

# Should all acutely ill medical patients be treated with antithrombotic drugs?

## A review of the interventional trials

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### Summary

After reports from observational studies suggesting an association between acutely ill medical patients and venous thromboembolism (VTE), interventional trials with anticoagulants drugs have demonstrated a significant reduction of VTE during and immediately after hospitalisation. Although several guidelines suggest the clinical relevance of reducing this outcome, there is a low tendency to use anticoagulants in patients hospitalised for acute medical illness. We speculated that such underuse may be dependent on a low perception that patients included in the trials are actually at risk of thromboembolism. Therefore, the aim of this study was to analyse the clinical settings included in the interventional trials and their relationship with thrombotic risk. Analysis of interventional trials revealed that the ma-

jority of patients included in the trials (about 80%) were affected by heart failure, acute respiratory syndrome or infections. Among these three illnesses, literature data shows an association with venous thrombosis only in patients with acute infections; this finding was, however, supported only by retrospective study. On the contrary, there is scarce or no evidence that heart failure and acute respiratory syndrome are associated with venous thrombosis. These data underscore the need of better defining the thrombotic risk profile of acutely ill medical patients included in interventional trials with anticoagulants.

### Keywords

Venous thrombosis, anticoagulants, medical patients

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## Introduction

Epidemiological studies have provided evidence of a high rate of thromboembolism in patients hospitalised in medical wards (1-3). Based on this, several clinical trials with anticoagulants including low-molecular-weight heparin (LMWH) and fondaparinux have been performed in patients hospitalised for acute medical illness to prevent thromboembolism (4-12). Interventional trials consistently showed that prophylaxis with anticoagulants reduces the risk of composite endpoints of deep venous thrombosis (DVT), pulmonary embolism (PE) and DVT-related death. These results prompted recommendation to the use anticoagulant prophylaxis in patients hospitalised for acute medical illness (13), but, despite this, there is a widespread underuse of anticoagulant prophylaxis in the medical wards of hospitals (14). This issue has been underscored by recent reviews, which, however, did not take into account the relationship between each clinical setting included in the interventional trials and the relative thrombotic risk in this setting (15-17).

Thus, compared to other clinical models in interventional trials with anticoagulants, acute medical illness represents an extremely heterogeneous setting with potentially wide range of thrombotic

risk. Hence, it is possible that the perception of thromboembolism risk varies according to the clinical presentation and that the prophylactic approach is influenced by the severity of disease. This argument could imply that clinical settings included in the interventional trials may carry a different thrombotic risk, but so far this issue has been only explored in part. Therefore, the aim of this study was to analyse the population included in the interventional trials and to discuss whether a different thrombotic risk may be result from the typology of acute medical illness.

## Methods

### Eligibility criteria

- Types of studies: Randomised clinical trials (RCTs) studying the effect of thromboembolism prophylaxis in medical patients. No language, publication date, or publication status restrictions were imposed.
- Types of intervention: Trials comparing the beneficial and harmful effects of antithrombotic drugs (LMWH and fondaparinux) vs. placebo.

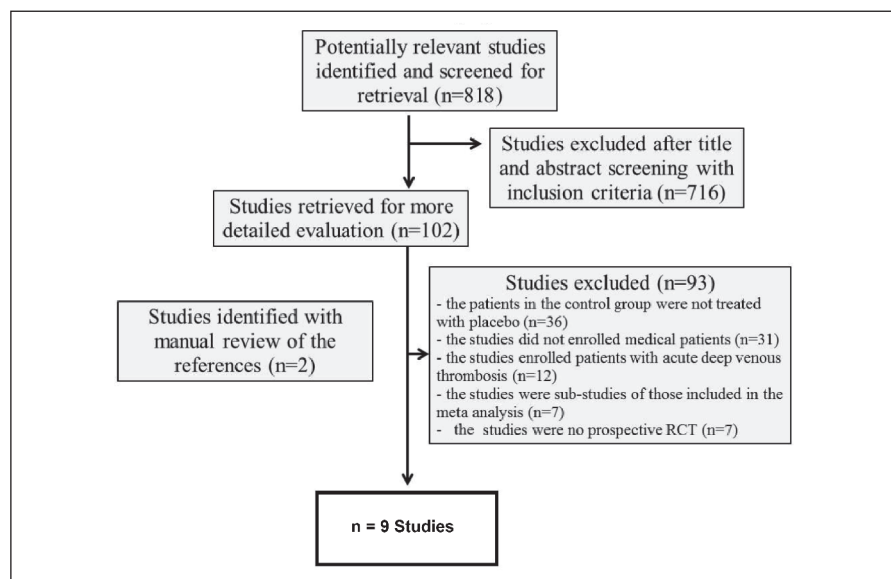


Figure 1: Study identification and selection progression.

Table 1: Characteristics of the patients included in the studies.

Study (Ref.)	N	Age	Males/ Females	HF NYHA n (%)	ARD	Infections	Cancer	Others	Primary endpoint
Dahan et al. Haemostasis 1986 (4)	270	80 ± 6.8	167/103	49 (18)	57 (21.1)	11 (4)	35 (12.9)	8 (2.9)	Frequency of lower limb DVT
MEDENOX N Engl J Med 1999 (5)	1102	73 ± 10.5	550/552	III: 274 (24.8) IV: 102 (9.6)	589 (53.4)	584 (52.9)	157 (14.2)	100 (9) RA 5 (0.5) IBD	VTE (DVT, PE or both)
Fraisse F et al. Am J Respir Crit Care Med 2000 (6)	223	68.1 ± 7.9	174/49	64 (28.7)	111 (49.7)	-	11 (4.9)	9 (4) previous DVT 52 (23.3)	Incidence of DVT diagnosed by venography
PREVENT Circulation 2004 (7)	3706	68.6 ± 11.4	1772/1909	III or IV: 1905 (51.4)	1121 (30.2)	1360 (36.7)	190 (5.1)	398 (10.7) RA 18 (0.5) IBD	Composite of symptomatic DVT, fatal or symptomatic nonfatal PE, sudden death, and asymptomatic DVT
Mahè I et al. Eur J Clin Pharmacol 2005 (12)	2474	76.3	1001/1473	637 (25.7)	545 (22)	532 (21.5)	343 (13.8)	47 (1.9) previous VTE	Overall mortality
ARTEMIS Br Med J 2006 (11)	849	74.7 ± 8.3	360/489	III or IV: 212 (24.9)	167 (19.6)	214 (25.2)	131 (15.4)	256 (30.1)	Composite of DVT and symptomatic VTE
Lederle FA et al. Am J Med 2006 (8)	280	71.7	276/4	69 (24.6)	-	96 (34.2) current pneumonia	26 (9.2)	13 (4.6) history of thromboembolism	All cause mortality
EXCLAIM Ann Intern Med 2010 (10)	5963	67.7 ± 12.3	2944/3019	III or IV: 1110 (18.6)	1805 (30)	1982 (33.2)	96 (1.6)	158 (2.6) RA 15 (0.2) IBD 338 (5.6) others	Composite of symptomatic or asymptomatic proximal DVT, symptomatic or fatal PE
LIFENOX N Engl J Med 2011 (9)	8307	65 ± 12	5211/3096	I or II: 416 (5) III or IV: 2124 (25.5)	-	4179 (56.8)	365 (4.4)	49 (0.5)	Rate of death from any cause

## Information sources

The studies were identified by searching electronic databases. This search was applied to Medline and Cochrane databases. The last search was run on December 2, 2012. Reference lists of all studies included in the present systematic review were screened for potential additional eligible studies.

## Search

We used the following search terms to search all trials registers and databases: deep venous thrombosis AND antithrombotic drugs AND medical patients.

## Study selection

Two authors (L.L., L.P.) independently reviewed all selected titles and abstracts. Studies were excluded if the title and/or abstract was not

appropriate for the aim of our review. Full texts were subsequently obtained for eligible studies or when the relevance of an article could not be excluded with certainty. Disagreement was resolved by consensus and by opinion of a third reviewer (F.V.), if necessary.

Selected studies were eligible if they met the following criteria: patients treated in Medicine wards for acute disease randomised to LMWH or fondaparinux vs. placebo. Only Prospective Randomised Controlled Trials were included in this analysis. Reviews, letters, case reports and non-human studies were excluded.

## Results

### Study identification and selection

The search of Medline, ISI Web of Science, SCOPUS and Cochrane database provided a total of 818 citations. Of these, 716 studies were discarded because after reviewing the abstracts it appeared that these papers clearly did not meet the selection criteria.

**Table 2: Intervention and method of diagnosis for DVT and PE in the analysed studies.**

Study (Ref.)	Study drug	Objective diagnosis of DVT (diagnostic tool if specified)	Objective diagnosis of PE (diagnostic tool if specified)	Primary endpoint
Dahan et al. Haemostasis 1986 (4)	LMWH	125 <sup>l</sup> fibrinogen scanning	Autopsy	Frequency of lower limb DVT
MEDENOX N Engl J Med 1999 (5)	Enoxaparin	Systematic ascending contrast venography of the legs. If venography was infeasible, venous ultrasonography	High-probability lung scanning, pulmonary angiography, or helical computed tomography or autopsy	VTE (DVT, PE or both)
Fraisse F et al. Am J Respir Crit Care Med 2000 (6)	Nadroparin	Venography performed at normal planned completion, in cases of early permanent discontinuation or during the study for positive, doubtful or uninterpretable Doppler ultrasonography	Venography and pulmonary angiography	Incidence of DVT diagnosed by venography
PREVENT Circulation 2004 (7)	Dalteparin	Venography or reports from compression ultrasonography or magnetic resonance imaging (MRI)	Ventilation-perfusion scanning, angiography, or computed tomography (CT) of the chest	Composite of symptomatic DVT, fatal or symptomatic non-fatal PE, sudden death, and asymptomatic DVT
Mahè I et al. Eur J Clin Pharmacol 2005 (12)	Nadroparin	Necropsy or suspected from daily clinical examination and confirmed by venography	Necropsy of deceased patients or suspected from daily clinical examination and confirmed by venography or pulmonary angiography	Overall mortality
ARTEMIS Br Med J 2006 (11)	Fondaparinux	Bilateral ascending venography of the legs	High probability lung scan, pulmonary angiography, or helical computed tomography, or autopsy	Composite of DVT and symptomatic VTE
Lederle FA et al. Am J Med 2006 (8)	Enoxaparin	Clinical suspicion plus a positive diagnostic test result	High probability ventilation/perfusion scan or diagnostic pulmonary angiogram or autopsy	All cause mortality
EXCLAIM Ann Intern Med 2010 (10)	Enoxaparin	Bilateral compression ultrasonography or venography	Computed tomography or ventilation-perfusion lung scanning. When available, autopsy	Composite of symptomatic or asymptomatic proximal DVT, symptomatic or fatal PE
LIFENOX N Engl J Med 2011 (9)	Enoxaparin	-	-	Rate of death from any cause

Study (Ref.)	N	Total patients evaluated	Total DVT		Asymptomatic DVT		Symptomatic DVT	
			A	P	A	P	A	P
Dahan et al. Haemostasis 1986 (4)	270	263	4/132 (3)	12/131 (9.1)	-	-	-	-
MEDENOX N Engl J Med 1999 (5)	1102	798	*17/272 (6.2) **44/263 (16.7)	41/263 (15.6)	-	-	3/272 (1.1) 6/263 (2.3)	4/263 (1.5)
Fraisse F et al. Am J Respir Crit Care Med 2000 (6)	223	169	13/84 (15.5)	24/85 (28.2)	-	-	-	-
PREVENT Circulation 2004 (7)	3706	2991	32/1508 (2.12)	64/1464 (4.3)	27/1507 (1.8)	53/1453 (3.6)	5/1759 (0.3)	11/1739 (0.6)
Mahè I et al. Eur J Clin Pharmacol 2005 (12)	2474	2474	9/1230 (0.73)	11/1244 (0.88)	-	-	0	0
ARTEMIS Br Med J 2006 (11)	849	644	18/321 (5.6)	29/323 (8.9)	18/321 (5.6)	29/323 (8.9)	0	0
Lederle FA et al. Am J Med 2006 (8)	280	280	-	-	-	-	5/140 (3.57)	8/140 (5.7)
EXCLAIM Ann Intern Med 2010 (10)	5963	4995	65/2485 (2.6)	105/2510 (4.2)	55/2485 (2.2)	75/2510 (3.0)	5/2485 (0.2)	20/2510 (0.8)
LIFENOX N Engl J Med 2011 (9)	8307	8307	-	-	-	-	-	-
Mean %	2574		6.6	10.2	3.2	5.2	1.06	1.43

Of the 102 remaining citations, 93 were excluded for the following reasons:

- the patients in the control group were not treated with placebo (23 studies vs. unfractionated heparin, 13 studies vs. other treatment [e.g. aspirin, oral anticoagulants])
- the studies did not enroll medical patients (n=31)
- the studies enrolled patients with acute DVT (n=12)
- the studies were sub-studies of those included in the analysis (n=7)
- the studies were no prospective RCT (n=7)

A total of nine studies met the inclusion criteria and were included in this systematic review.

The study identification and selection progression is summarised in ► Figure 1.

### Study characteristics

Baseline characteristics of patients included in the studies were summarised in ► Table 1.

All studies were written in English. The nine studies included ranged in size from 221 to 8,307 patients.

### Study end-points in placebo-treated patients

Clinical primary endpoints of the interventional trials with anti-thrombotic drugs included essentially symptomatic and asymptomatic DVT, PE, 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 considered separately (► Table 3). Thus, asymptomatic DVT was much more frequent than symptomatic DVT with a large variation ranging from as high as 28% to as low as 3% with an average of 4.7%. The rate of symptomatic DVT was much less with values from as high as 1.5% to as low as 0.8% and an average of 0.99%.

Compared to DVT, PE and DVT-related death were much lower with an event rate of 0.6% and 1.9%, respectively.

### Study population

Clinical characteristics of the study populations are illustrated in ► Table 1. Among the nine trials 50% included patients with an average age >70 years. Only five (5, 7, 10-12) of the selected studies included also patients with an age >75 years (mean 30%). Males and females were almost equally distributed in all trials. Even if clinical settings included in the trials were quite heterogeneous, about 80% of patients were affected by heart failure (HF), acute respiratory disease (ARD) and infections. HF was adequately defined inasmuch as patients were classified according to NYHA classes I-IV. However there was difference in the severity of HF as some trials included also patients with class NYHA I and II, who are unlikely to rest in the bed for a long time.

PE		VTE		DVT-related death		Death from any cause	
A	P	A	P	A	P	A	P
1/132 (0.75)	3/131 (2.29)	5/132 (3.78)	15/131 (11.4)	0	3/131 (2.29)	6/132 (4.54)	6/131 (4.5)
0	2/263 (0.8)	16/291 (5.5)	42/288 (14.5)	2/272 (0.7)	1/263 (0.4)	41/360 (11.4)	50/362 (13.9)
0	0	13/84 (15.4)	24/85 (28.2)	0	0	8/84 (9.5)	8/85 (9.4)
5/1759 (0.3)	4/1740 (0.2)	37/1759 (2.1)	68/1739 (3.9)	0/1829 (0)	2/1807 (0.11)	107/1747 (6.12)	103/1715 (6.0)
10/1230 (0.81)	17/1244 (1.36)	29/1230 (2.3)	38/1244 (3.0)	10/1230 (0.81)	17/1244 (1.36)	124/1230 (10.0)	128/1244 (10.2)
0	0	18/321 (5.6)	34/323 (10.5)	0 (0)	5/323 (1.5)	14/425 (3.3)	25/414 (5.88)
1/140 (0.71)	3/140 (2.1)	6/140 (4.2)	11/140 (7.8)	0	0	13/140 (9.2)	14/140 (10)
4/2485 (0.16)	7/2510 (0.27)	46/2485 (1.8)	81/2510 (3.22)	1/2485 (0.0)	2/2510 (0.1)	60/2975 (2.1)	65/2988 (2.2)
-	-	-	-	1/4171 (0.02)	1/4136 (0.02)	205/4171 (4.9)	199/4136 (4.8)
0.34	0.87	5.08	10.3	0.13	0.64	7.15	7.43

**Table 3: Rate of DVT, PE, VTE, DVT-related death and death from any cause in the selected studies.** A: active treatment, P: placebo. \* Enoxaparin 40 mg, \*\* Enoxaparin 70 mg.

ARD was another clinical setting which was mostly represented in the trials. Percentage of patients with ARD was > 50% of the entire cohort only in the Medenox, while it ranged between 20-40% in the other trials. None of the studies reported the association between ARD and venous thrombosis.

Infections were another important reason for hospitalisation and inclusion in the clinical trials. Unfortunately, the site, duration and severity of infections were not reported by any trial, therefore it is impossible to appreciate the different impact of infections on thrombosis. Furthermore, the percentage of included patients with infections differed greatly with values from as high as 52% to as low as 4%.

Other clinical settings which could predispose to venous thrombosis were less represented. Cancer was detected in 6% and a clinical history of DVT in 3.6% of the total population analysed. Other less represented clinical settings included rheumatoid arthritis and inflammatory bowel disease.

## Discussion

This review of interventional trials with anticoagulants confirms the existence of a venous thrombosis risk in acutely ill medical patients. DVT, particularly asymptomatic DVT, is the most important endpoint with an average rate of 5.2%, while PE and VTE-related death are less frequent with an average rate <1%.

An interesting finding of our review is that among the interventional trials the rate of thrombotic events in controls is greatly vari-

able with values which, in case of VTE, varied from as low as 3% to as high as 28%. There are some methodological issues which might account for such large variability. First, diagnosis of DVT and/or PE was performed with different methodologies with possible under- or over-estimation of clinical endpoints. Second, sample size of the trials was greatly variable with possible implication on the different DVT rate. Among the clinical variables patients' age should be considered an influencing factor as average age was greatly different among the trials; this may have influenced the rate of DVT, as thrombosis increases by advancing age (18, 19). Also relevant was the great variation in disease severity among the trials. This can be deduced by the rate of "death from any cause" which ranged from 2.2% to 13.9%.

We sought to address this specific issue by analysing the clinical settings included in the trials. The interventional trials with anti-thrombotic drugs included prevalently medical patients with HF, ARD or infections; these clinical settings represented >80% of patients included in the trials (► Figure 2). An important issue to be considered is whether each of these clinical settings is associated with venous thrombosis and whether the severity of clinical illness carries a higher risk.

HF is known to be associated with thrombosis, but the rate may be different according to the severity of the disease. Patients of class NYHA III and IV, who have serious HF, are recognised to be at higher risk of stroke while those of class I and II, who have mild HF, are at lower risk (11). Thus, the SAVE trial showed an inverse relationship between ejection fraction and risk of stroke with every 5% decrease in ejection fraction resulting in an 18% increase of

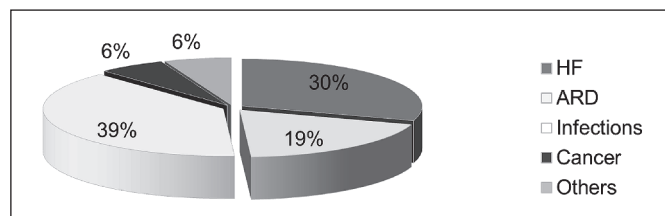


Figure 2: Clinical settings analysed in the trials.

stroke risk (20). HF may be also associated with venous thrombosis, but in this case there is also a relationship with the severity of the disease; in fact, one retrospective study showed that HF patients with an ejection fraction <20% were at high risk of developing DVT (21). Accordingly, the ARTEMIS trial (11) demonstrated a high rate of venous thromboembolism (VTE) (12.2%) in HF patients of class III and IV. This implies that the risk of venous thrombosis could be dishomogeneously distributed with a potentially lower risk of thrombosis for trials which included patients of classes NYHA I-II (4, 6, 8, 9, 12).

ARD is another setting frequently included in interventional trials. In the ARTEMIS trial the association between ARD and venous thrombosis was much lower compared with other settings, as only 5.5 % patients with ARD experienced venous thrombosis (11). However, analysis of another study which explored the association between ARD and venous thrombosis provided different results (6). During a follow-up of 11 days patients assigned to placebo experienced 28.3% DVT, which was diagnosed prevalently by venography. Clinical characteristics of patients included in this last study were well defined: in fact, patients suffered from severe ARD as indicated by the need of using mechanical ventilation. This difference in venous thrombotic rate suggests that the severity of ARD may be a strong predictor of venous thrombosis. ARD is characterised by inflammation and increased permeability of the lung that is associated with a constellation of clinical, radiologic and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension (22). Unfortunately, none of the interventional trials defined the entry criteria for patients with ARD, therefore it is not possible to appreciate the clinical characteristics of a large population included in such trials. As ARD severity was not specified in the inclusion criteria of the trials examined, we cannot exclude that this may have influenced the different rate of DVT.

Acute infection is another setting associated with venous thrombosis. Using a large database of medical records from general practice including 7,278 people, Smeeth et al. (23) demonstrated that infection of urinary tract increased the risk of DVT particularly in the first two weeks after exposure. Similarly to urinary tract infection, respiratory infections including pneumonia, acute bronchitis, chest infections and influenza increased the risk of DVT. Unfortunately the impact of other infections on DVT was not investigated, but the data reported would be in favour of a relationship between infections and DVT independently from the type of infection. Furthermore, it is of interest that the relationship between infections and DVT was not related to seasonal variation as the incidence of thromboembolism was equally distributed between warm and cold seasons. Finally, there

was no sign of age increasing the risk of DVT, as its incidence was similar in patients both older and younger than 60 years. In accordance with this finding, the ARTEMIS study (11) showed a high rate of venous thrombosis in patients with acute infections or inflammatory disease (11.4%). Also in case of infections, illness severity could display a different degree of thrombotic risk. Severe sepsis is, in fact, complicated by thrombosis as it is associated with activation of platelets and clotting system with an ensuing ongoing prothrombotic state (24). Even if a prothrombotic state has been observed in patients with subclinical endotoxaemia or mild infection, thrombotic complications are typically observed in patients with severe sepsis (25).

There has been some attempt to identify medical patients at higher risk of thrombosis. The Medenox (5) group, for instance, analysed the risk factors associated with VTE, but, with the exception of acute infective disease, none of the clinical settings causing hospitalisation was associated with VTE (26). Thus, in the multiple logistic analysis only age, previous VTE, cancer and infectious diseases were associated with an increased risk of DVT; surprisingly, chronic respiratory disease reduced the risk of DVT, but it is unclear if this finding reflects a link between chronic lung disease and DVT or is just a play of chance.

Other studies have sought to investigate risk assessment models helping to identify patients at higher risk of developing DVT, but the results are still inconclusive for several reasons including the retrospective nature of the study, inadequate follow-up and/or small sample size (2, 26, 27). The latest guideline (28) on this topic recommend anticoagulant prophylaxis in patients with cancer, previous DVT and age > 75 years because they are associated at high risk of thrombosis. However, apart from age, our analysis shows that they represent the minority of acutely ill medical patients. For the other risk categories, which represent the majority of acutely ill medical patients such as HF, ARD and infections, the suggested score appears inadequate because of lack of clinical definition and validation by prospective study. Identification of acutely ill medical patients at risk of venous thrombosis and validation of a score by a prospective study represent prerequisites for an appropriate prophylaxis with antithrombotic drugs in this setting.

In conclusion, our study suggests that underuse of anticoagulants in acutely ill medical patients may be dependent on a low perception of the thrombotic risk. This is attributable to the lack of prospective studies which evaluate the relationship between clinical settings such as HF, ARF and infections, which represent the majority of acutely ill medical patients, and venous thrombosis. Scoring the thrombotic risk of these settings will permit a better identification of candidates for anticoagulation prophylaxis.

#### Conflicts of interest

None declared.

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