APPROPRIATENESS

INTRODUCTION

Venous Thromboembolism (VTE) is a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The overall VTE rates worldwide are 100 per 100,000 populations/year, of which 70% are hospital acquired. In Asia, the incidence is increasing due to aging population, obesity, cancer and higher rate of major complex surgeries.

The occurrence of VTE often complicates the treatment course of hospitalised patients. In the absence of prophylaxis, VTE risk in medical patients is approximately 16%. However, DVT prophylaxis remains underused in hospitalised medical patients despite strong recommendations. In a study conducted by Goldhsber et al., only 42% received DVT prophylaxis within a month before the diagnosis of DVT in 2726 hospitalised patients. Thus, VTE risk assessment among medical inpatients is important to facilitate the initiation of thromboprophylaxis which includes pharmacological and non-pharmacological methods.

Despite accumulating scientific evidences to support the use of VTE risk assessment and appropriate thromboprophylaxis among medical inpatients, it is either neglected or prescribed unnecessarily by the physicians. A study from Iran demonstrated that approximately 47.2% of inpatients who presented with moderate to high risk of VTE had not been appropriately prescribed with prophylaxis, whereas 19.3% of low VTE risk patients were inappropriately instituted with prophylaxis.

Various VTE risk detection models were adapted in previous studies with methods developed to promote appropriate thromboprophylaxis prescribing. Unfortunately, most of these had adapted previous published risk assessment model that had yet to be validated or models with only agreement from institutional consensus. To our best knowledge, only two studies have stratified patients’ VTE risk with the use of validated risk assessment model, and subsequently, innovated electronic alert systems to improve appropriate prescribing of DVT prophylaxis. To date, Malaysian data in this area of research is scarce. Furthermore, electronic DVT alert system to encourage appropriate prophylaxis prescribing from previous study requires sophisticated technology and considerable financial resources, which may

RESULTS: Overall, 286 patients (n=142 pre-intervention versus n=144 post-intervention) were conveniently recruited. The prevalence of DVT prophylaxis use was 10.8%. Appropriate thromboprophylaxis prescribing increased from 64.8% to 68.1% post-DRAT implementation. Of note, among high DVT risk patients, DRAT intervention was observed to be a significant predictor of appropriate thromboprophylaxis use (14.3% versus 31.3%; adjusted odds ratio = 2.80; 95% CI 1.01 to 7.80; p<0.05).

Conclusion: The appropriateness of DVT prophylaxis use was suboptimal but doubled after implementation of DRAT intervention. Thus, an integrated risk stratification checklist is an effective approach for the improvement of rational DVT prophylaxis use.

KEY WORDS:
Deep vein thrombosis, appropriateness, prophylaxis, pharmacist, intervention

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be unlikely to be adapted widespread across many institutions especially in suburban regions in Malaysia that also admit patients at risk of VTE. Hence, by adopting validated risk assessment tool, this study aimed to evaluate the appropriateness use of DVT prophylaxis among medical inpatients in a Malaysian district hospital. It was also conducted to compare the appropriateness of DVT prophylaxis prescribing between usual care versus a pharmacist-driven DVT Risk Alert Tool (DRAT).

**METHODOLOGY**

*Subjects and data collection*

This was a prospective pre- and post-interventional, single-centre study conducted among patients admitted to medical wards in a district hospital in the state of Johor, Malaysia. Patients admitted to medical wards during the one-year study period were included in the study. Patient who received therapeutic or prophylactic anticoagulants prior to the current admission, hospitalised less than 24 hours, contraindicated to DVT prophylaxis treatment, and received therapeutic doses of anticoagulant for therapeutic purposes were excluded from the study.

The total population in this study was 1150 patients with 50% accounted for each pre and post-interventional study population. Under routine usual care, approximately 40% of patients would receive appropriate DVT prophylaxis. Considering the power of 90%, margin of error of 0.05, and postulating 60% of post-interventional group would receive appropriate DVT prophylaxis, a sample size of 130 patients each for pre- and post-interventions was obtained using Power and Sample Size (PS) Calculator.

*Pre-Interventional Study*

During the initial 3-month of pre-interventional study, patients admitted to medical wards from January 2016 till March 2016 that fulfilled the inclusion and exclusion criteria were recruited. As availability of pharmacists over the weekends in medical wards were inconsistent, the recruitment was done on a basis of convenient sampling. Potential study participants were screened from inpatient registry as well as reviewing their medical and medication charts. Every eligible patient seen by the pharmacists during the study period was given a description of the study and confidentiality assurance. Subsequently, VTE and bleeding risks were assessed by using structured DVT risk assessment tracking sheet consisting of two external validated risk assessment models: Padua Risk Assessment Model (RAM Score) and International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) Bleeding Risk Assessment Model.

The Padua Prediction RAM Score is one of the risk assessment model that has been developed to help stratify the VTE risk in hospitalised medical patients. It incorporates 15 risk factors within 11 items and it is one of the few VTE risk detection tool that has been external validated with the calculated sensitivity of 73.3% and a specificity of 51.9%. A score of four points or more is strongly associated with high risk of VTE and vice versa. On the other hand, IMPROVE Bleeding Risk Assessment Model remains the only evidence-derived and weighted bleeding risk model using 13 clinical and laboratory factors which has been external validated with calculated sensitivity of 33.97% and specificity of 81.47%. A cut-point score of seven or more is able to identify a high-risk patient group for major bleeds and non-major bleeds.

Patients' demographic data (age, gender, race, body weight, height), clinical status (current admission diagnosis), and their VTE medication data (types of DVT prophylaxis use, time of thromboprophylaxis initiated, if any, were collected via tabulated data collection sheet. Indication for DVT prophylaxis was determined by the pharmacists and reviewed by a medical specialist who had no direct involvement in the routine usual care of these patients to ensure the consistency of rating. Patients were then categorised as DVT prophylaxis indicated patients group (either pharmacological or non-pharmacological prophylaxis) if they fell into high VTE risk group with IMPROVE scores within the low risk group for bleeding. They were regarded as non-pharmacological DVT prophylaxis indicated if they scored as high risk for VTE and high risk for bleeding. Conversely, they were classified as not indicated for DVT prophylaxis if they had been stratified as low VTE risk. Patients were followed up until they were discharged from wards and physicians' self-approaches on DVT prophylaxis prescribing were assessed without altering the usual medical care for these patients. Appropriateness of DVT prophylaxis prescribing was then determined (Figure 1). This served as the pre-interventional result.

*Intervention (DRAT)*

In the second phase of the study (April to August 2016), by combining both external validated Padua Risk Assessment Model for the VTE risk assessment and IMPROVE Bleeding Risk Assessment Model for bleeding risk evaluation, DRAT Alert Card was developed by a team of pharmacists as a mode of intervention. This card was to be placed in patients’ ward medication administration chart during the intervention phase to alert treating physicians on the possible VTE risk, bleeding risk and recommended indication for DVT prophylaxis, if any. In addition, flyers detailing the interventional program were emailed to all attending physicians of the respective wards and presentations outlining the pharmacist-driven DRAT-alert card system were delivered to them as part of an initiatives to create awareness among physicians on the interventional program that was conducted during the intervention period.
Post-Intervention Study
During the subsequent 3-month post-interventional study (September 2016 to November 2016), patients admitted to medical wards who fulfilled the inclusion and exclusion criteria were again conveniently sampled. Informed consent was sought and strict confidentiality was maintained throughout the study period. Eligible patients were assessed on their VTE and bleeding risks using DVT risk assessment tracking sheet. Indication for thromboprophylaxis as defined in the pre-intervention study was also evaluated. Recommendation for initiating or stopping DVT prophylaxis was suggested by pharmacists by placing the DRAT Alert Card on patient’s ward medication administration chart (as separate sheet from the patient’s permanent medical records). The prescribing physician would then decide on the institution of thromboprophylaxis. Attending physicians held the final decision regarding patient’s management. Lastly, physicians’ approaches on DVT prophylaxis prescribing throughout interventional phase were assessed and patients were followed up until patients were discharged from wards. Similar to pre-intervention phase, appropriateness of prophylaxis prescribing was evaluated (Figure 1). This served as the post-interventional result.

Withdrawal Criteria
Patients would be discontinued from the study if they opted to withdraw from the consent, lost during follow up either due to deceased or transferred out to the other institutions or wards, developed condition or abnormality during the study period (e.g., patients with no known VTE prior to admission but were diagnosed of VTE during the study period who had been receiving therapeutic doses of anticoagulant or the development of active bleeding during hospital stay) that would compromise the safety of the patients or the quality of the data. All patients who withdrew from the study, if any were replaced.

Outcome Measures
Appropriateness in DVT prophylaxis prescribing was served as primary outcome measure. Results on the appropriateness of DVT prophylaxis prescribing between pre- and post-interventional study was compared and served as secondary outcome measure.

Statistical Analysis
Statistical analysis was performed using IBM SPSS version 21.0. Comparisons of the baseline demographic and clinical data between pre- and post-studies were analysed using Chi-square, Fisher’s Exact or Independent Sample t-test where appropriate. In addition, appropriateness of DVT prophylaxis use among medical inpatients between pre- and post-interventional studies was entered into univariate and multivariate logistic regression models to produce odds ratio (OR) with confidence interval (CI) of 95% where applicable. The levels of significance were expressed by p-value of less than 0.05.

Ethical Clearance
The study protocol was registered on the Malaysian National Medical Research Register (NMRR-15-1891-28427) and approved by the Malaysia Ministry of Health Medical Research Ethical Committee on 12 January 2016 [(7)KKM/NHSEC/P15-1562].

RESULTS
Out of 286 patients recruited for this study, 142 patients were enrolled into the pre-intervention phase, whereas another 144 patients were enrolled during the post-study. No patient was noted to develop significant adverse effect that required withdrawal from the study. Mean age of patient was 62.46±17.56 years old and approximately half of the patients were males. Mean body mass index (BMI) was 23.58±4.80 kgm⁻². There was no statistically difference between the baseline demographic and clinical characteristics between pre- and post-intervention groups (Table I). Throughout the study, subcutaneous injection (SC) of heparin was more widely used in medical wards as DVT prophylaxis (61%), followed by SC Enoxaparin (36%) and SC Fondaparinux (3%). There were no non-pharmacological DVT prophylaxis prescribed or noted for patient such as TED Stockings and early ambulation.

Overall, the prevalence of DVT prophylaxis use among hospitalised medical patients was 10.8%. Appropriate use of thromboprophylaxis showed to have a minimal increase from 64.8% in the pre-intervention group to 68.1% in the post-intervention group (p=0.559). Of note, when translating the data into subgroup analysis, among those at risk patients (DVT prophylaxis indicated group), a statistically significant increase on the appropriate thromboprophylaxis use was observed before and after the intervention (14.3% versus 31.3%, p=0.026). After adjusting and controlling the effects of potential confounders (Table II), DRAT intervention had been found to be one of the significant predictors towards appropriate thromboprophylaxis use among indicated medical inpatients. The number needed to treat (NNT) for DVT prophylaxis indicated medical patients was 5.87.

DISCUSSION
In the literature, DRAT alert card was the first DVT risk alert tool in Malaysia that utilised validated assessment models to stratify VTE and bleeding risks with recommendations on prophylaxis prescribing. Our study revealed that the DRAT intervention was able to significantly predict the appropriate use of DVT prophylaxis among medical patients at risk. By utilising DRAT, there is approximately three times greater chance that our at-risk patients would receive appropriate thromboprophylaxis. Our findings correlate with study conducted by Jered et al., in which pharmacist-led DVT risk assessment and prophylaxis recommendation program resulted in increased use of appropriate prophylaxis.⁷

Overall, the prescribing rate of DVT prophylaxis among indicated medical patients was suboptimal (14.3%) during pre-interventional phase. Similar low rate had also been observed in studies in other developing country in Asia.¹¹ As VTE is usually clinically silent, physicians may not appreciate the immediate effectiveness of thromboprophylaxis.¹² In addition, studies had shown that clinical awareness of VTE risk in medical patients was low when compared to surgical patients.¹³ As a result, physicians tend to pay more attention in the treatment of admission diagnosis while prophylaxis was more often to be overlooked.¹⁴ By applying DRAT during 3-month period of post-interventional phase, our study showed a significant two-fold increment to 31.3% in appropriate thromboprophylaxis prescribing among at risk
medical patients. DRAT implementation appeared to be an effective clinical decision support tool by providing objective risk assessment scorings to assist in appropriate prophylaxis management among at risk patients. A study from the United States found that appropriate prophylaxis prescribing increased significantly after initiating of at least 6-month of interventional program. Taking the previous data into consideration, longer time would be needed to monitor the sustained effect of DRAT card to show its true effectiveness.

Preventing VTE in elderly population is particularly challenging. Theoretically, VTE risk increased exponentially with age. Hence, management with appropriate thromboprophylaxis should be expected high in this group of population. In contrast, our study demonstrated that beside DRAT intervention, age was another significant predictors for appropriate prophylaxis prescribing. In comparison with middle-age group, appropriate DVT prophylaxis was found not effectively implemented among at risk older population. This discrepancy could be described by the discouraging complex condition with multiple risks among elderly medical patients. Hence, physicians’ concern on higher risk of bleeding formed significant barriers toward prophylaxis implementation. Nevertheless, findings from clinical trials suggest that when extrapolating to geriatric population, the benefit of DVT prophylaxis often outweigh the risk provided some basic precautions were observed. This included the individualized benefit to risk assessment utilizing objective clinical scorings such as DRAT intervention in our study.

Another noteworthy point from our study was when combining both prophylaxis indicated patients and non-indicated patients, the overall rate of appropriate DVT prophylaxis prescribing was found only slightly higher, by 3.3% post-DRAT implementation. This could be explained by almost all of those considered as appropriate DVT prophylaxis users (91.3%) evaluated in pre-interventional phase was contributed by those from low DVT risk patients who were not being prescribed with DVT prophylaxis in actual practice. Thus, the frequency of appropriate DVT prophylaxis users would be high as there might be a proportion of actual low risk patients at VTE risk stratification.

<table>
<thead>
<tr>
<th>Study Characteristics</th>
<th>Pre Intervention (N=142)</th>
<th>Post Intervention (N=144)</th>
<th>p-value#</th>
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<tr>
<td><strong>Age (years)</strong></td>
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<tr>
<td>Young (&lt;35)</td>
<td>10 (7.1)</td>
<td>16 (11.1)</td>
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<td>33 (23.2)</td>
<td>42 (29.2)</td>
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<td>Old (≥ 60 years)</td>
<td>99 (69.7)</td>
<td>86 (59.7)</td>
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<td><strong>Gender</strong></td>
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<tr>
<td>Male</td>
<td>74 (52.1)</td>
<td>67 (46.5)</td>
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<tr>
<td>Female</td>
<td>68 (47.9)</td>
<td>77 (53.5)</td>
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<td>Malay</td>
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<td>91 (63.2)</td>
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<td>Chinese</td>
<td>43 (30.3)</td>
<td>34 (23.6)</td>
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<tr>
<td>Indian</td>
<td>17 (12.0)</td>
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<td>Others</td>
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<td><strong>BMI (kgm⁻²)</strong></td>
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<td>10 (6.9)</td>
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<td>79 (54.9)</td>
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<td>Obese (≥30)</td>
<td>18 (12.7)</td>
<td>6 (4.2)</td>
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<td><strong>DVT Risk Assessment</strong></td>
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<tr>
<td>Padua RAM Score (Mean ± SD)</td>
<td>2.63 (±1.93)</td>
<td>2.62 (±1.99)</td>
<td>0.970</td>
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<tr>
<td>Low Risk (RAM &lt; 4)</td>
<td>86 (60.6)</td>
<td>77 (53.5)</td>
<td>0.226</td>
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<tr>
<td>High Risk (RAM ≥ 4)</td>
<td>56 (39.4)</td>
<td>67 (46.5)</td>
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<td><strong>Bleeding Risk Assessment</strong></td>
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<tr>
<td>IMPROVE Score (Mean ± SD)</td>
<td>2.48 (±1.62)</td>
<td>2.25 (±1.74)</td>
<td>0.258</td>
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<td>Low Risk (IMPROVE &lt; 7)</td>
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<td>139 (96.5)</td>
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<tr>
<td>Low Risk (IMPROVE ≥ 7)</td>
<td>2 (1.4)</td>
<td>5 (3.5)</td>
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<td><strong>DVT Prophylaxis Indication Assessment</strong></td>
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<td>Indicated</td>
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<td>67 (46.5)</td>
<td>0.226</td>
</tr>
<tr>
<td>Non-Indicated</td>
<td>86 (60.6)</td>
<td>77 (53.5)</td>
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</tbody>
</table>

Data given as number (percentage) unless otherwise indicated
# χ² test, Fisher’s Exact test or Independent Sample t-test where applicable
* p-value <0.05 considered statistically significant
SD, standard deviation
had not been routinely assessed by the prescribers during pre-interventional phase. As a result, the overall effect from the DRAT intervention from our study could have been underrepresented. However, from another perspective, the inclusion of low risk patient into the study (for comparison) was important as it reflected the true population of medical patients who were admitted with a variability of VTE risks.

The NNT calculated for at risk patients was 5.87. This suggested that for every 6 DRAT cards placed on prophylaxis indicated patients, one patient would receive DVT prophylaxis. A review by Michael et al showed that one VTE could be prevented for every 22 patients treated with pharmacologic prophylaxis (NNT: 22).\(^1\)\(^8\) Hence, it could be postulated that for every 132 DRAT cards placed on prophylaxis indicated patient, one VTE case could be prevented. As VTE is common in hospitalised medical inpatients, with many patients not displaying significant signs and symptoms,\(^1\) the improvement from DRAT implementation could put a positive impact on safety of the patients and assist in the reduced occurrence of VTE.

**STUDY LIMITATION**

In this study, no non-pharmacological DVT prophylaxis prescribed or noted for patients. Early ambulation may have been encouraged by the prescribers but were not documented. Thus, this may underestimate the frequency of non-pharmacological prophylaxis. Prescribers may have accepted the pharmacists’ intervention of DVT prophylaxis and encouraged patient for early ambulation without documentation in progress notes of patients, but with just verbally. Nonetheless, a written order is very important to ensure that appropriate and accurate medical order is being delivered to the patient. Data on appropriate DVT prophylaxis use was lower may have been due to underreporting of non-pharmacological prophylaxis. Moreover, as this was a quasi-experimental pre-post study adopting convenient sampling, it was not feasible to randomly recruit study participants into both intervention and control groups. However, selection biases could be overcome in this study as comparability of baseline characteristics of both groups was examined and confirmed under bivariate statistical analysis.

**CONCLUSION**

Appropriateness of the use of DVT prophylaxis in our study was suboptimal but improved after the pharmacist-driven DRAT intervention, particularly among those with high risk medical inpatients. Integrated risk stratification checklist is an effective approach for the improvement of rational DVT prophylaxis use. Future studies of longer duration should be conducted and compared to establish the best practice for a pharmacist-driven thromboprophylaxis risk alert model.

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**REFERENCES**

Original Article


