Risk-assessment algorithm and recommendations for venous thromboembolism prophylaxis in medical patients

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Abstract: The risk for venous thromboembolism (VTE) in medical patients is high, but risk assessment is rarely performed because there is not yet a good method to identify candidates for prophylaxis.

Purpose: To perform a systematic review about VTE risk factors (RFs) in hospitalized medical patients and generate recommendations (RECs) for prophylaxis that can be implemented into practice.

Data sources: A multidisciplinary group of experts from 12 Brazilian Medical Societies searched MEDLINE, Cochrane, and LILACS.

Study selection: Two experts independently classified the evidence for each RF by its scientific quality in a standardized manner. A risk-assessment algorithm was created based on the results of the review.

Data synthesis: Several VTE RFs have enough evidence to support RECs for prophylaxis in hospitalized medical patients (eg, increasing age, heart failure, and stroke). Other factors are considered adjuncts of risk (eg, varices, obesity, and infections). According to the algorithm, hospitalized medical patients ≥40 years-old with decreased mobility, and ≥1 RFs should receive chemoprophylaxis with heparin, provided they don't have contraindications. High prophylactic doses of unfractionated heparin or low-molecular-weight-heparin must be administered and maintained for 6–14 days.

Conclusions: A multidisciplinary group generated evidence-based RECs and an easy-to-use algorithm to facilitate VTE prophylaxis in medical patients.

Keywords: embolism and thrombosis, risk factors, prevention and control, heparin, risk-assessment, guideline

Introduction

Venous thromboembolism (VTE) represents a spectrum of diseases that include deep vein thrombosis, central venous catheters associated thrombosis (CVC-thrombosis), and pulmonary embolism (PE). Both clinically symptomatic and asymptomatic episodes of VTE are common in hospitalized patients (Goldhaber and Tapson 2004), and are associated with high mortality (Maffei et al 1980; Anderson et al 1991; Lindblad et al 1991; Golin et al 2002). Autopsy studies have shown that approximately 10% of all inpatients deaths are due to PE, but only a small proportion of PE are suspected before death (Pineda et al 2001; Yoo and Mendes 2004). Until the mid 90s, most studies focused on surgical patients, given their high incidence of VTE. As a consequence, the notion about the need for VTE prophylaxis in surgical populations gained acceptance. More recently, randomized controlled trials have highlighted the fact that the risk of VTE in patients with medical conditions is similar to that of some surgical patients (Bergmann and Neuhart 1996; Harenberg et al 1996; Lechler et al 1996; Samama et al 1999; Kleber et al 2003; Leizorovicz et al 2004). Additionally,

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some epidemiological studies have demonstrated that more than half of patients who develop symptomatic VTE have medical, not surgical conditions (Goldhaber et al 2000). In the registry RIETE (Monreal et al 2004), only 28% of acutely ill medical patients with decreased mobility had received prophylaxis, while 67% of surgical patients did. During the follow-up of these patients, both PE and fatal bleedings were more common in medical patients, underlying the need for adequate prophylactic regimens in this particular subset of patients. Therefore, the analysis of the importance of risk factors in hospitalized medical patients is crucial to define the risk-benefit of VTE prophylaxis utilization. A systematic review of risk factors for VTE was performed, evaluating the current evidence about the factors that could justify the use of VTE prophylaxis in this population. The evidence about the effectiveness of VTE prophylaxis in these specific groups was also reviewed, and evidence-based recommendations were incorporated into an easy-to-use risk-assessment algorithm for VTE.

Methods

Literature search

A computer-based literature search was performed independently by two investigators to identify studies evaluating the following conditions as risk factors for thrombosis in acutely ill medical patients: active rheumatologic diseases (ARD) and inflammatory bowel disease (IBD), acute myocardial infarction (AMI), admission to ICU, age, cancer, chemotherapy and hormonotherapy, central venous catheters (CVC), cerebral vascular accident (CVA), congestive heart failure (CHF), diabetes, hormonal contraception (HC) and hormonal replacement therapy (HRT), hypertension, infections, nephrotic syndrome, obesity, paresis and/or paralysis of the lower extremities, peripheral vascular disease, pregnancy and puerperium, previous VTE, reduced mobility, respiratory diseases (eg, chronic obstructive pulmonary disease [COPD], respiratory insufficiency, and respiratory infections), tobacco use, and thrombophilias. We also evaluated the efficacy of methods of VTE prophylaxis in acutely ill medical patients, including low dose unfractionated heparin (LDUH), low molecular weight heparins (LMWH), and mechanical methods of prophylaxis. We searched the English language and non-English language literature by using MEDLINE, LILACS databases, and the Cochrane Central Register of Controlled Trials from the earliest searchable dates through August 2004. Annals of important meetings were also searched for abstracts from 1998 onwards. The reference lists of published reviews were also evaluated.

Data collection

Inclusion criteria for the systematic review were established before the literature search. We included randomized-controlled trials, cohorts, and case-control studies with at least 10 subjects evaluating risk factors or efficacy of prophylactic methods for VTE. Two authors read all retrieved studies and made the final decision on which studies met the inclusion criteria. All data were abstracted independently and in duplicate by two of the authors using a standardized data collection form. Discrepancies in the data abstracted were resolved by consensus among the authors and the working committee.

Levels of evidence

The level of evidence of each study was classified based on the American Heart Association, American College of Cardiology, and European Society of Cardiology (AHA/ACC/ESC) guidelines for the management of patients with supraventricular arrhythmias (Blomstrom-Lundqvist et al 2003). These criteria were adapted to allow evaluation of studies about efficacy of methods of VTE prophylaxis and risk factors for VTE. Tables 1A and 1B show the levels of evidence and Table 2 shows the strength of recommendations.

Table 1 Classification of levels of evidence for the studies

1A **Level of evidence**	**Studies about risk factors**
A	Evidence derived from several RCTs, cohorts using screening methods for VTE and/or case-control studies suggesting that the risk factor is directly associated with the disease.
B	Evidence derives from a limited number of RCTs, cohorts and/or case-control studies, or with conflicting information and/or divergence of opinion that the risk factor is directly associated with the disease.
C	Evidence from RCTs, cohorts and/or case-control studies, that the risk factor is NOT directly associated with the disease.
1B **Level of evidence**	**Studies about treatment, prevention or etiology**
A	Evidence derived from RCTs.
B	Evidence derived from RCTs with methodologic flaws, or published only as abstracts, or nonrandomized studies, or observational registries.
C	Primary basis for the recommendations was expert's consensus.

Abbreviations: RCTs, randomized controlled trials; VTE, venous thromboembolism.

Table 2 Classification of recommendations

Strength of recommendations	Recommendations based on evidence and expert opinion
Class I	Conditions for which there is evidence for and/or agreement of opinion that the procedure (or treatment) is useful/effective.
Class II	Conditions for which there is little evidence for and/or divergence of opinion that the procedure (or treatment) is useful/effective. a The weight of evidence or opinion favors the procedure (or treatment). b Usefulness/efficacy is less established by evidence or opinion.
Class III	Conditions for which there is evidence for and/or agreement of opinion that the procedure (or treatment) is NOT useful/effective and in some cases may be harmful.

Results

Risk factors

Each risk factor was evaluated separately as much as possible. The risk factors for VTE in clinical patients, according to the level of evidence, are listed in Table 3. Table 4 shows the frequency of VTE in hospitalized patients with various medical conditions.

Active rheumatologic diseases and inflammatory bowel disease\

Although rheumatologic diseases represent a heterogeneous group of patients, they have usually been considered at-risk for thrombosis because incidences of VTE of 10% to 30% have been demonstrated in hospitalized patients with active rheumatologic diseases (Cohen and Quinlan 2000; Alikhan et al 2003; Rahim et al 2003). Cogo and colleagues (1994) in an analysis of 540 patients with suspected DVT, detected systemic lupus erythematosus (SLE) as a risk factor for VTE (OR 4.3; 95% CI 3.1–5.5). However, Orger and colleagues (1997) in a very similar study with 277 patients, found different results (OR 0.7; p = NS), that were confirmed in a case-control study with 1,272 SLE patients (OR 1.6; p = NS) (Samama 2000). In the secondary analyses of the MEDENOX study about the importance of risk factors, the association of VTE with rheumatologic diseases was not statistically significant (RR 1.6; 95% CI 0.96–2.69, p = 0.11). Based on these data, active rheumatologic diseases as a group, and SLE in particular, are not clearly related to increased VTE risk. However, lupus anticoagulant (LA) and anticardiolipin (ACL) antibodies are frequently found in rheumatologic patients and are definitely related to thrombotic phenomena. Fijnheer and colleagues (1996), studying 173 SLE patients, found that LA was associated with VTE with an OR of 6.4 (95% CI 2.7–15.4).

Arterial and venous thromboses are common clinical findings in patients with Behcet' disease (BD) (Koc et al 1992). ACL has been found in as many as 30% of these patients (Zouboulis et al 1993), but other studies demonstrate vascular thrombosis even when an ACL antibody is not found (Kiraz et al 1999; Mader et al 1999). A HLA-B51 positive is associated with a higher risk of VTE (OR 4.2; 95% CI 1.1–16.3) and a HLA-B35 has a protective effect (OR 0.2; 95% CI 0.04–0.92) (Kaya et al 2002).

IBD was evaluated by Bernstein and colleagues (2001) in a retrospective cohort including 2,857 patients with Crohn's disease (CD) and 2,672 with ulcerative colitis (UC). Compared with controls both CD and UC patients had increased risk for DVT (RR 4.7; 95% CI 3.5–6.3 in CD and RR 2.8; 95% CI 2.1–3.7 in UC) and for PE (RR 2.9; 95% CI 1.8–4.7 in CD and RR 3.6; 95% CI 2.5–5.2 in UC) (Kaya et al 2002). Miehsler and colleagues (2004) studied 618 patients with IBD, 243 patients with rheumatoid arthritis and equal number of gender and aged-matched control. The authors found that IBD was significantly associated with a higher chance of developing VTE (OR 3.6; 95% CI 1.7–7.8; $p < 0.001$), but that rheumatoid arthritis was not (OR 0.7; 95% CI 0.2–2.9; p = NS).

Table 3 Risk factors for VTE in medical patients according to the level of evidence

A	B
Age ≥ 55 years	Active rheumatologic diseases
AMI	Inflammatory bowel diseases
Cancer	Infections
Chemotherapy	Obesity
CHF class III or IV	Peripheral arterial insufficiency
CVC and PAC	Reduced mobility
HCVA	Varices/chronic venous insufficiency
Hormonotherapy	
HRT and HC	
ICU admission	
ICVA	
Nephrotic syndrome	
Paresis/paralysis of legs	
Pregnancy and puerperium	
Previous VTE	
Severe respiratory diseases	
Thrombophilias	

Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; CVC, central venous catheters for general use and hemodialysis catheters; HC, hormonal contraceptives; HCVA, hemorrhagic cerebral vascular accident; HRT, hormonal replacement therapy; ICU, intensive care unit; ICVA, ischemic cerebral vascular accident; PAC, pulmonary artery catheters; VTE, venous thromboembolism.

Table 4 Frequency of DVT in hospitalized patients according to their medical condition

Condition	DVT (%)
CVA	28–75
CHF class III or IV	15–71
AMI	10–63
Nephrotic syndrome	14–43
ICU admission	25–31
Active rheumatologic diseases	10–30
Severe respiratory diseases	9–29
Infection	7–16

Abbreviations: AMI, acute myocardial infarction; CVA, cerebral vascular accident; CHF, congestive heart failure; DVT, deep venous thrombosis; ICU, intensive care unit.
Note: Frequency based on studies using screening for DVT in patients without prophylaxis.

In summary, IBD, BD, and positive LA and ACL antibodies in SLE patients should be considered as risk factors for VTE (EVIDENCE A). Active rheumatologic diseases as a group receive a level of evidence B, while SLE without LA or ACL and rheumatoid arthritis should not be considered as risk factors for VTE.

Acute myocardial infarction

The risk for VTE in acute coronary syndromes' patients is high, but the specific evaluation of VTE risk in this setting has become difficult because the use of heparin and other medications that interfere directly with the coagulation system is now routine. Most data about VTE risk in acute coronary syndromes come from old studies, with small number of patients, comparing placebo with some kind of prophylaxis. One study showed an incidence of DVT as high as 62.5%, when the treatment for AMI was basically absolute bedrest for 5 days (Zawilska et al 1989). In a study comparing LDUH with placebo, PE was detected in 12.2% (5/41) in the placebo group, compared with 0/37 in the heparin group (Emerson and Marks 1977). AMI should therefore, be considered a risk factor for VTE (EVIDENCE A).

Admission to ICU

Several studies that employed screening for DVT in critically ill patients showed that admission to an ICU is a risk factor for VTE (RR 1.8 to 2.9) (Cade 1982; Ibarra-Perez et al 1988; Hirsch et al 1995; Goldberg et al 1996; Marik et al 1997; Kapoor et al 1999; Fraisse et al 2000; Goldhaber et al 2000). The incidence of DVT in clinical ICUs is very high, particularly in patients receiving no prophylaxis (25% to 31%), compared with those that receive some form of prophylaxis (11 to 16%) (EVIDENCE A) (Cade 1982; Kapoor et al 1999; Fraisse et al 2000; Goldhaber et al 2000). Besides, PE is found in up to 27% of ICU patients that undergo autopsy. Although PE contributes to death in about 12% of ICU patients, it is suspected before death in only 30% of the cases. ICU patients have in general 2 to 4 additional risk factors for VTE, not including reduced mobility (Ryskamp and Trottier 1998; Geerts and Selby 2003). Nevertheless, according to several reports, the utilization of prophylaxis in ICU patients had been quite irregular (Ibrahimbacha and Alnajjar 1998; Levi et al 1998; Ryskamp and Trottier 1998; Rocha and Tapson 2002; Geerts and Selby 2003; Lacherade et al 2003; Rocha et al 2003).

Age

Several epidemiologic studies have shown that the incidence of VTE increases exponentially with aging. It is not clear if the reasons for this are changes in clotting mechanisms or the presence of thrombogenic comorbidities (Anderson et al 1991; Silverstein et al 1998). In a study conducted in Oslo, the incidence of VTE increased from 1:10,000 at age 20 to 1:1,000 at age 50 (Strekerud et al 1998). Other studies showed different age cutoffs for significant increase in risk of VTE: RR 1.75 for age >65 years, 1.51 for age >75 years and 2.0 for age >85 years (Kniffin et al 1994; Alikhan et al 2004; Oger 2000). In the study EPI-GETBO, the authors screened 234 medical patients on the day of admission with Doppler ultrasound, and found that the prevalence of asymptomatic DVT, among patients older than 80 years, reached 17.8% (95% CI 8.5–32.6) and the incidence 6.0 per 1,000 patients-day (95% CI, 0–12.7) (Oger et al 2002a). In the study performed in the community of Worcester, MA, the risk of VTE almost doubled at each decade from the 5th decade on (RR 1.9) and the incidence of VTE was 62:100,000, starting at age 50 (Anderson et al 1991). For the same age, others studies showed an incidence of VTE reaching 100:100,000 (Silverstein et al 1998; Hansson et al 1999). Therefore, we conclude that there is a progressive increase in VTE risk with advancing age, and that age over the 5th decade should be considered as an additional risk factor for VTE in medical patients (EVIDENCE A).

Cancer, chemotherapy, and hormonotherapy

Association between cancer and thromboembolism is known since 1865, when Trousseau described migratory thrombophlebitis as a sign for underlying pancreatic cancer (EVIDENCE A). Since then, many others neoplasias have been associated with VTE (Table 5) (Pinzon et al 1986; Thodiyil and Kakkar 2002). This high incidence of

Table 5 Relative risk for VTE in different neoplasias

Origin	Patients with VTE	Total of patients	RR (95% CI)
Head and neck	35	20,924	0.29 (0.2–0.4)
Bladder	180	74,517	0.42 (0.36–049)
Breast	469	186,273	0.44 (0.4–0.48)
Esophagus	64	147,42	0.76 (058–0.97)
Cervix	53	102,36	0.90 (0.68–1.18)
Liver	121	229,38	0.92 (0.76–1.110)
Prostate	1230	218,743	0.98 (0.93–1.04)
No cancer	46.848	8,177,634	1.0
Rectum	417	65,837	1.11 (1.0–1.22)
Lung	1.504	232,764	1.13 (1.07–119)
Colon	1.320	168,832	1.36 (1.29–1.44)
Renal	278	34,376	1.41 (1.25–1.59)
Stomach	280	32,655	1.49 (1.33–1.68)
Lymphoma	537	52,042	1.80 (1.65–1.96)
Pancreas	488	41,551	2.05 (1.87–2.24)
Ovarium	327	26,406	2.16 (1.93–2.41)
Leukemia	591	47,234	2.18 (2.01–2.37)
Brain	184	13,529	2.37 (2.04–274)
Uterus	226	11,606	3.34 (2.97–3.87)

VTE may be explained not only by the hypercoagulability but also by the action of some antineoplastic agents and the frequent venous catheterization. In some studies the higher incidences of DVT were observed in patients with pancreas, ovarium, liver, and brain cancer, while others indicate breast, lung, genital, urinary, stomach and colon cancers as the most frequently related to VTE (Coon 1976; Bussani and Cosatti 1990; Sorensen et al 1998). In a series of 21.530 autopsies, 29% of the patients had cancer and the most common were ovarium, extrahepatic biliary tree, and stomach (34.6%, 31.7%, and 15.2%, respectively), while esophagus, larynges, leukemia, and lymphoma had the lower prevalences (Coon 1976; Bussani and Cosatti 1990; Sorensen et al 1998).

Chemotherapy and hormonotherapy may also be thrombogenic (EVIDENCE A). However, it's difficult to separate the effect of the treatment from the effect of the cancer itself. Several studies have shown that VTE is more common during chemotherapy in breast cancer patients, compared with the period without treatment (6.8% vs 17.6%) (Goodnough et al 1984; Levine et al 1988; Saphner et al 1991; Pritchard et al 1996). Saphner and colleagues (1991) observed a higher incidence of VTE when tamoxifen was used. In a study with mieloma patients, Zangari and colleagues (2001) observed that addition of thalidomide to chemotherapy was associated with an important increase in DVT incidence (28% vs 4%, $p = 0.002$).

Central venous catheters

Several variables are implicated in the increased thrombogenicity associated with central venous catheters (CVC-thrombosis) and DVT in patients using catheters (Table 6). Given the high variability of catheter-related factors and underlying diseases, studies evaluating CVC-thrombosis are quite heterogeneous. Besides, the diagnostic methods for thrombosis and the primary objectives of these studies are extremely variable, which make it difficult to group then in order to make specific recommendations. For these reasons, we discuss thrombosis prophylaxis according to the purpose of the catheter: for chemotherapy in cancer patients, for parenteral nutrition (PN) and for general use in ICU patients. We briefly discuss also the evidence for pulmonary artery catheters and hemodialysis catheters as risk factors for thrombosis.

Several studies show that the incidence of thrombosis is higher in the catheterized veins than in contralateral veins (Raad et al 1994; Durbec et al 1997b; Mian et al 1997; Martin et al 1999; Joynt et al 2000). Besides, in RCTs of prophylaxis, the incidence of CVC-thrombosis is 5%–18% in the groups that receive prophylaxis and 4%–62% in the groups that do not receive prophylaxis. Therefore, central venous catheters constitute additional

Table 6 Factors associated with venous thrombosis in patients with catheters

Variables	Relative risk
Catheterization of femoral vein[1]	4.7–6.0 (OR 7.7–23.5)
Catheterization of axilary, subclavian or internal jugular veins[2]	3.9–11.6
Catheterization of femoral vein vs. subclavian or internal jugular veins[3]	4.7–7.4
Catheterization of internal jugular vein vs. subclavian vein[4]	4.1
Catheterization of left subclavian vein vs. right subclavain vein[5]	1.2
Infusion of parenteral nutrition vs. other solutions[6]	2.6
Catheter material (polyvinyl or polyethylene vs. polyurethane or silicone)[7]	3.6–6.0
Catheter duration[8]	1.04
Number of attempts to insertion (one vs. two)[9]	11.8
Long-term central catheters vs. long-term peripherakl catheters[10]	2.2
Catheters in patients with anti-thrombin III deficiency[11]	OR 8.4
Catheters in patients with factor V Leiden[12]	2.3

Notes: [1](Trottier et al 1995; Durbec et al 1997a; Mian et al 1997; Joynt et al 2000); [2](Kerr et al 1990; Martin et al 1999); [3](Trottier et al 1995; Merrer et al 2001); [4](De et al 1997; Timsit et al 1998); [5](Gould et al 1993; De et al 1997); [6](Koksoy et al 1995); [7](Bozzetti et al 1983; Monreal et al 1994); [8](Brismar et al 1981; Ibrahim et al 2002); [9](Koksoy et al 1995); [10](Kuriakose et al 2002), [11](Lokich and Becker, 1983; De et al 1995); [12](Van Rooden et al 2004)

risk factors for VTE in clinical patients (Heit et al 2000) in general and in oncologic patients (Bern et al 1990; Balestreri et al 1995; De et al 1997) in particular (EVIDENCE A).

Pulmonary artery catheters (Swan-Ganz)

The rate of clot formation in pulmonary artery catheters is time dependent and ranges from 66% to almost 100% in noncoated catheters with heparin (Hoar et al 1981; Chastre et al 1982; Mangano 1982; Mollenholt et al 1987). Nevertheless, the frequency of thrombotic complications reported varies considerably, depending on the method of detection of the thrombus (Elliott et al 1979). Similarly to other CVC, pulmonary artery catheters lead to a 4.5 higher relative risk of thrombosis of the catheterized vein as compared with the contralateral veins (Meredith et al 1993), and constitute an additional risk factor for VTE (Rocha et al 2003) (EVIDENCE A).

Hemodialysis catheters

Although moderate to severe renal insufficiency is associated with higher risk of bleeding (Lohr and Schwab 1991), thromboembolic events are also quite common in patients with renal failure. Chronic hemodialysis patients present high incidence of thrombophilias, frequently utilize recombinant erithropoetin, which may have a prothrombotic effect and present also VTE risk factors that are less commonly recognized, such as hyperhomocysteinemia, endothelial dysfunction and markers of systemic inflammation (Casserly and Dember 2003). In a study of the US Renal Data System with 76,718 renal failure patients on chronic dialysis in 1996, the incidence of PE was 149.9/100,000, while the incidence of PE in the general US population was 24.6/100,000 (Tveit et al 2002). Furthermore, thrombosis of the venous access is another well established condition in these patients, affecting arterial-venous fistulas, grafts and double-lumen catheters for hemodialysis (Fan and Schwab 1992). These catheters are most commonly used as temporary vascular accesses but in some instances, allow hemodialysis for longer periods (Shusterman et al 1989). Catheter malfunction is quite common and the incidence of CVC-thrombosis in these patients is up to 46% (Fan and Schwab 1992; Beenen et al 1994), however, the need for catheter removal is rare. Also, the cannulation of subclavian veins lead more frequently to thrombosis and/or stenosis than the cannulation of internal jugular veins (Vanherweghem et al 1986; Beenen et al 1994; Agraharkar et al 1995), particularly on the left side (Clark et al 1990). Thus, there is evidence that hemodialysis catheters, similarly to other CVC constitute an additional risk factor for VTE (EVIDENCE A).

Cerebral vascular accident

Hospitalized patients with CVA present one of the highest rates of VTE among general medical patients, ranging from 28% to 75% and affecting particularly the paralyzed limb (McCarthy et al 1977). In a retrospective cohort were analyzed 1,953 patients with hemorrhagic CVA and 15,599 patients with ischemic CVA (Gregory and Kuhlemeier 2003). The authors found a prevalence of VTE four-fold higher for patients with hemorrhagic CVA and even after controlling for severity of disease and duration of hospitalization, hemorrhagic CVA was an independent risk factor for VTE with an OR of 2.6 (95% CI 1.5–4.6). In another study, PE was found to be the immediate cause of death in 5% of stroke patients (Pambianco et al 1995). For these reasons both ischemic and hemorrhagic CVA must be considered important risk factors for VTE (EVIDENCE A).

Congestive heart failure

Many studies have shown that CHF is related to VTE, especially in patients with reduced mobility. In a case-control study with 790 patients, CHF increased significantly the risk for VTE (OR 2.6; 95% CI 1.4–4.7) (Howell et al 2001). Besides, the lower the ejection fraction the higher the risk of VTE: OR 38.3 for EF <20%; 2.8 for EF from 20% to 40%, and 1.7 for EF >45%. In a cohort study with 1,250 patients, Heit and colleagues (2000) detected CHF as an independent risk factor for VTE in patients presenting with fatal PE at autopsy (OR 2.8; 95% CI 1.8–4.2). Samama, in another case-control study, also identified CHF as a risk factor for VTE in ambulatorial patients (OR 2.9; 95% CI 1.5–5.6) (Samama 2000). Even in patients treated with anticoagulants due to a previous VTE episode, CHF was considered an independent risk factor for new VTE episodes (OR 2.3; 95% CI 1.1–5.0) (Douketis et al 2000). Although an analysis of the MEDENOX study failed to consider CHF as an independent risk factor for VTE, the risk associated with CHF was observed to be higher among patients with more severe functional compromise (RR 0.87; 95% CI 0.6–1.3 for New York Heart Association [NYHA] class III and RR 1.3; 95% CI 0.74–2.34 for NYHA class IV). CHF must be considered an important risk factor for VTE, particularly among patients with NYHA classes III and IV (EVIDENCE A).

Hormonal contraception and hormonal replacement therapy

HRT and HC increase the risk for VTE by 2 to 6 times (EVIDENCE A). Recently, two well designed RCTs confirmed the association between VTE and HRT (Hulley et al 1998; Rossouw et al 2002). In the HERS Study (Heart and Estrogen/progestin Replacement Study), 2,763 women with coronary disease were followed prospectively and an increase in the risk for VTE was noted among those women treated with estrogen and progesterone (RR 2.7; 95% CI 1.4–5.0 for VTE and RR 2.8; 95% CI 0.9–8.7 for PE). A few years later, in the Women's Health Initiative (WHI), the group receiving HRT had a RR of 2.1 (CI 95% 1.6–2.8) for the development of VTE when compared to the placebo group. The risk is higher in the first year of HRT use (Perez et al 1997; Hoibraaten et al 1999; Miller et al 2002), especially in the presence of previous history of VTE (Hoibraaten et al 2000). Scarabin and colleagues (2003) showed that the risk of VTE was higher with oral, compared with transdermic, administration of HRT (RR 4.0; 95% CI 1.9–8.3).

Several observational studies and some RCTs have documented a RR 3 to 6 times higher in HC users, compared with nonusers (EVIDENCE A) (Jick et al 1995; Lewis et al 1996; Douketis et al 1997; Vandenbroucke et al 2001). In a multicentric, international case-control study including 1,143 cases of VTE and 2.998 controls, HC was associated with an OR of 4.1 (95% CI 3.1–5.6) in European women and to an OR of 3.2 (95% CI 2.6–4.1) in women from developing countries (WHO 1995). As for HRT, the risk is higher during the first year of use (Suissa et al 1997; Lidegaard et al 1998), and it seems also higher for the 3rd generation hormones (desogestrel and gestoden) (Kemmeren et al 2001).

Infections

Several cohorts and prospective randomized trials have indicated the association between infections and VTE. However, most patients included in these studies have lung infections and are described in the specific section about respiratory diseases. The SIRIUS study (Samama 2000) included 1,272 ambulatory patients and demonstrated that infection is a risk factor for VTE (OR 1.95; 95% CI 1.31–2.92). However, in this study the site of the infections are not reported. Kierkegaard and colleagues (1987) studied 101 acutely ill patients with labeled fibrinogen and found that those with pneumonia or cardiac diseases had an incidence of DVT of 20% while the patients with other diagnoses had an incidence of DVT of only 4%. In this study, 4 of the 22 patients with pneumonia had DVT, while none of the patients with urinary tract infection, bronchitis, acute enterocolitis or sepsis developed DVT. In the prospective registry 'DVT FREE', Goldhaber and Tapson (2004) evaluated 5,451 patients with acute DVT confirmed by Doppler ultrasound, demonstrating that 22% of the patients had an infection as one of the comorbidities (pneumonia in 7%, sepsis in 5%, and other infections in 10%). They also showed that thoracic infections were more common among those with PE and DVT, than among those with DVT alone (10% vs 8% $p = 0.04$). Alikhan and colleagues (2004) analyzed the data of 866 patients of the MEDENOX study, demonstrating that the acute infections were one of the main risk factors for VTE in the univariate (RR 1.47; 95% CI 1.47–2.14) and multivariate analyses (OR 1.74; 95% 1.12–2.75). These data suggest that infections are an additional and frequent risk factor for VTE, especially in hospitalized patients (EVIDENCE A for pulmonary infection and B for the other infections).

Nephrotic syndrome

The association between nephrotic syndrome (NS) and thromboembolic events is recognized since 1837 (Trew et al 1978). Until the 70s, some authors suggested that renal vein thrombosis was possibly the cause of the NS (Kendall et al 1971; Bennett 1975). Nevertheless, several studies confirmed that the thrombotic episodes are a consequence of the factors leading to the hypercoagulability found on the NS (Llach et al 1975, 1980; Noel et al 1979; Llach 1985; Bellomo et al 1993) The global incidence of thrombosis in NS is 43% (Bellomo and Atkins 1993), but PE and DVT affect about 11% of the patients (Nickolas et al 2003). The frequency of renal vein thrombosis in the membranous NS, in adults, varies among studies from 5% to 60% (Orth and Ritz 1998; Nickolas et al 2003). These episodes are symptomatic in only 10% of the cases (Orth and Ritz 1998), and all episodes can be accurately detected by computed tomography (Gatewood et al 1986). Rostoker and colleagues (1995) reviewed 13 prospective studies, including 682 patients with NS, showing that the incidence of renal vein thrombosis was 21.4% (95% CI 18%–25%). These authors reviewed also three other studies with 148 patients and found that incidence of PE was 14% (95% CI 9%–21%). Thromboembolic phenomena, particularly renal vein thrombosis, are more common with membranous lesions (Wagoner et al 1983; Llach 1985; Nickolas et al 2003), and possibly when serum albumin is <2g/dL (Kauffmann et al 1978; Kuhlmann et al 1981; Robert et al 1987; Nickolas et al 2003). For hospitalized patients with reduced mobility, NS is a risk factor for VTE (EVIDENCE A).

Obesity

There are many studies that evaluate obesity direct or indirectly as a risk factor for VTE leading to some debate about the importance of it as a risk factor. Alikhan and colleagues (2004), analyzing the data of the MEDENOX study, did not find a significant correlation between obesity and VTE (RR 1.04; 95% CI 0.69–1.60). Grady and colleagues (2000), evaluating women with body mass index (BMI) above 27, also failed to find such a correlation. It is important to mention that in both studies the identification of obesity as a risk factor was a secondary objective and the analysis was done post hoc. Besides, the definition of obesity currently accepted as the BMI $\geq$30 Kg/m^2, is not used in all studies. For example, in a study of consecutive out-patients with clinical suspicion of VTE, Cogo and colleagues (1994) defined obesity as 30% excess above ideal body weight and did not find that obesity was a risk factor for VTE. Heit and colleagues (2000), in a population based case-control study reached the same conclusion.

On the other hand, several studies do implicate obesity as a risk factor for VTE. Blaszyk and colleagues (1999) found in an autopsy study (n = 7,227) a higher incidence of VTE in obese (67%) than in nonobese (14%), RR 2.97 (95% CI 1.78–4.93). Four prospective cohort studies support theses findings, with RR ranging from 2.0 to 3.92 (Cogo et al 1994; Goldhaber et al 1997, 1983; Hansson et al 1999). Although there is some debate, the evidence from prospective trials evaluating risk factors support the correlation between obesity and VTE. Nevertheless, the RR for obesity is relatively low (between 2 and 3) but increases significantly when there are additional risk factors for VTE. Indeed, the RR rises from 2 to 10 with the use of HC in obese patients (Abdollahi et al 2003). In summary, we conclude that obesity is an important coadjuvant for the development of VTE (EVIDENCE B).

Paresis/paralysis of the lower extremities

There is supporting evidence that paresis or paralysis of the lower extremities is associated with VTE, even when not secondary to CVA (EVIDENCE A). In a study with 143 patients that developed acute hemiplegia, the incidence of VTE was 26% and the risk was higher during the first 4 weeks (Rentsch 1987). Pottier and colleagues (2002) studied the presence of risk factors among 450 hospitalized medical patients and found that paralysis was associated with an increased chance of VTE (calculated OR 12.5; 95% CI 1.5–104.5). The same result was seem in a case-control study with 620 patients older than 65 years (OR 2.1; 95% CI 1.0–4.1) (Weill-Engerer et al 2004). Patients with paresis or paralysis of the legs must be considered as at-risk for VTE, particularly during the acute setting (EVIDENCE A).

Peripheral vascular diseases

The impact of varices of the lower extremities as an additional risk factor for VTE in medical patients is controversial. There are few studies evaluating the theme and there is no evidence that surgical treatment of the varicose veins decreases the potential risk of VTE. Kakkar and colleagues (1970) showed that the incidence of VTE by labeled fibrinogen in surgical patients with mild to severe varices was 56.5%, leading to a RR of 2.3. The reason for such a high incidence of VTE in patients with varices is not known but one of the possibilities is that the varices may be a consequence of previous and undiagnosed DVT. Recently, Heit and colleagues (2000) demonstrated in a population-based, case-control study that varices are associated with risk of VTE in medical patients, but the risk decreases with age: OR 4.2 at age 45, 1.9 at age 60 and 0.9 at age 75. In another analysis of the same data (Heit et al 2002), the attributable risk of VTE to varices was 6%; but after adjustments for other confounders, such as hospitalization, trauma, cancer and chemotherapy, CHF and CVA, CVC or pacemaker, the risk associated with varices became zero. Some cohort studies also failed to demonstrate an independent association between varices and VTE (Goldhaber et al 1983; Kierkegaard et al 1987). On the other hand, prospective studies with good methodology (Alikhan et al 2003; Oger et al 1997) and case control studies (Samama 2000; Pottier et al 2002) showed that varices (OR $\geq$ 2.5 and RR 4.2) and venous insufficiency (OR $\geq$ 1.7) were significantly associated with VTE in medical patients. Furthermore, one case-control study in ambulatory patients with clinical suspicion of DVT or PE showed that peripheral arteriopathy was related to an higher chance of VTE (OR 1.9) (Cogo et al 1994). Therefore, peripheral venous and arterial diseases may be considered as cofactors for the development of thrombosis (EVIDENCE B).

Pregnancy and puerperium

Pregnancy is a well known condition related to increased risk of thrombosis (Samama 2000), that persists even a few months after delivery (EVIDENCE A). It is estimated that the risk for VTE during pregnancy increases 3 to 4 times, probably because of the increase in procoagulant factors, such as factor VIII and in the resistance to activated protein C. Samuelsson and Hagg (2004), in a population-based study with more than 24,000 women, reported an incidence of VTE during

pregnancy and postpartum of 103:100,000 (95% CI 55–177). Besides, fatal PE remains one of the most important complications during pregnancy and puerperium, especially in those women older than 40 years (Franks et al 1990).

Previous VTE

Previous VTE has been consistently described as a risk factor for the development of VTE in several scenarios: hospitalized and ambulatorial patients and in the general population (EVIDENCE A). The case-control study SIRIUS (Samama 2000) revealed a strong tendency to new thrombotic events in ambulatorial patients with previous history of VTE (OR 15.6). In a prospective study, Oger and colleagues (1997) showed that medical patients with suspected DVT and history of VTE had increased chance of confirming the diagnosis by venography (OR 1.7). In 2003, Tosseto and colleagues (2003) also demonstrated increased risk of VTE in individuals with previous history of this condition (OR 6.8). A case-control study showed that previous history was an important risk factor for VTE also in hospitalized medical patients (OR 4.7) (Bonifacj et al 1997). Another case-control study showed that in hospitalized medical patients older than 64 years-old, previous VTE was independently associated with the development of VTE during hospitalization (OR 3.4) (Weill-Engerer et al 2004). In the analysis of VTE risk factors based on the MEDENOX study (Alikhan et al 2004), previous history was associated with the development of VTE, in univariate (RR 1.8; $p = 0.02$) and multivariate logistic regression (RR 2.1; $p = 0.02$). Thus, previous history of thrombosis should be considered as an additional risk factor for VTE in medical patients (EVIDENCE A).

Reduced mobility

It is not known exactly what level and duration of immobility is associated with increased risk of VTE. What is recognized is that when important risk factors are present, even subtle reductions in mobility increase the overall risk of VTE. It is believed that when patients are able to ambulate to the bathroom or on the hallways, but have to come back, for any reason (eg, need for intravenous infusions or oxygen therapy, generalized weakness, pain, or dyspnea on exertion), and stay in bed or chair while hospitalized with an acute illness, they are at-risk for VTE.

Some studies tried to identify the loss of mobility as the main factor leading to VTE. Motykie and colleagues (2000) evaluated 1,000 patients with Doppler ultrasound for suspected DVT and noted that there was a significant correlation between loss of mobility for more than 3 days and development of DVT. In a large case-control study with 1,272 ambulatory patients, Samama (2000) showed that standing for more than 6 hours and resting in bed or chair were associated with an increased odds of VTE (OR 1.9; 95% CI 1.1–3.1 and OR 5.6; 95% CI 2.3–13.7, respectively). Similarly, Heit and colleagues (2000) showed that hospitalization or admission to a long-term care facility increased the risk of VTE (OR 8.0; 95% CI 4.5–14.2). Other studies identify the reduction of mobility as a risk factor for VTE, but the definition of decreased mobility is either not clearly stated or it is quite variable, including complete bed rest for ≥ 5 days (Anderson et al 1992), partial or complete bedrest for at least 10 days (Harenberg et al 1996), reduced mobility for more than half of the day, at least during 7 days (Lechler et al 1996). Other authors noted that more serious loss of mobility, such as the incapacity to walk independently for more than 10 meters were frequently associated with the development of VTE (Alikhan et al 2003). In a recent case-control study of hospitalized patients older than 65 years, reduced mobility was an independent risk factor for VTE (OR 1.73 to 5.64), depending on the degree of immobility (Table 7) (Weill-Engerer et al 2004). The risk was higher in patients with more severe limitation of mobility (bedrest vs wheel-chair) and when the loss of mobility was recent (<15 days vs ≥30 days).

Based on presented data, we believe that the patient who stays in bed or chair for more than half of the day (excluding sleep time) must be considered as having reduced mobility and is at-risk for VTE (EVIDENCE B). The immobility that is more recent and severe is more strongly associated with the development of VTE.

Respiratory diseases

Respiratory diseases such as COPD and pneumonia are frequently cited as VTE risk factors, but studies evaluating specifically the impact of these conditions in the incidence of VTE are rare. Besides, the diagnosis of VTE in COPD patients is usually a challenge because PE may present simply as worsening of dyspnea in a patient with chronic respiratory failure. On the study performed in the community of Worcester, MA, the diagnosis of COPD was present in 18% of those with DVT and in 34% of patients with PE (Anderson et al 1991). In autopsy studies, DVT has been diagnosed in 18% to 51% of COPD patients, giving an OR of 1.6 for emphysema as compared with controls with median age >81 years-old (Mitchell et al 1968; Janssens et al 2001). In prospective cohorts of patients with exacerbation of COPD, DVT was detected in 9% of patients by venography

Table 7 Reduced mobility as a risk factor for VTE

Degree of immobility	OR	95% CI	P
Normal	1.0	-	-
Limited	1.73	1.08–2.75	0.02
Wheel-chair ≥ 30 days	2.43	1.37–4.30	0.002
Bedrest ≥ 30 days	2.73	1.20–6.20	0.02
Wheel-chair 15–30 days	3.33	1.26–8.84	0.02
Bedrest 15–30 days	3.37	1.00–11.29	0.05
Wheel-chair <15 days	4.32	1.50–12.45	0.007
Bedrest <15 days	5.64	2.04–15.56	0.0008

and/or labeled fibrinogen (Prescott et al 1981), in 11% by Doppler ultrasound (Schonhofer and Kohler 1998; Erelel et al 2002), and in 29%, when combining ventilation-perfusion scanning and Doppler ultrasound (Mispelaere et al 2002). Patients treated for VTE with oral anticoagulation in a RCT were analyzed, and the authors demonstrated that chronic respiratory diseases increased the risk for recurrence of VTE (OR 1.91; 95% CI 0.85–4.26) (Douketis et al 2000). On the other hand, the analyses of patients with risk factors for VTE in the MEDENOX study surprisingly revealed that chronic respiratory disease was not significantly associated with an increased risk (OR 0.6; 95% CI 0.38–0.92)(Alikhan et al 2004). However, it is worthy noticing that these analyses were performed post hoc and based on secondary objectives of the MEDENOX study.

Prospective controlled studies evaluating the efficacy of VTE prophylaxis are helpful in identifying pulmonary conditions as risk factors for VTE because the rates of thrombosis can be compared between patients on control and treatment groups. Belch and colleagues (1981), in a small study with patients with thoracic infection or CHF, showed a significant difference in the incidence of DVT diagnosed by labeled fibrinogen, favoring LDUH (5,000 IU 8–8h) versus placebo (4% vs 26%, respectively, $p < 0.01$). In another RCT, patients with exacerbation of COPD, requiring ventilatory support (the majority with thoracic infection), were randomized to LMWH (nadroparin 3,800 IU AXa or 5,700 IU AXa) or placebo (Fraisse et al 2000). Those receiving LMWH had significantly lower incidence of VTE, when compared with placebo (28.2% vs 15.5% respectively, $p = 0.045$). In the study THE-PRINCE (Kleber et al 2003), patients with severe respiratory diseases (SRD) or CHF were randomized to enoxaparin 40 mg/daily or LDUH 5,000 IU three times daily. The authors demonstrated that the incidence of VTE by venography was high in all patients, without significant differences among all patients receiving enoxaparin and LDUH (8.4% vs 10.4%), or among patients with SRD (7.1% vs 5.9%). The definition of SRD in this study was the presence of abnormalities in the pulmonary function tests, arterial blood gas analyses or both, and at least one of the following conditions: acute exacerbation of COPD, severe secondary pulmonary hypertension, pneumonia, interstitial lung disease, lung cancer and/or metastasis and life expectancy of less than 2 months. This description is broad enough to include the main pulmonary diagnoses that are associated with an increase risk of VTE in hospitalized medical patients, and was therefore, incorporated to our algorithm instead of each pulmonary disease separately. In summary, there is some controversy about the role of specific respiratory diseases as risk factors for VTE in hospitalized medical patients. However, in general, patients presenting diagnostic criteria for SRD have increased risk for VTE (EVIDENCE A).

Thrombophilias

Hereditary thrombophilias, particularly antithrombin III (ATIII), protein C (PC) and protein S (PS) deficiencies, and factor V Leiden (FVL) are well known risk factors for VTE. Several case-control studies and some prospective registries show level A evidence for these thrombophilias as risk factors for thrombosis (Table 8). In a recent prospective registry of thrombophilic families, the incidence of VTE was 16% among relatives with thrombophilia, against 1% among those without thrombophilia (RR 15.7; 95% CI 9.6–28.0) (Vossen et al 2004). In a multicenter study with 233 Italian families, Bucciarelli and colleagues (1999) showed that ATIII deficiency is associated with a higher risk for VTE than other genetic conditions (RR 4.4 for ATIII vs FVL, 2.6 for ATIII vs PS, and 1.9 for ATIII vs PC). Simioni and colleagues (1999) reported that conditions such as surgery, trauma, immobilization, pregnancy, puerperium, and hormonal contraception increase the risk for thrombosis in patients with ATIII, PS or PC deficiencies. Mutation of the prothrombin gene has also been associated with increased risk for VTE in different populations (OR 2.0 to 11.5) (Poort et al 1996; Brown et al 1997; Cumming et al 1997; Hillarp et al 1997; Kapur et al 1997; Leroyer et al 1998; Souto et al 1998; Aznar et al 2000). It is appropriate to conclude that hereditary thrombophilias confer additional risk for VTE in hospitalized patients (EVIDENCE A).

Hyperhomocysteinemia (HHC) has been considered a risk factor not only for arterial disease, but also for venous thrombosis. In 1998, den Heijer and colleagues (1998) reviewed 8 case-control studies in a meta-analysis, and showed correlations between fasting HHC and VTE (OR 2.5; 95% CI 1.8–3.5), and methionine-induced HHC

Table 8 Annual incidence and VTE risk in hereditary thrombophilias

Author, year	Patients/ controls	Design	ATIII	PC	PS	FVL	MPG	Combination
Finazzi and Barbui 1994	28/53†	PC/8 years	12.0%	2.80%	3.30%	-	-	-
Pabinger et al 1994	44/49	PC	-	2.50%	3.50%	-	-	-
Koster et al 1995	474/474	CC	OR 2.2–5.0	OR 3.1–6.5	OR 0.7–1.6§	-	-	-
Poort et al 1996	442/463	CC	-	-	-	-	OR 2.8	-
Kapur et al 1997	50/50	CC	-	-	-	-	OR 11.5	-
Hillarp et al 1997	99/282	CC	-	-	-	-	OR 3.8	-
Cumming et al 1997	219/164	CC	-	-	-	-	OR 5.4	-
Brown et al 1997	504	RC	-	-	-	OR 5.8	OR 2.0	-
Faioni et al 1997	327/317	CC	-	-	OR 2.4	-	-	-
Leroyer et al 1998	366/400	CC	-	-	-	x	OR 3.7	OR 4.8
Souto et al 1998	116/201	CC	-	-	-	-	OR 3.1	-
Middeldorp et al 1998	437	RC	-	-	-	0.45%. RR 4.2	-	-
Martinelli et al 1998	150/723	RC	RR 8.1	RR 7.3	RR 8.5	RR 2.2	-	-
Mateo et al 1998	583	RC	OR 21.2	OR 12.6	OR 19.9	-	-	OR 9.0
Sanson et al 1999	94/208†	PC/3 years	1.60%	1.00%	0.40%	-	-	-
Bucciarelli et al 1999	233/513	RC	1.07%	0.54%	0.50%	0.30%		
Simioni et al 1999	793	RC	x	x	x	0.11%. RR 2.5		0.40%. RR 10.6
Rodeghiero and Tosetto 1999	15109	TC	-	OR 1.7	-	RR 3.3	-	-
van Boven et al 1999	48/44	CC	1.10%	-	-	x	x	4.60%
Aznar et al 2000	229/246	CC	-	-	-	OR 6.9	OR 2.4	-
Lensen et al 2000	233	RC	-	-	-	0.56%	-	-
Middeldorp et al 2001	247/470†	PC/3.3 years	-	-	-	0.58%	-	-
Folsom et al 2002[a]	14358	PC/8.1 years		RR 3.36				
Folsom et al 2002[b]	335/668	CC	-	-	-	OR 3.7	-	-
Simioni et al 2002	131/313-248*	PC/4 years	-	-	-	0.17%. RR 6.6	-	-
Oger et al 2002[b]	621/406	CC	-	-	-	OR 3.2¥	-	-
Vossen et al 2004	846/1212	CC	-	x	x	0.15%	-	0.84%

Abbreviations: ATIII, antithrombin III deficiency; CC, case-control; FVL, factor V Leiden; MPG, mutation of the prothrombin gene; OR, odds ratio; PC, prospective cohort; PC, protein C; PS, protein S; RC, retrospective cohort; RR, relative risk; TC, transversal cohort.
Notes: †Patients/asymptomatic holders; *Patients/asymptomatic holders-controls; §Not a risk factor; ¥Not a risk factor for age >70 years (OR 0.8; 95% CI 0.4–1.7); xThrombophilias evaluated in combination.

and VTE (OR 2.6; 95% CI 1.6–4.4). Furthermore, the risk seems to be even higher in patients older than 60 years (OR 4.4; 95% CI 1.9–9.8) (Ray 1998). Thus, HHC should be considered a risk factor for VTE (EVIDENCE A).

Other risk factors

Although some conditions, such as, systemic arterial hypertension, diabetes mellitus and tobacco smoking are cited occasionally as potential risk factors for VTE, we did not find enough evidence to justify their inclusion on the list of factors that predispose hospitalized medical patients to the development of venous thrombosis.

VTE prophylaxis

Compared with surgical patients, there are few studies evaluating VTE prophylaxis in medical patients. Besides, the great range of clinical conditions and variations in individual characteristics make it difficult to create a single recommendation suitable for all patients or even define if there is superiority of one type or one particular regimen of heparin over the others. Table 9 shows the evidence-based recommendations for prophylaxis, as they are found in the literature, for specific conditions and not for medical patients as a group. Table 9 also shows that, in most studies, the regimens of heparin involve high prophylactic doses: LDUH 5.000 IU every 8 hours, enoxaparin 40 mg daily, dalteparin 5.000 IU daily or nadroparin also in high doses (3.800 IU for patients with less than 70 kg and 5.700 IU for those weighing 70 kg or more). All these studies have proved the efficacy of these regimens in decreasing the incidence of VTE. This leads to the initial conclusion that medical patients benefit from high prophylactic doses of heparin. Therefore, these high prophylactic doses are the ones recommended (GRADE I) for most hospitalized medical patients on the algorithm (Figure 1). Only a few studies, usually with very few patients and some methodological flaws (Harenberg et al

Table 9 Evidence-based recommendations for VTE prophylaxis in patients with specific medical conditions Ψ

Condition	Method	Evidence	Recommendation	Dose
Previous VTE + risky condition	LDUH	C[1]	I	5.000 IU 8–8h
	LMWH	C[2]	I	Dalteparin (5.000 IU/day) or enoxaparin (40 mg/day)
Chronic venous insufficiency/varices	Enoxaparin	A[3]	IIa	40 mg/day
	Dalteparin	A[4]	IIa	5.000 IU/day
Obesity + risky conditions	Enoxaparin	B[5]	IIa	40 mg/day
	Dalteparin	A[6]	IIa	5.000 IU/day
Thrombophilias + risky conditions	LDUH, LMWH or Warfarin	B[7]	I	5.000 IU 8–8h or dalteparin (5.000 IU/day) or enoxaparin (40 mg/day) or warfarin (RNI 2–3)
HRT/HC + risky conditions	LDUH	C[8]	I	5.000 IU 8–8h
	LMWH	C[9]	I	Dalteparin (5.000 IU/day) or enoxaparin (40 mg/day)
CHF	LDUH	A[10]	I	5.000 IU 8–8h
	Enoxaparin	A[11]	I	40 mg/day
	Dalteparin	A[12]	I	5.000 IU/day
AMI	LDUH	B[13]	I	5.000 IU 12–12h or full dose
	Dalteparin	B[14]	I	120 IU/Kg
	Ambulation	B[15]	IIa	–
	ES	B[16]	IIa	–
Ischemic CVA	LDUH*	A[17]	I or III	5.000 IU 8–8h or 12–12h
	LMWH*	B[18]	I or III	Dalteparin (2.500 IU 12–12h) or enoxaparin (40 mg/day)
	ES**	B[19]	IIb	–
	IPC + LDUH***	B[20]	IIb	IPC + HNF 5.000 IU 12–12h
Hemorrhagic CVA	INITIAL phase:			
	LDUH or LMWH	B[21]	III	CONTRAINDICATED
	ES/IPC** and***	B[22]	IIb	–
	LATE phase: LDUH or LMWH****	C[23]	IIb	–
Acute rheumatological diseases/IBD	Enoxaparin	B[24]	I	40 mg/day
	Dalteparin	A[25]	I	5.000 IU/day
Severe respiratory diseases	LDUH	A[26]	I	5.000 IU 8–8h
	Enoxaparin	A[27]	I	40 mg/day
	Dalteparin	A[28]	I	5.000 IU/day
	ES	B[29]	IIa	Continuous
Infections	LDUH	B[30]	I	5.000 IU 8–8h or 12-12h
	Enoxaparin	A[31]	I	40 mg/day
	Dalteparin	A[32]	I	5.000 IU/day

Condition	Method	Evidence	Recommendation	Dose
Nephrotic syndrome	Enoxaparin	B[33]	I	40 mg/day
Neoplasias	Enoxaparin	B[34]	IIa	40 mg/day
Admission to ICU	LDUH	B[35]	I	5.000 IU 12–12h
	Enoxaparin	B[36]	I	40 mg/day
	Nadroparin	B[37]	I	3.800 IU or 5.700 IU/day
	ES/IPC** and***	B[38]	IIa	–
CVC for PN	LDUH	A[39]	IIb	5.000 IU 6-6h or 12–12h SC, or 1U/mL – 3 U/mL in PN
CVC in cancer	Dalteparin	A[40]	I	2.500 IU/day
patients†	Nadroparin	B[41]	IIa	2.850UI a 7.600 IU/day
	Warfarin*****	B[41]	IIb	1mg/day

Notes: §Nadroparin and LDUH were equivalent, but more patients in the nadroparin group died (2.8% vs 1.2%; p = 0.02);
†In cancer patients, hospitalized and with reduced mobility, prevail the recommendations related to the clinical situation not to the catheter.
*In patients with a well defined deficit with reduced mobility, and cerebral hemorrhage excluded with CT or NMR – RECOMMENDATION I. RECOMMENDATION III for systematic use in all patients due to the increased risk of bleeding.
**Lower efficacy in very high-risk patients.
***Attention to the IPC contraindications, like arterial peripheral disease.
****Prophylaxis may be considered after 10 days of the onset, provided patient is clinically and radiologically stable.
*****Patients with high risk for bleeding must be excluded (liver metastasis or use of fluoracil and derivates).
ΨHigh prophylactic doses: LDUH 5.000 IU every 8 hours, enoxaparin 40 mg daily, dalteparin 5.000 IU daily or nadroparin (3.800 IU for <70 kg and 5.700 IU ≥70 kg) daily are the ones recommended (GRADE I) for most hospitalized edical patients on the algorithm.
Abbreviations: CHF congestive heart failure; AMI, acute myocardial infarction; CVA, cerebral vascular accident; ARD, active rheumatological disease; IBD, inflammatory bowel disease; ICU, intensive care unit; VTE, venous thromboembolism; LMWH, low molecular weigh heparin, LDUH, low dose unfractionated heparin; ES, elastic stockings; IPC, intermittent pneumatic compression; CVC, central venous catheter and PN, parenteral nutrition.
Citations: [1](Harenberg et al 1996), [2](Samama et al 1999; Leizorovicz et al 2004), [3](Alikhan et al 2003), [4](Leizorovicz et al 2004), [5](Alikhan et al 2003), [6](Leizorovicz et al 2004), [7](Sanson et al 1999; Simioni et al 1999), [8](Harenberg et al 1996), [9](Leizorovicz et al 1999), [10](Belch et al 1981; Harenberg et al 1996, 1999; Lechler et al 1996; Kleber et al 2003), [11](Lechler et al 1996; Harenberg et al 1999; Samama et al 1999; Kleber et al 2003), [12](Leizorovicz et al 2004), [13](Emerson and Marks 1977; Pitt et al 1980; Zawilska et al 1989; Scala et al 1990), [14](Scala et al 1990), [15](Miller et al 1976), [16](Kierkegaard and Norgren 1993), [17](McCarthy et al 1977; McCarthy and Turner 1986; Sandercock et al 1993; IST 1997; Bath et al 2000), [18](Prins et al 1989; Hillbom et al 1999; Bath et al 2000; Counsell and Sandercock 2001), [19](Prasad et al 1982; Muir et al 2000; Mazzone et al 2004), [20](Kamran et al 1998), [21](Dickmann et al 1988; Boeer et al 1991), [22](Prasad et al 1982; Kamran et al 1998; Muir et al 2000; Mazzone et al 2004), [23](Dickmann et al 1988; Boeer et al 1991), [24](Alikhan et al 2003), [25](Leizorovicz et al 2004), [26](Belch et al 1981; Ibarra-Perez et al 1988; Kleber et al 2003), [27](Harenberg et al 1999; Alikhan et al 2003; Kleber et al 2003), [28](Leizorovicz et al 2004), [29](Ibarra-Perez et al 1988), [30](Gardlund 1996; Harenberg et al 1996), [31](Samama et al 1999), [32](Leizorovicz et al 2004), [33](Sarasin and Schifferli 1994; Rostoker et al 1995), [34](Alikhan et al 2003; Zangari et al 2004), [35](Cade 1982; Kapoor et al 1999; Goldhaber et al 2000), [36](Goldhaber et al 2000), [37](Fraisse et al 2000), [38](Ibarra-Perez et al 1988; Cook et al 2000; Jimenez et al 2001; Rocha et al 2003), [39](Randolph et al 1998; Klerk et al 2003), [40](Monreal et al 1996; Klerk et al 2003), [41](Van Rooden et al 2004), [42](Bern et al 1990; Couban et al 2002; Heaton et al 2002; Klerk et al 2003).

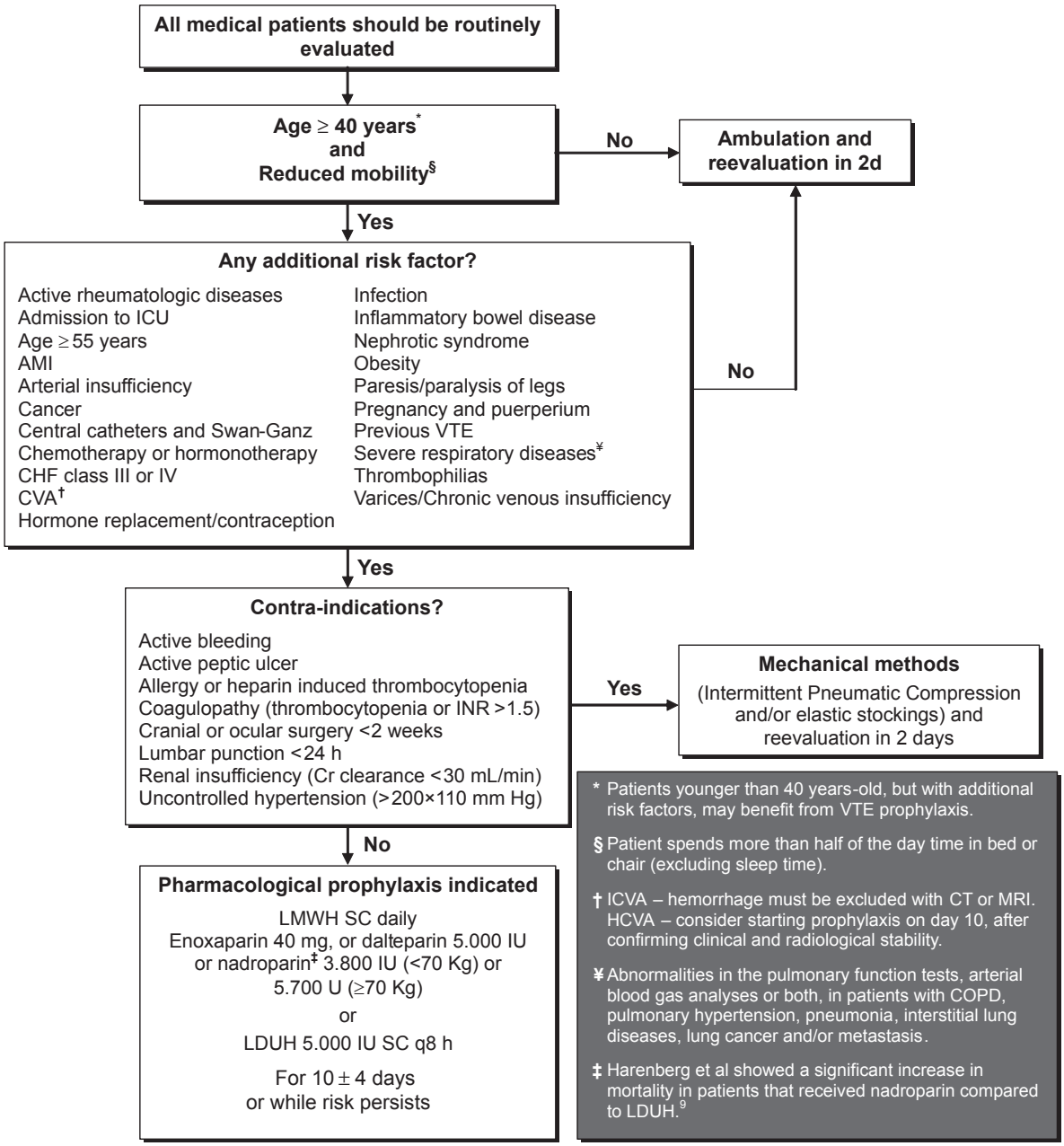

Figure 1 Algorithm for VTE prevention in hospitalized medical patients.

1996; Lechler et al 1996; Samama et al 1999; Leizorovicz et al 2004) have shown that low prophylactic doses of heparin have efficacy. Besides, in the MEDENOX study (Samama et al 1999) that compared the high (40 mg) and low (20 mg) prophylactic doses of enoxaparin with placebo, only the higher dose reduced significantly the incidence of VTE. In the groups receiving 20 mg of enoxaparin, the incidence of DVT detected by phlebography was similar to that of the placebo group (14.5% vs 15.0%). Finally, a large randomized placebo-controlled trial, published after this review had been concluded (Cohen et al 2006) showed that fondaparinux, a synthetic, selective inhibitor of factor Xa, at a dose of 2.5 mg/day subcutaneously for 14 days was also effective for the prevention of VTE in older acutely ill medical patients.

Four important RCTs evaluated VTE prophylaxis in medical patients as a group (Harenberg et al 1996; Lechler et al 1996; Samama et al 1999; Leizorovicz et al 2004). Together they included 7,735 patients, with average ages of 68 to 74 years-old. Diseases and conditions listed as risk factors are presented on Table 10. The most common

Table 10 The most common diseases and risk factors for VTE found in four large RCTs about efficacy of prophylaxis in hospitalized medical patients[1–4]

Disease/Risk factor	%
Congestive heart failure	30–52
Respiratory disease	24–53
Infection	20–54
Obesity	27–53
Varices	22–27
Cancer	4.6–20
Active rheumatologic disease	7.6–11
Past history of VTE	3.4–8.4
Estrogen therapy	1.4–1.8
Bowel inflammatory disease	0.5–0.8

Notes: [1]Harenberg et al 1996; [2]Lechler et al 1996; [3]Samama et al 1999; [4]Leizorovicz et al 2004.

reasons for admission were CHF, respiratory insufficiency and infection. The most common risk factors were obesity, varices, cancer, active rheumatologic disorders and previous VTE. Enoxaparin (Lechler et al 1996; Samama et al 1999), dalteparin (Leizorovicz et al 2004), nadroparin (Harenberg et al 1996), and LDUH (Harenberg et al 1996; Lechler et al 1996) were used in these studies. Harenberg and colleagues (1996) compared nadroparin 3.600 IU with LDUH 5.000 IU, every 8 hours in 1,968 medical patients. Although there were no differences on the efficacy of prophylaxis or on the rate of bleeding, more patients in the nadroparin group died (2.8% vs 1.2% in LDUH group, $p = 0.02$). However, Fraisse and colleagues (2000) evaluated nadroparin as VTE prophylaxis in 223 patients with acute exacerbation of COPD requiring mechanical ventilation and demonstrated the efficacy of this LMWH against placebo, without increased bleeding or death rates.

Another important issue is how long the prophylaxis should be maintained. It is common belief among physicians that as soon as the patient is able to ambulate, the risk is over and prophylaxis could be discontinued. However, there is no support in the literature for this, and in all studies that included hospitalized medical patients with risk factors to VTE, prophylaxis was maintained for at least 6 to 14 days (Harenberg et al 1996; Lechler et al 1996; Samama et al 1999; Kleber et al 2003; Leizorovicz et al 2004). In the PREVENT (Leizorovicz et al 2004) study, authors are specific about the point that all patients received the medication (dalteparin or placebo) for 14 days, even if they were discharged earlier. Besides, in the MEDENOX (Harenberg et al 1996; Lechler et al 1996; Samama et al 1999; Leizorovicz et al 2004) and in the PREVENT (Leizorovicz et al 2004) studies, patients were reevaluated several weeks after prophylaxis was finished, and symptomatic VTE episodes were detected. We have not found any studies testing prophylaxis for less than 6 days. Until new data is available, it's recommended that VTE prophylaxis be maintained for at least 6 to 14 days. There is only one study that we are aware of—the EXCLAIM study (Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients with Prolonged Immobilization)—that has evaluated the extension of prophylaxis beyond 14 days in medical patients. The preliminary results of this study were recently presented at the XXIth Congress of the International Society on Thrombosis and Haemostatis and suggest the extension of VTE prophylaxis with enoxaparin 40 mg/day for an additional 28 days, is beneficial for acutely ill medical patients that remain with severely impaired mobility and for those with moderate impairment of mobility plus ≥75 years-old, cancer, or history of VTE. The final manuscript has not yet been published.

Some conditions represent contraindications to heparin use and must have their risk weighed against the potential benefit of the prophylaxis. Active bleeding, allergies, and previous type II heparin induced thrombocytopenia are absolute contraindications; thrombocytopenia for other reasons, coagulopathies, recent surgeries, specially cranial and ocular, lumbar puncture, uncontrolled hypertension, active pepticulcer without bleeding, and renal failure with clearance lower than 30 mL/min are also considered contraindications (Leizorovicz et al 2004; Samama et al 1999). In patients with mild to moderate renal failure, LDUH is preferred over LMWH for VTE prophylaxis in medical patients, based on level C of evidence (Class IIa). If LMWH are chosen for patients with renal insufficiency, the measurement of anti-Xa activity is recommended to adjust LMWH doses (Hulot et al 2004).

Conclusion

In summary, VTE prophylaxis is recommended for acutely ill, hospitalized medical patients, age 40 years or older, with reduced mobility and at least one additional risk factor for VTE, as suggested in the algorithm below (Figure 1). Patients younger than 40 years of age, but presenting with important risk factors, may benefit from prophylaxis. When the algorithm for risk assessment indicates that VTE prophylaxis is recommended, LMWH once a day (enoxaparin 40 mg, dalteparin 5.000 IU, nadroparin 3.800 IU if ≤70 Kg or 5.700 IU if >70 Kg) or LDUH 5.000 UI SC every 8 h should be used and maintained for 6 to 14 days, even if the patient resumes ambulation or has early discharge. For patients older than 60 years, fondaparinux 2.5 mg once a day is also an option.

If there is contraindication for pharmacological prophylaxis, mechanical methods of prophylaxis may be considered. However, all patients must be frequently reevaluated for the appearance of new indications or contraindications for prophylaxis during the hospitalization.

Key points

- Hospitalized medical patients have increased risk of thromboembolic complications.
- Our multidisciplinary group created an easy-to-use algorithm to facilitate the implementation of evidence-based recommendations for prophylaxis of hospitalized medical patients into practice.
- In the absence of contraindications, hospitalized medical patients that are older than 40 years of age, have reduced mobility and at least one additional risk factor for VTE should be given high prophylactic doses of LDUH or LMWH for 6 to 14 days.

For the working committee

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