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RESEARCH ARTICLE

EVALUATION OF VENOUS THROMBO-EMBOLISM PROPHYLAXIS IN PATIENTS UNDERGOING MAJOR ORTHOPEDIC SURGERIES (HIP & KNEE) IN EGYPT.

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Abstract

Venous thrombo-embolism (VTE) is a major health threat despite the availability of various prophylactic regimens with favourable benefit-risk ratio. Guidelines on thrombo-embolic disorders and their management are also available. However, there are still gaps between guidelines and real life clinical practice. Patients undergoing major orthopedic surgeries are at high risk of developing VTE. Our study aims to compare real life VTE prophylaxis received by patients to the recommendations set by international ACCP guidelines (2008) during hospitalization and after hospital discharge and to detect the possible reasons for discrepancies. The study was a local, multicenter, longitudinal, non-interventional study with 4-6 weeks follow-up for patients undergoing major orthopedic surgeries and included a total of 3 visits; admission visit, discharge visit, and a follow-up visit. Each of the twenty active wards recruited around 10 to 15 consecutive patients. When this study was conducted, data was compared to what was recommended by ACCP 2008 guidelines to assess compliance. Our results shows that real life VTE prophylaxis was compliant to ACCP 2008 guidelines in a majority of patients both during hospitalization (96.6%; 95% CI: 94.7, 98.6%) and after hospital discharge (73.3%;

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95% CI: 68.4, 78.2%). Reasons for non-compliance to guidelines during hospitalization included late starting of VTE prophylaxis, not prescribing VTE prophylaxis and prescribing other anti-thrombotic agents not recommended by the guidelines. Reasons for post discharge non-compliance included no prophylaxis, longer or shorter prophylaxis and prescribing other anti-thrombotic agents not recommended by the guidelines. VTE prophylactic medications prescribed for patients who underwent major orthopedic surgery were compliant to ACCP 2008 guidelines during hospitalization and after hospital discharge.

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Introduction:-

Venous thrombo-embolism (VTE) is recognized to be a major global health problem resulting in significant morbidity and mortality [1, 2]. In Europe and North America, the approximate incidence of VTE is 160 per 100'000 annually for Deep vein thrombosis (DVT) and for symptomatic non-fatal PE, the incidence is 20 per 100,000 while incidence of fatal pulmonary embolism (PE) stands at 50 per 100 000 [3, 4]. Sudden death is the initial clinical presentation in almost one quarter of patients with PE [5-7]. In a study conducted in Egypt, 39.2% of enrolled medical and surgical patients were at high risk for VTE. In the same study, surgical patients were found to be at higher risk than medical patients [8].

Major orthopedic surgery remains a condition at high risk of VTE. In patients who undergo major orthopedic surgeries, venous thrombo-embolism occurs with an incidence reported to be 41 to 85% for asymptomatic DVT, 5 to 36% for proximal DVT, and 0.1 to 1.0% for fatal PE, in the absence of effective VTE prophylaxis. Patients who undergo lower limb arthroplasties and hip fracture surgery have the highest incidence of VTE among surgical patients due mostly to vessel trauma, venous stasis in the limb, immobility, age and other VTE risk factors [9, 10].
VTE prophylaxis has traditionally been considered for patients undergoing surgery until hospital discharge (typically 5-14 days). However, results of several studies have shown that a significant number of patients experience DVT or PE during the 6 weeks following orthopedic surgery. And accordingly, as extended risk became will recognized, prolonged VTE prophylaxis duration of up to 6 weeks is suggested as a more effective regimen to prevent VTE in patients undergoing orthopedic surgery especially for those at high risk of developing VTE. In addition to identifying patients who are at high risk, key challenges include choosing a relatively safe, convenient and effective prophylaxis regimen to ensure patient compliance and clinical benefits [11-13].

Anticoagulants drugs used for VTE prophylaxis include unfractionated heparins (UFH), low molecular weight heparins (LMWH), fondaparinux and vitamin K antagonists (VKA). These drugs can reduce the risk of developing VTE by 60% or more. In addition, direct oral anticoagulants (DOACs) are used for VTE prophylaxis and for treatment of established VTE. However, their use will depend on assessing expected clinical benefit versus the probable risk of bleeding [14, 15].

Evidence based guidelines for VTE prevention have been available for more than 20 years. Hospitalized patients usually have at least one VTE risk factor. Without prophylaxis, around 40 to 60% of patients undergoing major orthopedic surgeries will develop hospital-acquired DVT according to several factors including; advanced age, type and duration of surgery, post-operative infections in addition to reduced mobility after discharge. Around 10% of hospital deaths result from pulmonary embolism [9, 16].

Proven methods of pharmacological prophylaxis for patients undergoing elective total hip replacement (THR) or elective total knee replacement (TKR) include; LMWH, fondaparinux, adjusted-dose VKA or DOACs.[15]While mechanical methods of prophylaxis include; graduated elastic compression (GEC) stocking, intermittent pneumatic compression (IPC) devices and foot impulsive devices (FID) [15-18].

The aim of the study is to describe real life VTE prophylaxis in Egypt and to compare it to the recommendations of international guidelines in patients undergoing major orthopedic surgeries; TKR, THR, and hip fracture surgeries (HFS).

Subjects and Methods:-

Site and patient selection:-

Selection of investigators:

The participating physicians were orthopedic surgeons operating in orthopedic or trauma wards from private or public hospitals/clinics in different governorates in Egypt.

Selection of patients:

Each of the twenty active wards recruited around 10 to 15 consecutive patients. All patients who were undergoing major orthopedic surgeries and fulfilling all eligibility criteria were asked to participate. For those who refused to take part in the study, the reason was recorded in the screening log. This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments. Prior to a patient's participation in the study, a written Informed Consent Form was signed, name filled in and personally dated by the patient or by the his legally acceptable representative and by the person who conducted the Informed Consent discussion. A copy of the signed and dated written Informed Consent Form was provided to the patient.

Eligibility criteria:

Inclusion criteria:

- Males and females > 21 years of age.
- Admitted to orthopedic ward to undergo THR, TKR or HFS.
- Patients willing to sign data release consent.

Exclusion criteria:

- Patients having suffered multiple traumas including visceral lesions and involving the vital prognosis.
- Patients having suffered a previous VTE within the last 6 months.
- Patients receiving long-term therapy with an anticoagulant agent for any reason other than surgery).
- Patients currently participating in a clinical trial.

Study design:-

The study is a local, multicenter, non-interventional on the therapeutic strategy, longitudinal study with 4-6 weeks follow-up after major orthopedic surgery and includes a total of 3 visits; visit 1 (admission visit) , visit 2 (discharge visit) and visit 3 (follow-up visit). The enrollment duration was up to 12 months, and data was collected using paper CRFs. Investigators complied with the regulations for the spontaneous reporting of Adverse Drug Reactions.

Statistical considerations:-

Analysis population(s)

- Enrolled population: all subjects included in the study.
- Eligible (Descriptive) population: subject who satisfied the inclusion/exclusion criteria.
- Follow-up Analysis Population: eligible subjects who have follow-up data for the 1ry study endpoint "Post discharge VTE prophylaxis 4 – 6 weeks".

Statistical power and sample size justification:

Reference to previous studies that investigated the prophylaxis of VTE in orthopedic surgery patients, the percentage of in-hospital patients undergoing orthopedic surgeries (including THA and TKA) had received appropriate VTE prophylaxis in adherence to ACCP guidelines ranges from 52.4% to 73.8% (average is 63%). We expected this percentage in Egypt to be not less than 60%. Assuming that 60% of patients would receive a prophylaxis in compliance to guidelines, enrolment of 300 patients would provide a 95% CI precision rate of 5.54% (54.5%-65.5%)

Statistical methods:-

Data was analyzed using the software, Statistical Package for Social Science, (SPSS) version 19. Frequency distribution with its percentage and descriptive statistics with mean and standard deviation were calculated. Percentages of compliant patients were calculated with 95% CI. Chi-square, t-test, correlations were done whenever needed.

P values of less than 0.05 were considered significant.

Results:-

A total of 327 patients were recruited from 20 active sites. The study was initiated in July 2012 (first patient included) and was completed in March 2014 (last patient completed). Out of included patients, 326 (99.7%) were eligible patients who constituted the descriptive population as one patient (0.3%) was aged less than 21 years. Of them, 137 (42%) were males and 189 (58%) were females. The mean age of eligible patients was 60.6± 13.4 years.
At enrolment visit, medical history was reported in 172 (52.8%) patients while not reported in 154 (47.2%) patients. Diabetes mellitus was the most frequent medical history as reported in 86 (26.4%) patients, followed by hypertension in 45 (13.8%) patients, renal insufficiency in 17 (5.2%), varicose veins in 14 (4.3%), hepatic diseases in 13 (4.0%), coronary artery diseases in 8 (2.5%), rheumatoid arthritis in 4 (1.2%) while thrombophilias, stroke and cancer were reported in 3 patients each. Analysis of the physical status (PS) according to the American Society of Anesthesiologists (ASA) revealed that, out of 326 patients, 120 (36.8%) were normal health patients "ASA PS1", 174 (53.4%) were having a mild systemic disease "ASA PS2" while 32 (9.8%) were having a severe systemic disease "ASA PS3". Pre-operative blood labs showed normal figures within normal ranges for platelets, INR and serum creatinine.

Of the eligible patients, 128 (39.3%) were admitted to orthopedic ward to undergo knee arthroplasty, 99 (30.4%) patients were admitted to undergo hip arthroplasty and the same number of patients were also admitted to undergo hip fracture surgery (Figure 1).

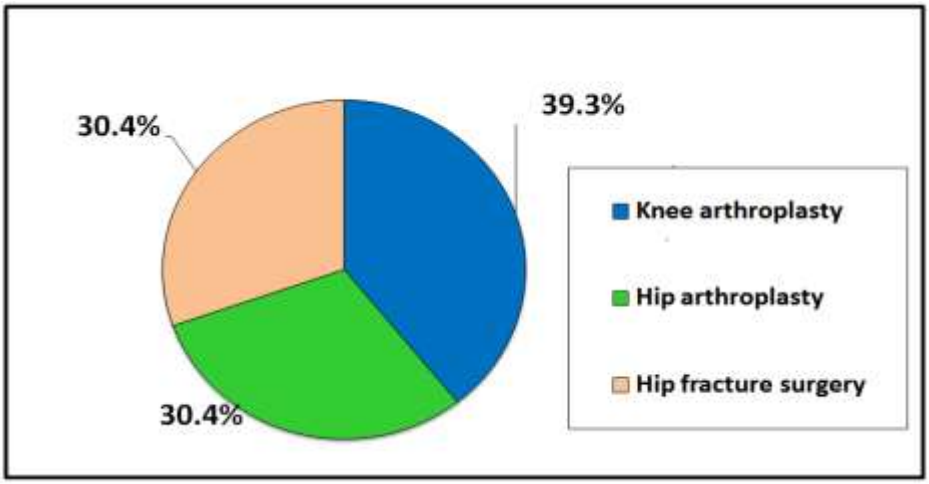


Figure 1:- Types of surgical procedures

Arthroplasty was the type of intervention in 245 (75.2%) patients while osteosynthesis was the intervention in 81 (24.8%) patients.

Regional "Spinal" anesthesia was the most frequently used anesthesia for surgery as reported in more than half of the patients; 192 (58.9%), followed by regional "Epidural" with Catheter in 78 (23.9%) patients, general anesthesia in 52 (16.0%) patients while regional "Epidural" anesthesia without Catheter was reported in 4 (1.2%) patients.
During hospitalization, out of 326 (100%) patients, 324 (99.4%) were prescribed VTE prophylaxis while only 2 patients (0.6%) were not prescribed VTE prophylaxis. The main reasons for not prescribing prophylaxis as reported by physicians were; fear of “Heparin induced thrombocytopenia” in one patient and non-compliance in the other patient.

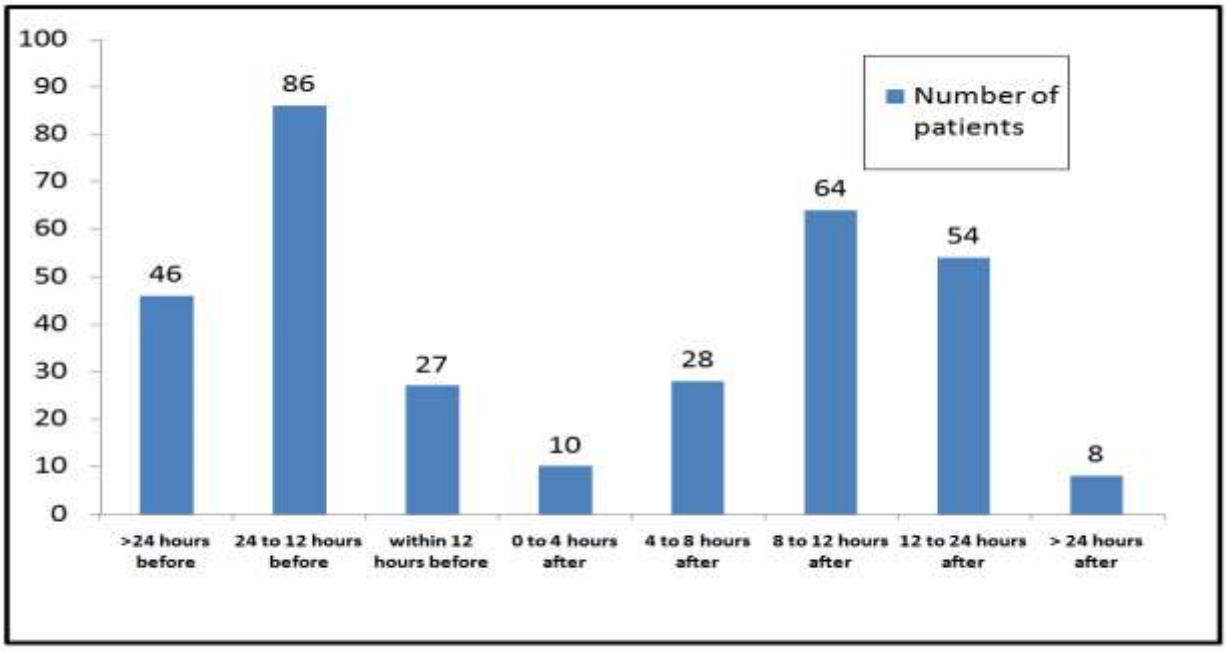
LMWH was the most frequently prescribed medication for VTE prophylaxis during hospitalization as it was prescribed for 297 (91.1%) patients, followed by OAC warfarin, rivaroxbanand dabigatran for 26 (8.0%) patients while one patient (0.3%) was prescribed another anti-thrombotic agent (Table 1).

Table 1:- VTE prophylaxis medications during hospitalization

Class	Count	%	Generic name	Count	%	Dose	Count	%
LMWH	297	91.1	Enoxaparin	280	85.9	40 mg	259	92.5*
						60 mg	4	1.4*
						80 mg	17	6.1*
			Nadroparin	16	4.9	0.3 mg	16	4.9
			Tinzaparin	1	0.3	2500 IU	1	0.3
OAC	26	8.0	Rivaroxaban	21	6.4	10 mg	21	6.4
			Dabigatran	5	1.5	150 mg	5	1.5
No prophylaxis	2	0.6	NA	2	0.6	NA	2	0.6
Another anti-thrombotic Agent	1	0.3	NA	1	0.3	NA	1	0.3
Total	**326**	**100**						
***** *Percentages were calculated from the number of patients prescribed Enoxaparin*								

Further, timing of the 1st VTE pharmacologic treatment was as follows; 46 (14.1%) patients have received their 1st VTE prophylaxis medications more than 24 hours before surgery, 86 (26.4%) patients have received it 12 to 24 hours before surgery, 27 (8.3%) within 12 hours before surgery, 10 (3.1%) have received the prophylaxis within 4 hours after surgery, 28 (8.6%) received the prophylaxis from 4 to 8 hours after surgery, 64 (19.6%) received prophylaxis from 12 to 24 hour after surgery and 8 (2.5%) patients have received their 1st VTE prophylaxis medications more than 24 hours after the surgery (Figure 2).

Figure 2:- Timing of 1st administration of pharmacological treatment for VTE prophylaxis



In addition, one or more mechanical methods for VTE prophylaxis were used during hospitalization as an adjunct to pharmacological prophylaxis for 69 (21.2%) patients, while no mechanical methods were used for 257 (78.8%) patients. The most frequently used mechanical method during hospitalization was bandages which were used in 52 (16.0%) patients followed by intermittent pneumatic compression in 34 (10.4%) patients and graduated elastic compression stockings in 15 (4.6%) patients.

Out of 326 patients, real life VTE prophylaxis received by 315 patients (96.6%; 95% CI: 94.7, 98.6%) was compliant to ACCP 2008 guidelines while that received by 11 (3.4%) patients was considered non-compliant to the guidelines (Figure 3).

Eleven patients were non-compliant to ACCP 2008 guidelines as the late starting of VTE prophylaxis "> 24 hours after surgery" in 8 (72.7%) cases, not prescribing VTE prophylaxis during hospitalization in 2 (18.2%) cases and prescribing other anti-thrombotic agents not recommended by ACCP 2008 in one (9.1%) case.

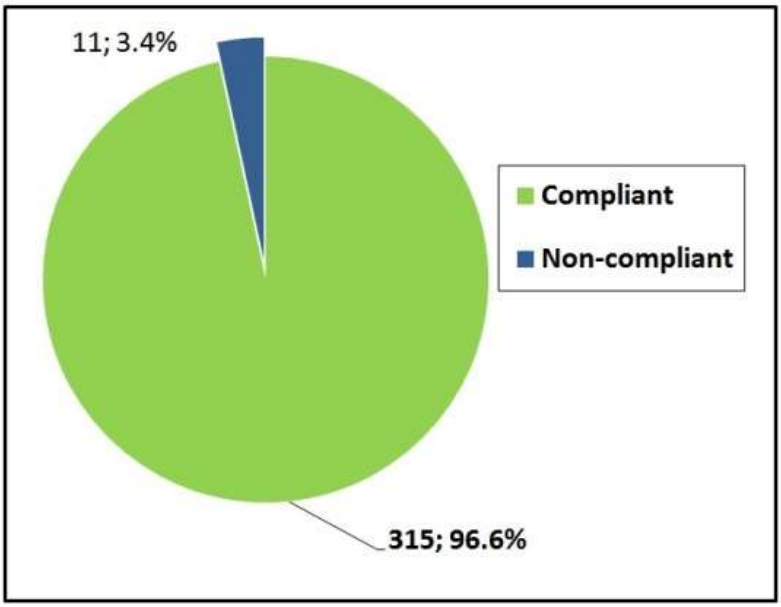


Figure 3:- Compliance of VTE Prophylaxis during Hospitalization to (ACCP 2008) guidelines

VTE prophylaxis was prescribed for 283 (86.8%) patients for the post discharge period while not prescribed for 43 (13.2%) patients. Physicians' reasons for not prescribing VTE prophylaxis for post discharge period as per ACCP 2008 guidelines for the 43 patients were that extended prophylaxis was not medically justified in 36 (83.7%) patients while bleeding tendency was the reason in 7 (16.3%) patients.

It is also worth pointing out that the follow-up analysis population included only 318 (97.3%) patients who were eligible and having follow-up data for the 1^{ry} study endpoint; as 5 (1.5%) patients were lost to follow-up and 3 (0.9%) patients died. Out of the 318 patients, post-discharge VTE prophylaxis medications were taken as prescribed by 261 (82.1%) patients, not taken as prescribed by 17 (5.3%) patients while 40 patients (12.6%) were not prescribed VTE prophylaxis for post-discharge period.

Of those who didn't take their post discharge VTE prophylaxis as prescribed, 5 (31.25%) patients didn't take it due to economic reasons, prophylaxis was discontinued for bleeding in 4 (25%) patients, while the non availability of drugs prescribed at pharmacy were the reasons for3 (18.75%) patients. In contrast , "No or partial re-imbursement by Health system", "Self-injection non-possibility/ No-one to perform the injection", "Omission" and " Definitive prophylaxis discontinuation for medical reason (DVT)" were chosen by 1 (6.25%) patient per each reason.

Besides, for post discharge period, VTE prophylaxis medications were prescribed for 278 (87.4%) patients while not prescribed for 40 (12.6%) patients.

LMWH was the most frequently prescribed medication post discharge as it was prescribed for 229 (72.0%) patients, followed by OAC for 48 (15.1%) patients while one patient (0.3%) was prescribed another anti-thrombotic agent (Table 2).

Table 2:- VTE prophylaxis medications post discharge

Class	Count	%	Generic name	Count	%	Dose	Count	%
LMWH	229	72.0	Enoxaparin	228	71.7	40 mg	212	93.0*
						60 mg	4	1.8*
						80 mg	12	5.2*
			Tinzaparin	1	0.3	2500 IU	1	0.3
OAC	48	15.1	Rivaroxaban	38	11.9	10 mg	38	11.9
			Dabigatran	10	3.1	150 mg	6	60**
						220 mg	4	40**
No prophylaxis	40	12.6	NA	40	12.6	NA	40	12.6
Another anti-thrombotic Agent	1	0.3	NA	1	0.3	NA	1	0.3
Total	**318**	**100**						

***** *Percentages were calculated from the number of patients prescribed Enoxaparin*
****** *Percentages were calculated from the number of patients prescribed dabigatran*

Mechanical methods for VTE prophylaxis were used post discharge as an adjunct to medication-based prophylaxis for 26 (8.2%) patients while no mechanical methods were used for 292 (91.8%) patients.
Graduated elastic compression stockings were used by 16 (5.0%) patients while bandages were used by10 (3.1%) patients.

Out of 318 (100%) patients, real life VTE prophylaxis received by 233 patients (73.3%; 95% CI: 68.4, 78.2%) was compliant to ACCP 2008 guidelines while that received by 85 (26.7%) patients was considered non-compliant to the guidelines (Figure 4).

Out of the 85 (100%) ACCP 2008 non-compliant cases, reasons for non-compliance were not prescribing post discharge VTE prophylaxis in 40 (47.1%) cases, long duration of post-discharge VTE prophylaxis (more than 35 days) in 32 (37.6%) cases, short duration of post-discharge VTE prophylaxis (less than 10 days) in 12 (14.1%) cases and prescribing other anti-thrombotic agents not recommended by ACCP 2008 in one (1.2%) case.

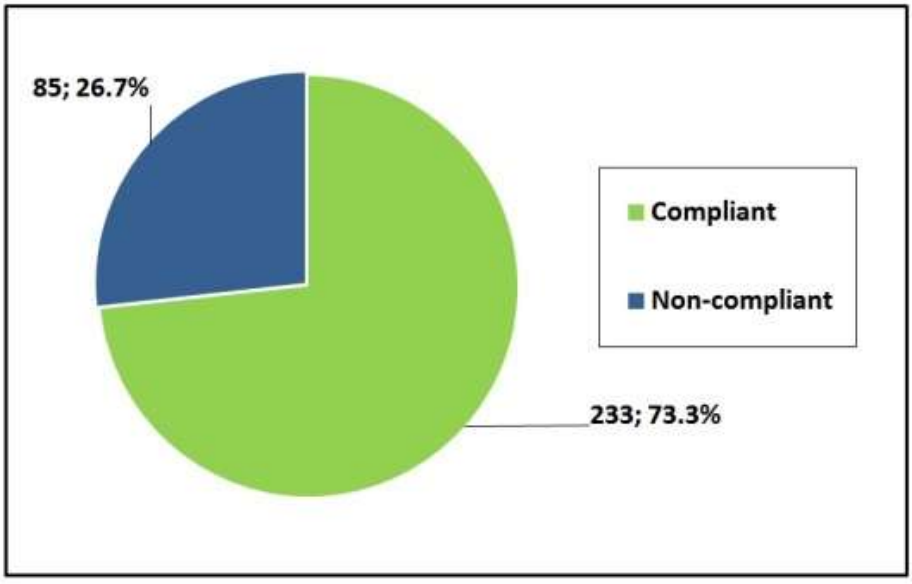


Figure 4:- Compliance of VTE Prophylaxis post discharge to (ACCP 2008) guidelines

Discussion:-

VTE is a major cause of morbidity and mortality in hospitalized patients, especially those admitted to orthopedic surgeries. Numerous randomized controlled trials showed that using thrombo-prophylaxis in hospitalized patients at risk for VTE is safe, effective in addition to being cost-effective [3, 5, 6].

But, though effective strategies for prevention of VTE are widely available, these strategies remain underused; mainly in developing countries and the question whether the implementation of guidelines of VTE prophylaxis for surgical patients influenced the prescription of prophylaxis by the medical staff or improved the outcome of the patients still have no clear answer [19]. In addition, the discrepancy between guidelines and real life is a worrisome challenge which should be evaluated for further steps to be taken.

Our study results showed that during hospitalization, real life prophylaxis received by (96.6%; 95% CI: 94.7, 98.6%) of the patients was compliant to ACCP 2008 guidelines. However relatively lower the VTE prophylaxis received, after hospital discharge, by (73.3%; 95% CI: 68.4, 78.2%) of the patients was compliant to the guidelines.
Reasons for non-compliance to guidelines during hospitalization included late starting of VTE prophylaxis "> 24 hours after surgery", not prescribing VTE prophylaxis during hospitalization and prescribing other anti-thrombotic agents not recommended by the guidelines. On the other hand, reasons for post discharge non-compliance included not prescribing post discharge VTE prophylaxis at all, longer than recommended duration of prophylaxis (more than 35 days), shorter than recommended duration of prophylaxis (less than 10 days) and prescribing other anti-thrombotic agents not recommended by the guidelines.

Low molecular weight heparin was the most frequently prescribed medication during hospitalization and after discharge followed by Oral anti-coagulants. Mechanical methods for VTE prophylaxis were used for some patients during hospitalization and after hospital discharge as an adjunct to medication-based prophylaxis.

Arnold et al and Ageno et al, showed that surveys of prophylaxis use point to the percentage of medical and surgical patients receiving prophylaxis ranges from 38 to 94 according to the type of illness or procedure [19-21].

In a study conducted in the United States to evaluate the use of guidelines on thromboprophylaxis in surgical and medical patients, it was found that around two thirds of confirmed VTE cases could have been potentially prevented ACCP guidelines were followed [20].

The most common reasons given for inadequate prophylaxis were lack of prophylaxis (47.7%), inadequate duration (22.7%), and incorrect type of prophylaxis (20.5%). Surprisingly, a tendency has also been reported for prophylaxis to be administered less frequently with increasing VTE risk level [22].These results may reflect physician concerns that the risk of bleeding may be greater in very high-risk patients. Despite ample documentation of VTE risk in hospitalized medical patients, such patients are less likely to receive appropriate thrombo-prophylaxis.

In a prospective registry, conducted in 5,451 patients with confirmed DVT, only 22.2% of medical patients received prophylaxis compared with 46.9% of the surgical cohort [23, 24].

Similarly, IMPROVE registry of acutely ill medical patients, reported that only 39% of patients hospitalized for 3 days or more received VTE prophylaxis. In the United States, in a tertiary care center, 75% of admitted patients (for medical services) were at high risk for developing VTE while only 43% of them received prophylaxis [25].

As a result of an educational program to improve compliance, 79% of patients were identified to be at risk for VTE and an improvement is prophylaxis rate was observed as the rate reached72%.[(21)] In a study of 272 critically ill medical patients, pharmacologic prophylaxis (alone or combined with mechanical methods) was used in 38% of patients. This resulted in 55% risk reduction of in hospital death [26].

Clinical recommendations and guidelines alone are not enough to improve clinical outcomes but treating physicians should be aware about the recommendations and the risk for patients if not allowed. Factors influencing physicians' adherence to guidelines are still not clear but several there barriers that can obstruct physicians' adherence to guidelines [27].

These barriers include; limited willingness of treating physician to follow guidelines and resistance to changing established practices. In addition, lack of awareness and disagreement with guidelines are major barriers to compliance. Moreover, casual awareness is not enough but sufficient familiarity and knowledge to apply recommendations are needed. In addition, guidelines and recommendations need to be integrated into hospital protocols in order to facilitate physicians' compliance [28].

To the best of our knowledge, this study was the first study conducted in Egypt to evaluate the followed VTE prophylaxis regimens in patients undergoing major orthopedic surgeries.

From our data we can conclude that VTE prophylactic treatment prescribed for most of our patients who underwent major orthopedic surgery during hospitalization was compliant to ACCP 2008 guidelines and percentage of compliance was relatively low in the post discharge period. However, the previously mentioned barriers for compliance should be taken into consideration in future research in order to reach higher compliance rates.

Disclosure:
The authors do not have any conflict of interest regarding this work.

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