Review

Antithrombotic drugs in acutely ill medical patients: review and meta-analysis of interventional trials with low-molecular-weight heparin and fondaparinux

Lorenzo Loffredo*[1], Ludovica Perri[1], Elisa Catasca[1], Maria Del Ben[1], Francesco Angelico[1] & Francesco Violi[1]

Practice Points

- Venous thromboembolism (VTE) represents a severe complication for acutely ill hospitalized medical patients.
- Deep venous thrombosis and VTE are significantly reduced in hospitalized medical patients treated with antithrombotic drugs.
- Only 0.8% of the acutely ill hospitalized medical patients, not treated with antithrombotic drugs will develop pulmonary embolism.
- Antithrombotic drugs do not reduce the rate of pulmonary embolism, VTE-related death or death from any other cause.
- Antithrombotic drugs significantly enhance hemorrhages in hospitalized medical patients.

SUMMARY Venous thromboembolism (VTE) represents a severe complication for acutely ill hospitalized medical patients. Despite several guidelines suggesting that prophylactic measures significantly reduce the risk of VTE, there is a scarce tendency to use antithrombotic drugs in these patients. We performed a meta-analysis of the interventional trials with antithrombotic drugs (low-molecular-weight heparin and fondaparinux) to oversee the clinical effectiveness and bleeding complications. A total of eight randomized controlled trials, including 16,524 patients, were analyzed. This meta-analysis suggests that in acutely ill medical patients, compared with controls, prophylaxis with antithrombotic drugs may be of clinical benefit in VTE (odds ratio [OR]: 0.512; 95% CI: 0.41–0.64; $p < 0.001$) and deep venous thrombosis (OR: 0.520; 95% CI: 0.41–0.67; $p < 0.001$); furthermore, there is no effect

[1]I Clinica Medica, Sapienza University, Viale del Policlinico 155, 00161, Rome, Italy
*Author for correspondence: Tel.: +39 064 997 0103; Fax: +39 064 997 0103; lorenzo.loffredo@uniroma1.it

Future Medicine part of fsg

on pulmonary embolism, VTE-related death and death from any other cause, and significant enhancement of hemorrhages (OR: 1.465; 95% CI: 1.2–1.79; p < 0.001). Future clinical trials should better define the risk factors for VTE in order to provide the optimal care for acutely ill medical patients.

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) is a major cause of morbidity and mortality in hospitalized medical patients [1,2].

VTE prophylaxis with antithrombotic drugs (such as unfractionated heparin, low-molecular-weight heparin [LMWH], or fondaparinux) or mechanical leg compression has been recommended for many of these patients [1,2].

In accordance with the PADUA classification [3], American College of Chest Physicians guidelines [1] defined the at-risk population for VTE. Despite these recommendations and data coming from interventional trials showing that prophylaxis with anticoagulants reduces the risk of DVT, VTE and PE [4–6], there is a large underuse of this therapy in the medical hospital wards [7,8]. In the IMPROVE study, only 60% of patients judged to be at risk of VTE received prophylaxis [9]. As a result, it is not possible to exclude that there is uncertainty as to whether prophylaxis with anticoagulants really provides a clinical benefit without serious risk of bleeding.

Therefore, the aim of this study was to review the interventional trials with antithrombotic drugs (LMWH and fondaparinux) in patients hospitalized for acute medical illness analyzing the balance between clinical effectiveness and bleeding complications and to draw data, which may be useful in planning future trials in this setting.

Methods

Eligibility criteria

Types of studies

Randomized clinical trials studying the effect of thromboembolism prophylaxis in medical patients. No language, publication date or publication status restrictions were imposed.

We conducted all analyses according to the intention-to-treat principle. For trials with a factorial design, we based the main results on two-way analyses, where all trial participants

Table 1. Characteristics of the patients included in the meta-analysis.

Study (year)	n	Age (mean ± SD)	Males/ females	HF, n (%)	ARD, n (%)	Infections, n (%)	Cancer, n (%)	Jadad score	Primary end point of the study	Ref.
Dahan *et al.* (1986)	270	80 ± 6.8	167/103	49 (18)	57 (21.1)	11 (4)	35 (12.9)	3	Rate of lower limb DVT	[14]
MEDENOX (1999)	1102	73 ± 10.5	550/552	376 (34.2)	589 (53.4)	584 (52.9)	157 (14.2)	4	Venous thromboembolism	[15]
Fraisse *et al.* (2000)	223	68.1 ± 7.9	174/49	64 (28.7)	111 (49.7)	–	11 (4.9)	4	Incidence of DVT	[19]
PREVENT (2004)	3706	68.6 ± 11.4	1772/1909	1905 (51.4)	1121 (30.2)	1360 (36.7)	190 (5.1)	3	Composite of symptomatic DVT, fatal or symptomatic nonfatal PE, sudden death and asymptomatic DVT	[16]
Mahé *et al.* (2005)	2474	76.3	1001/1473	637 (25.7)	545 (22)	532 (21.5)	343 (13.8)	3	Overall mortality	[18]
ARTEMIS (2006)	849	74.7 ± 8.3	360/489	212 (24.9)	167 (19.6)	214 (25.2)	131 (15.4)	3	Composite of DVT and symptomatic venous thromboembolism	[17]
Lederle *et al.* (2006)	280	71.7	276/4	69 (24.6)	–	96 (34.2) current pneumonia	26 (9.2)	4	All-cause mortality	[20]
LIFENOX (2011)	8307	65 ± 12	5211/3096	2540 (30.6)	–	4179 (56.8)	365 (4.4)	5	Death from any cause	[21]

ARD: Acute respiratory disease; DVT: Deep venous thrombosis; HF: Heart failure; PE: Pulmonary embolism.

Table 2. Study drug and method of diagnosis for deep venous thrombosis and pulmonary embolism in the trials included in the meta-analysis.

Study (year)	Study drugs	Diagnostic tool for DVT	Diagnostic tool for PE	Ref.
Dahan *et al.* (1986)	LMWH	^{125}I fibrinogen scanning	Autopsy	[14]
MEDENOX (1999)	Enoxaparin	Venography or venous ultrasonography	Lung scanning, pulmonary angiography, helical computed tomography or autopsy	[15]
Fraisse *et al.* (2000)	Nadroparin	Venography	Venography and pulmonary angiography	[19]
PREVENT (2004)	Dalteparin	Venography, compression ultrasonography or MRI	Ventilation/perfusion scanning, angiography, or computed tomography of the chest	[16]
Mahé *et al.* (2005)	Nadroparin	Necropsy or venography	Necropsy , venography or pulmonary angiography	[18]
ARTEMIS (2006)	Fondaparinux	Venography	Lung scan, pulmonary angiography, helical computed tomography or autopsy	[17]
Lederle *et al.* (2006)	Enoxaparin	Clinical suspicion confirmed by diagnostic test	High probability ventilation/perfusion scan, diagnostic pulmonary angiogram or autopsy	[20]
LIFENOX (2011)	Enoxaparin	Not specified	Not specified	[21]

DVT: Deep venous thrombosis; LMWH: Low-molecular-weight heparin; PE: Pulmonary embolism.

receiving antithrombotic drugs were compared with all participants not receiving it.

Types of intervention

Trials comparing the beneficial and harmful effects of antithrombotic drugs (LMWH and fondaparinux) versus placebo.

■ Information sources

The studies were identified by searching electronic databases. This search was applied to Medline, ISI Web of Science, SCOPUS and the Cochrane database. The last search was run on 2 February 2013. Reference lists of all studies included in the present systematic review were screened for potential additional eligible studies.

■ Search

We used the following key words to search all trials registers and databases:

("heparin, low-molecular-weight" [MeSH Terms] OR ("heparin" [All Fields] AND "low-molecular-weight" [All Fields]) OR "low-molecular-weight heparin" [All Fields] OR ("low" [All Fields] AND "molecular" [All Fields] AND "weight" [All Fields] AND "heparin" [All Fields]) OR "low molecular weight heparin" [All Fields]) OR ("fondaparinux" [Supplementary Concept] OR "fondaparinux" [All Fields]) AND (medical [All Fields] AND ("patients" [MeSH Terms] OR "patients" [All Fields])) AND ("venous thrombosis" [MeSH Terms] OR ("venous" [All Fields] AND "thrombosis" [All Fields]) OR "venous thrombosis" [All Fields] OR ("deep" [All Fields] AND "vein" [All Fields] AND "thrombosis" [All Fields]) OR "deep vein thrombosis" [All Fields]) AND Randomized Controlled Trial [ptyp] deep vein thrombosis AND low molecular weight heparin AND medical patients.

■ Study selection

Two authors (L Loffredo and L Perri) independently reviewed titles and abstracts generated by the search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis. For potentially eligible studies, or if the relevance of an article could not be excluded with certitude, we procured the full text. Disagreements were resolved by discussion between L Loffredo and L Perri; if no agreement was reached, a third author (F Violi) decided.

Studies were included if they involved: patients sheltered in medical wards for acute disease randomized to LMWH or fondaparinux versus placebo. Reviews, case reports, editorials, commentaries, letters, review articles, guidelines or secondary prevention trials and nonhuman studies were also excluded from the analysis.

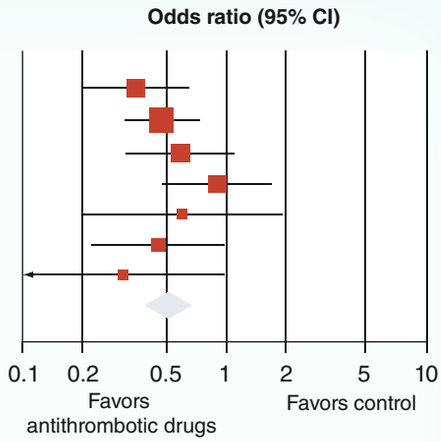
■ Data extraction & quality assessment

Quality assessment was detected by means of the Jadad scale [10]. This scale rates the following characteristics of studies:

- If the study was defined as randomized;
- The method used to generate the sequence of randomization;

Ⓐ

Model	Study name	Odds ratio	Lower limit	Upper limit	p-value	Events/total Treated	Events/total Control
	MEDENOX	0.361	0.197	0.660	0.001	16/291	40/288
	PREVENT	0.485	0.316	0.745	0.001	32/1759	64/1739
	ARTEMIS	0.602	0.327	1.108	0.103	18/321	29/323
	Mahé *et al.*	0.914	0.489	1.708	0.777	19/1230	21/1244
	Lederle *et al.*	0.611	0.195	1.916	0.398	5/140	8/140
	Fraisse *et al.*	0.465	0.218	0.992	0.048	13/84	24/85
	Dahan	0.310	0.097	0.987	0.048	4/132	12/131
Fixed		0.520	0.407	0.664	0.000	107/3957	198/3950



Ⓑ

Model	Study name	Odds ratio	Lower limit	Upper limit	p-value	Events/total Treated	Events/total Control
	MEDENOX	0.342	0.122	0.963	0.042	5/291	14/288
	PREVENT	0.469	0.300	0.734	0.001	29/1759	60/1739
	ARTEMIS	0.714	0.224	2.274	0.569	5/321	7/323
	Fraisse	0.413	0.103	1.653	0.211	3/84	7/85
Fixed		0.466	0.321	0.677	0.000	42/2455	88/2435

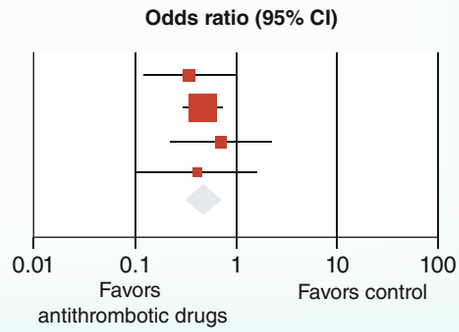


Figure 1. Forest plots for outcomes of (A) deep venous thrombosis and (B) proximal deep venous thrombosis in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

- If the study was defined as 'double-blind';
- If it used an identical placebo;
- If there was a description of withdrawals and drop-outs [10].

A score of 5 points defined high-quality studies; 3–4 points defined medium-quality studies; ≤2 points defined low-quality studies.

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement issued in 2009 [11].

Statistical analysis

To evaluate the effect of antithrombotic drugs in acutely ill medical patients on cardiovascular events, we treated the results of each randomized controlled trial as dichotomous frequency data. We considered a p-value <0.05 to be significant. Odds ratios (ORs) and 95% CIs were calculated. These data were pooled using a fixed-effect model (the Mantel–Haenszel method) [12]. Statistical heterogeneity was calculated by I^2 index [10]. The I^2 value estimates the amount of variance across studies due to heterogeneity rather than chance. We considered the following scores: I^2 <30% for mild heterogeneity; 30–50% for moderate heterogeneity; and >50% for severe heterogeneity.

The software Comprehensive Meta Analysis (version 2.2.064; Biostat Inc., FL, USA) supported the analysis.

The presence of publication bias was evaluated by using the Egger tests (reporting the one-tailed p-value) [13]. If publication bias exists, the Egger test p-value is <0.05.

Results

Study identification & selection

The search of Medline and the Cochrane database provided a total of 818 citations. Of these, 716 studies were discarded after reviewing the

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	0.493	0.044	5.468	0.565	1/291	2/288
	PREVENT	0.448	0.155	1.292	0.137	5/1759	11/1739
	Lederle *et al.*	0.539	0.176	1.651	0.279	5/140	9/140
Fixed		0.489	0.235	1.018	0.056	11/2190	22/2167

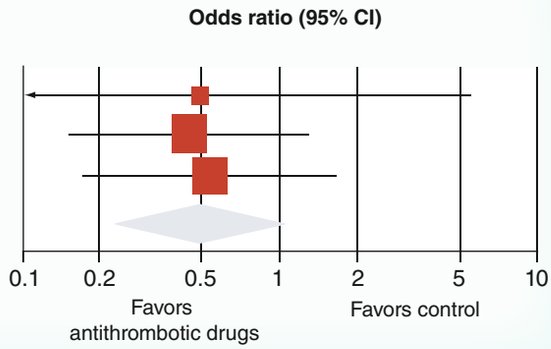


Figure 2. Forest plots for outcomes of symptomatic deep venous thrombosis in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

abstracts, because it appeared that these papers clearly did not meet the selection criteria.

Of 102 remaining citations 94 were excluded for the following reasons:

- The patients in the control group were not treated with placebo (23 studies vs unfractioned heparin, 13 studies vs other treatment [e.g., aspirin or oral anticoagulants]);
- The studies did not enrolled medical patients (n = 31);
- The studies enroll patients with acute DVT (n = 12);
- The studies were substudies of those included in the meta-analysis (n = 7);
- The studies were not prospective randomized clinical trials (n = 6);
- The studies analysed VTE after an initial course of prophylactic treatment with antithrombotic drugs (n = 2).

A total of eight studies met the inclusion criteria and were included in this systematic review [14–21].

Study characteristics

The eight selected studies ranged from 221 to 8307 patients. Baseline and clinical characteristics of the study populations are illustrated in the Table 1. All of the trials included patients with an average age >50 years. Males and females were almost equally distributed in all trials. Even if clinical settings included in the trials were quite heterogeneous, approximately 80% of patients were affected by heart failure or acute respiratory disease or infections.

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	0.361	0.199	0.653	0.001	17/272	41/263
	PREVENT	0.482	0.301	0.770	0.002	27/1507	53/1453
	ARTEMIS	0.602	0.327	1.108	0.103	18/321	29/323
Fixed		0.471	0.344	0.646	0.000	62/2100	123/2039

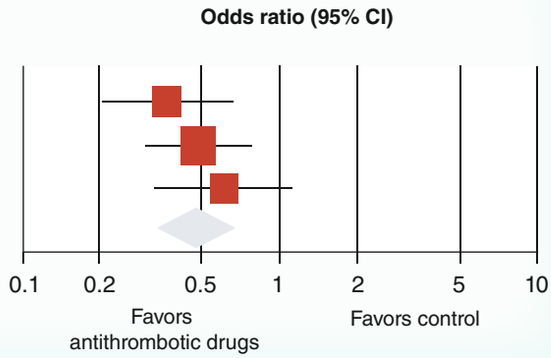


Figure 3. Forest plots for outcomes of asymptomatic deep venous thrombosis in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	1.197	0.009	4.112	0.294	0/291	2/288
	PREVENT	1.237	0.332	4.615	0.751	5/1759	4/1740
	ARTEMIS	0.090	0.005	1.635	0.104	0/321	5/323
	Mahé *et al.*	0.592	0.270	1.297	0.190	10/1230	17/1244
	Lederle *et al.*	0.329	0.034	3.197	0.338	1/140	3/140
	Dahan *et al.*	0.326	0.033	3.172	0.334	1/132	3/131
Fixed		0.562	0.309	1.020	0.058	17/3873	34/3866

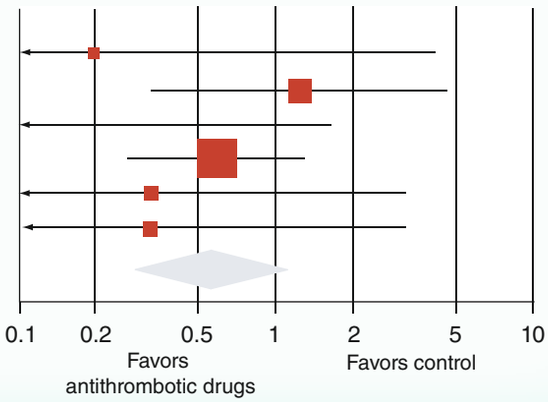


Figure 4. Forest plots for outcomes of pulmonary embolism in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

Clinical primary end points of the interventional trials with antithrombotic drugs included essentially symptomatic and asymptomatic DVT, pulmonary embolism, DVT-related death and death from any cause. The methodological approach for the diagnosis of DVT was based on venography or compression ultrasonography or both, while PE was diagnosed by ventilation/perfusion scanning, pulmonary angiography or computed tomography (Table 2). The rate of DVT was almost different if symptomatic or asymptomatic events were separately considered. Thus, asymptomatic DVT was much more frequent compared with symptomatic ones with a large variation ranging as high as 28% to as low as 3% with an average of 4%.

Meta-analysis of interventional trials

■ DVT

DVT included symptomatic, asymptomatic, distal and proximal vein thrombosis. Seven studies, including 7907 patients, assessed the effect of antithrombotic drugs on the risk of DVT. The incidence rate for DVT was 3.85% (2.70 vs 5.01% in patients treated with antithrombotic drugs and controls, respectively).

Compared with controls, DVT events were significantly reduced with antithrombotic drugs (OR: 0.520; 95% CI: 0.41–0.67; p < 0.001) (Figure 1A) with an absolute risk reduction (ARR) of 2.3%. No heterogeneity (I^2 = 0; p = 0.449) and evidence of publication bias (Egger test; p = 0.433) among trials was observed. Furthermore, antithrombotic drugs were able to reduce DVT when only the proximal tract was considered (Figure 2).

■ Symptomatic DVT

Symptomatic DVT included distal and proximal vein thrombosis. Three studies, including 4357 patients, assessed the effect of antithrombotic drugs on the risk of symptomatic DVT.

The incidence rate for symptomatic DVT was 0.75% (0.5 vs 1.0% in patients treated with antithrombotic drugs and controls, respectively).

No significant reduction for symptomatic DVT was observed comparing patients treated with antithrombotic drugs versus controls (Figure 2). No heterogeneity (I^2 = 0; p = 0.973) and evidence of publication bias (Egger test, p = 0.467) among trials was observed.

■ Asymptomatic DVT

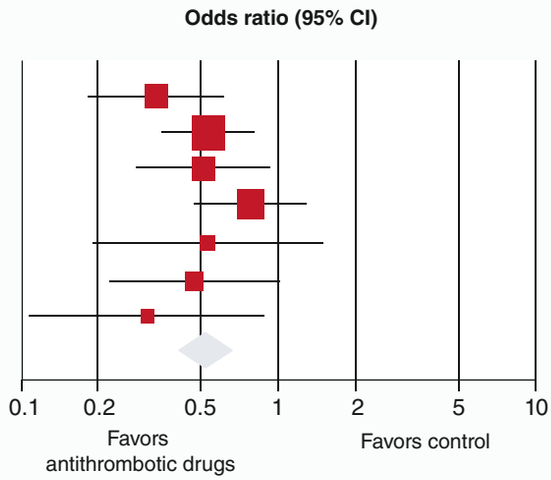
Asymptomatic DVT included distal and proximal vein thrombosis. Three studies, including 4139 patients, assessed the effect of antithrombotic drugs on the risk of asymptomatic DVT.

The incidence rate for asymptomatic DVT was 4.4% (2.95 vs 6.0% in patients treated with antithrombotic drugs and controls, respectively).

Compared with controls, DVT events were significantly reduced with antithrombotic drugs (OR: 0.471; 95% CI: 0.34–0.65; p < 0.001) with ARR of 3.05% (Figure 3). No heterogeneity

Ⓐ

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	0.332	0.182	0.604	0.000	16/291	43/288
	PREVENT	0.528	0.352	0.792	0.002	37/1829	68/1807
	ARTEMIS	0.505	0.279	0.914	0.024	18/321	34/323
	Mahé *et al.*	0.766	0.470	1.251	0.287	29/1230	38/1244
	Lederle *et al.*	0.525	0.189	1.462	0.217	6/140	11/140
	Fraisse *et al.*	0.465	0.218	0.992	0.048	13/84	24/85
	Dahan *et al.*	0.304	0.107	0.864	0.025	5/132	15/131
Fixed		0.512	0.408	0.642	0.000	124/4027	233/4018



Ⓑ

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	0.297	0.107	0.822	0.019	5/291	16/288
	PREVENT	0.500	0.329	0.760	0.001	34/1829	66/1807
	ARTEMIS	0.410	0.143	1.178	0.098	5/321	12/323
	Fraisse *et al.*	0.413	0.103	1.653	0.211	3/84	7/85
Fixed		0.454	0.319	0.645	0.000	47/2525	101/2503

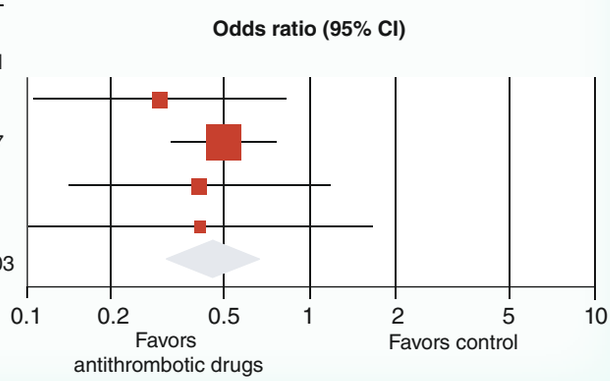


Figure 5. Forest plots for outcomes of (A) venous thromboembolism and (B) major venous thromboembolism in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

(I^2 = 0; p = 0.495) and evidence of publication bias (Egger test, p = 0.496) among trials was observed.

■ Pulmonary embolism

Six studies, including 7739 patients, assessed the effect of antithrombotic drugs on the risk of PE, defined as fatal plus nonfatal PE. The rate of PE in placebo group was 0.6%.

The incidence rate for PE was 0.65% (0.43 vs 0.87% in patients treated with antithrombotic drugs and controls, respectively).

No significant reduction for PE was observed comparing patients treated with antithrombotic drugs versus controls (Figure 4). No heterogeneity (I^2 = 0, p = 0.495) and evidence of publication bias (Egger test, p = 0.077) among trials was observed.

■ VTE

Seven studies, including 8045 patients, assessed the effect of antithrombotic drugs on the risk VTE (defined as DVT and PE).

The incidence rate for VTE was 4.4% (3.1 vs 5.8% in patients treated with antithrombotic drugs and controls, respectively).

VTE events were significantly reduced with the addition of antithrombotic drugs compared with placebo (OR: 0.512; 95% CI: 0.41–0.64; p < 0.001) (Figure 5A) and were associated with an ARR of 2.7%. No heterogeneity (I^2 = 0; p = 0.461) and evidence of publication bias (Egger test, p = 0.152) among trials was observed.

Furthermore, we analyzed the major VTE, defined as proximal DVT (symptomatic or

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	1.941	0.175	21.532	0.589	2/272	1/263
	PREVENT	0.197	0.009	4.114	0.295	0/1829	2/1807
	ARTEMIS	0.090	0.005	1.635	0.104	0/321	5/323
	LIFENOX	0.992	0.062	15.859	0.995	1/4171	1/4136
	Dahan *et al.*	0.139	0.007	2.709	0.193	0/132	3/131
	Mahé *et al.*	0.592	0.270	1.297	0.190	10/1230	17/1244
Fixed		0.533	0.274	1.036	0.064	13/7955	29/7904

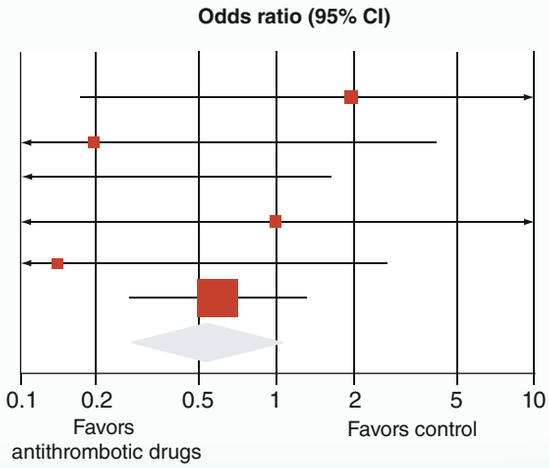


Figure 6. Forest plots for outcomes of venous thromboembolism-related death in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

asymptomatic) and PE, confirming that antithrombotic drugs were able to reduce this outcome (Figure 5B).

VTE-related death

Six studies, including 15,859 patients assessed the effect of antithrombotic drugs on the risk of VTE-related death.

The incidence rate for VTE-related death was 0.26% (0.16 vs 0.36% in patients treated with antithrombotic drugs and controls, respectively).

No significant differences were observed for VTE-related death comparing antithrombotic drugs with placebo (Figure 6). No heterogeneity (I^2 = 0; p = 0.548) and evidence of publication bias (Egger test, p = 0.242) among trials was observed.

Death from any cause

Eight studies, including 16,516 patients assessed the effect of antithrombotic drugs on the risk of death from any cause.

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	0.802	0.516	1.247	0.327	41/360	50/362
	PREVENT	1.021	0.772	1.350	0.883	107/1747	103/1715
	ARTEMIS	0.530	0.272	1.035	0.063	14/425	25/414
	LIFENOX	0.961	0.787	1.173	0.694	199/4171	205/4136
	Fraisse *et al.*	1.013	0.362	2.838	0.980	8/84	8/85
	Lederle *et al.*	0.921	0.416	2.038	0.840	13/140	14/140
	Dahan *et al.*	0.992	0.312	3.159	0.989	6/132	6/131
	Mahé *et al.*	0.978	0.753	1.259	0.864	124/1230	128/1244
Fixed		0.942	0.831	1.069	0.356	512/8289	539/8227

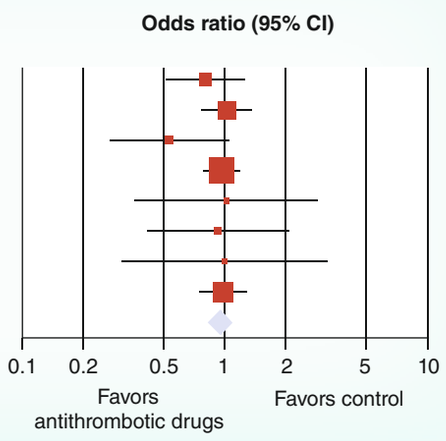


Figure 7. Forest plots for outcomes of death from any cause in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

Table 3. Definition of bleeding in the trials included in the meta-analysis.

Study (year)	Objective diagnosis of major bleeding	Objective diagnosis of minor bleeding	Ref.
Dahan *et al.* (1986)	–	–	[14]
MEDENOX (1999)	Bleeding overt and associated with the need for transfusion of two or more units of packed red cells or whole blood, or with a decrease in the hemoglobin concentration of 2 g/dl or more from baseline, or if bleeding was retroperitoneal, intracranial or fatal	Hemorrhage overt but did not meet the other criteria for major hemorrhage	[15]
Fraisse *et al.* (2000)	Hemorrhages overt and associated with a decrease in hemoglobin concentration of 2 g/dl or more compared with the baseline value, when it necessitates a transfusion of two or more units of packed red cells, when it was retroperitoneal or intracranial, or when the investigator decided to end the treatment with heparin because of his judgement on the benefit/risk ratio	Those not considered major	[19]
PREVENT (2004)	Any bleeding episode that led to hospitalization or transfusion	–	[16]
Mahé *et al.* (2005)	–	–	[18]
ARTEMIS (2006)	Fatal bleeding, bleeding in a critical location, bleeding leading to surgical intervention, or overt bleeding associated with a drop in hemoglobin concentration of ≥20 g/l or leading to transfusion of two or more units of red blood cells	Clinically relevant overt bleeding not meeting the criteria for major bleeding	[17]
Lederle *et al.* (2006)	As defined by the bleeding severity index	–	[20]
LIFENOX (2011)	Overt bleeding associated with one of the following: death; the need for transfusion of at least two units of packed red cells or whole blood; a fall in the hemoglobin level of ≥20 g/l; the requirement for a major therapeutic intervention to stop or control bleeding; or a bleeding site that was retroperitoneal, intracranial or intraocular	Overt bleeding that did not meet the criteria for major hemorrhage but was associated with clinical features defined in the protocol	[21]

The incidence rate for major VTE was 6.4% (6.2 vs 6.5% in patients treated with antithrombotic drugs and controls, respectively).

Compared with placebo, prophylaxis with antithrombotic drugs did not reduce the events for death from any cause (Figure 7). No heterogeneity (I^2 = 0; p = 0.801) and evidence of publication bias (Egger test, p = 0.146) among trials was observed.

Hemorrhages

Total hemorrhages included fatal, major and minor bleedings. Eight studies, including 16,787 patients, assessed the effect of antithrombotic drugs on the risk of total hemorrhages. Major and minor bleeding were heterogeneously defined as reported in Table 3.

The rate of total bleeding was higher in patients treated with anticoagulants compared with those treated with placebo (3.1 vs 2.2% in patients treated with antithrombotic drugs and controls, respectively). However, there were huge differences in bleeding rate which ranged from as high as 23% to as low as 1% in the anticoagulant-treated arm. Compared with placebo, total hemorrhage events were significantly enhanced with antithrombotic drugs (OR: 1.465; 95% CI: 1.2–1.79; p < 0.001) (Figure 8) and were associated with an absolute risk increase of 1.1%. No heterogeneity (I^2 = 0; p = 0.801) and evidence of publication bias (Egger test, p = 0.146) among trials was observed.

Major hemorrhages

Seven studies, including 16,524 patients, assessed the effect of antithrombotic drugs on the risk of major hemorrhages.

The incidence rate for major hemorrhages was 0.5% (0.6 vs 0.4% in patients treated with antithrombotic drugs and controls, respectively).

Compared with placebo, prophylaxis with antithrombotic drugs did not reduce the events for major hemorrhages (Figure 9).

No heterogeneity (I^2 = 0; p = 0.457) and evidence of publication bias (Egger test, p = 0.150) among trials was observed.

Minor hemorrhages

Six studies, including 16,244 patients assessed the effect of antithrombotic drugs on the risk of minor hemorrhages.

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	1.269	0.848	1.899	0.247	62/360	51/362
	PREVENT	2.144	1.133	4.057	0.019	30/1848	14/1833
	ARTEMIS	2.377	0.830	6.807	0.107	12/425	5/414
	LIFENOX	1.515	1.091	2.105	0.013	91/4171	60/4136
	Mahé *et al.*	1.386	0.822	2.337	0.221	34/1230	25/1244
	Lederle *et al.*	0.391	0.075	2.052	0.267	2/140	5/140
	Fraisse *et al.*	1.590	0.811	3.118	0.177	25/108	18/113
	Dahan	0.326	0.033	3.172	0.334	1/132	3/131
Fixed		1.465	1.201	1.788	0.000	257/8414	181/8373

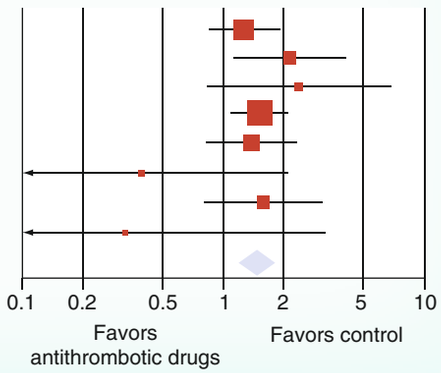


Figure 8. Forest plots for outcomes of total hemorrhages in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

The incidence rate for minor hemorrhages was 0.8% (2.5 vs 1.7%) in patients treated with antithrombotic drugs and controls, respectively).

Compared with placebo, minor hemorrhage events were significantly enhanced with antithrombotic drugs (OR: 1.474; 95% CI: 1.2–1.84; p < 0.001) (Figure 10) and were associated with an absolute risk increase of 0.8%.

No heterogeneity (I^2 = 0; p = 0.734) and evidence of publication bias (Egger test, p = 0.098) among trials was observed.

This systematic review of interventional trials with antithrombotic drugs confirms the existence of a high rate of VTE, defined as DVT and PE, in patients hospitalized for acute medical illness. VTE includes both DVT and PE. However, stratifying DVT as symptomatic and asymptomatic (including distal and proximal vein thrombosis), the first is less frequent (with an average rate of 1% in controls) than the latter (with an average rate of 6%). Recently, the REPOSI study [22], which included patients much older than those enrolled in the interventional

Model	Study name	Statistics for each study				Events/total	
		Odds ratio	Lower limit	Upper limit	p-value	Treated	Control
	MEDENOX	1.749	0.681	4.494	0.246	12/360	7/362
	PREVENT	2.985	0.807	11.045	0.101	9/1848	3/1833
	ARTEMIS	0.974	0.061	15.624	0.985	1/425	1/414
	LIFENOX	1.444	0.669	3.115	0.349	16/4171	11/4136
	Mahé *et al.*	0.337	0.035	3.240	0.346	1/1230	3/1244
	Lederle *et al.*	0.391	0.075	2.052	0.267	2/140	5/140
	Fraisse *et al.*	2.157	0.526	8.851	0.286	6/108	3/113
Fixed		1.453	0.911	2.318	0.116	47/8282	33/8242

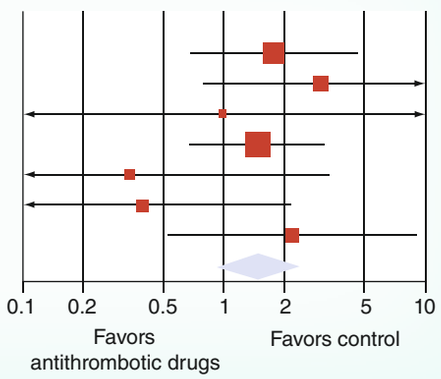


Figure 9. Forest plots for outcomes of major hemorrhages in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

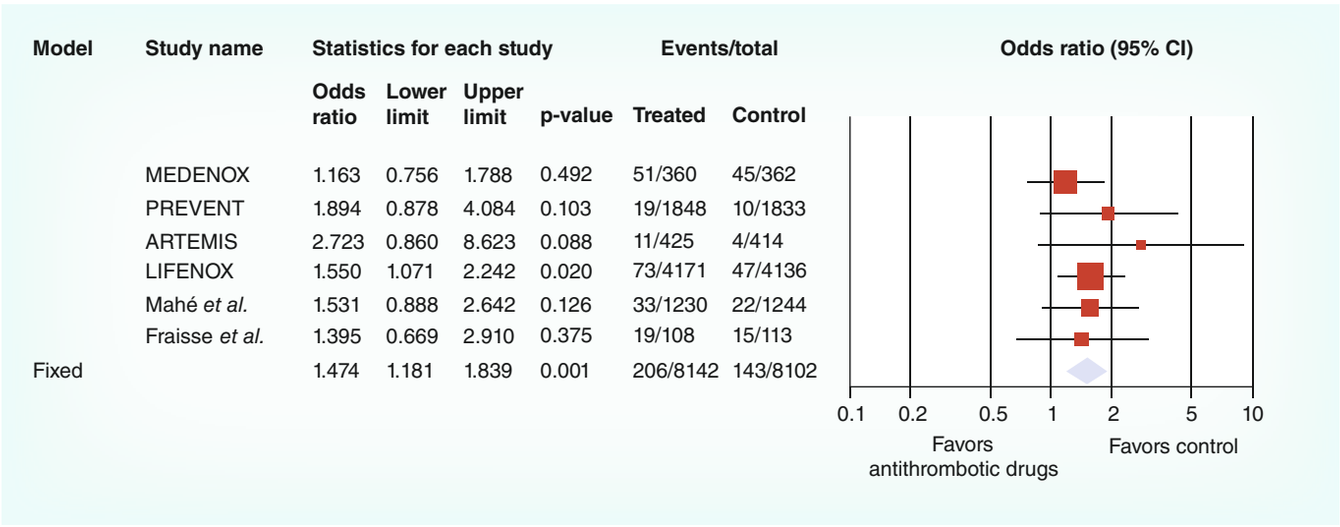


Figure 10. Forest plots for outcomes of minor hemorrhages in studies of antithrombotic drugs (low-molecular-weight heparin and fondaparinux) versus placebo.

trials with anticoagulants, found that during the hospital stay the rate of symptomatic DVT was a little bit lower (0.5%) compared with the rate observed in the interventional trials [23]. This would suggest that in the real world of acutely ill medical patients the rate of symptomatic DVT is relatively low even in case of very old people [23].

Even if this analysis of interventional trials with antithrombotic drugs in patients hospitalized for acute medical illness is consistent with a significant reduction of thrombotic events, its impact on clinical outcomes seems almost variable with a scarce effect on hard end points such as PE, VTE-related death and death from any other cause. This result was also confirmed by Lederle *et al.* in a previous meta-analysis conducted in hospitalized medical patients and those with stroke [24].

An interesting finding in our meta-analysis is that among the interventional trials the rate of thrombotic events in controls is greatly variable with values which vary from as low as 3.0% to as high as 28% in VTE cases. It remains to be established, however, The reason for such a great variability of VTE rates among the trials could derive from different methodologies used to diagnose DVT and/or PE. Recently, we analysed this issue for the interventional studies of this meta-analysis [25], showing that these trials included prevalently medical patients with heart failure, acute respiratory disease or infections; these clinical settings represented >80% of patients included in these trials [25]. An important issue is whether each of these clinical settings is associated with venous thrombosis and whether the severity of clinical illness carries a higher VTE risk [25]. Future trials should further explore this issue.

Another possible explanation for the great variability of VTE could derive from the different methodological issues used to diagnose DVT and/or PE; different methodologies could under- or over-estimate clinical end points. Furthermore, the different patient ages should be considered as a cause of great variability of VTE incidence among the trials. The rate of VTE increases by advancing age [26,27]; furthermore, several trials suggested that heparin is less beneficial in patients younger than 75 years old [28–30].

We also analyzed the impact of anticoagulants on minor and major bleedings that could be observed during the follow-up. Thus, our meta-analysis showed a significant increase of minor bleeding in patients given anticoagulants. Major bleeding, however, occurred in approximately 0.6% of patients but it should be taken into account that the average age of patients was often <70 years. Therefore it cannot be excluded that the rate of major bleeding could be even higher in general population.

Even if differences in clinical characteristics could account for the large variation in the thrombotic rate observed in the interventional trials, our meta-analysis demonstrates a clinical benefit of anticoagulants in acutely ill

medical patients. However, the clinical impact of such treatment is inhomogeneous among the thrombosis-related end points. We observed, in fact, that while DVT is consistently reduced and clinically relevant, the effect on hard end points, such as VTE-related death, death from any cause and PE, seems to be scarce or modest.

Better definition of acute medical illness at high risk of venous thrombosis is mandatory before performing future trials with anticoagulants.

Conclusion & future perspective

Nowadays we cannot definitively answer whether to treat acutely ill medical patients or not. At the moment, there are no data that lead us to recommend a widespread use of antithrombotic drugs in acutely ill medical patients. Future prospective studies are needed to evaluate the risk/benefits of antithrombotic drugs and to clarify if the severity of clinical settings is a prerequisite to distinguish patients at higher risk of DVT in order to provide the optimal care for these patients.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- of interest

1 Kahn SR, Lim W, Dunn AS *et al.* Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, (9th ed): American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141(Suppl. 2), e195S–e226S (2012).

- **Recent guidelines for antithrombotic therapy and prevention of thrombosis in medical patients.**

2 Guyatt GH, Eikelboom JW, Gould MK *et al.* Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141(Suppl. 2), e185S–e194S (2012).

- **Recent guidelines for antithrombotic therapy and prevention of thrombosis in medical patients.**

3 Barbar S, Noventa F, Rossetto V *et al.* A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J. Thromb. Haemost.* 8(11), 2450–2457 (2010).

- **Scale to identify medical patients at risk of thrombosis.**

4 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.* 151(5), 933–938 (1991).

5 Heit JA, O'Fallon WM, Petterson TM *et al.* Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch. Intern Med.* 162(11), 1245–1248 (2002).

6 Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. *Arch. Intern. Med.* 160(22), 3415–3420 (2000).

7 Wittkowsky AK. Effective anticoagulation therapy: defining the gap between clinical studies and clinical practice. *Am. J. Manag. Care* 10(Suppl. 10), S297–S306; discussion S312–397 (2004).

8 Cohen AT, Tapson VF, Bergmann JF *et al.* Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 371(9610), 387–394 (2008).

9 Tapson VF, Decousus H, Pini M *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 132(3), 936–945 (2007).

10 Jadad AR, Moore RA, Carroll D *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control. Clin. Trials* 17(1), 1–12 (1996).

11 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 6(7), e1000097 (2009).

12 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl Cancer Inst.* 22(4), 719–748 (1959).

13 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315(7109), 629–634 (1997).

14 Dahan R, Houlbert D, Caulin C *et al.* Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. *Haemostasis* 16(2), 159–164 (1986).

15 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. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N. Engl. J. Med.* 341(11), 793–800 (1999).

16 Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 110(7), 874–879 (2004).

17 Cohen AT, Davidson BL, Gallus AS *et al.* Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* 332(7537), 325–329 (2006).

18 Mahé I, Bergmann JF, D'azemar P, Vaissie JJ, Caulin C. Lack of effect of a low-molecular-weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double-blind study. *Eur. J. Clin. Pharmacol.* 61(5–6), 347–351 (2005).

19 Fraisse F, Holzapfel L, Couland JM *et al.* Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD.

The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am. J. Respir. Crit. Care Med.* 161(4 Pt 1), 1109–1114 (2000).

20 Lederle FA, Sacks JM, Fiore L *et al.* The prophylaxis of medical patients for thromboembolism pilot study. *Am. J. Med.* 119(1), 54–59 (2006).

21 Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann JF. Low-molecular-weight heparin and mortality in acutely ill medical patients. *N. Engl. J. Med.* 365(26), 2463–2472 (2011).

22 Marcucci M, Iorio A, Nobili A *et al.* Prophylaxis of venous thromboembolism in elderly patients with multimorbidity. *Intern. Emerg. Med.* (2013) (Epub ahead of print).

23 Violi F, Perri L, Loffredo L. Interventional trials with anticoagulants in acutely ill medical patients: a methodological pitfall? *Intern. Emerg. Med.* (2013) (Epub ahead of print).

24 Lederle FA, Zylla D, Macdonald R, Wilt TJ. Venous thromboembolism prophylaxis in hospitalized medical patients and those with stroke: a background review for an American College of Physicians Clinical Practice Guideline. *Ann. Intern. Med.* 155(9), 602–615 (2011).

■ **Meta-analysis conducted in hospitalized medical patients and those with stroke showed no benefit for venous thromboembolism-related death and death from any cause in patients treated with antithrombotic drugs.**

25 Violi F, Perri L, Loffredo L. Should all acutely ill medical patients be treated with antithrombotic drugs? A review of the interventional trials. *Thromb. Haemost.* 109(4), 589–595 (2013).

■ **Underscores the need of better defining the thrombotic risk profile of acutely ill medical patients included in interventional trials with anticoagulants.**

26 Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. *Thromb. Haemost.* 83(5), 657–660 (2000).

27 Oger E, Bressollette L, Nonent M *et al.* High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. *Thromb. Haemost.* 88(4), 592–597 (2002).

28 Hull RD, Schellong SM, Tapson VF *et al.* Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann. Intern. Med.* 153(1), 8–18 (2010).

29 Kucher N, Leizorovicz A, Vaitkus PT *et al.* Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. *Arch. Intern. Med.* 165(3), 341–345 (2005).

30 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 randomised clinical trials. *Thromb. Haemost.* 83(1), 14–19 (2000).