Assessment of the Risk and Prophylactic Treatment of Venous Thromboembolism in the Elderly

F. Couturaud, K. Lacut, C. Leroyer, D. Mottier

Groupe d'Etude de la Thrombose de Bretagne Occidentale (GETBO), Brest, France

Key Words

Venous thromboembolism · Elderly ·
Thromboprophylaxis

Abstract

Numerous large randomized controlled trials have assessed the benefit of prophylactic anticoagulation for venous thromboembolism in selected patients. However, few trials were conducted in elderly patients, as this issue was not addressed in this specific population, or as elderly patients were excluded of these studies. Therefore, as the risk of a first episode of venous thromboembolism (in surgical and in medical setting) and the risk of a major anticoagulant-related bleeding are both increased in elderly subjects, the results of the main available studies can not be extrapolated to this population. Consequently, in practice, the balance between expected benefit and risk of prophylactic anticoagulation should be carefully assessed for each individual elderly patient taking in account the specific risk of venous thromboembolism in elderly in the absence of anticoagulation, the risk of anticoagulant related bleeding according to the type of anticoagulant treatment and the intrinsic risk of bleeding of elderly subjects and, lastly, the available guideline recommendations. In order to improve such evaluation, it is

anticipated that further prophylactic studies are needed in elderly patients. In addition, the development of anticoagulation clinics and new oral anticoagulants should help to reduce anticoagulant related bleeding for an equivalent, or an increased, benefit.

Copyright © 2004 S. Karger AG, Base

Introduction

Historically, numerous trials have been initially conducted in surgical setting, leading for years to strong consensual recommendations on the indication and on the modalities of primary prevention of venous thromboembolism (VTE). In the last decade, the results of randomized trials provided major data on the efficacy of thromboprophylaxis in medical patients. The recognition of a particularly increased risk of venous thromboembolism in elderly, although it was suspected from decades, has been only recently confirmed. However, few data are available on the optimal strategy of prophylaxis of venous thromboembolism in these patients as only few large well designed randomized controlled trials have been performed addressing this specific issue. As life expectancy is increasing in developed countries, venous thromboembolism prophylaxis in the elderly will arise as a major public health problem for the next decades and large randomized well designed trials are needed in order to eval-

KARGER

Fax +41 61 306 12 34
E-Mail: karger@karger.ch
www.karger.com

© 2004 S. Karger AG, Basel
1424-8832/04/0336-0362\$21.00/0

Accessible online at:
www.karger.com/pht

Francis Couturaud
Groupe d'Etude de la Thrombose de Bretagne Occidentale (GETBO)
Equipe d'accueil
CHU La Cavale Blanche
29609 Brest, France

Tel: +02 98 34 73 63; Fax: +02 98 34 79 44; E-mail: francis.couturaud@chu-brest.fr

uate the benefit and the risk of thromboprophylaxis in this setting.

Risk of Venous Thromboembolism

Frequency

The risk of venous thromboembolism is increased in hospitalized and ambulatory elderly patients. In surgical setting, VTE is an important complication of major surgery, occurring in 19% of patients before 60 years, in 36% over 60 years and in 65% over 70 years without prophylaxis. According to the 6th ACCP Consensus Conference on Antithrombotic therapy, elderly patients are consequently classified as high risk patients for whom thromboprophylaxis is warranted [1].

Although VTE occurs in 80% of cases in medical setting, few data was available until recently [2]. In the large study of Samama et al. evaluating the efficacy and the risk of thromboprophylaxis using enoxaparin versus placebo in 1102 medical patients over 40 years, the incidence of VTE reaches 20% in the placebo group of patients over 80 years and less than 4% in placebo group of patients under 70 years [3].

In ambulatory patients, data on the risk of VTE is also now available. In a large community-based study conducted in France, Oger et al. reports an annual incidence of VTE of 1.83 per 1,000 in the entire cohort, whereas the annual incidence of VTE reaches 10 per 1,000 in patients of 75 years and older [2]. These results are consistent with another study evaluating the incidence of VTE in patients who were hospitalized for another reason than VTE: at the admission of patients, asymptomatic VTE was diagnosed in 17.8% of patients over 80 years whereas no VTE was detected in patients under 55 years [4]. Nursing home patients might also have an increased risk of VTE [5].

Mortality

The mortality of acute VTE in elderly is increased: 16% of patients over 80 years died early after the diagnosis of VTE in comparison with 2% before 40 years in the study of Anderson et al., a difference that is confirmed and increased over 3.5 years of follow-up [6]. There is also a trend of a higher proportion of symptomatic pulmonary embolism in elderly: in patients over 70 years, pulmonary embolism is the manifestation of VTE in 70% of cases in comparison with 55% of cases under 70 years [5]. Co-morbidity and massive haemorrhage are also more frequent in elderly.

Risk Period for VTE

In contrast with surgical patients, it remains undetermined when begins the risk period for VTE in medical patients. Indeed, the findings of a high prevalence of VTE at

the time of admission to hospital for an acute medical illness other than suspected VTE suggests that for some of these patients, and particularly elderly, the risk of VTE is increased prior to hospitalisation [4]. In elderly, this might due to a lower mobility; however, the demonstration of an increased risk of VTE in chronically institutionalized immobilized patients remains uncertain [7]. Another explanation lies in the fact that acute medical illnesses, that are associated with an increased risk of VTE, occur days prior to hospitalization.

Age as an Independent Risk Factor of VTE

It remains undetermined if, in the association between aging and an increased risk of VTE, age is an independent or a confounding risk factor of VTE [8,9]. Particularly, if venous stasis and vascular breakdown are associated with acquired conditions, such as prolonged immobilisation due to cerebral ischemia, congestive heart failure, acute respiratory failure, dehydration or surgical procedure [10], conversely, some conditions as well as aging may induce a hypercoagulable state in elderly. Thus, some coagulation factors have been found elevated in elderly such as factor VII, fibrinogen and more interesting factor VIII [11]. A hyperhomocysteinemia has also been observed in elderly in relation to folate and B6-B12 vitamin deficiency [12]. Lastly, Ridker reported an increased prevalence of factor V Leiden in elderly [13]; conversely, Oger et al. recently found that factor V Leiden was no longer associated with an increased risk of VTE in patients of 70 years and more [14].

Thus, although it remains undetermined if age is an independent risk factor of VTE or not, the risk of VTE in the elderly is elevated in an extent that warrants thromboprophylaxis. However, the potential benefit must be weighted with the risk of prevention.

Anticoagulant-Related Risk of Bleeding

The mainstay of thromboprophylaxis in medical and surgical patients is anticoagulant therapy. Anticoagulants such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) and antivitamin K have been extensively evaluated and are recommended as referent methods in most patients [1,15]. However, if the risk of VTE is increased in elderly in the absence of anticoagulation, the risk of bleeding while on anticoagulant therapy is also higher in such population. Major data on the risk of bleeding is provided by trials on long term oral anticoagulation. In these studies, age over 65 is associated with an increased risk of major haemorrhage; although conflicting, aging is found to be an independent risk factor of bleeding after adjustment to anticoagulation intensity, other medical conditions and other medications [15]. In addition, intracranial bleeding remains a

considerable concern in these patients, mainly due to a high risk of falls [16]. On heparin, elderly have also an increased risk of bleeding as creatinine clearance is decreased [17].

In addition, the risk of major bleeding with thromboprophylaxis differs between surgical and medical settings: during anticoagulant prophylaxis with UFH or LMWH, most studies in medical patients report a frequency of 1% or less of major haemorrhage [3,18,19] whereas major bleeding occurs in more than 1 to 2% of patients in surgical setting [1,20]. Experimental studies suggested a lower risk of bleeding with LMWH compared with UFH, however, recent randomized trials and meta-analysis on the efficacy and risk of anticoagulation in prevention and treatment of VTE failed to demonstrate convincing evidence of a reduction of the risk of bleeding with LMWH compared to UFH [19,21]. Although promising, new anticoagulants, such as ximelagatran or fondaparinux, are not associated with a decreased risk of bleeding in surgical patients [20,22]. Lastly, non pharmacological prophylactic methods, such as compression stockings, intermittent pneumatic compression and early mobilization, are limited as adjunctive method to anticoagulant prophylaxis [1].

Efficacy of Thromboprophylaxis in Randomized Trials

The main benefit associated with thromboprophylaxis is prevention of VTE and the main risk is bleeding. However, no large well design randomized trials have been conducted in elderly of 65 years or more in surgical as well as in medical setting; consequently, the benefit and the risk of thromboprophylaxis in elderly should be weighted on the basis of epidemiological studies on the risk of VTE and on the risk of bleeding in this population, as well as the results of major randomized trials evaluating thromboprophylaxis in selected population, although old patients and or those with renal dysfunction were often excluded.

There is strong evidence that surgical patients over 60 years should be classified as high risk patients for VTE. In such category, a reduction of more than 60% of the risk of VTE on low-dose UFH or LMWH is demonstrated. If LMWH are more convenient, as these molecules are administered once a day and there is no need for monitoring, however, in elderly, low-dose UFH administered subcutaneously twice a day should be preferred to LMWH if creatinine clearance is less than 30 ml/minute [1]. The optimal duration is uncertain; a minimum of 7 to 10 days is recommended. After total hip replacement, 3 additional weeks of thromboprophylaxis are warranted [23]. However, major bleeding remain a concern in surgical patients and, particularly, in elderly. If extended duration of thromboprophylaxis appears beneficial for preventing VTE after total hip replacement in

selected patients, this result should not be extrapolated to the elderly. New anticoagulants, such as fondaparinux or ximelagatran, have been shown to be very efficient in reducing the risk of VTE. However, current studies suggest that these molecules are not associated with a lower risk of bleeding: Fondaparinux is found to be more efficient than LMWH but is associated with an increased risk of bleeding whereas ximelagatran is not inferior to LMWH in reducing the risk of VTE as well as the risk of bleeding [20,22]. Moreover, these new treatments are contraindicated in patients with renal insufficiency (i.e.; creatinine clearance < 30 ml/minute), a condition that is frequent in the elderly.

In medical setting, major data is now available although the specific issue of efficacy and risk of prophylactic anticoagulation in elderly has not been directly addressed in most study. In internal medicine setting, the study of Samama et al. shows a risk reduction of VTE of 63% with 40 mg enoxaparin compared to 20 mg enoxaparin or placebo in patients over 40 years who are hospitalized for an acute medical illness without an increased risk of major bleeding [3]. The risk reduction is 87% in patients of 80 years and older. In this study, the risk of major bleeding is not different between the three arms of treatment (40 mg versus 20 mg of enoxaparin versus placebo) [3]. Similar results have been also found in patients hospitalized for acute myocardial infarction and ischemic stroke as well as in internal medicine in the meta-analysis of Mismetti et al [19]. Based on available data, enoxaparin administered 40 mg once day is the treatment of choice for the prevention of VTE in patients over 40 years and hospitalized for an acute medical illness. In patients with renal failure (creatinine clearance < 30 ml/minute) and low weight (definition of low weight varies according to randomized trials), these conditions being frequent in elderly, subcutaneous low-dose UFH is a safe alternative. In contrast to surgical patients, the risk of bleeding in elderly is not a major concern. However, two important questions remain undetermined in medical patients: when should be started prophylactic anticoagulation in medical patients and for how long time? Indeed, the finding of a high frequency of VTE in elderly at the time of their admission to hospital for another reason than a suspicion of VTE suggests that thromboprophylaxis should be started prior to hospitalization [4]. In addition, the risk of VTE persists after discharge of patients in medical unit (7% at three months) [3]. These observations suggest that the duration thromboprophylaxis should be extended after discharge in some patients; an ongoing study is evaluating four additional weeks of enoxaparin in medical patients (EXCLAIM study).

Conclusion

VTE is a major health problem in elderly. Because the risk of VTE is high in such population, prophylactic anticoagulation, which has demonstrated a high efficacy, is indicated in surgical as well as medical setting. However, the risk of anticoagulant-related bleeding is also elevated in elderly particularly in surgical setting. For determining the optimal strategy of thromboprophylaxis, the benefit, the risk and the efficacy of treatment need to be based on epidemiological and randomized trials. In elderly more than others, two important questions are not resolved: first, in contrast with surgical patients, the optimal time of initiation of thromboprophylaxis in medical patients remains undeter-

mined; second, both in surgical and medical setting, the optimal duration of prophylactic anticoagulation needs to be defined as the risk of VTE persists over three months. Ongoing and further randomized trials are needed in order to provide additional important data helping physicians for optimizing prevention of VTE in elderly.

References

- 1 Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001;119: S132-175.
- 2 Oger E, for the EPI-GETBO Study Group. Incidence of venous thromboembolism: a community-based study in Western France. *Thromb Haemost* 2000;83:657-660.
- 3 Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999;341:793-800.
- 4 Oger E, Bressollette L, Nonent M, et al. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. The TADEUS Project. *Thromb Haemost* 2002;88:592-597.
- 5 Heit JA, Silvestein MD, Mohr DN, et al. The epidemiology of venous thromboembolism in the community. *Thromb haemost* 2001;86:452-463.
- 6 Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;151: 933-938.
- 7 Gatt ME, Paltiel O, Bursztyrn M, et al. Is prolonged immobilization a risk factor for symptomatic venous thromboembolism in elderly bedridden patients? Results of a historical-cohort study. *Thromb haemost* 2004;91:538-543.
- 8 Cogo A, Bernardi E, Prandoni P, et al. Acquired risk factors for deep vein thrombosis in symptomatic outpatients. *Arch Intern Med* 1994;154: 164-168.
- 9 Landefeld CS, McGuire E, Cohen AM. Clinical findings associated with acute proximal deep vein thrombosis: a basis for quantifying clinical judgement. *Am J Med* 1990; 88:388-392.
- 10 Petermans J, Zicot M. La pompe musculo-veineuse de la personne âgée. *J Mal Vasc* 1994;19: 115-8.
- 11 Mari D, Mannucci PM, Coppola R, Bottasso B, Bauer KA, Rosenberg RD. Hypercoagulability in centenarians : the paradox of successful aging. *Blood* 1995;85:3144-3149.
- 12 den Heijer JA, Koster T, Blom HJ, et al. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. *N Engl J Med* 1996;334:759-762.
- 13 Ridker PM, Glynn RJ, Miletich JP, Goldhaber SZ, Stampfer MJ, Henkens CH. Age-specific incidence rates of venous thromboembolism among heterozygous carriers of factor V Leiden mutation. *Ann Intern Med* 1997;126:528-531.
- 14 Oger E, Lacut K, Le Gal G, et al. Is APC resistance a risk factor for venous thromboembolism in patients over 70 years? *Thromb Haemost* 2002; 88:587-591.
- 15 Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998;105:91-99.
- 16 Man-Son-Hing M, Nichol G, Lau A, et al. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;159:677-685.
- 17 Campbell NR, Hull RD, Brant R, et al. Aging and heparin-related bleeding. *Arch Intern Med* 1996; 156:857-860.
- 18 Dahan R, Houlbert D, Caulin C, et al. Prevention of deep vein thrombosis in elderly medical inpatients by a low molecular weight heparin: a randomized double blind trial. *Haemostasis* 1986;16: 159-164.
- 19 Mismetti P, Laporte-Simitsidis S, Tardy B, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular weight heparins: a meta-analysis of randomized clinical trials. *Thromb haemost* 2000;83:14-19.
- 20 Turpie AGG, Bauer KA, Eriksson BI, Lassen MR for the Steering Committees of the Pentasaccharide Orthopedic Prophylaxis Studies. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. A Meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 2003;163:1833-1839.
- 21 Dolovitch L, Ginsberg J, Douketis J, Holbrook A. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism. *Arch Intern Med* 2001;160:181-188.
- 22 Eriksson BI, Agnelli G, Cohen AT, et al. METHRO III Study Group. Direct thrombin inhibitor melagatran followed oral ximelagatran in comparison with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement. *Thromb Haemost* 2003;89:288-296.
- 23 Kearon C. Duration of venous thromboembolism prophylaxis after surgery. *Chest* 2003;124:386S-392S.