Eastern Journal of Medicine 14 (2009) 73-77

Review Article

Thromboprophylaxis in the general medical patients: making sense of the current guidelines and controversial issues

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Abstract: There is sufficient data for thromboprophylaxis in surgical patients. If we follow these guidelines for medically ill patients it would result in giving anticoagulants to a large number of patients. The guidelines are based upon prevention of asymptomatic DVT as an endpoint. The number of such patients who develop symptomatic DVT is very small. It would be worthwhile studying the risk factors for DVT in those with symptomatic DVT. We could then target thromboprophylaxis at a selected group of acutely ill medical patients who would benefit most by this intervention.

Key words: Tromboprophlaxis, current guidelines, controversial issues

The American college of chest physicians (ACCP) guidelines for thromboprophylaxis have been presented in 2004 and revised in 2008 (1). These guidelines are based on an extensive body of literature which has studied the issue of thromboprophylaxis in surgical patients. Therefore the guidelines give very clear and extensive recommendations for surgical patients. The ACCP guidelines point out that 70-80% of fatal PEs actually occur in the non surgical setting. Hospitalization for an acute medical illness is associated with an eight fold increase in venous thromboembolism. However the guidelines in respect to the patients with general medical disorders are in the main derived from experience from their surgical counterparts. The experience in surgical patients has been sought to be extrapolated to create similar guidelines for the medical patient. These guidelines form the basis for various other national guidelines and recommendations.

The ACCP guidelines have been further simplified from its 2004 guideline to divide the patients into three broad groups (table 1).

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As seen above the guidelines have done away with the descriptive nature of the previous risk group recommendations. The current guidelines have simplified the decision process whereby the patients are broadly classified into broad risk groups based upon their reason for admission. The guidelines do not recommend an individualized scoring system as for other conditions such as disseminated intravascular coagulation. Such scoring systems for venous thromboembolism (VTE) have not been validated and do not adequately identify patients who would not develop (VTE).

The absolute numbers of patients who develop deep vein thrombosis (DVT/VTE) after admission for an acute medical condition are still small despite the increased risk of thrombosis as compared to the general population. Symptomatic DVT is seen in < 1% of medical patients1. Thus all medical patients are included in the low and moderate risk groups of the ACCP guidelines (table 1). The guidelines estimate that low risk patients have a less than 10% risk of DVT without thromboprophylaxis. The corresponding figure for the moderate risk patients is 10-40%1. This risk has been arrived at from studies which have included asymptomatic DVT (diagnosed using venography or Doppler ultrasound) as an endpoint. This endpoint is based on the assumption that there is a concordance between assymtomatic DVT and clinically important (VTE).

Table 1. The ACCP guidelines: Risk stratification in 2004 and 2008

ACCP 2004 risk groups	
Low risk	Under the age of 40, No adverse risk factors*, will require general anesthesia for less than 30 minutes, and are undergoing minor elective, abdominal, or thoracic surgery.
Moderate risk	Undergoing minor surgery who have additional risk factors* or those age 40 to 60 who will require general anesthesia for more than 30 minutes and have none of the above risk factors.
High risk	Those >60 years of age undergoing surgery as well as those age 40 to 60 with additional risk factors*.
Highest risk	patients with multiple risk factors*, as well as those undergoing hip or knee arthroplasty or hip fracture surgery, and those with major trauma or spinal cord injury.
ACCP 2008 risk groups	
Low risk	Minor surgery in mobile patients; Medical patients who are fully mobile
Moderate risk	Most general, open gynecologic, or urologic surgery patients; Medical patients bed rest or sick
High risk	Hip or knee arthroplasty, hip fracture surgery, spinal cord injury

*Additional risk factors include one or more of the following: advanced age, cancer, prior venous thromboembolism, obesity, heart failure, paralysis, or presence of a molecular hypercoagulable state (eg, protein C deficiency, factor V Leiden)

Table 2. Placebo-controlled trials of LMwH for VTE prophylaxis in medically ill patients 2

Author, year (trial)	Treatment	Number of patients	Days of prophylaxis	Primary outcome (VTE)	Incidence of VTE inplacebo group (%)	Incidence of VTE in plrophylaxis group (%)	Relative risk of VTE in prophylaxis group
Samama et al. 1999 MEDENOX	Enoxaparin	866	6-14	days 1-14	14.90	5.50	0.37 (P<0.001)
Leizorovicz et al. 2004 PREVENT	Dalteparin	3,706	14	Days 1-21	4.96	2.77	0.55 (P = 0.0015)
Cohen et al. 2006 (ArTeMis)	Fondaparinux	849	6-14	Days 1-15	10.5	5.6	0.53 (P = 0.029)

The ACCP 2008 guidelines for medically ill patients are as follows (presented here verbatim from the published guidelines):

For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with low-molecular-weight heparin (LMWH) (Grade 1A), low-dose unfractionated heparin (LDUH) (Grade 1A), or fondaparinux (Grade 1A). For medical patients with risk factors for VTE, and for whom there is a contraindication to anticoagulant thromboprophylaxis, we recommend the optimal use of mechanical thromboprophylaxis with graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) (Grade 1A).

The evidence for use of LMWH in medical patients are derived largely from the MEDENOX (enoxaparin), PREVENT (dalteparin) and ARTEMIS (fondaparinux) trials (table 2) 2.

Additionally a COCHRANE review for thromboprophylaxis in general medical patients meta analysed 13 studies with total of 22,141 pateints of which 9 studies compared heparin with placebo and 4 studies compared LMWH with LDUH[3]. The COCHRANE review excluded trials which also included surgical patients, patients with myocardial infarction, studies with bias towards stroke patients and studies using non standardised means to detect DVT. In the analyses of studies comparing heparin with placebo, heparin reduced the risk of DVT by 60% (RR 0.40, 95% CI 0.31-0.53, p< 0.00001) and pulmonary embolism (PE) by 42% (RR 0.58,95% CI 0.43-0.80, p= 0.00007). There was a non significant reduction in mortality and incidence of fatal PE among patients receiving heparin. There was a significantly increased risk of bleed among patients receiving heparin (RR 2.18, 95% CI 1.28-3.72, p= 0.004).

There was no statistically significant difference in outcome among patients receiving LMWH or LDUH. There was a statistically insignificant trend towards better outcome among patients receiving LMWH and statistically significant 72% risk reduction in major bleeding when LMWH was used. Heparin causes a significant amount of both major and minor bleed (0.5% and 3.7%) compared to the placebo group (0.2 and 2 % major and minor bleed respectively). Use of LMWH reduced the risk of major bleed top 0.3%.There are no head to head trials comparing the various LMWH and it is recommended to use manufacturer prescribed doses.

The duration of prophylaxis is still controversial. The results of the EXCLAIM trial are still awaited. Interim results presented as abstracts appear to suggest that a longer duration of prophylaxis would be beneficial in reducing the risk of VTE. The ACCP guidelines for thromboprophylaxis duration are largely confined to orthopaedic patients and recommend using prophylaxis for 10-35 days(1). In other surgical patients where thromboprophylaxis is recommended, this should be continued till patient is fit to be discharged. This should be true of medical patients as well.

1. Special considerations

The vitamin K antagonists are not recommended on account of a variable pharmacokinetic profile. Medically ill patients have variable food intake and other concomitant medication which would interfere with adequate anticoagulation with the oral anticoagulants. Oral anticoagulants have a very narrow therapeutic range below which they are ineffective and above which there is increased risk of bleeding. Similarly aspirin and other antiplatelet agents were used previously and still recommended in some guidelines for thromboprophylaxis in surgical patients. However randomised trials have shown them to be inferior to the anticoagulant therapy. They also increase the risk of bleed when used in combination with the oral anticoagulants. Therefore the ACCP guidelines do not recommend their use in thromboprophylaxis. Several patients would have a compromised renal function. Low molecular weight heparins and fondaparinux are excreted through the kidneys and they are expected to bio accumulate in case of poor renal clearance. This bioaccumulation varies among the various low molecular weight heparins and is least with standard prophylactic doses of dalteparin. It is therefore recommended to use the LMWH with least bioaccumulation or use such agents when monitoring for their effects is available. In our institution we recommend LDUH with aPTT monitoring in such patients(1).

The ACCP guidelines do not recommend routine thromboprophylaxis in cancer patients undergoing chemotherapy as there is no evidence that such intervention improves survival. The rates of both asymptomatic DVT and symptomatic VTE range from 2-4% in cancer patients with indwelling venous catheters1. Larger studies did not find any difference in outcome among those cancer patients receiving thromboprophylaxis and those not receiving thromboprophylaxis. Thus the use of thromboprophylaxis in patients who have indwelling catheters is not recommended. Use of thromboprophylaxis in those cancer patients who require surgery or are acutely ill are governed by the general guidelines for perioperative patients and acutely ill medically patients.

Mechanical measures of anticoagulation are an attractive concept as they can be used without fear of bleed. These devices are available as graduated compression stockings, intermittent pneumatic pumps or the venous foot pump. These have been found to be effective in several studies are a useful adjunct to the anticoagulant therapy. However they have several limitations to widespread use. In particular, they do not have any single standard for manufacture or evaluation of effectiveness nor have they been specifically studied in any blinded trial. More often than not they are used in appropriately. Their effect on pulmonary embolism and mortality is not known. Therefore their use is currently recommended1 provided care givers choose correct sizes and educate their patients as regards correct

Table 3. Observational studies evaluating rates of VTE prophylaxis 2

Author, year (trial)	Number of patient	Patients receiving any formof VTE prophylaxis (%)
Goldhaber and Tapson 2004	Total 2,726	42
(DVT FREE study)	(medical patients: 1,362)	
	(surgical patients: 1,364)	
Kahn et al. 2007 CURVE study	1,894	23
Tapson et al. 2007 IMPROVE study	6,824	61
Cohen et al. 2008 ENDORSE study	35,329	53
	(medical patients: 15,487)	(medical patienst 45;
	(surgical patients: 19,842)	surgical patients 59)

application and care. Adherence to manufacture guidelines regarding use of individual mechanical thromboprophylaxis devices is also advised (1).

2. What are the implications of the current ACCP guidelines in care of medically ill patients?

The medical wards are generally populated by acutely ill individuals who would have atleast 1 risk factor as enumerated in the current guidelines. A fairly increasing proportion of elderly patients with indwelling catheters and varying degrees of immobility render most of the patients in medical wards eligible for thromboprophylaxis. Approximately 40% of medically ill patients have three or more risk factors for thrombosis2. Data using asymptomatic DVT as an endpoint have shown that thromboprophylaxis is a cost effective and economical intervention to avoid the dreaded complication of pulmonary embolism. Therefore the guidelines recommend that medically ill patients at risk of VTE should receive thromboprophylaxis. In spite of presence of guidelines and extensive evidence for benefits of thromboprophylaxis the actual use of thromboprophylaxis in medically ill patients is very low (table 3)2.

As seen from the studies summarised in table 3, large numbers of patients eligible for thromboprophylaxis based upon eligibility criteria in the ACCP guidelines did not receive the same. Measures to increase compliance with these guidelines including the use of audit and feedback, automated computerized reminders to the treating physician have been suggested (1).

3. So why are we hesitant to use thromboprophylaxis in our general medical patients?

Not withstanding that the guidelines appear to be primarily directed towards surgical patients, in real life practice physicians do not encounter many symptomatic DVTs and PEs among admitted patients. The ACCP guidelines are built on the premise that there is a relationship between asymptomatic DVTs detected by traditional methods and subsequent symptomatic DVT and PE. The basis of this premise is based upon studies in surgical patients and the guidelines acknowledge at the very outset that further studies would be required to test this hypothesis. It would perhaps be fallacious to base the guidelines on an outcome which might not be clinically relevant.

The absolute number of patients who develop symptomatic VTE in medically ill patients is very small (<1%)1. Therefore any reduction in VTE even if statistically significant is actually a very small number. The number needed to treat (NNT) to prevent one PE is 345 with no effect on all cause mortality(1). Trials evaluating cost effectiveness of thromboprophylaxis are based upon asymptomatic DVT outcomes. Therefore there is a need to critically evaluate the guidelines for thromboprophylaxis in medically ill patients (6).

4. Which general medical patients should receive thromboprophylaxis?

The Sirius trial (4). tried to identify risk factors for VTE in the general medical population seen in an outpatient setting. In this population (defined as patients who had not undergone surgery or application of a plaster cast to the lower extremities within the 3 weeks preceding inclusion in study) intrinsic factors such as history of VTE,

venous insufficiency, chronic heart failure, obesity, immobile standing position, history of more than 3 pregnancies, and triggering factors such as pregnancy, violent effort, or muscular trauma, deterioration of general condition, immobilization, long-distance travel, and infectious disease were significantly more frequent in the patients with thrombosis (odds ratio, >1; P<.05).

The landmark MEDENOX trial was further analysed to identify those patients admitted to the wards who would be at an increased risk of VTE (5). In univariate analysis , they were able to identify 4 risk factors, namely age> 75years, prior history of VTE, cancer and acute infection. Among the acute medical illnesses requiring admission, respiratory failure, both acute and chronic had the least risk. Factors such as heart failure, hormonal therapy, varicose veins, and obesity were not associated with an increased risk of VTE. Age > 75 years was associated with 1.3 times greater risk of VTE than a 60 year old. However on multivariate analysis, the risk factor with the greatest risk for VTE was prior history of VTE and risk factor with lowest risk was age >75 (in relation to each other among the 4 risk factors identified). Another interesting finding was that the number of risk factors in a given patient did not matter either. Cancer is a risk factor for thrombosis. As pointed out earlier however patients with cancer receiving chemotherapy and hormonal therapy do not require thromboprophylaxis. Those patients with cancer confined to bed would require thromboprophylaxis.

5. Conclusion

The current ACCP guidelines for thromboprophylaxis in medically ill patients are somewhat all encompassing in nature. It recommends the use of thromboprophylaxis in these patients based on data derived from surgical patients. These recommendations are based on the premise that asymptomatic DVT translates to clinically relevant VTE which as yet remains to be proven in the general medical patient. Thus we may advise thromboprophylaxis in acutely ill medical patients confined to bed based upon current guidelines. The evidence for the same is somewhat weaker compared to the robust data in surgical patients. As seen from analyses of the MEDENOX patients there might be a much more selected group of acutely ill medical patients who would benefit most from thromboprophylaxis.

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