on the AR of the patient so the variability in the prescriptions might be reduced as well.

Concerning complications associated to thromboprophylaxis, there were no major safety issues related to the use of heparin and although two patients developed major bleeding, in both of them, pharmacological prophylaxis was not indicated.

On the other hand, although body weight data for VTE prophylaxis is not essential, it must be taken into account that this information during hospitalisation may be required for the administration of another drug whose dose does depend on body weight; so it is imperative that it should be collected as other analytical data in the Emergency medical record [17].

Regarding study limitations, the sample size was small due to the exclusion of a considerable number of patients who were prescribed the anticoagulant drugs with therapeutic purposes. In this group of patients omission of treatment and dosing errors were also observed, but this information was not included in the study. The 2007 PRETEMED guide is not officially implemented in the hospital, so the proposed risk factors and their weight in the final score should have been agreed beforehand with the professionals working in that department. The reason why we did not seek this consensus was not to reveal to the ED that their prescriptions

were being evaluated using the PRETEMED guide in order to avoid biased results. The guide is easily available online and the usual pattern of use could have been intentionally modified.

CONCLUSION

The PRETEMED guide is a useful tool that facilitates risk stratification of VTE in patients with medical conditions due to the existence of a table of well-defined risk calculation. Although the guideline is not officially implemented in the hospital, the existence of similar percentages of patients both under and overestimated could suggest that the individual risk is not been valued enough.

From our point of view, in order to achieve effective implementation of guidelines, it is essential that clinicians themselves assess the situation in their area and be aware of that need. Therefore, the carrying out of observational studies, despite their limitations, is useful in knowing routine clinical practice and identifying strengths and weaknesses, thus promoting multidisciplinary activities that ultimately result in better therapy for the patient.

Acknowledgements. The authors would like to thank Samantha Wilkinson for her invaluable help in editing the English manuscript.

REFERENCES

1. Calderón, E., Rivero L., Gutiérrez S. & Medrano F.J. (2008) *Farm. Hosp.* **32**: 259-60.
2. Haines, S.T. (2010) *Am. J. Health Syst. Pharm.* **67** (Suppl 6): S3-8.
3. Francis, C.W. (2007) *N. Engl. J. Med.* **356**: 1438-44.
4. Goldhaber, S.Z. & H. Bounameaux (2012) *Lancet*. **379**:1835-46.
5. Geerts, W.H., D. Bergqvist, G.F. Pineo, J.A. Heit, C.M. Samama, M.R. Lassen, *et al.* (2008) *Chest.* **133** (6 Suppl): 381S-453S.
6. Scottish Intercollegiate Guidelines Network. *Prevention and management of venous Thromboembolism A national clinical guideline*. Available at: <http://www.sign.ac.uk/pdf/ sign 122.pdf>. Accessed October 09, 2011.
7. Venous thromboembolism: reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. National Institute for Health and Clinical Excellence. Available at: <http://www.nice.org.uk/nicemedia/live/12695/47195/47195.pdf>. Accessed October 10, 2011.
8. Health Care Guideline: Venous Thromboembolism Prophylaxis. Institute for Clinical Systems Improvement. Available at: <http://www.icsi.org/venous_thromboembolism_prophylaxis__2__guideline_/venous_thromboembolism_prophylaxis__guideline__47057.html>. Accessed December 12, 2011.
9. Guía PRETEMED 2007. Guía de práctica clínica basada en la evidencia sobre prevención de enfermedad tromboembólica venosa en patología médica. SADEMI y SAMFyC. Available at: <http://www.sademi.com/actividades/publicaciones/guia_medica_pretemed_2007.pdf>. Accessed September 9, 2011.
10. Geerts, W.H., G.F. Pineo, J.A. Heit, D. Bergqvist, M.R. Lassen, C.W. Colwell, *et al.* (2004) *Chest.* **126** (3 suppl): 338S–400S.
11. Tomás, S., M. Chanovas, F. Roqueta & The Work Group EVADUR-SEMES (2010) *Emergencias.* **22**: 415-28.
12. Prevention of thromboembolic venous disease in medical patients (PRETEMED). Available at: <http://pmmp.cnki.net/Resources/CDDPdf/evd%5Cbase%5CNational%20Guideline%20Clearinghouse%5C%E4%B8%B4%E5%BA%8A%E5%AE%9E%E8%B7%B5%E6%8C%87%E5%8D%97%5C727.pdf>. Accessed September 9, 2011.
13. Schulman, S. & C. Kearon (2005) *J. Thromb. Haemost.* **3**: 692-4.
14. Cohen, A.T., V.F. Tapson, J.F. Bergmann, S.Z. Goldhaber, A.K. Kakkar, B. Deslandes, *et al.* (2008) *Lancet.* **371**: 387-94.
15. Blann, A.D. & Lip G.Y.H. (2006) *Brit. Med. J.* **332**: 215-9.
16. Hirsh, J, G. Guyatt, G.W. Albers, R. Harrington & H.J. Schünemann (2008) *Chest.* **133**: 71S-109S.
17. de Lorenzo-Pinto, A. & L. García-Diz (2011) *Med. Clin. (Barc).* **137**: 259-61.