Safety and effectiveness of thromboprophylaxis use in hospitalized elderly medical patients at a Saudi tertiary care center

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ABSTRACT

Introduction: Appropriate prescribing of thromboprophylaxis according to guidelines’ recommendations can heighten over- or underutilization risk. The study intended to evaluate the safety and effectiveness of appropriate/inappropriate thromboprophylaxis use among hospitalized elderly medical patients.

Methods: A retrospective observational cohort study was conducted, including patients who were ≥60 years old, hospitalized for an acute medical illness that required hospitalization in a medical ward for >48 h, and received thromboprophylaxis. Against the American College of Chest Physicians guidelines, the thromboprophylaxis use appropriateness was assessed.

Results: A total of 370 patients met the inclusion criteria, in 71.9% of whom thromboprophylaxis use was appropriate. The mean age of the included patients was 75 years (±9.1), and 72.4% of them were at high risk of venous thromboembolism (VTE), and almost all these patients received appropriate thromboprophylaxis. The occurrence of bleeding was significantly higher in the appropriate use group during hospitalization than the inappropriate use group (11.7% vs. 2.9%, \( p = 0.009 \)); the majority of these bleeding events were classified as major. There were no differences in VTE events during hospitalization or 90 days all-cause mortality between the two groups.

Conclusion: The study demonstrates high prescribers’ compliance with recommendations in high-risk patients. In patients at low risk for VTE, the overutilization of thromboprophylaxis did not increase their bleeding risk. This study suggests that the benefits of thromboprophylaxis in elderly patients, regardless of their VTE risk, may outweigh the risk of bleeding.

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1. Introduction

Venous thromboembolism (VTE), including both pulmonary embolism (PE) and deep venous thrombosis (DVT), is a serious con-

condition that is associated with increased preventable morbidity and mortality (Kesieme et al., 2011; Leizorovicz et al., 2004; Samama, 2000). It remains a common complication among surgical and nonsurgical hospitalized patients (Cohen et al., 2008; Goldhaber et al., 2000; O’Donnell, 2003; Wang et al., 2011). VTE is still one of the leading causes of preventable hospital deaths in the United States and developing countries (Maynard, 2016; Stone et al., 2017). In the United States, VTE affects 300,000–600,000 individuals and causes approximately 100,000 deaths annually (Beckman et al., 2010). A multinational study that enrolled 68,183 hospitalized patients from 32 countries (including 154 patients from Saudi Arabia) reported that more than half of the hospitalized patients were at risk of VTE (Cohen et al., 2008).

Overall, the risk of VTE increases with age, especially in hospital-
ized elderly patients (Alikhan et al., 2004; Khalafallah et al.,
Incidence of VTE was notably increased in hospitalized elderly versus younger patients (Heit et al., 2001; Spencer et al., 2014; Tritescher and Aujesky, 2017). Several risk assessment models (RAMs) have been evaluated to determine the risk of VTE in hospitalized medically ill patients (Darzi et al., 2020). These RAMs help practitioners identify hospitalized patients at high risk for developing VTE during hospitalization, including the Padua prediction score (Barbar et al., 2010). Thromboprophylaxis is known to reduce the incidence of VTE, especially in those high-risk patients (Alikhan et al., 2004; Cohen et al., 2006; Leizorovicz et al., 2004; Wang et al., 2011). Thus, the 2012 American College of Chest Physicians (ACCP) and the 2018 American Society of Hematology (ASH) guidelines recommend using thromboprophylaxis for all medically ill hospitalized patients who are at high risk of VTE (Kearon et al., 2016; Schinemann et al., 2018). The guidelines’ recommendation of mechanical devices or pharmacological agents for thromboprophylaxis is based mainly on patients’ risk of bleeding (Kearon et al., 2016; Schinemann et al., 2018). Although most older adults are at increased risk of VTE requiring thromboprophylaxis, they also have a higher risk of bleeding, which is exacerbated by the use of pharmacological thromboprophylaxis (Cohen et al., 2006; Lacut et al., 2008; Leizorovicz et al., 2004).

Clinical guidelines’ recommendations help guide practice, but it is more important to apply these guidelines. Low adherence to guidelines’ recommendations remains a major issue in hospitals (Henke et al., 2020). Previous reports have indicated a low compliance rate with VTE prophylaxis guidelines (Henke et al., 2020). Studies have estimated that only 24–53% of medical patients receive appropriate thromboprophylaxis (Amin et al., 2007; Cohen et al., 2008; Grant et al., 2018; Kahn et al., 2007; Taher et al., 2011; Tapson et al., 2007; Wang et al., 2011). The overutilization of pharmacological thromboprophylaxis may expose patients to an unnecessary risk of bleeding. At the same time, the underutilization may expose patients to an avoidable risk of VTE. The risk of bleeding remained the major holdback for practitioners who are afraid of over thromboprophylaxis, especially in elderly hospitalized patients. The decision of whether to use pharmacological thromboprophylaxis must balance the benefits of avoiding a VTE event and the risk of bleeding. Moreover, inappropriate thromboprophylaxis utilization becomes more critical in a frail population, such as elderly patients, who are normally at a higher risk of VTE and bleeding.

Because the elderly population has generally been underrepresented in pharmacological thromboprophylaxis clinical studies (Cohen et al., 2006; Kucher et al., 2005; Leizorovicz et al., 2004; Samama et al., 1999), uncertainty remains about whether the benefits and risks of thromboprophylaxis can be generalized to these patients, on whom few studies have focused. Furthermore, the inappropriate utilization of thromboprophylaxis in elderly medical patients may expose them to a higher, yet preventable, risk of VTE or anticoagulation-related bleeding or death. Accordingly, this study was conducted to evaluate the safety and effectiveness of thromboprophylaxis use among elderly medical patients. In addition to assessing the impact of the appropriateness of thromboprophylaxis use on patients’ safety and efficacy outcomes.

2. Material and methods

2.1. Study design and setting

A retrospective observational cohort study was conducted at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia, from October 2019 to March 2020. The KAMC is a tertiary care academic medical center with about 1,500 beds. We evaluated the effectiveness and safety outcomes of appropriate and inappropriate thromboprophylaxis use according to the ACCP recommendations. Ethical approval was obtained from the institutional review board at King Abdullah International Medical Research Center.

2.2. Study population

All patients admitted to medical floors at KAMC were assessed for inclusion in the study. Patients who were ≥ 60 years old, admitted for an acute medical illness that required hospitalization in a medical ward for > 48 h and received pharmacological or mechanical thromboprophylaxis were included. We excluded patients who received treatment doses of anticoagulant for other reasons, had active bleeding on admission or had a VTE diagnosis within 48 h of admission.

2.3. Data collection

Data were collected from patients’ electronic medical records. Data about patients’ demographics, the reason for admission, pre-existing comorbidities, and VTE risk factors based on the Padua prediction score were retrieved. Data on the use of thromboprophylaxis and patients’ outcomes were followed up from admission date (index date) to the patient’s discharge or death.

2.4. Appropriateness of prescribing VTE prophylaxis

The appropriateness of thromboprophylaxis use was evaluated against the recommendations of the ACCP 9th edition guidelines (Kearon et al., 2016). Based on the VTE risk level reflected in Padua prediction score (Barbar et al., 2010), patients were categorized as high-risk if they had a Padua score of ≥ 4 points and thus were recommended for thromboprophylaxis based on ACCP guidelines (Kearon et al., 2016). Prescribed thromboprophylaxis was considered “appropriate” if the patient was eligible (high-risk) and received proper VTE prophylaxis (type and dose), while “inappropriate” if the patient was ineligible but received thromboprophylaxis.

2.5. Study outcomes

2.5.1. Major and minor bleeding

Based on the International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding in nonsurgical patients, bleeding was categorized. (Schulman and Kearon, 2005) Major bleeding was identified if the patient had fatal bleeding; symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome; bleeding causing a drop in hemoglobin level of 2 g/dL or more, or bleeding leading to transfusion of two or more units of whole blood or red cells. Minor bleeding was defined as any bleeding event that did not fit the criteria for major bleeding.

2.5.2. Venous thromboembolism (VTE) and all-cause death

VTE was defined as the occurrence of DVT or PE or both during hospitalization, confirmed by one of the following: (1) PE diagnosis using perfusion scanning and computed tomography, or pulmonary angiography; (2) DVT diagnosis using Doppler ultrasonography; or (3) cause of death related to VTE in patient’s medical record. All-cause death was defined as death documentation from any cause during hospitalization and up to 90 days after hospital discharge.
2.6. Statistical analysis

Descriptive statistics were used to describe patients’ characteristics. The t-test and chi-square test were used to assess differences between the two groups’ baseline characteristics and incidence of bleeding (major or minor), VTE, and all-cause death in patients who received thromboprophylaxis appropriately or inappropriately. An α of < 0.05 was used for statistical significance. The data were coded, checked for accuracy, and analyzed using the SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

From October 2019 through March 2020, 700 elderly patients were admitted for at least 48 hours and initially screened for eligibility. Of these patients, 370 elderly patients met the inclusion criteria. The mean age of the included patients was 75 years (±9.1), and 43.2% were female. The majority of the included patients were overweight, with an average BMI of 27 kg/m², and obese patients (BMI > 30 kg/m²) accounted for 29.2% of the total population. Thromboprophylaxis use was appropriate in 266 patients (71.9%), while 104 patients (28.1%) inappropriately received thromboprophylaxis. Almost all patients (102 patients; 98.1%) who were not supposed to receive thromboprophylaxis but did, whereas only 2 were high-risk patients who received an inappropriate dose or type of thromboprophylaxis.

Both groups’ baseline characteristics were similar, differing only in mean age, presence of active cancer, and VTE history, which were significantly higher in patients who received appropriate thromboprophylaxis. The majority of the included patients (72.4%) were at high risk of VTE (Padua score ≥ 4), and almost all these patients received appropriate thromboprophylaxis. Hypertension, diabetes mellitus, and chronic kidney disease were present in 79.5%, 76.2%, and 35.4% of the included patients, respectively. The most commonly used thromboprophylaxis method was pharmacological (98.1%), with unfractionated heparin being the most prescribed anticoagulant for included patients (83.5%). Table 1 gives the patients’ baseline characteristics.

The incidence of bleeding events during hospitalization was higher in patients who received appropriate thromboprophylaxis than in those who inappropriately received thromboprophylaxis (31 vs. three patients; 11.7% vs. 2.9%, p = 0.009). Major bleeding affected 22 of the 31 patients who had bleeding events in the appropriate thromboprophylaxis group (8.3%) and accounted for all bleeding events in the inappropriate thromboprophylaxis group (p = 0.064). No differences were seen in VTE incidence during hospitalization between the two groups (4% vs. 1.1%). Likewise, the difference in all-cause mortality within 90 days between the two groups (15.4 vs. 10.6%) was not significant (Table 2).

4. Discussion

This study evaluated the real-world safety and effectiveness of thromboprophylaxis use among elderly medical patients and the impact of the appropriateness of thromboprophylaxis use on patients’ outcomes. The majority of the included patients had a high risk for VTE (72.4%), and almost all of these appropriately received thromboprophylaxis. The incidence of bleeding events was significantly lower in patients who inappropriately received thromboprophylaxis. The majority of those patients were already at low risk for VTE than in patients who appropriately received thromboprophylaxis, for whom the majority were at high risk for VTE. In contrast, no difference was observed between the two groups in the incidence of VTE or death from any cause.

| Patients’ characteristics | Overall | Patients with appropriate thromboprophylaxis, n (%) | Patients with inappropriate thromboprophylaxis, n (%) | P-value* |
|--------------------------|---------|-----------------------------------------------|--------------------------------------------------|--------|
| Number of patients       | 370 (1.0) | 266 (71.9) | 104 (28.1) | –      |
| Age in years, mean (SD)  | 75.0 (9.1) | 76.1 (8.9) | 72.2 (8.8) | <0.001 |
| Female gender            | 160 (43.2) | 122 (45.9) | 38 (36.5)  | 0.104  |
| BMI (kg/m²), mean (SD)   | 26.9 (7.3) | 26.7 (7.6) | 27.4 (6.4) | 0.057  |
| High risk of VTE         | 268 (72.4) | 266 (100) | 2 (1.9)    | 0.104  |
| Pre-existing comorbidities| 294 (79.5) | 210 (79.0) | 84 (80.8)  | 0.697  |
| Hypertension             | 282 (76.2) | 201 (75.6) | 81 (77.9)  | 0.637  |
| Diabetes mellitus        | 131 (35.4) | 98 (36.8)  | 33 (31.7)  | 0.355  |
| Chronic kidney disease   | 108 (29.2) | 78 (29.3)  | 30 (28.9)  | 0.928  |
| Obesity (BMI > 30 kg/m²) | 92 (24.9)  | 69 (25.0)  | 23 (22.1)  | 0.452  |
| Heart failure            | 43 (11.5)  | 33 (12.4)  | 10 (9.6)   | 0.444  |
| Thyroid disorder         | 34 (9.2)   | 33 (12.4)  | 1 (1.0)    | <0.001 |
| Active cancer            | 35 (9.5)   | 33 (12.0)  | 2 (2.0)    | 0.002  |
| History of VTE           | 5 (1.4)    | 5 (1.9)    | 0 (0.0)    | 0.159  |
| Thrombophilic condition  | 47 (12.7)  | 47 (17.7)  | 20 (19.2)  | –      |
| Reason for admission     | 42 (11.4)  | 39 (14.7)  | 3 (2.9)    | –      |
| Pneumonia                | 38 (10.3)  | 28 (10.5)  | 10 (9.6)   | –      |
| Urinary tract infection  | 28 (7.6)   | 24 (8.9)   | 4 (3.9)    | –      |
| Stroke                   | 21 (5.7)   | 20 (7.5)   | 1 (1.0)    | –      |
| Respiratory diseases     | 16 (4.3)   | 8 (3.0)    | 8 (7.7)    | –      |
| Sepsis                   | 14 (3.8)   | 9 (3.4)    | 5 (4.8)    | –      |
| Decompensated heart failure | 144 (38.9) | 91 (34.2) | 53 (31.0) | –      |
| Acute kidney injury      | 309 (83.5) | 225 (84.6) | 84 (80.8)  | –      |
| Other                    | 54 (14.6)  | 36 (13.5)  | 18 (17.3)  | –      |
| VTE prophylaxis used     | 7 (1.9)    | 5 (1.9)    | 2 (1.9)    | –      |

Results are presented as frequency (percentage) unless otherwise indicated.
Abbreviations: VTE, venous thromboembolism; SD: standard deviation; BMI: body mass index.
1 P-values were from chi-Square test for categorical data or t-test for continuous data, unless indicated.
2 Patients were classified as high risk for VTE if their Padua score was ≥ 4.
This study found overutilization of thromboprophylaxis in 27.5% of the included patients, a figure similar to the proportion of patients who inappropriately received thromboprophylaxis in the ENDORSE study conducted by Cohen et al. (Cohen et al., 2006). Although this proportion was much better than the 91.6% reported by Grant et al. (Grant et al., 2018), it was much higher than the overutilization rate reported in previous studies (Table 3) (Kahn et al., 2007; Taher et al., 2011). However, this study’s findings must be interpreted with caution when compared to previous studies. Since the purpose and the design of this study differed from those earlier studies focusing on the appropriateness of using thromboprophylaxis without investigating the impact of the appropriateness of thromboprophylaxis use on patients’ outcomes. It is also worth mentioning that the overall appropriateness of therapy for the current research was previously reported in another study (Alabdulkarim et al., 2020).

The incidence of bleeding events in our study was 9.2%, with most events seen among patients who appropriately received thromboprophylaxis (11.7% vs. 2.9%). However, bleeding risk is known to increase threefold in elderly patients (≥85 years) using thromboprophylaxis from the risk seen in patients aged 40 years or younger (Darzi et al., 2020). The mean age of the included patients using appropriate thromboprophylaxis was significantly higher than the inappropriate group (76.1 vs. 72.2, p < 0.001). This increased age could have contributed to the higher incidence of bleeding among patients using thromboprophylaxis, even when appropriate to their VTE risk score. The bleeding rate reported in this study exceeded the rates reported previously in a retrospective study (Wang et al., 2011). In the prior study, the rate of bleeding in this study exceeded the rates reported previously in a retrospective study of 0.18) (Wang et al., 2011). Other studies reported lower rates (1.6% vs. 1.54%, p = 0.80, minor bleeding 13.10% vs. 12.25%, p = 0.018) (Wang et al., 2011). Other studies reported lower rates of bleeding of 0–7.2% in patients receiving thromboprophylaxis compared with 10.4% among those using UFH (Kleber et al., 2003). Most of the previous thromboprophylaxis efficacy trials were compared with placebo before using the Padua prediction score RAM to stratify high-risk VTE patients (Cohen et al., 2006; Kucher et al., 2005; Samama et al., 1999). Moreover,

Table 2
Venous thromboembolic and bleeding events based on the appropriateness of utilized thromboprophylaxis.

| Outcome                              | Overall (n = 370) | Appropriate thromboprophylaxis (n = 266) | Inappropriate thromboprophylaxis (n = 104) | P-value |
|--------------------------------------|------------------|------------------------------------------|--------------------------------------------|--------|
| Bleeding – during hospitalization    | 34 (9.2)         | 31 (11.7)                                | 3 (2.9)                                    | 0.009  |
| Major                               | 25 (6.8)         | 22 (8.3)                                 | 3 (2.9)                                    | 0.064  |
| VTE – during hospitalization        | 12 (3.2)         | 11 (4.1)                                 | 1 (1.0)                                    | 0.309  |
| All-cause mortality within 90 days  | 52 (14.1)        | 41 (15.4)                                | 11 (10.6)                                  | 0.229  |

Numbers are presented as number of patients with events (percentage). Abbreviations: VTE, venous thromboembolism.

Table 3
Summary of studies investigating the appropriateness of thromboprophylaxis based on guidelines.

| Study               | Year | Overall Eligible and received | Not eligible and did not receive | Inappropriate Overall Not eligible but received (overutilization) | Eligible but did not receive (underutilization) |
|---------------------|------|--------------------------------|---------------------------------|---------------------------------------------------------------|-------------------------------------------------|
| CURVE23             | 2006 | 450 (23.8)                      | 278 (61.7)                      | 172 (38.2)                                                   | 1,444 (76.2)                                    |
| Amin et al.24       | 2007 | 66,479 (31.9)                   | 66,479 (100)                   | –                                                            | 129,625 (66.1)                                   |
| IMPROVE25           | 2007 | 7640 (50.4)                     | 7640 (100)                     | –                                                            | 7516 (49.6)                                     |
| ENDORSE6            | 2008 | 15,487 (41.5)                   | 6119 (39.5)                    | 9368 (90.5)                                                 | 21,869 (58.3)                                   |
| AVAIL ME26          | 2011 | 339 (40.1)                      | 334 (98.5)                     | 5 (1.5)                                                      | 506 (59.9)                                      |
| Wang et al.17       | 2011 | 5932 (53.2)                     | 5932 (100)                     | –                                                            | 5203 (46.8)                                     |
| Grant et al.27      | 2018 | 12,864 (28.7)                   | 5682 (44.2)                    | 7182 (35.8)                                                 | 31,911 (71.3)                                   |

Note: VTE risk assessment and bleeding assessment tools were not consistent among the studies.
Numbers are presented as number of patients (percentage).
1 Only patients that received thromboprophylaxis were included in the study.
2 These are estimates based on the published proportions.

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VTE definitions among these studies were not consistent: some included symptomatic and others symptomatic and asymptomatic VTE events, potentially leading to significant discrepancies between current findings of VTE’s incidence versus previous reports (Cohen et al., 2006; Kucher et al., 2005; Samama et al., 1999).

Despite this study’s goal of shedding light on some perspectives that may improve current practice, it did have some limitations. Its retrospective nature may limit its generalizability and the causal relationship of its findings, which goes beyond the purpose of the study. Besides, the overall number of included subjects was smaller than the numbers included in previous studies. The number of patients receiving thromboprophylaxis inappropriately was almost the third of the patients who appropriately received thromboprophylaxis. Only the risk of VTE was assessed using the Padua scoring system, without calculating subjects’ bleeding risk, which might have influenced our safety findings. The risk of bleeding for patients who received mechanical thromboprophylaxis was based on clinical documentation in the patients’ records rather than on a scoring system. No specific scoring system was currently followed on clinical documentation in the patients’ records rather than on a scoring system.

Based on the current and previous studies (Henke et al., 2020, La Regina et al., 2016), thromboprophylaxis use in low-risk patients was not associated with an additional risk of bleeding, which raises an important question regarding the actual bleeding risk in elderly medically ill patients. Are we avoiding a minimal risk of bleeding in patients at low risk of VTE while exposing patients at high risk of VTE to an avoidable risk of VTE? Especially among elderly patients without contraindication for thromboprophylaxis.

5. Conclusion

This study provided evidence from the real-world about the safety and effectiveness outcomes of appropriate or inappropriate thromboprophylaxis use among a cohort of elderly medical patients in Saudi Arabia. The overutilization of thromboprophylaxis among elderly hospitalized medical patients at low risk for VTE and no contraindications for thromboprophylaxis use was not associated with additional bleeding risk. Although a valid medical practice recommended in guidelines, implementing RAMs for VTE in addition to RAMs for bleeding risk could help better stratify patients’ eligibility for thromboprophylaxis. Thus, potentially reducing the risk of VTE without exposing patients to a higher risk of bleeding. We suggest that clinicians may reconsider the benefits of using thromboprophylaxis in all hospitalized elderly medical patients who have no contraindication for thromboprophylaxis, regardless of their risk for VTE and bleeding. Such an approach could help avoid the current high prevalence of underutilization of thromboprophylaxis among high-risk patients the world over. However, a larger multicenter and international prospective study is needed to assess the actual risk of bleeding with thromboprophylaxis and whether that risk can be outweighed by the benefits of preventing an additional VTE event.

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