

The AVAIL NE Study: A Multinational Assessment of Venous Thromboembolism Prophylaxis and Management in the Near East Region

Abdalla Awidi^{1,*},¹⁰ Ahmed K. Yassin², Fayez Abillama³

¹ Jordan University Medical School, Cell Therapy Center and University Hospital, Amman, Jordan

²Hawler Medical University, Erbil, Iraq ³Lebanese American University Medical Center, Rizk Hospital, Beirut, Lebanon

ARTICLE INFO

Article Type: Research Article

Article History: Received: 16 Apr 2018 Accepted: 24 Jun 2018

Keywords. Pulmonary Embolism Venous Thromboembolism Venous Thrombosis

ABSTRACT

Background: Venous Thromboembolism (VTE) is a global cause of morbidity and mortality with annual incidence rates between 0.75 and 2.69 per 1000 individuals in the population. Despite the large variety of VTE prophylactic solutions and the availability of several guidelines for their use, appropriate prophylaxis practices are not ideal in many healthcare facilities around the world.

Objectives: The present study aimed to evaluate the extent of administration of the recommended prophylactic treatment to hospitalized patients at risk of VTE according to local protocols and/or national/international guidelines.

Methods: This observational, cross-sectional study was conducted on 1256 medical and surgical patients from 26 sites across the Near East region. The patients' records were screened for the fulfillment of inclusion/exclusion criteria during a single visit. The proportion of medical and surgical patients who were at risk of VTE and the thromboprophylactic measures employed by physicians for these patients were assessed.

Results: The results demonstrated that 559 patients (52.2%) did not require thromboprophylaxis. Yet, 17.8% were inappropriately administered a prophylactic treatment. Out of the 512 patients at risk of VTE, 443 were eligible for drug prophylaxis. However, 50%received the recommended treatment. Furthermore, significant variations were observed among centers in different countries regarding prophylactic measures in critically ill, cancer, chronically immobilized, and non-orthopedic surgery patients.

Conclusion: Despite the universal acknowledgment of the seriousness of VTE, the employment of thromboprophylaxis remains suboptimal in the Near East region. A considerable number of hospitalized patients are not receiving any VTE prophylaxis or are given inappropriate treatments. Further studies are required to assess and compare compliance rates prior to and following the implementation of such quality improvement projects.

1. Background

Venous Thromboembolism (VTE), defined as Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE), is a global cause of morbidity and mortality with annual incidence rates between 0.75 and 2.69 per 1000 individuals in the population (1). There are many predisposing risk factors that may account for its persistently high incidence, including age, obesity, pregnancy, immobility, and hospitalization (2). VTE was initially thought to be

a complication of major surgery, with a risk of 20 - 30% reported for such patients. However, studies have now demonstrated that up to 73% of hospitalized patients are at risk of developing VTE, and that as many as 26% of patients admitted to a general medical ward develop VTE in the absence of prophylaxis (3, 4).

Approximately half of all VTE cases occur during or shortly following a hospital stay (5). In a recent review by Raskob et al., VTE associated with hospitalization was revealed to be a leading burden of all diseases, measured in Disability-Adjusted Life Years (DALYs) (1). VTE is now regarded as the most important preventable cause of

^{*}Corresponding author: Abdalla Awidi, Jordan University Hospital, Amman, Jordan; Tel: +96-2-795277455

Email: abdalla.awidi@gmail.com.

death in hospitalized patients. Many healthcare facilities have adopted international guidelines (6, 7) and risk assessment/prevention protocols to reduce the incidence of hospital-acquired VTE (8). Recent advances in modern medicine have also led to development of multiple effective prophylactic interventions for VTE.

2. Objectives

While several studies have assessed the use of VTE prophylaxis in the Middle East (9-12), the current state of prophylaxis in the Near East region requires additional investigation. Thus, the present study aims to evaluate the proportion of hospitalized patients at risk of VTE as well as physicians' adherence to the local protocols and/or national/ international guidelines for VTE prophylaxis.

3. Patients and Methods

3.1. Study Design and Patient Population

This multinational, cross-sectional, observational study aimed to assess the prevalence of VTE risk and thromboprophylactic practices in hospitalized patients. This study was scheduled to recruit 1600 - 2200 patients from multiple sites across four countries in the Near East region, namely Lebanon, Syria, Jordan, and Iraq. VTE prophylaxis audit was done for all medical centers included in this investigation, representing the main hospitals in the listed countries. Approval of the study protocol by each hospital's respective institutional review board was obtained prior to study initiation.

The enrolled subjects were male and female medical and surgical patients. Medical patients were required to meet the following inclusion criteria: $aging \ge 40$ years and being admitted to hospital for treatment of a serious medical illness. The inclusion criteria for surgical patients were also aging at least 18 years and having undergone a surgical operation requiring either general or epidural anesthesia lasting for at least 45 minutes. The patients were excluded if they had missing hospital charts, refused to provide informed consent forms, were initially admitted for the treatment DVT or PE, or were hospitalized for a minor operation (anesthesia lasting for less than 45 minutes) with no other qualifying acute medical conditions.

3.2. Case Report Form and Data Collection

Given the observational nature of the study, no modifications to the standard of care were carried out. A standardized Case Report Form (CRF) was filled out by independent observers at each hospital during one predefined visit. The CRF included information about the inclusion and exclusion criteria, patients' demographics, weight, height, and reason for admission, presence of other risk factors, presence of any contraindications for thrombo-prophylaxis, presence of bleeding risk factors, serum creatinine level, patients' degree of immobility, type of administrated thrombo-prophylaxis, and concomitant medications. All sites were visited to check for informed consent forms, CRF completion, and consistency.

3.3. Statistical Analysis

Patient classification utilized in the 2012 ACCP

antithrombotic therapy and prevention of thrombosis guide were adopted for the current study (7). Continuous data were represented as mean, Standard Deviation (SD), minimum, maximum, and median with 95% Confidence Interval (CI). In addition, summary data were reported globally and by country for both medical and surgical cohorts. Furthermore, categorical data were summarized into number and percentage of the population, whereas quantitative data were represented as mean and SD. Chi-square test was used to detect any association between the categorical variables. In case the expected values within cells were lower than 5, Fisher's exact test was used. Besides, student's t-test was employed to compare quantitative variables. All statistical tests were performed using the SPSS statistical software, version 18 at 5% significance level.

4. Results

4.1. Participants' Characteristics and Reasons for Hospitalization

This study was performed on 26 hospitals from different areas across four countries in the Near East region. A total of 1256 participants were enrolled; 482 from Lebanon, 308 from Syria, 280 from Jordan, and 186 from Iraq. The patients were sub-grouped into 782 medical patients (62.3%) and 474 surgical ones (37.7%). However, 185 patients (14.7%) were excluded from the final analysis as the type of surgery was not specified (Table 1).

With the exception of age, the demographic and baseline characteristics of both cohorts were generally similar. According to the results, the mean age of the medical patients was significantly higher than that of the surgical patients (63.2 ± 13.6 years vs. 49.9 ± 18.3 years, P < 0.001). The two cohorts were similar with regards to gender composition, with males comprising 49.9% (n = 393) of the medical patients and 49.0% (n = 234) of the surgical ones (P = 0.76). The reasons for hospital admission among medical and surgical patients have been presented in Table 1.

4.2. VTE Risk Factors and Prophylaxis

Totally, 34.7% of the medical patients (n = 271) compared to only 12.7% of the surgical patients (n = 60) had multiple risk factors for VTE. The most prevalent VTE risk factor was acute infection among medical patients (n = 186; 24.5%), but active cancer among surgical ones (n = 65; 14.4%) (Table 2).

Out of the 1071 patients included the final analysis (782 medical and 289 surgical patients), 512 ones (47.8%) were deemed to be at risk of VTE according to the ACCP guidelines (medical: n = 385, 75.2% vs. surgical: n = 127, 24.8%). Yet, only 443 at-risk patients (86.5%) were eligible to receive pharmacological prophylaxis. However, only 52.7% of these patients received such a treatment, and a mere 50% of such treatments were concordant with ACCP 2012 recommendations. On the other hand, 191 patients (17.8%) received pharmacological prophylaxis despite the lack of indications, and only 15 of the 440 patients (3.4%) who were eligible for mechanical prophylaxis received the intervention.

The number of patients receiving any prophylactic treatment and the proportion of administration of the ACCP-recommended prophylaxis for each of the participating

Table 1. Reasons for Admission in Medical and Surgical Wards					
Reason for Admission	Number (%)				
Medical ward (n = 782)					
Infectious disease	111 (17.4)				
Acute respiratory failure	89 (13.9)				
Heart failure	37 (5.8)				
Other cardiovascular diseases	80 (12.6)				
Malignancy	102 (16.1)				
Ischemic stroke	36 (5.7)				
Acute pulmonary infection	76 (12.0)				
Hemorrhagic stroke	6 (0.9)				
Hematological disease	54 (8.5)				
Rheumatologic/inflammatory disease	11 (1.7)				
Neurological disease (stroke excluded)	43 (6.8)				
Urinary tract infection	34 (5.4)				
Endocrine/metabolic disease	19 (3.0)				
GI/hepatobiliary	86 (13.5)				
Renal disease	49 (7.7)				
Other medical conditions	28 (4.4)				
Surgical ward (n = 474)					
Hip replacement	20 (5.5)				
Knee replacement	10 (2.7)				
Hip fracture	10 (2.7)				
Curative arthroscopy	3 (0;8)				
Other orthopedic trauma	35 (9.6)				
Colon/small bowel	41 (11.1)				
Rectosigmoid	11 (3.0)				
Gastric	22(6.0)				
Hepatobiliary	41 (11.1)				
Urologic	40 (11.0)				
Vascular	19 (5.2)				
Thoracic	15 (4.1)				
Gynecologic	16 (4.4)				
Obstetric	11 (3.0)				
Other	94 (25.5)				
Surgery invasiveness					
Minimal	114 (25.1)				
Open surgery	326 (74.9				
Reason for surgery					
Surgery for cancer	73 (16.5)				

countries have been depicted in Figures 1 and 2, respectively. The results revealed no statistically significant differences among the countries regarding the proportion of patients receiving the ACCP-recommended prophylaxis (P = 0.87; Figure 1A). However, statistically significant differences were observed among the countries with respect to the proportion of critically ill (P < 0.001; Figure 1B), cancer (P < 0.05; Figure 1C), and chronically immobilized (P < 0.05;0.01; Figure 1D) patients receiving the ACCP-recommended prophylaxis. As for orthopedic surgery, there were statistically significant differences between the proportion of patients receiving any thrombo-prophylaxis and the recommended VTE prophylaxis (P = 0.001, Figure 2A). As for non-orthopedic surgery, there were no statistically significant differences between the proportion of patients receiving any thrombo-prophylaxis and the recommended VTE prophylaxis (P > 0.005, Figure 2B).

A significantly lower proportion of patients had no contraindications to thromboprophylaxis in the medical group compared to the surgical group (83.5% vs. 92.1%, P < 0.001). The commonly reported reasons for contraindications included significant renal impairment (medical: 10.0% vs. surgical: 1.3%) and a high risk of bleeding (medical: 7.0% vs. surgical: 2.4%), both of which were significantly more prevalent in the medical cohort (P < 0.001) (Table 3).

4.3. Type of Prophylaxis

The majority of thromboprophylactic treatments administered to medical and surgical patients were pharmacological. All types of thromboprophylaxis have been presented in details in Table 1. Accordingly, mechanical prophylaxis was primarily reserved for surgical patients and included the use of intermittent pneumatic compression (1.6%) as well as graduated compression stockings (2.2%).

5. Discussion

The current study demonstrated that a large proportion of hospitalized patients were at risk of developing VTE, and

Table 2. The Risk Factors of VTE in all Patients					
Risk Factors	Medical Patients	Surgical Patients	Total		
	Number (%)	Number (%)	Number (%)		
Patients with more than one risk factor	271 (34.7)	60 (12.7)	331 (26.4)		
Acute respiratory failure	61 (8.1)	1 (0.2)	62 (5.1)		
Acute inflammatory disorder	27 (3.6)	6 (1.3)	33 (2.7)		
Acute infection	186 (24.5)	24 (5.3)	210 (17.3)		
Active cancer	129 (17.1)	65 (14.4)	194 (16.1)		
Cancer therapy	92 (12.2)	18 (4.0)	110 (9.1)		
Recent ischemic stroke	39 (5.1)	5 (1.1)	44 (3.6)		
Chronic pulmonary disease	87 (11.5)	12 (2.7)	99 (8.2)		
Chronic heart failure	122 (16.1)	23 (5.1)	145 (12.0)		
Previous venous thromboembolism	12 (1.6)	7 (1.6)	19 (1.6)		
Varicose veins/insufficiency	30 (4.0)	15 (3.3)	45 (3.7)		
Thrombophilia	2 (0.3)	2 (0.4)	4 (0.3)		
Previous superficial venous thrombosis	2 (0.3)	3 (0.7)	5 (0.4)		
Contraceptives/hormone replacement therapy	4 (0.5)	2 (0.4)	6 (0.5)		
Long-term immobility	60 (7.9)	24 (5.3)	84 (7.0)		
Pregnancy (within three months)	1 (0.1)	13 (2.9)	14 (1.2)		
Obesity	77 (10.2)	41 (9.1)	118 (9.8)		
Central venous catheter	12 (1.6)	9 (2.0)	21 (1.7)		



(A), critically ill (B), cancer (C), and chronically immobilized medical patients (D) at risk of venous thromboembolism. *The data included at-risk patients with a high risk of bleeding.

many did not receive the appropriate prophylactic treatment according to the best practices on VTE prophylaxis in the area. Approximately half of all enrolled patients (47.8%) were deemed to be at risk of VTE, which is consistent with the previous reports (4, 13). Furthermore, the findings suggested that medical patients were more prone to



Figure 2. Prophylaxis Use in (A) Orthopedic Surgical Patients at Risk of Venous Thromboembolism and (B) Non-Orthopedic Surgical Patients at Risk of Venous Thromboembolism.

developing VTE, with a higher proportion of these patients presenting with multiple risk factors. This is in line with the previous reports, including the research by Piazza et al., which demonstrated that medical patients were at a higher risk of VTE (14).

Based on the present study results, application of the ACCP-recommended pharmacological prophylaxis was moderate across all centers (21.9 - 52%, P < 0.001). This was comparable to the results obtained in the ENDORSE and IMPROVE studies (4, 15). While the majority of medical patients were eligible for pharmacological prophylaxis (82.1%), adherence to ACCP recommendations was moderate at best (46.8% - 54.8%). Despite the generally higher adherence to ACCP guidelines in the surgical cohort, the observed rates (62.3%) were still suboptimal. This deviation from ACCP recommendations was especially encountered in patients who had undergone non-orthopedic surgeries. The superior adherence to the ACCP guidelines by orthopedic surgeons is not unexpected given that major orthopedic surgeries are a leading predisposing factor to VTE (16), and the benefits of prophylaxis for this type of surgery have been widely recognized. Furthermore, the

Reason for Contraindication	Medical Patients	Surgical Patients	Total	P value
	Number (%)	Number (%)	Number (%)	
No contraindications to thromboprophylaxis	649 (83.5)	431 (92.1)	1080 (86.7)	< 0.001
Currently receiving LMWH/UFU/VKA	14 (1.8)	2 (0.4)	16 (1.3)	0.038
Hypersensitivity to LMWH	1 (0.1)	1 (0.2)	2 (0.2)	0.235
High risk of bleeding	53 (7.0)	11 (2.4)	64 (5.3)	0.001
Acute infectious endocarditis	5 (0.7)	0 (0.0)	5 (0.4)	0.068
Significant renal impairment	78 (10.0)	6 (1.3)	84 (6.7)	< 0.001
Intracranial hemorrhage	8 (1.0)	1 (0.2)	9 (0.7)	0.166
Low platelet count (< 100 K/µL)	32 (4.1)	4 (0.8)	36 (2.9)	0.001
Known bleeding disorder	9 (1.2)	2 (0.4)	11 (0.9)	0.227
Active gastrointestinal bleeding	26 (3.3)	2 (0.4)	28 (2.2)	0.001
Hepatic impairment	12 (1.5)	1 (0.2)	13 (1.0)	0.039
Esophageal varices	3 (0.3)	0 (0.0)	3 (0.2)	-

results indicated that mechanical prophylaxis was largely unused despite the indication of such treatments in a large number of patients. The overall application of ACCPrecommended mechanical prophylaxis was markedly lower than the rates observed for pharmacological treatments (1.1 - 7.7%, P < 0.001).

The present study findings revealed significant variations among the participating countries regarding prophylactic practices in critically ill, cancer, chronically immobilized, and non-orthopedic surgery patients. These differences could be attributed to several factors, including differences in physicians' awareness levels, availability of guidelines, implementation of risk assessment/prevention protocols by the participating centers, and availability of necessary resources. However, no significant variations were observed in ACCP-recommended prophylaxis practices among orthopedic patients, suggesting that orthopedic surgeons across the Near East region are similarly aware of the surgery-associated risk of VTE and the importance of thromboprophylaxis. Low rates of compliance have been previously attributed to several physician-related factors, including safety concerns regarding the use of anticoagulants (17). This was especially prevalent while treating cancer patients (18). However, the low use of VTE prophylaxis observed in the present study cannot be solely attributed to such factors. In some instances, patients were inappropriately administered a thrombo-prophylactic treatment. It is likely that despite the availability of several VTE prevention guidelines, physicians' mistakes might have contributed to the observed compliance rates.

Several guidelines that outline the appropriate methods of prophylaxis for DVT and VTE are currently available. However, the persistence of VTE in hospitals across the world suggests that the implementation of these recommendations into clinical practice is a challenge. Fortunately, studies have been conducted to assess different strategies to improve compliance. For instance, a study by Al-Tawfig et al. indicated that implementation of a quality improvement project that included development of a protocol, monitoring prophylactic practices, and feedback raised compliance from 63% to 100% (19). Indeed, a systematic review by Toother et al. revealed that active strategies, including regular reminders and assistance for clinicians in providing appropriate prophylaxis, appeared to be more effective than the passive dissemination of clinical practice guidelines (20). Given these findings, widespread implementation of such protocols in healthcare centers in the Near East region is recommended to boost compliance. These protocols should ideally include the following components: conducting a local audit of the current prophylactic practices followed by a feedback to demonstrate the importance and relevance of VTE prophylaxis to physicians, continually on-going educational programs to improve awareness, and introducing a system (computer- or paper-based) to remind physicians to assess VTE risk and facilitate prescription.

There are several limitations to the current study that should be addressed. As a result of the cross-sectional design, the duration of adherence to the recommended prophylaxis throughout patients' full hospital stay could not be assessed. The number of hospitals that used a formal prophylaxis VTE protocol was not determined, as well. Availability of this information might have provided additional insights into the underlying cause of variation in compliance. Moreover, studies following patients up through their whole hospital stay are recommended to monitor patients' compliance with the prescribed VTE prophylaxis.

5.1. Conclusions

Despite the universal acknowledgment of the seriousness of VTE and the importance of thromboprophylaxis, the employment of such practices remains suboptimal in the Near East region. The present study findings indicated that a considerable number of hospitalized patients were not provided with any VTE prophylaxis or were given inappropriate treatments. The results also revealed that mechanical prophylaxis was under-utilized. Hence, a regional strategy is to evaluate VTE risk and implement multi-component interventional platforms to remind physicians to assess VTE risk and facilitate appropriate prophylactic prescriptions. Future studies can then assess and compare compliance rates prior to and following the implementation of such quality improvement projects.

Acknowledgements

There is no acknowledgements.

Authors' Contribution

All authors participated in study design, data collection, statistical analysis, and manuscript preparation.

Funding/Support

This study was sponsored and funded by Sanofi, which was involved in the design and collection of the data.

Financial Disclosure

There is no financial disclosure.

References

- Day ISCfWT, Raskob G, Angchaisuksiri P, Blanco A, Buller H, Gallus A, *et al.* Thrombosis: a major contributor to the global disease burden. *Journal of Thrombosis and Haemostasis*. 2014;**12**(10):1580-90.
- Anderson Jr FA, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23_suppl_1):I-9-I-16.
- Abdel-Razeq H. Venous thromboembolism prophylaxis for hospitalized medical patients, current status and strategies to improve. *Annals of thoracic medicine*. 2010;5(4):195.
- Cohen AT, Tapson VF, Bergmann J-F, Goldhaber SZ, Kakkar AK, Deslandes B, *et al.* Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *The lancet.* 2008;**371**(9610):387-94.
- Spencer FA, Emery C, Joffe SW, Pacifico L, Lessard D, Reed G, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. Journal of thrombosis and thrombolysis. 2009;28(4):401.
- National Institute of health and care excellence (NICE). 2010 [updated 2010; cited]; Available from: https://www.nice.org. uk"www.nice.org.uk.
- Guyatt GH, Akl EA, Crowther M, Schünemann HJ, Gutterman DD, Lewis SZ. Introduction to the ninth edition: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2):48S-52S.
- Maynard G, Stein J. Designing and implementing effective venous thromboembolism prevention protocols: lessons from collaborative

efforts. Journal of thrombosis and thrombolysis. 2010;29(2):159-66.

- Awidi A, Obeidat N, Magablah A, Bsoul N. Risk stratification for venous thromboembolism in hospitalized patients in a developing country: a prospective study. *Journal of thrombosis* and thrombolysis. 2009;28(3):309.
- 10. Mokhtari M, Salameh P, Kouchek M, Kashani B, Taher A, Waked M, *et al.* The AVAIL ME Extension: a multinational Middle Eastern survey of venous thromboembolism risk and prophylaxis. *Journal of Thrombosis and Haemostasis.* 2011;9(7):1340-9.
- 11. Taher AT, Aoun J, Salameh P. The AVAIL ME study: a multinational survey of VTE risk and prophylaxis. *Journal of thrombosis and thrombolysis.* 2011;**31**(1):47-56.
- 12. Zeitoun AA, Dimassi HI, El Kary DY, Akel MG. An evaluation of practice pattern for venous thromboembolism prevention in Lebanese hospitals. *Journal of thrombosis and thrombolysis*. 2009;**28**(2):192.
- Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2):e195S-e226S.
- Piazza G, Seddighzadeh A, Goldhaber SZ. Double trouble for 2,609 hospitalized medical patients who developed deep vein thrombosis: prophylaxis omitted more often and pulmonary embolism more frequent. *Chest.* 2007;**132**(2):554-61.
- 15. Tapson VF, Decousus H, Pini M, Chong BH, Froehlich JB, Monreal

M, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest.* 2007;**132**(3):936-45.

- Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e278S-e325S.
- Kakkar AK, Davidson BL, Haas SK, Investigators Against Thromboembolism Core G. Compliance with recommended prophylaxis for venous thromboembolism: improving the use and rate of uptake of clinical practice guidelines. *Journal of thrombosis* and haemostasis : JTH. 2004;2(2):221-7.
- Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, *et al*. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;**100**(10):3484-8.
- Al-Tawfiq JA, Saadeh BM. Improving adherence to venous thromoembolism prophylaxis using multiple interventions. *Ann Thorac Med.* 2011;6(2):82-4.
- Tooher R, Middleton P, Pham C, Fitridge R, Rowe S, Babidge W, et al. A systematic review of strategies to improve prophylaxis for venous thromboembolism in hospitals. *Annals of surgery*. 2005;241(3):397-415.