Review Article

Thrombo-prophylaxis in acutely ill medical and critically ill patients

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Abstract

Thrombo-prophylaxis has been shown to reduce the incidence of pulmonary embolism (PE) and mortality in surgical patients. The purpose of this review is to find out the evidence-based clinical practice criteria of deep vein thrombosis (DVT) prophylaxis in acutely ill medical and critically ill patients. English-language randomized controlled trials, systematic reviews, and meta-analysis were included if they provided clinical outcomes and evaluated therapy with low-dose heparin or related agents compared with placebo, no treatment, or other active prophylaxis in the critically ill and medically ill population. For the same, we searched MEDLINE, PUBMED, Cochrane Library, and Google Scholar. In acutely ill medical patients on the basis of meta-analysis by Lederle *et al*. (40 trials) and LIFENOX study, heparin prophylaxis had no significant effect on mortality. The prophylaxis may have reduced PE in acutely ill medical patients, but led to more bleeding events, thus resulting in no net benefit. In critically ill patients, results of meta-analysis by Alhazzani *et al*. and PROTECT Trial indicate that any heparin prophylaxis compared with placebo reduces the rate of DVT and PE, but not symptomatic DVT. Major bleeding risk and mortality rates were similar. On the basis of MAGELLAN trial and EINSTEIN program, rivaroxaban offers a single-drug approach to the short-term and continued treatment of venous thrombosis. Aspirin has been used as antiplatelet agent, but when the data from two trials the ASPIRE and WARFASA study were pooled, there was a 32% reduction in the rate of recurrence of venous thrombo-embolism and a 34% reduction in the rate of major vascular events.

Keywords: Critically ill, deep vein thrombosis, heparin, mortality, thrombo-prophylaxis

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Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are collectively referred as venous thrombo-embolism (VTE). These fatal conditions are common, but preventable complications of hospitalization. In surgical patients, thrombo-prophylaxis has been shown to reduce the incidence of fatal PE and the rate of death from any cause. The literature evidence on the benefit of anticoagulation in acutely ill medical and critically ill patient is scarce. A lot of new evidence has been reported in last the 5 years regarding VTE prophylaxis. A number of randomized controlled trials along with meta-analysis have challenged the indicated role of anticoagulation in all acutely ill medical patients. Until now, it was thought that one form of heparin is superior to another in critically ill patients, but that too has been challenged in recent trials. The purpose of this review is to find out the evidence-based clinical practice criteria of short-term and long-term DVT prophylaxis, and the current role of newer oral anticoagulants and antiplatelet agents in acutely ill medical and critically ill patients.

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Data Search

We sought to include all published literature from January 2008 to September 2013 and indexed in one

of the following databases advanced PUBMED, MEDLINE, Cochrane Library, and Google Scholar search engine with following criteria: (1) Design: Systematic review/meta-analysis/randomized controlled trial; (2) Population: Medical or surgical critically ill patients older than 18 years, acutely ill medical patients older than 18 years including patients with stroke but excluding patients with acute coronary syndrome; (3) Intervention: Any heparin thrombo-prophylaxis compared with any other strategy or no prophylaxis; (4) Use of newer oral anticoagulants; (5) Outcomes: Any VTE outcomes (e.g. DVT or PE, whether symptomatic or asymptomatic), major bleeding, heparin induced thrombocytopenia (HIT), or mortality.

A critically ill patient for the purpose of this review is one with multiorgan failure and requiring intensive care support for the same.

We searched the advanced PUBMED, MEDLINE, Cochrane Library and Google Scholar in which term "VTE" was searched as Medical Subject Heading (Mesh) and term "prevention and control" and "prophylaxis" was used as Mesh subheading. We further applied Boolean query using keywords acutely ill, medically ill and critically ill patients. Filters were applied, which included time limit of 5 years and included human subjects only. Thirty-six articles were shortlisted and finally reviewed articles were further narrowed to two meta-analysis and five randomized controlled trials as illustrated in Figure 1 and Table 1.

Studies of heparin prophylaxis that were done specifically in patients with acute myocardial infarction were excluded because full-dose anticoagulation has been shown to be beneficial in acute coronary syndromes for reasons other than VTE prophylaxis.

Pathophysiology

Anticoagulants are active in the low-flow, low-shear venous vasculature where fibrin-rich clots form whereas anti-platelets are active, in high-flow, high-shear arterial circulation, where platelet adhesion and aggregation are more important.[1] At present, available anticoagulants for DVT prophylaxis include as listed in Table 2.

Heparin prophylaxis prevents asymptomatic, surveillance-detected deep venous thrombosis in hospitalized medical and critically ill patients. People with untreated proximal DVTs (some of which are asymptomatic) die more often than those without it that makes prophylaxis for all hospitalized patients logical, but any real benefits are still unproven. Medical educators have managed to teach a generation of physicians that deep venous thrombosis is synonymous with PE, but the truth is far more complex. As we know, the spectrum of VTE extends from DVT to PE. This spectrum extends further from symptomatic DVT, asymptomatic DVT on one hand and on other hand to symptomatic PE and asymptomatic PE. The limitation with current studies is that screening methods of DVT are used to assess the efficacy of oral or subcutaneous anticoagulants. Hence, asymptomatic DVT are picked up and as a result incidence of asymptomatic DVT is high in the published studies. However, once asymptomatic DVT is detected, the patients in the placebo group are also given anticoagulants that is, typically therapeutically anti-coagulated, thereby lowering the risk of thrombus propagation, embolization, and subsequent PE; hence, the natural history of VTE is altered. Thus, a paradox exists, such that asymptomatic DVT rates reported in trials using screening (before symptoms arise) are likely to be higher than rates of symptomatic DVT that would be identified in practice redundant. However, the rates of symptomatic PE reported in trials using screening detection of DVT (given that these DVT are typically treated when identified) are likely to be lower than the rates of symptomatic PE that would be identified in practice. Hence, studies have not shown mortality benefit.

On the other hand, PE is detected clinically, or is an incidental finding as computed tomography angiography is not used routinely. Thus the, incidence of PE is also low in these studies due to two factors; one is due to alteration in the natural history of VTE and the other due to the lack of screening methods for PE. The scenario in medical and critically ill patient was unclear before 2010; there were a lot of myths around thromboprophylaxis in this group of patients.

The article will review, the current evidence-based development in thrombo-prophylaxis in

I. Critically ill patients,
II. Acutely ill medical patients,
III. Extended-duration thrombo-prophylaxis in medically ill patients with the current role of newer oral anticoagulants.

Deep vein thrombosis prophylaxis in critically ill patients

The incidence of symptomatic or asymptomatic DVT without thrombo-prophylaxis is 13-31% of medical-surgical critically ill patients.[2] In observational studies of Intensive Care Unit (ICU) patients receiving

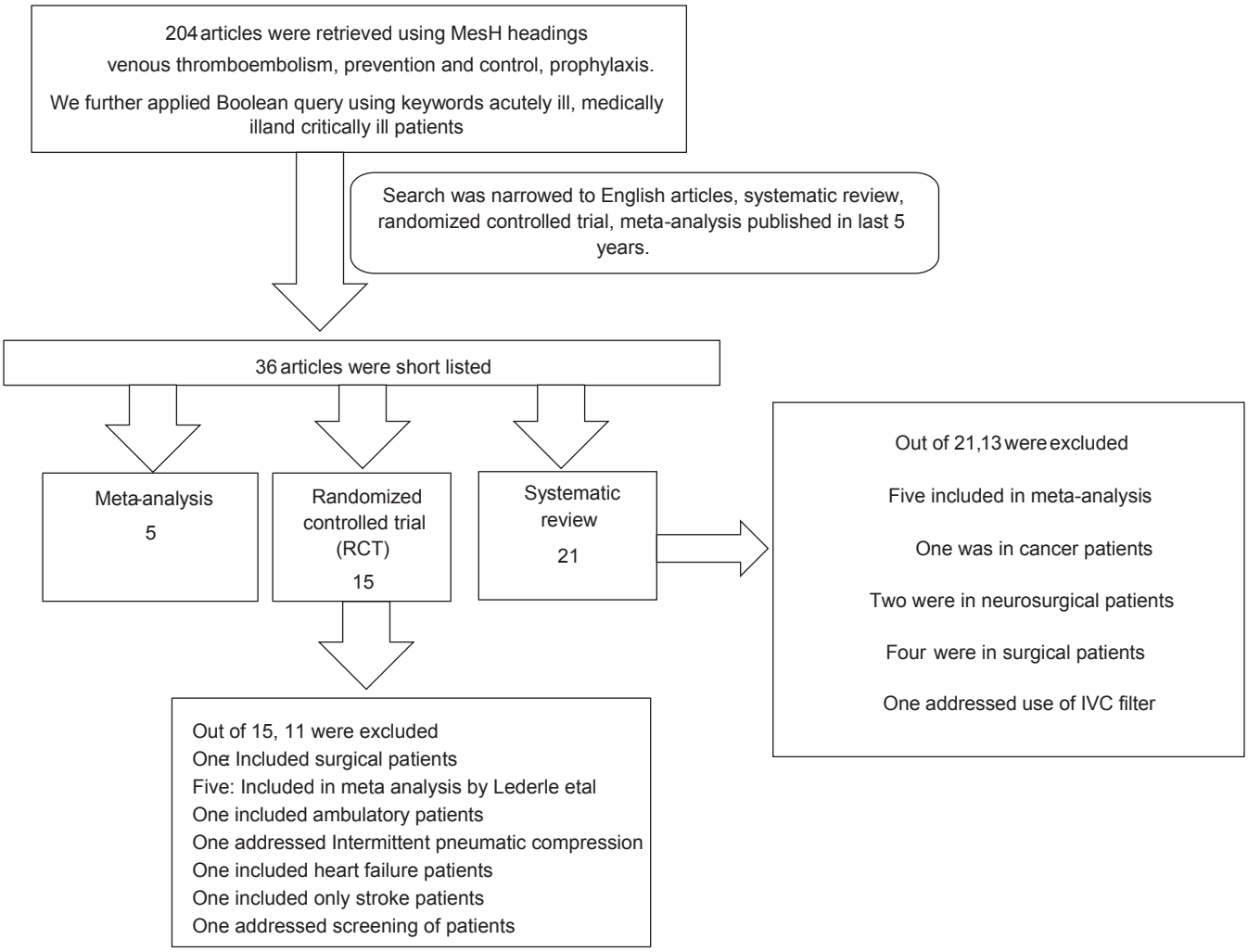

Figure 1: Schematic presentation of literature search strategy

low-molecular-weight heparin (LMWH), the frequency of VTE at any site ranged from 5.1% to 15.5% and bleeding complications from 7.2% to 23.1%, respectively.[3] Critically ill patients are at higher risk of VTE due to underlying severe illness, sedative drugs, invasive lines, and prolonged immobilization. Outside the ICU, clinically important DVTs are sometimes defined as symptomatic events that lead to objective radiologic confirmation and treatment.[4,5] However, the concept of symptomatic DVT is challenging in critically ill patients, because they cannot reliably communicate symptoms due to impaired consciousness from drugs or their underlying illness. Furthermore, physical signs, such as unilateral leg edema, are uncommon because ICU patients are supine, frequently have bilateral edema, and structured physical examination has been shown to have no diagnostic utility for DVT in medical-surgical critically ill patients. Therefore, thrombo-prophylaxis is must in ICU patients. Low-dose unfractionated heparin (UFH) compared with placebo was effective in reducing asymptomatic DVT by approximately 50%, based on the first randomized clinical trial (RCT) as early as 1982 in this group of the population.[6]

Meta-analysis comparing UFH/LMWH vs placebo

A meta-analysis by Alhazzani *et al*. has made the blurred picture somewhat clear.[7] The main objective of this systematic review was to incorporate the RCTs comparing heparin (UFH or LMWH) thrombo-prophylaxis strategies with each other or no prophylaxis in medical-surgical critically ill patients on any of the following outcomes: DVT, PE, major bleeding, HIT, and mortality. There have been in all seven trials in critically ill patients till date involving a total of 7226 patients. Medical and surgical critically ill patients were enrolled in three trials,[6,8,9] two trials enrolled medical ICU patients,[10,11] one trial enrolled medical ICU patients with chronic obstructive pulmonary disease,[12] and one trial enrolled surgical ICU patients.[13] Two trials compared UFH with placebo,[6,10] one trial compared LMWH with placebo,[12] 4 trials compared LMWH with UFH.[8,9,11,13]

Table 1: Summary of meta-analysis and randomized controlled trials discussed

Trials	Medically ill	Critically ill	Inference	Limitations
Meta-analysis by Lederle *et al.*	40 unique randomized trials involving >52,000 patients were identified Of these, 21 were conducted in medical patients Of which 10 compared prophylaxis with heparin or related agents with no heparin 9 compared LMWH with UFH and 2 compared different durations of LMWH prophylaxis 19 trials were conducted in patients with acute stroke The primary outcome was all-cause mortality up to 120-day after randomization Secondary outcomes (all to 120-day) included symptomatic DVT; all PE; fatal PE; all bleeding events; major bleeding events; and for mechanical prophylaxis, skin damage	-	In medical patients, heparin prophylaxis had no significant effect on mortality, may have reduced PE in medical patients and all patients combined, and led to more bleeding and major bleeding events, thus resulting in little or no net benefit. No differences in benefits or harms were found according to type of heparin used	In current studies systematic screening for DVT is conducted Thus the incidence of asymptomatic DVT in the ICU setting is found to be high Hence natural history of VTE is altered
LIFENOX study	A double-blind, placebo-controlled, randomized trial to assess the effect of subcutaneous enoxaparin (40 mg daily) as compared with placebo-over 10±4 days in patients on mechanical compressive device. The primary outcome measure was death from any cause among hospitalized, acutely ill medical patients at participating sites in China, India, Korea, Malaysia, Mexico, Philippines, and Tunisia Important aspect of this study was the participation of Asian countries		Among 4171 patients randomized to enoxaparin 40 mg subcutaneously for 10-day, plus or minus 4-day, all-cause 30-day mortality was 4.9%; among 4136 randomized to placebo for the same duration, it was 4.8% (relative risk: 1.0; $P=0.83$)	Comprehensive estimation of the incidence of asymptomatic deep vein thrombosis or nonfatal pulmonary embolism was beyond the scope of the study. There was no difference in the rate of symptomatic deep vein thrombosis, but the very low rates suggest underreporting by participating centers
Meta-analysis by Alhazzani *et al.*		Seven trials involving 7226 critically ill patients	Any heparin prophylaxis compared with placebo reduces the rate of DVT and PE, but not symptomatic DVT. Major bleeding risk and mortality rates were similar Compared with UFH, LMWH reduces the rate of pulmonary embolism and symptomatic PE but not DVT, symptomatic DVT, major bleeding or mortality	These estimates are derived from trials that as earlier discussed did not conduct systematic PE screening. Most of the events were clinically suspected and objectively confirmed, although these trials did not use a standardized diagnostic approach for PE
MAGELLAN trial	Patients were randomized to receive s.c. enoxaparin, 40 mg OD, for 10±4 days and oral placebo for 35±4 days or to receive subcutaneous placebo for 10±4 days and oral rivaroxaban, 10 mg OD, for 35±4 days The primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic VTE up to day 10 (non-inferiority test) and up to day 35 (superiority test) The principal safety outcome was the composite of major or clinically relevant non-major bleeding		Rivaroxaban was non-inferior to enoxaparin for standard-duration thrombo-prophylaxis. Extended-duration rivaroxaban reduced the risk of VTE	Rivaroxaban was associated with an increased risk of bleeding
EINSTEIN programme	This program consisted of three randomized trials of rivaroxaban One for the treatment of acute deep-vein thrombosis (the acute DVT study) One for the treatment of acute pulmonary embolism (the acute PE study) One for continued treatment in patients who have received treatment for acute deep-vein thrombosis or pulmonary embolism (the continued treatment study) Rivaroxaban safety and effectiveness were evaluated in three clinical studies totaling 9478 patients with DVT or PE. Patients were randomly assigned to receive rivaroxaban, enoxaparin and warfarin, or placebo. The studies measured recurrent DVT, PE or death after randomization		Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation	These benefits come at a price; rivaroxaban costs $3000 a year, as compared to about $200 for warfarin. Rivaroxaban can cause major bleeding, but thus far, observed rates of major bleeding events caused by rivaroxaban have not exceeded the rates of major bleeding caused by warfarin
ASPIRE and WARFASA study	Two recent clinical trials WARFASA study and the ASPIRE study, evaluated aspirin as compared with placebo in patients with unprovoked VTE who had completed initial treatment with heparin followed by warfarin or a minimum of 6 weeks (most received therapy for at least 3 months). Both studies used identical low-dose aspirin regimens (100 mg/day)		When data from these two trials were pooled, there was a 32% reduction in the rate of recurrence of VTE and a 34% reduction in the rate of major vascular events	With fewer patients recruited than originally planned, the ASPIRE trial by itself was not powered to show a significant reduction in the primary outcome. When combined, with the WARFASA study a clear effect is evident

DVT: Deep vein thrombosis; VTE: Venous thrombo-embolism; PE: Pulmonary embolism; LMWH: Low-molecular-weight heparin; UFH: Unfractionated heparin; OD: Once daily

[Figure 2]. The combined results of these seven trials are mentioned as below:

(i) Heparin (UFH [two trials] and LMWH [one trial]) compared to placebo reduces the rate of DVT and PE (risk ratio [RR], 0.52 [95% confidence interval (CI), 0.28, 0.97]; $P = 0.04$; $I^2 = 0\%$) but not symptomatic DVT (RR, 0.86 [95% CI, 0.59, 1.25]; $P = 0.43$). Major bleeding and mortality rates were similar. As compared to placebo patients had similar bleeding rates, mortality, and symptomatic DVT.[7]

(ii) Compared with UFH, LMWH reduced rates of PE (RR, 0.62 [95% CI, 0.39, 1.00]; $P = 0.05$; $I^2 = 53\%$) and symptomatic PE (RR, 0.58 [95% CI, 0.34, 0.97]; $P = 0.04$) but not DVT (RR, 0.90 [95% CI, 0.74, 1.08]; $P = 0.26$; $I^2 = 0\%$), symptomatic DVT (RR, 0.87 [95% CI, 0.60, 1.25]; $P = 0.44$; $I^2 = 0\%$), major bleeding (RR, 0.97 [95% CI, 0.75, 1.26]; $P = 0.83$; $I^2 = 0\%$), or mortality (RR, 0.93 [95% CI, 0.82, 1.04]; $P = 0.20$; $I^2 = 31\%$).[7]

Limitations

These estimates are derived from trials that as earlier discussed did not conduct systematic PE screening. Most of the events were clinically suspected and objectively confirmed. There are limitations to the data in this systematic review. Of the seven included trials, two trials reported only one type of VTE outcome,[6,13] two trials did not report bleeding,[6,10] two trials did not report mortality[6,10] and five trials did not report HIT.[6,10-13] The primary outcome in most of these trials was lower extremity DVT.

Table 2: Agents available for VTE prophylaxis

Type of agent	Dosage-DVT prophylaxis	DVT treatment	Special circumstance
Unfractionated heparin	5000 U s.c. BD/TDS	80 U/kg bolus followed by 18 U/kg/h	Renal failure: Dose modification Increased incidence of HIT
LMWH Enoxaparin Dalteparin	40 mg s.c. OD 5000 U s.c. OD	1 mg/kg s.c. BD 5000 U s.c. BD	Renal failure: Enoxaparin-0.5 mg/kg s.c. BD Dalteparin: No dosage modification
Fondaparinux	2.5 mg s.c. OD	Weight based normogram	C/I in patients with CrCl<30 ml/min
Rivaroxaban	20 mg PO OD	15 mg PO BD	To be avoided in patients with renal failure

CrCl: Creatinine clearance; LMWH: Low-molecular-weight heparin; VTE: Venous thrombo-embolism; DVT: Deep vein thrombosis; HIT: Heparin induced thrombocytopenia

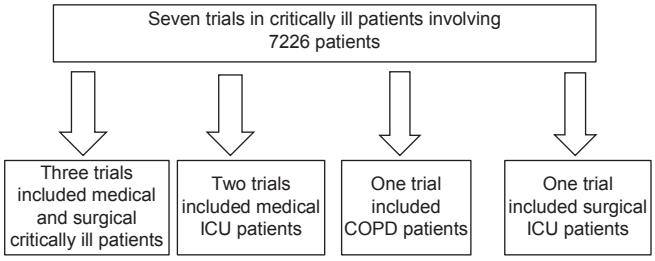

Figure 2: Schematic representation of trials in critically ill patients

Clinical take away in critically ill patients

On the basis of the above meta-analysis, evidence to date suggests that any type of heparin thrombo-prophylaxis decreases DVT and PE in medical-surgical critically ill patients, and LMWH compared with bid UFH decreases PE and symptomatic PE. Major bleeding and mortality rates do not appear to be significantly influenced by heparin thrombo-prophylaxis in the ICU setting. No one form of heparin is superior to other as advertised by pharmaceutical companies. Meanwhile, all relevant clinical outcomes of thrombo-prophylaxis and their associated economic consequences should be considered. As well as considerations of drug availability, patient comfort, and ease of administration should guide decisions regarding thrombo-prophylaxis in critically ill patients.

Deep vein thrombosis prophylaxis in medically ill patients

Several randomized trials have reported reductions in asymptomatic DVT from heparin prophylaxis in hospitalized medical patients.[12,14-16] This surrogate outcome is much more common than clinically evident disease, and its value has been questioned previously.[17-19] There has been a lot of controversy in this field and various trials until date had showed conflicting results. Meta-analysis by Lederle *et al*.[20] and subsequently a randomized controlled trial by Kakkar *et al*.[21] have thrown some light in this area of interest. In subsequent section, both of these studies will be discussed.

Meta-analysis for benefits of thromboprophylaxis

A recent meta-analysis published by Lederle *et al*. systematically reviewed randomized trials that addressed the benefits and risks of VTE prophylaxis in hospitalized adult nonsurgical patients, including trials done in various categories of medical patients and in patients with acute stroke. Forty unique randomized trials involving >52,000 patients were ultimately identified. Of these 21 were conducted in medical patients, of which 10 compared prophylaxis with heparin or related agents with no heparin,[12,14-16,19,22-25] 9 compared LMWH with UFH,[8,26-33] and 2 compared different durations of LMWH prophylaxis.[34,35] Nineteen trials were conducted in patients with acute stroke, of which 8 compared heparin prophylaxis with no heparin,[36-43]

five compared LMWH with UFH,[44-48] three compared mechanical with no mechanical prophylaxis,[49-51] and three had unique designs.[52-54] All studies used UFH or LMWH, except one that used fondaparinux,[24] so the term "heparin" was used to describe these studies [Figure 3]. The primary outcome was total mortality up to 120-day after randomization. Secondary outcomes (all to 120-day) included symptomatic DVT; all PE; fatal PE; all bleeding events; major bleeding events; and for mechanical prophylaxis, skin damage.

i. In medical patients (10 trials; 20,717 participants), comparing heparin prophylaxis versus placebo did not significantly reduce the primary outcome of total mortality but did result in fewer PEs (odds ratio [OR], 0.69 [95% CI, 0.52-0.90]) and more bleeding events (RR 1.34 [CI, 1.08-1.66])[20]
ii. Heparin prophylaxis did not significantly affect any outcomes in patients with acute stroke (eight trials; 15,405 participants), except for an increase in major bleeding events (OR, 1.66 [CI, 1.20-2.28])[20]
iii. In stroke patients, no statistically significant differences were observed in the analysis for mortality, symptomatic DVT, or PE, but mechanical prophylaxis caused more instances of lower extremity skin damage (RR, 4.02 [CI, 2.34-6.91])-an increase of 39 events/1000 patients treated (CI, 17-77 events)[20]
iv. No statistically significant differences in clinical outcomes were observed in the 14 trials that compared UFH with LMWH.[20]

In medical patients, heparin prophylaxis had no significant effect on mortality, may have reduced PE in medical patients and all patients combined, and led to more bleeding and major bleeding events, thus resulting in little or no net benefit. No differences in benefits or harms were found according to type of heparin used. Mechanical prophylaxis provided no benefit and resulted in clinically important harm to patients with stroke.

LIFENOX trial

An important study post this meta-analysis was a study by Kakkar *et al*.,[21] in which Asian countries were participants and it looked after mortality as the primary endpoint in acutely ill hospitalized medical patients. It was a double-blind, placebo-controlled, randomized trial was conducted to assess the effect of subcutaneous enoxaparin (40 mg daily) as compared with placebo-both administered for 10 ± 4 days in patients who were wearing elastic stockings with graduated compression-on the rate of death from any cause among hospitalized, acutely ill medical patients. Patients were hospitalized for acute decompensated heart failure, severe systemic infections, or active cancer. Both groups wore knee-high elastic graduated compression stockings during the treatment phase of the trial. Among 4,171 patients randomized to enoxaparin 40 mg subcutaneously for 10-day, plus or minus 4-day, all-cause 30-day mortality was 4.9%; among 4,136 randomized to placebo for the same amount of time, it was 4.8% (RR, 1.0; 95% CI, 0.8-1.2; $P = 0.83$).[21] No difference in the rate of fatal PE.[21] No difference in the rate of major hemorrhagic events, although enoxaparin trended toward harm (0.4% vs. 0.3%).[21]

Taken together, these studies strongly suggest that individualized risk-benefit assessment is necessary to maximize benefit and minimize harm of VTE prevention efforts in medically ill patients. This need for clinical judgment is best reflected in the recently released 2012 American College of Chest Physician guidelines:[55]

"For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thrombo-prophylaxis with LMWH, low-dose UFH bid, low-dose UFH tid, or fondaparinux"

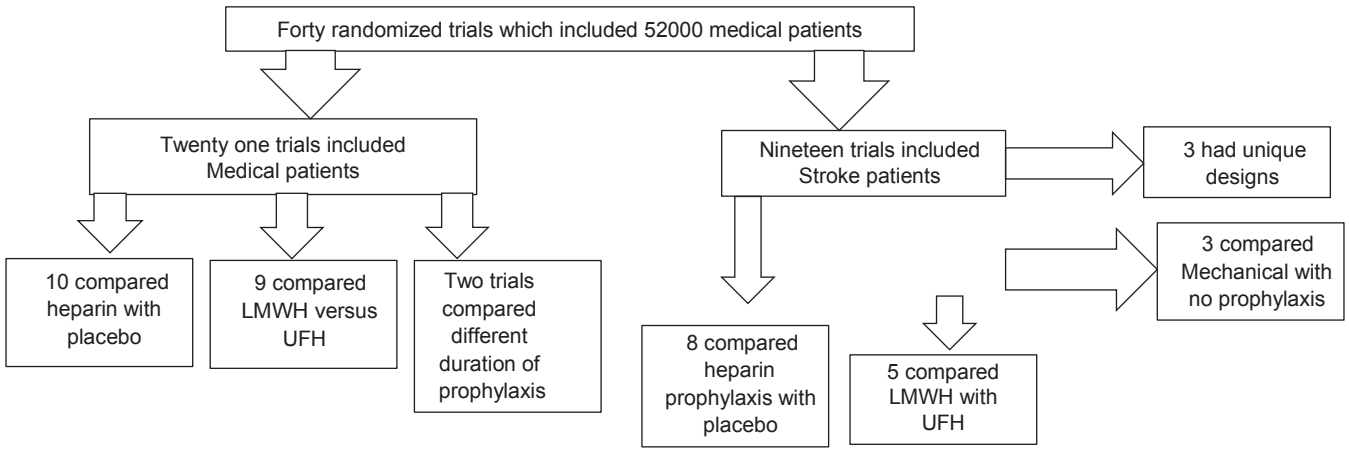

Figure 3: Schematic representation of trials in acutely ill medical patients

and "For acutely ill hospitalized medical patients at low-risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis".

The risk assessment can be given as per Padua Risk Assessment model which was suggested by Barbar *et al*. in which patients with higher Padua Risk Score ≥4 have a high incidence of DVT.[56] Barbar *et al*. used a modification of the Kucher score, the Padua VTE risk model, to assess medical inpatients in a prospective cohort study conducted in an Italian hospital over a 2-year period [Table 3].[56]

Clinical takeaway

The reflex has been to use prophylaxis on even low-risk patients for venous thrombo-embolism. Maybe we should be making decisions about who should be receiving pharmacologic prophylaxis based on factors other than the fact that they are in the hospital for an acute medical illness.

Extended-duration thrombo-prophylaxis

Acute VTE is a common disorder with annual incidence of approximately 1 or 2 cases/1000 in the general population.[57,58] The risk of recurrence remains even after the treatment ends and can reach up to 5-10% during the 1st year.[59-61] Major concern is how long to give oral anticoagulants for patients with post VTE episode, as too long duration of anticoagulation is associated with increased bleeding risk. Here, comes the role of two agents in extended-duration thrombo-prophylaxis that is, rivaroxaban and Aspirin which will be discussed in the subsequent section.

Rivaroxaban

Rivaroxaban is an orally active direct factor X an inhibitor and is the first oral anticoagulant molecule approved to treat and reduce the recurrence of blood clots since the approval of warfarin nearly 60 years ago. Rivaroxaban already had Food and Drug Administration (FDA) approval for prevention of DVT and PE after knee or hip replacement surgery (July 2011), and for stroke prevention in people with non-valvular atrial fibrillation (November 2011). The U.S. FDA approved rivaroxaban for a new indication for treating DVT or PE and for long-term prophylaxis of recurrent DVT and PE on the basis of EINSTEIN Program and MAGELLAN trial.[62,63]

MAGELLAN trial

MAGELLAN trial was a multicenteric, randomized, double-blind trial, and authors evaluated the efficacy and safety of oral rivaroxaban administered for an extended period, as compared with subcutaneous enoxaparin administered for a standard period, followed by placebo.[62] Authors randomly assigned patients 40 years of age or older who were hospitalized for an acute medical illness to receive subcutaneous enoxaparin, 40 mg once daily, for 10 ± 4 days and oral placebo for 35 ± 4 days or to receive subcutaneous placebo for 10 ± 4 days and oral rivaroxaban, 10 mg once daily, for 35 ± 4 days. The primary efficacy outcomes were the composite of asymptomatic proximal or symptomatic VTE up to day 10 (non-inferiority test) and up to day 35 (superiority test). In acutely ill medical patients, rivaroxaban was non-inferior to enoxaparin for standard-duration thrombo-prophylaxis. Extended-duration rivaroxaban reduced the risk of VTE. Rivaroxaban was associated with an increased risk of bleeding.

EINSTEIN program

This program consisted of three randomized trials of rivaroxaban.[64,65] Rivaroxaban safety and effectiveness were evaluated in three clinical studies totaling 9,478 patients with DVT or PE. Patients were randomly assigned to receive rivaroxaban, enoxaparin and warfarin, or placebo. The studies measured recurrent DVT, PE or death after randomization. Rivaroxaban is as efficacious as enoxaparin with warfarin for treating DVT and PE [Figure 4]. Unlike warfarin, rivaroxaban does not require initial "overlap" or "bridging" with heparin/enoxaparin, and also does not require blood level monitoring thus simplifying treatment. Rivaroxaban can cause major bleeding, observed rates of major bleeding events caused by rivaroxaban have not exceeded the rates of major bleeding caused by warfarin, and may well be lower (1% compared to 1.7% overall). Prothrombin complex concentrate seems to reverse the effects of rivaroxaban, and could be used as an antidote.

Table 3: Padua risk assessment model[56]

Points	Condition
3	Cancer, past VTE, reduced mobility, thrombophilic condition
2	Trauma or surgery in the past month
1	≥70, CHF, AMI, ischemic CVA, BMI≥30, hormones, other*

*Acute infectious disorder or rheumatological disorder. PRAM score≥4; patient at higher risk of VTE. VTE: Venous thrombo-embolism; AMI: Acute myocardial infarction; CHF: Congestive heart failure; BMI: Body mass index; CVA: Cerebro-vascular accident

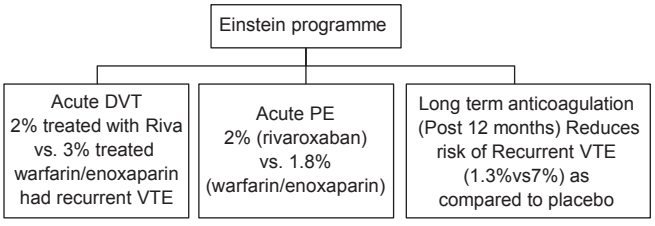

Figure 4: Summary of EINSTEIN program

Rivaroxaban dosage is 15 mg BD in the acute phase for 3 weeks followed by 20 mg OD [Table 4].

Aspirin

The dual benefit of Aspirin in both arterial and venous circulations might be expected. Atherosclerosis is a risk factor for unprovoked VTE, and patients with idiopathic VTE are at increased risk for subsequent arterial cardiovascular events. Two recent clinical trials, WARFASA and ASPIRE evaluated aspirin as compared with placebo in patients with unprovoked VTE who had completed initial treatment with heparin followed by warfarin for a minimum of 6 weeks (most received therapy for at least 3 months).[66,67] Both studies used identical low-dose aspirin regimens (100 mg/day). Together, these two studies indicate that aspirin reduces by one third the rate of recurrence of venous thrombo-embolism as well as the rate of major vascular events, a composite outcome of venous thrombo-embolism, stroke, myocardial infarction, or cardiovascular death. These benefits were attained with low-risk of bleeding. Before physicians consider Aspirin prescription for patients who have had acute unprovoked VTE, it is important that:

The patient should be treated effectively with anticoagulation for at least 3 months, to avoid the high risk of early recurrence. For patients who then wish to stop anticoagulation, a switch to aspirin at a dose of 100 mg daily will reduce by one-third the risk of recurrent VTE. The advantage of Aspirin is, that not only decreases the cardiovascular event but also attenuate the early burst of thrombosis recurrence after cessation of oral anticoagulation [Table 5].

Conclusions

Despite abundant literature supporting the benefits of VTE thrombo-prophylaxis, the absolute clinical impact in acutely ill medical patients is uncertain. It suggests that in medically ill patients at moderate risk for DVT, NNT is 1000 i.e. it means you have to treat 1000 people with the drug to prevent one additional bad outcome. All acutely ill medical patients should not be offered DVT prophylaxis; only patients with risk factors as per Padua Risk Assessment score should be offered DVT prophylaxis. The results in this low-to-moderate risk population should by no means be extended to critically ill patients, who (the best evidence suggests) have a high risk for DVT and PE, and should receive pharmacologic prophylaxis unless contraindicated. In critically ill patients, any form of heparin is better than placebo, but no one form of heparin is superior to other (UFH vs. LMWH). Rivaroxaban is an oral anticoagulant, which can be given in acute VTE with no bridging needed. Rivaroxaban is FDA approved for DVT thrombo-prophylaxis in acutely ill medical patients. Aspirin can be used for dual prevention of venous and arterial thrombosis for extended therapy.

Table 4: Myths broken by new evidence

Myths before 2010	Current evidence	Evidence
DVT prophylaxis to be given in all hospitalized, acutely ill medical patients	DVT prophylaxis to be given in acutely ill hospitalized patients who are at high risk of thrombosis	Lederle *et al.*, LIFENOX study, ACCP guidelines 2012
LMWH superior to UFH in critically ill patients	All form of heparin are equivalent	Alhazzani *et al.*
Warfarin only oral anticoagulant available	Rivaroxaban is an oral anticoagulant recommended	EINSTEIN programme and MAGELLAN trial
Aspirin only as antiplatelet agent	Aspirin both for acute and venous thrombosis	ASPIRE and WARFASA trial

DVT: Deep vein thrombosis; LMWH: Low-molecular-weight heparin; UFH: Unfractionated heparin; ACCP: American College of Chest Physician

Table 5: Clinical takeaway

Type of patients	Inference/clinical take away
Medically ill	DVT prophylaxis not to be given in all acutely ill medical patients. Only patients with high risk of thrombosis on the basis of Padua risk score (≥4) should be given prophylaxis In medical patients, heparin prophylaxis had no significant effect on mortality, may have reduced PE in medical patients and all patients combined, and led to more bleeding and major bleeding events, thus resulting in little or no net benefit Graduated compression stockings do more harm than benefit in medically ill patients
Critically ill	DVT prophylaxis to be given in all critically ill patients No one form of heparin is superior to another in critically ill patients Major bleeding and mortality rates do not appear to be significantly influenced by heparin thrombo-prophylaxis in the ICU setting Drug availability, patient comfort, cost and ease of administration, should guide decisions regarding thrombo-prophylaxis in critically ill patients
Rivaroxaban-in medically ill patients	Rivaroxaban can be used in the acute treatment of DVT and for long term anticoagulation and thrombo-prophylaxis in acutely ill medical patients In acutely ill medical patients, rivaroxaban was non-inferior to enoxaparin for standard-duration thrombo-prophylaxis Extended-duration rivaroxaban reduced the risk of VTE. Rivaroxaban was associated with an increased risk of bleeding
Aspirin: For extended-duration thrombo-prophylaxis	Findings of the ASPIRE study pooled with WARFASA study; provide consistent evidence that low-dose aspirin is beneficial in preventing recurrent VTE and major vascular events in patients who have had a first episode of unprovoked VTE

DVT: Deep vein thrombosis; PE: Pulmonary embolism; ICU: Intensive care unit; VTE: Venous thrombo-embolism

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