Agreement of Four Competing Guidelines on Prevention of Venous Thromboembolism and Comparison with Observed Physician Practices

A Cross-sectional Study of 1,032 Medical Inpatients

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OBJECTIVE: To assess the degree of agreement between four competing guidelines regarding the recommendation for prophylactic heparin therapy and to report to what extent actual practice agreed with or differed from the recommendations made before these guidelines were disseminated.

DESIGN: Four French guidelines were applied to data from a cross-sectional study conducted before their dissemination.

SETTING: Twenty-six medical units of a teaching and a non-teaching hospital.

PATIENTS: One thousand thirty-two medical inpatients.

MAIN MEASUREMENTS: Interguideline agreement rated by the κ coefficient and percentage of patients receiving prophylactic heparin treatment.

RESULTS: The percentage of patients requiring prophylactic treatment ranged from 35.4% to 54.6% (overall κ coefficient, 0.65 [0.63 to 0.68]), depending on the guideline. The four guidelines agreed in recommending prophylactic heparin treatment in 330 patients (32.0%). The corresponding rate of prophylactic treatment use was 57.0% (188/330). None of the guidelines recommended prophylactic heparin treatment in 385 patients (37.3%). The physicians did not order prophylactic treatment in 80.3% of these patients (309/385). The guidelines disagreed in recommending prophylactic treatment in 317 patients (30.7%). The corresponding rate of prophylactic treatment use was 32.8% (104/317).

CONCLUSION: The four guidelines agreed in 69.3% of patients but physician practices were already quite appropriate in these patients before the guidelines were disseminated. Active dissemination of the guidelines can be expected to improve physician practices in the treatment of these patients, but likely with limited impact. In contrast, the four guidelines disagreed in 30.7% of patients. Further clinical trials are needed in this subgroup of patients.

KEY WORDS: venous thrombosis; pulmonary embolism; practice guidelines; heparin; low molecular weight.

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Venous thromboembolism is a common clinical problem among hospitalized patients.¹ The clinical silence of deep vein thrombosis and the potential mortality of pulmonary embolism make prevention the most suitable response to this disease.² However, a strategy for venous thromboembolism prophylaxis in medical inpatients has not been clearly established, except for particular conditions such as recent myocardial infarction and acute stroke.² The multiplicity and combination of risk factors involve heterogeneous levels of venous thromboembolism risk, making the assessment of the risk-benefit ratio of thromboprophylaxis difficult for different subpopulations of medical patients. Although the findings of recent studies have shown that prophylactic heparin treatment provides an overall risk reduction of deep vein thrombosis in general medical inpatients,^{3,4} further data are needed to determine precisely which patients could benefit from thromboprophylaxis. Despite the lack of definitive data on which subpopulations of medical patients require prophylaxis, the need for written policies aiming at preventing venous thromboembolism in hospitals has been widely promulgated.² Indeed, several studies of nonsurgical patients have evidenced a high prevalence of over- and undertreatment and substantial variations in physician practices.^{5,6}

In France, four competing clinical practice guidelines were disseminated between 1998 and 2000 in order to provide clinicians with guidance on the appropriate use of prophylactic heparin treatment in patients hospitalized in medical departments.⁷⁻⁹ Unfortunately, there are some differences in the recommendations of these competing guidelines, resulting from variations in combinations of risk factors. These differences are disquieting because a major reason for developing these clinical guidelines was to reduce inappropriate variations in the use of prophylactic heparin treatment. However, the implications of these differences for the number of patients recommended prophylactic heparin treatment have never been quantified. Another key reason for developing these clinical guidelines was to improve physicians' practices in prevention of venous thromboembolism. The potential impact of clinical guidelines depends on many factors, including baseline appropriateness of physician practices prior to the dissemination of the guidelines.^{10,11} Hence, guidelines should focus on indications for which physicians' practices are inappropriate, if they are to lead to improvement in patient outcomes.¹²

The aims of this study were 1) to assess the degree of agreement between these four guidelines regarding the recommendation for prophylactic heparin therapy and

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2) to report to what extent baseline practice agreed with or differed from recommendations before these guidelines came into use.

PATIENTS AND METHODS

Study Design

Data were obtained from a 1-day cross-sectional study carried out in 1998, before the four guidelines were disseminated.

Settings

The study was conducted in the 13 medical units of a teaching hospital of 1,500 acute beds and in the 13 medical units of a nonteaching hospital of 500 acute beds. The hospitals were both located in urban areas in the Alps (France).

Patients

Patients who were 18 years of age or older and present on the day of the study in adult medical units were enrolled in the study. Patients in day care units, intensive care units, and emergency departments were excluded, as were those who required long-term anticoagulant therapy because of atrial fibrillation, prosthetic heart valve, stroke, or atherosclerosis, and those who had presented symptomatic deep vein thrombosis (confirmed by an intraluminal filling defect on venography or by compression ultrasound examination) or pulmonary embolism (confirmed by a high-probability ventilation perfusion lung scan, a spiral computed tomographic scan, or an abnormal finding on angiography) upon admission. We did not perform systematic ultrasonographic screening on the day of admission. Patients who had had a major surgical procedure within the previous 4 weeks were also excluded because they were not considered by clinical guidelines addressing prevention of venous thromboembolism in internal medicine patients. In addition, the efficacy of low-molecular weight heparin in preventing postoperative venous thromboembolism has been extensively established.^{13,14}

Data Collection

Data were prospectively collected from medical charts by 26 physicians independent of those in charge of the patients. They were given formal training and standardized instructions on definitions and data collection methods. They used a standard data abstract form that included information on sociodemographic characteristics, venous thromboembolism risk factors, duration, and types of thromboprophylaxis. The following factors were recorded: history of venous thromboembolism, body mass index, current cancer, genetic or acquired thrombophilia, respiratory insufficiency that did not require ventilatory support, congestive heart failure (which was documented in the

medical chart as clinically diagnosed congestive heart failure according to the Framingham criteria, an ejection fraction of less than 40%, or both, at or before admission), hormone therapy (estrogen replacement therapy, antiandrogen, tamoxifen), varicose veins, acute stroke or lower-limb paralysis, systemic disease and/or inflammatory bowel disease, immobilization (defined as bedridden or confinement to wheelchair), myocardial infarction (defined by chart documentation of acute chest pain with increase in cardiac enzyme level [creatinine kinase level greater than twice the upper normal value or serum creatine kinase MB fraction above 0.05] or evidence of a new acute myocardial infarction on an electrocardiogram serum [defined as 1 mm of ST segment elevation in 2 or more limb leads, or 2 mm of ST segment elevation in 2 or more precordial leads, or Q wave, or new or presumed left bundle-branch block]), pregnancy or recent delivery, and acute infectious disease. Patients were considered to be receiving prophylactic treatment for venous thromboembolism if they received unfractionated or low-molecular weight heparin. The use of a low dose of warfarin was also considered as an appropriate prophylactic treatment in two patients with metastatic cancer receiving chemotherapy.¹⁵ A high level of interobserver reliability had been evidenced for most items of the data abstract form in a pilot study. Data related to patient characteristics, risk factors, and method of prophylaxis were entered in a computer database.

Applying the Guidelines

The four competing guidelines were applied retrospectively to the electronic database of patient characteristics and risk factors, using ad hoc STATA do-files (STATA Corporation, College Station, Tex). The Tenon hospital guidelines were developed using a three-round Delphi survey of 32 French physicians who were specialized in internal medicine, vascular medicine, neurology, cardiology, oncology, nephrology, pneumology, and pharmacology.⁸ The three other guidelines had been based on informal consensus of local panel experts who were specialized in internal medicine, vascular medicine, and pharmacology. Two experts involved in the development of the Lunéville hospital guidelines and one expert involved in the development of the Assistance Publique-Hôpitaux de Paris (AP-HP) guidelines had also participated in the three-round Delphi survey of the Tenon hospital guidelines. The development process of the Grenoble hospital guidelines and the Lunéville hospital guidelines had integrated the results of a local physician practice survey. The results of an uncontrolled before-and-after study showed that the implementation of the Tenon hospital guidelines was followed by improvement in physician practices.¹⁶ Another uncontrolled before-and-after study showed that the implementation of the Grenoble hospital guidelines was followed by a significant decrease in the rate of deep vein thrombosis systematically detected by ultrasound examination of lower limbs (J.L., J.-L.B., et al., unpublished data). Table 1 summarizes

Table 1. Content of the Four Guidelines on Prophylaxis of Venous Thromboembolism

Tenon Hospital Guidelines ⁸		Assistance Publique-Hôpitaux de Paris guidelines ⁷	
Use of low-molecular weight heparin is proposed for patients hospitalized for more than 24 hours in a medical unit:		Use of low-molecular weight heparin is proposed for patients hospitalized in a medical unit:	
A. Who have at least one high-risk condition:		A. Who have at least one major risk factor:	
Recent myocardial infarction		Recent myocardial infarction	
Recent paralysis of lower limb(s)		Recent paralysis of lower limb(s)	
Congestive heart failure		Previous deep vein thrombosis or pulmonary embolism	
Malignancy (especially abdominal or metastatic)		Thrombophilia (deficiency of antithrombin III, protein C, or protein S, antiphospholipid antibody, prothrombin G20210A gene mutation)	
Polycythemia or hyperviscosity state			
Previous deep vein thrombosis or pulmonary embolism			
Thrombophilia (deficiency of antithrombin III, protein C, or protein S, antiphospholipid antibody, prothrombin G20210A gene mutation)			
B. Who have two or more risk conditions (B.1.) or one risk condition associated with two or more aggravating factors (B.2.)		B. Who have one minor risk condition (B.1.) and one minor risk factor (B.2.)	
B.1. Risk conditions	B.2. Aggravating factors	B.1. Risk conditions	B.2. Risk factors
Nephrotic syndrome (albumin <20 g/l)	Immobility (bedridden)	Congestive heart failure	Age >60
Inflammatory bowel disease	Severe dehydration	Respiratory insufficiency	Obesity
Severe infection	Obesity (BMI ≥30)	Malignancy (abdominal or thoracic)	Varicose veins
Respiratory insufficiency	Varicose veins	Severe infection	Bedridden
Ovarian stimulation	Age >60	Nephrotic syndrome	Pregnancy
	Pregnancy	Systemic disease	Puerperium
	Puerperium	Inflammatory bowel disease	High-dose estrogen therapy
	Oral contraceptives	Myeloproliferative disease	Antiphospholipid antibody
	Estrogen therapy	Severe dehydration	Lupus anticoagulant
	Long travel	Critical ischemia of lower limb	
Lunéville Hospital Guidelines⁹		Grenoble Hospital Guidelines (submitted for publication)	
Use of low-molecular weight heparin is proposed for patients hospitalized in a medical unit who have a score over 4 (score = number of level 3 risk factors × 3 + number of level 2 risk factors × 2)		Use of low-molecular weight heparin is recommended in patients hospitalized in medical unit who have:	
Level 3 risk factors		A. One major risk factor:	
Previous deep vein thrombosis		Recent myocardial infarction	
Previous pulmonary embolism		Recent paralysis of lower limb(s)	
Recent paralysis of lower limb(s)		Previous deep vein thrombosis or pulmonary embolism within 5 years	
Myeloproliferative disease		B. Three or more risk factors or two risk factors and immobilization (defined as confinement to bed or to bed and wheelchair)	
Systemic disease			
Thrombophilia		Risk factors:	
Long-term immobilization		Malignancy	
Level 2 risk factors		Congestive heart failure	
Age >65		Respiratory insufficiency	
Pregnancy or puerperium		Severe infection	
Congestive heart failure, recent myocardial infarction		Systemic disease	
Chest infection or severe infection		Inflammatory bowel disease	
Varicose veins		Recent major surgical procedure	
Obesity		Pregnancy or puerperium	
Recently bedridden		Age >70	
Nephrotic syndrome		Varicose veins	
Oral contraceptives or estrogen therapy		Obesity	
Severe dehydration		Estrogen therapy	
Respiratory insufficiency		Thrombophilia (deficiency of antithrombin III, protein C, or protein S)	
Malignancy (pelvic, abdominal, or thoracic)		Antiphospholipid antibody or lupus anticoagulant	
Central venous catheter		Long travel	

the content of each set of clinical practice guidelines. Because of the limitations of our data, we considered that patients having congestive heart failure or respiratory insufficiency met the criteria of the guidelines with no regard to the severity of these conditions.

Statistical Analysis

The proportions of patients requiring prophylactic heparin treatment according to each guideline were estimated by using an exact 95% confidence interval. The degree of agreement between guidelines was quantified by using the κ coefficient.¹⁷ Statistical analyses were performed using STATA 6.0 software.

RESULTS

Patient Characteristics and Physician Practices

A total of 1,323 patients were hospitalized in the internal medicine units of the two hospitals on the day of the study. Of these, 291 patients (22.0%) were excluded for the following reasons: diagnosis of pulmonary embolism or deep vein thrombosis upon hospitalization in 67 cases (5.1%), major surgical procedure within the previous 4 weeks in 122 cases (9.2%), long-term anticoagulant treatment in 98 cases (7.4%), and age less than 18 years of age in 4 cases (0.3%). Finally, 1,032 patients were included in the study. The median number of patients included by ward was 26 (interquartile range, 16 to 53). Women comprised 52.5% of the patients, and the mean age was 67.6 years (standard deviation, 19.1) (Table 2). The three most common risk factors were age over 70 years (54.8%), immobilization (38.6%), and congestive heart failure (24.3%). Overall, 162 patients (15.7%) had no risk factors, 280 (27.1%) one risk factor, 293 (28.4%) two risk factors, and 297 (28.8%) three or more risk factors. Three hundred sixty-eight patients (35.7%) were given prophylactic treatment. Fifty-four patients (5.2%) who received aspirin, 5 patients (0.5%) who received platelet aggregation inhibitors, and 106 patients (10.3%) who used elastic compression stockings alone were considered as receiving no pharmacological prophylaxis. None of the patients used pneumatic compression stockings.

Agreement Between the Guidelines

The proportion of patients for whom prophylactic heparin treatment would have been recommended ranged from 35.4% to 54.6%, depending on which guideline was used (Table 3). The four guidelines agreed in recommending the use of prophylactic heparin treatment in 330 patients (32.0%). None of the guidelines recommended prophylactic heparin treatment in 385 patients (37.3%), and the four guidelines disagreed in 317 patients (30.7%). The overall κ coefficient for interguideline agreement was 0.65 (95% confidence interval [CI], 0.63 to 0.68). The highest levels of agreement in pairwise comparisons were found between

Table 2. Patient Characteristics and Physician Practices (N = 1,032)

	n	%
Characteristics		
Female	542	52.5
Age, y		
<60	321	31.1
60 to 64	67	6.5
65 to 69	78	7.6
≥70	566	54.8
Median length of stay (interquartile range), days	8	3–17
Risk factor		
Confinement to wheelchair	258	25.0
Bedridden	140	13.6
History of venous thromboembolism	93	9.0
Recent paralysis of lower limb(s)	54	5.2
Malignancy	174	16.8
Recent myocardial infarction	44	4.3
Congestive heart failure	251	24.3
Respiratory insufficiency	114	11.0
Infection	168	16.3
Systemic disease/inflammatory bowel disease	46	4.5
Hormone therapy	25	2.4
Obesity	66	6.4
Varicose veins	155	15.0
Genetic or acquired thrombophilia	29	2.8
Pregnancy	1	0.1
Prophylactic heparin treatment	368	35.7
Low-molecular weight heparin	329	31.9
Unfractionated heparin	37	3.6
Low dose of warfarin	2	0.2

the Grenoble hospital and the Lunéville hospital guidelines ($\kappa = 0.74$) on one hand and between the AP-HP and Tenon hospital guidelines ($\kappa = 0.80$) on the other hand (Table 4).

Agreement of Observed Practices with Recommendations

The rate of agreement of observed physician practices was 68.1% (703/1032; 95% CI, 65.2 to 70.9) with the Lunéville hospital guidelines, 68.2% (704/1032; 95% CI, 65.3 to 71.0) with the Grenoble hospital guidelines, 60.4% (624/1032; 95% CI, 57.4 to 63.5) with the Tenon hospital guidelines, and 61.6% (636/1032; 95% CI, 58.8 to 64.6)

Table 3. Number of Patients (Percentage and 95% Confidence Interval) Requiring Prophylactic Heparin Treatment According to Each Guideline (n = 1,032)

Guidelines	Number of Patients	Percentage (95% Confidence Interval)
Lunéville Hospital	365	35.4 (32.4 to 38.4)
Grenoble Hospital	446	43.2 (40.2 to 46.3)
Tenon Hospital	560	54.3 (51.2 to 57.3)
Assistance Publique-Hôpitaux de Paris	564	54.6 (51.5 to 57.7)

Table 4. Pairwise Comparisons of the Number (%) of Patients Requiring Prophylactic Heparin Treatment (N = 1,032)

First Guideline/ Second Guideline	Prophylactic Heparin Treatment				κ
	Recommended by Neither Guideline	Recommended by Both Guidelines	Only Recommended by the First Guideline	Only Recommended by the Second Guideline	
Grenoble/Lunéville	562 (54.4)	341 (33.0)	105 (10.2)	24 (2.3)	0.74
Grenoble/AP-HP*	428 (41.5)	406 (39.3)	40 (3.9)	158 (15.3)	0.62
Grenoble/Tenon	425 (41.2)	399 (38.7)	47 (4.5)	161 (15.6)	0.60
Lunéville/AP-HP*	459 (44.5)	356 (34.5)	9 (0.9)	208 (20.1)	0.59
Lunéville/Tenon	458 (44.4)	351 (34.0)	14 (1.3)	209 (20.2)	0.58
AP-HP*/Tenon	418 (40.5)	510 (49.4)	54 (5.2)	50 (4.8)	0.80

* Assistance Publique-Hôpitaux de Paris guidelines.

with the AP-HP guidelines. Overall, the actual rate of prophylaxis increased according to the number of guidelines recommending prophylactic heparin therapy (Fig. 1). Physician practices were already appropriate in 69.5% (497/715) of patients for whom the guidelines agreed: before the dissemination of the guidelines, 57.0% (188/330) of patients had already been ordered prophylactic treatment when the four guidelines agreed to recommend thromboprophylaxis, and 80.3% (309/385) were not given prophylactic treatment when none of the guidelines recommended thromboprophylaxis.

DISCUSSION

Main Findings and Implications

Our study has yielded two main results. First, it has shown that strictly applying four commonly available guidelines shows wide variations in the proportions of patients recommended prophylactic heparin treatment

(range, 35.4% to 54.6%). Consequently, the guidelines disagree in recommending thromboprophylaxis in 30.7% of our study patients. These findings are in accordance with previous studies reporting that competing guidelines addressing various medical conditions differ greatly in their implications for the numbers of patients treated.^{18,19}

The reasons for variations in guidelines are related to the lack of robust scientific evidence, variations in the process of guideline development, and the limitations of expert panel methods. The paucity of scientific evidence is a major limiting factor to the validity and consistency of guidelines.²⁰ Indeed, randomized controlled trials are currently lacking or conflicting for a wide range of indications of prophylactic heparin treatment encountered in daily practice such as immobilization^{4,21} or acute infection.^{4,22} The four guidelines also differed in content and implications because of variations in the process of development. Indeed, our study has emphasized that guidelines sharing the same development process give similar advice. Hence, the highest levels of agreement were observed between the Tenon hospital guidelines and the AP-HP guidelines ($\kappa = 0.80$), which relied exclusively on expert panels, and between the Lunéville and the Grenoble hospital guidelines ($\kappa = 0.74$), which were primarily based on the results of a survey of physician practices.

Guidelines may be inconsistent even for expert panels looking at the same scientific evidence and using the same consensus method.²³ The reliability of expert panel methods, including the RAND-UCLA Appropriateness Method, which has been described as the most systematic and meticulous expert panel method, has been questioned.²⁴ Expert panels are confused when the number of case scenarios to be considered is too high and unwieldy.²⁴ In addition, the results of expert panels have been shown to be sensitive to the composition of the panel (physician specialties, use of the procedure by the experts).^{25,26}

Second, the four guidelines failed in anticipating the needs of clinicians. Indeed, clinicians had already ordered prophylactic anticoagulant treatment in 35.7% of patients hospitalized in adult internal medicine units, before the dissemination of the guidelines. Moreover, physician practices were appropriate in 69.5% of patients for whom the

FIGURE 1. Actual rate of prophylactic heparin therapy according to the number of guidelines recommending prophylactic treatment (n = 1,032).

guidelines agreed. A key reason for developing clinical practice guidelines is the expectation that they could improve physician behavior.¹² Hence, the room for improving physician practices in prevention of venous thromboembolism was limited given the high baseline level of appropriateness of practices in these consistent indications. In contrast, clinicians must still make their own decisions about heparin prophylaxis in 30.7% of patients, despite the dissemination of these guidelines. Surveying physician practices before developing guidelines may highlight the indications for which physicians need recommendations.²⁷ Indeed, guidelines may reinforce appropriate practices but with a limited impact in indications where practices are already in accordance with scientific evidence or expert opinion. Guidelines should rather focus on clinical indications characterized by inappropriate variations in physician practices.

Strengths and Weaknesses

Care was taken to reduce the risk of variations in guidelines related to external factors such as publication of new evidence, country of development, and rater subjectivity.

First, the four guidelines were published between 1998 and 2000 and probably relied on the same evidence. Hence, it was unlikely that inconsistencies in the number of patients recommended for prophylactic heparin treatment reflect the impact of new evidence that has appeared in the interval between publication of the guidelines.

Second, we applied only French guidelines to our data because guidelines for one country may not be appropriate for others.²⁸ Obviously, risk factors for venous thromboembolism and efficacy of pharmacological prophylaxis are similar throughout developed countries. However, clinical guidelines involve other considerations such as patient preferences, costs, and health care system, which differ from one country to another.²⁹ Consequently, the results of panel expert methods may vary depending on the members' country.^{25,30}

Third, clinical guidelines were applied to the electronic database of patient characteristics and risk factors, using ad hoc STATA do-files. This process determined whether each guideline recommended prophylactic heparin treatment for every patient, avoiding rater subjectivity.

Another strength of our study is that physician practices were prospectively gathered prior to the dissemination of the clinical guidelines. Hence, our findings reflected spontaneous physician practices in prevention of venous thromboembolism without contamination by the guidelines. This allowed us to assess the potential impact of the clinical guidelines.

Some limitations of our study should be acknowledged. First, we have made several assumptions in applying the guidelines because of a lack of information on some criteria or vagueness in the guidelines. This might have led to overestimating the proportion of patients for whom prevention was recommended according to the guidelines. Nevertheless, our results are likely to reasonably reflect the relative

differences between the guidelines in the number of patients treated, which was the aim of this study.

Second, the ideal objective comparison of guidelines would involve prospective clinical trials comparing patient outcomes. However, studies testing the impact of guidelines are costly, lengthy, and difficult to conduct.²⁸ Moreover, there is no clear agreement on which outcome measure is relevant when assessing effectiveness of pharmacological thromboprophylaxis.³¹ Hence, alternative ways of comparing guidelines should be used. Comparison of guidelines based on semantic analysis of their content is complex and does not reflect the frequencies of indications encountered in daily practice. In contrast, our method of comparison of clinical guidelines has the advantage of being objective and of taking the actual frequencies of indications into account.

Third, our study was conducted in two French hospitals, a factor that may undermine the generalizability of these findings. However, the prevalence of risk factors for venous thromboembolism, especially for bed rest, was close to that reported in a study carried out in 16 acute care hospitals in central Massachusetts.¹

The advice given by these competing guidelines addressing prevention of venous thromboembolism in medical inpatients differs in 30.7% of patients. The reasons for these variations are the paucity of scientific evidence, variations in the development process, and the limitations of expert panel methods. Further randomized clinical trials are needed to determine which subgroups of these patients could benefit from prophylactic heparin treatment. In contrast, the guidelines agreed in 69.3% of patients but physician practices were already quite appropriate in these patients, before dissemination of the guidelines. Hence, the room for improvement of physician practices by implementing these guidelines was limited. Physician practices should be surveyed before developing guidelines in order to highlight clinical situations for which recommendations are needed.

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