Assessment of Rivaroxaban versus Enoxaparin for Therapeutic Efficacy and Clinical Safety in Renally Compromised Cancer Patients

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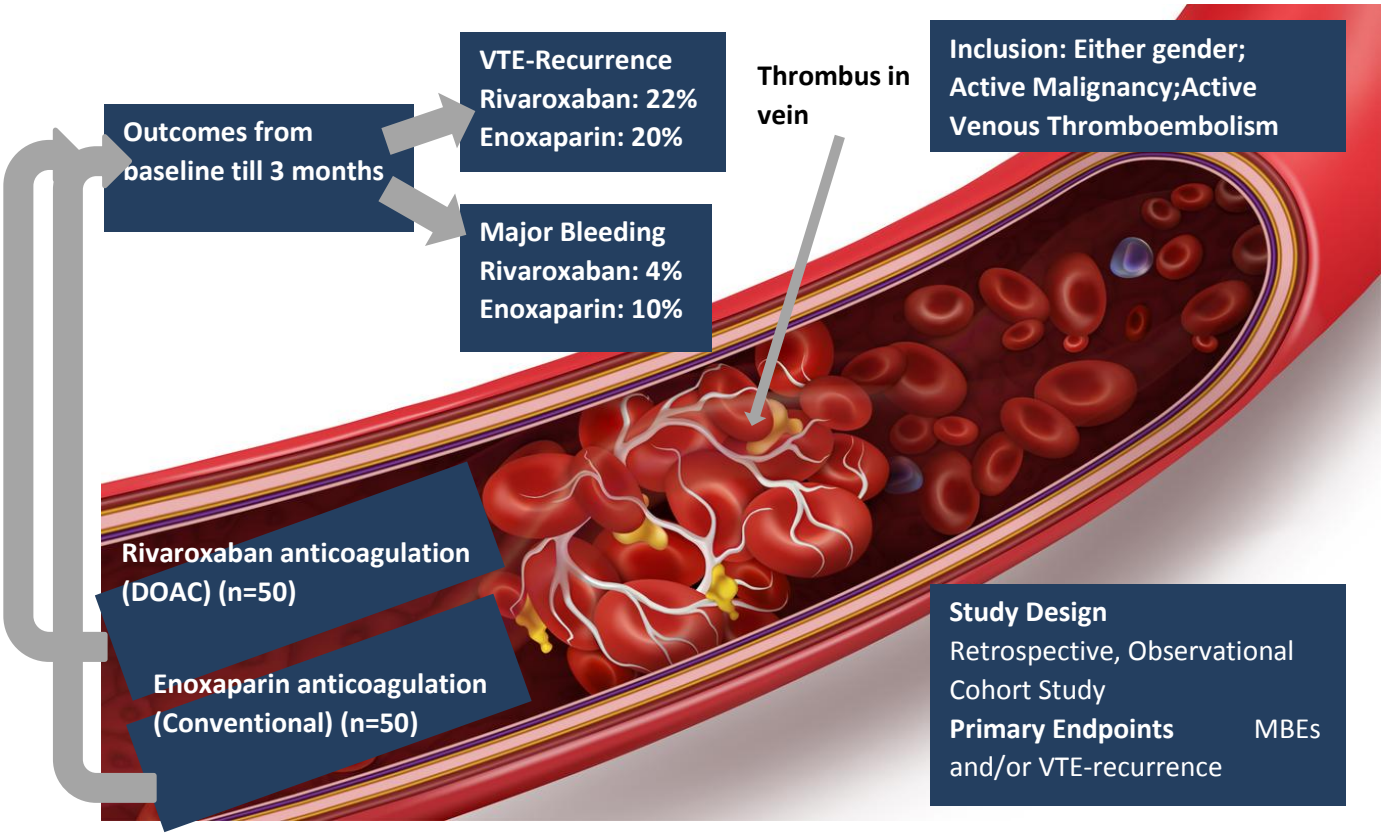
Abstract

Rivaroxaban used for treating cancer-associated venous thromboembolism (Ca-VTE) may be associated with major bleeding events (MBEs) and VTE-recurrences. A few studies were focused on its use in renally compromised cancer patients. This study aimed to assess the therapeutic efficacy and clinical safety of rivaroxaban *vs.* enoxaparin in Ca-VTE patients with and without renal impairment. An analysis on fixed-oral-dose rivaroxaban versus traditional enoxaparinwas performed in terms of clinical safety and therapeutic efficacy in Ca-VTE diagnosed patients of either group *i.e.,* with and without renal impairmentat ShaukatKhanum Memorial Cancer Hospital & Research Centre, Peshawar, enrolled from 2016 to 2020. Primary safety and efficacy outcomes were MBEand VTE-recurrence respectively, assessed at baseline and after 3 months of treatment. Among 100 patients, 50% received rivaroxaban and remaining 50% enoxaparin treatment. Higher MBE rate was associated with enoxaparin *vs.* rivaroxaban treated arm with an insignificant difference (10% *vs.* 4%; 95% CI; *P*=0.09). However, rivaroxaban users had a higher but insignificant VTE-recurrence rate as compared to enoxaparin users (32% *vs.* 20%; 95% CI; *P*=0.23). The overall rate of MBEs and VTE recurrence was comparatively higher in renally impaired patients.Conclusively, the study revealed that the risk of recurrent VTE and MBE increases witha corresponding alteration in renal function of Ca-VTE patients. In treating Ca-VTE (with or without renal impairment), rivaroxaban may be a better alternative to enoxaparin with high safety and of comparable efficacy profile. Drug dosage adjustment playsa significant role inreducing the risk of bleeding with enoxaparin.

Keywords

Cancer-Associated Venous Thromboembolism (Ca-VTE); Renal Impairment; Rivaroxaban; Enoxaparin; Safety; Efficacy; Drug Dosage Adjustment

Graphical Abstract



I. INTRODUCTION

Venous thrombo-embolism (VTE) is associated with poor prognosis, high mortality, and morbidity rate in cancer patients, carrying a 4-7 folds higher risk for deep venous thrombosis (DVT) and pulmonary embolism (PE), compared to the age-matched control patients per annum.[1, 2] Additionally, renal impairment is identified as another risk factor for VTE in those cancer patients.[3] Therefore, adequate and timely management of cancer-associated venous thromboembolism (Ca-VTE) is of foremost concern in the care of cancer patients with and/or without renal impairment.

In the last few decades, advancements made in the management of Ca-VTE are considerable. Besides low molecular weight heparin (LMWH), other anticoagulants are also available showing promising efficacy in the treatment Ca-VTE.[4-6] Due to its inconvenient administration on a daily or twice-daily basis, substantial cost, and/or development of hematoma at the injection site, patients show poor compliance with LMWH.[7] Furthermore, proper dosing in elderly and renally impaired patients is problematic due to its variable pharmacokinetics.[8]

Due to above mentioned problems with LMWH, direct oral anticoagulants (DOACs) *i.e.*, rivaroxaban, apixaban, and edoxaban, are considered as an alternate option to it. Rivaroxaban is a factor Xa inhibitor which received approval in 2012, for the treatment of VTE following the EINSTIEN-DVT and EINSTIEN-PE trials.[9, 10]It has a rapid onset of action and peak anticoagulant effect in 2-4 hours after the first administered dose. Furthermore, considering its feasible pharmacokinetic and pharmacodynamic properties, the need for its anticoagulation monitoring is not critical on a routine basis.[11, 12]As per pharmacokinetic studies, with its dual elimination mode, two-third of its dose excretes in an inactivated form through renal and hepatobiliary pathways. However, one-third in its unchanged active form undergoes renal excretion.[13]In renally compromised patients having abnormal creatinine clearance (CrCl), a decreased clearance will leads to high plasma

concentration of rivaroxaban. Studies have shown that increase in the concentration of rivaroxaban also enhanced the area under the plasma concentration-time curve (AUC) of 44%, 52%, and 64% in patients with mild (CrCl 50-80 ml/min), moderate (CrCl 30-49 ml/min) and severe renal impairment (CrCl 15-29 ml/min), respectively.[14] Likewise, the half-life of rivaroxaban was extended up to 0.4, 0.7, and 1.2 hours, respectively. As rivaroxaban excretes partially via the renal route, therefore, dose adjustment before administration can play significant role to optimize its therapeutic efficacy and clinical safety in such patients.[15]

Based on meta-analyses, randomized control trials (RCTs) conducted on cancer population *i.e.*, EINSTEIN-DVT and PE, RECOVER, AMPLIFY, and Hokusai-VTE, have suggested that the DOACs (rivaroxaban, apixaban, and edoxaban) were found as a non-inferior option to LMWH in VTE management.[16-21] On the contrary, however, two RCTs *i.e.*, SELECT D and Hokusai-VTE showed that, DOACs are of better efficacy but inferior safety with the higher bleeding rate when compared with LMWHs.[22, 23]

On the basis of findings mentioned in the above quoted trial studies, the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) have adopted DOACs' use *i.e.*, rivaroxaban and edoxaban in their recommended guidelines.[24, 25] These recommendations, however, are still less common and uneven in the current data. In the light of limited available literature, we designed a single centered study to evaluate the clinical safety and therapeutic efficacy of rivaroxaban *vs.* enoxaparin in the management of Ca-VTE in cancer population with and without renal impairment.

II. MATERIAL AND METHODS

IIa.Study Design

This single centered cohort study was conducted at ShaukatKhanum Memorial Cancer Hospital (SKMCH), Peshawar, utilizing a cancer registry data with effect from March 2016 to December 2020. The study was approved from the International Review Board (IRB) of the hospital, aiming to evaluate the therapeutic efficacy and clinical safety of rivaroxaban in comparison with enoxaparin for VTE treatment in cancer patients with and without renal impairment. Patients under consideration were analyzed at two points of the study *i.e.*, baseline and 3-months follow-up after providing with the required treatment regimens.

IIb.Study Subjects

Patients were included, if they were positively diagnosed as cancer patients, ready to participate with the provision of formal written consent, belonged to either gender, cancer patients underwent surgery or not, had an active and major diagnosis or clinical suspicion of cancer with DVT or PE.[20] The major ineligibility criteria were, patients having chronic and significant measurable bleeding > 48 hours, recent CNS bleed or hemorrhagic CNS metastasis, major bleeding (>2 units transfused in 24 hours), severe platelets dysfunction, head trauma, neuraxial anesthesia, underlying hemorrhagic coagulopathy, and long-term antiplatelet therapy.[20]

IIc. Study Protocol

IRB approval was granted by IRB of ShaukatKhanum Memorial Cancer Hospital & Research Center, Lahore on 28th February 2020. Patients were identified and relevant clinical parameters were obtained from patients' electronic health records using the Hospital's Management Information System (MIS). Data abstraction was completed on December 12, 2020. Variables evaluated included: demographics, weight, cancer type, cancer status, renal status, dosage adjustment, and various laboratory parameters at the time of VTE diagnosis and consequently up to 3 months of initiation of anticoagulation therapy.

IId. Study Endpoints

The primary efficacy endpoint was the laboratory-confirmed VTE incidence both new and/or recurrent after a 3-month follow-up that is radiologically determined via CT scans, X-rays, and/or Doppler ultrasounds. The primary safety endpoint was the incidence of major bleeding episodes up to 3 months after initiation of anticoagulation therapy. The safety endpoint was assessed through several pathological tests including coagulation profile *i.e.*, International Normalized Ratio (INR), Activated Partial Thromboplastin Time (aPTT), and Prothrombin Time (PT).

Rivaroxaban and enoxaparin therapeutic doses were given and subsequently analyzed for clinical safety and therapeutic efficacy in two groups, with and without renal impairment. The assessments of relevant set of parameters were performed at the baseline and after 3 months of the said treatment.

IIe.Statistical Methods

Statistical analysis of the obtained data was performed using SPSS version 21.0 and Graph-Pad Prism version 8.0.1 software with respect to demographics and clinical variables of interest. Continuous variables are represented as mean (standard deviation [SD]) while categorical variables as n (%). Correlation between the set(s) of data and group comparison was made using appropriate tests such as Student's *t*-test, chi-square test, and a Kaplan-Meier curve (to determine survival over time). The level of significance was set at $P<.05$ and confidence interval (CI)=95% with all *P-VALUES* 2 sided to determine the difference between the subjected parametric values.

III. RESULTS

A single centered study was employed to assess cancer patients fulfilling the eligibility criteria at SKMHRC between 2016 to 2020, whereby, 100 confirmed diagnosed cases of cancer-associated venous thromboembolism (Ca-VTE) treated with selected anticoagulants were assessed. Of the total, 50 patients with renal impairment were treated with rivaroxaban and enoxaparin (25 each), and the same was followed for 50 control patients.

IIIa.Patients' Demographics

The demographics and clinical characteristics assessed were nearly comparable between the groups (Table 1). Gender *(xP-VALUE .2*), active malignancy *(P-VALUE .4)*, renal status *(P-VALUE .5)* and stage of impairment *(P-VALUE .7)* were of insignificant difference between both treatment arms. Most of the subjects had an active malignancy at the time of VTE diagnosis. However, weight of subjects *(P-VALUE .05)* and their malignancy type (*P-VALUE .06*) were comparable and significantly different. Furthermore, gastrointestinal (GI) cancer was a profound cancer type among both treatment groups.

IIIb. VTE Recurrence

In the prevention of recurrent VTE, rivaroxaban was almost similar to enoxaparin in patients with either renally impaired or with normal renal function (rivaroxaban, 16 cases [32%], enoxaparin, 10 cases [20%]; 95% of CI, *P-VALUE=.3*). The study also revealed that the rate of incidence of VTE recurrence was 15% and 11% in patients with renal impairment and normal renal function, respectively as shown in table 2. Kaplan-Meier curve (Figure 1) shows the step-wise VTE recurrence rate over 3 months of duration for both groups treated with either type of anticoagulants.

Table 1. Demographics and Clinical Characteristics of Study Subjects (n=100).

Variable	Group		
	Enoxaparin	**Rivaroxaban**	***P*-VALUE**
	***n*=50**	***n*=50**	
Demographics			
Gender			0.23[a]
Male	22 (44)	27 (54)	
Female	28 (56)	23 (46)	
Weight	22.6±4.3	23.2±5.2	0.05[b]
Co-Morbid			
Renal Status			0.5[a]
Impairment	25 (50)	25 (50)	
No Impairment	25 (50)	25 (50)	
Impairment stage			0.7[a]
Mild	15 (60)	9 (36)	
Moderate	5 (20)	12 (48)	
Severe	5 (20)	4 (16)	
Malignancy Status			
Cancer Type			0.06[a]
Breast	4 (8)	7 (14)	
Prostate	4 (8)	1 (2)	
Gastro-intestinal	12 (24)	13 (26)	
Kidney	4 (8)	3 (6)	
Miscellaneous	26 (52)	26 (52)	
Active Cancer			0.42[a]
Yes	41 (82)	43 (86)	
No	9 (18)	7 (14)	

Values expressed n (%), Mean, Standard Deviation (SD), and *P-VALUE*.[a]Pearson chi-square test; [b]Student's*t*-test

Table 2. Parametric Assessment in the Study Populationfor Clinical Safety and Efficacy by Treatment Groups (n=100).

Variable	Treatment Groups		
	Rivaroxaban *n*=50	**Enoxaparin *n*=50**	***P-VALUE***
Recurrent VTE (n/N (%)			
Total of recurrent VTE	16	10	
Normal renal function	7/16 (43)	4/10 (40)	0.36
Renal impairment	9/16 (56)	6/10 (60)	0.36
Major Bleeding (n/N (%)			
Total of major bleeding events	2	5	
Normal renal function	0/2 (0)	1/5 (20)	0.31
Renal impairment	2/2 (100)	4/5 (80)	0.41

Abbreviation: VTE, Venous Thromboembolism. Values expressed n/N (%) and P-VALUE. Person chi-square test

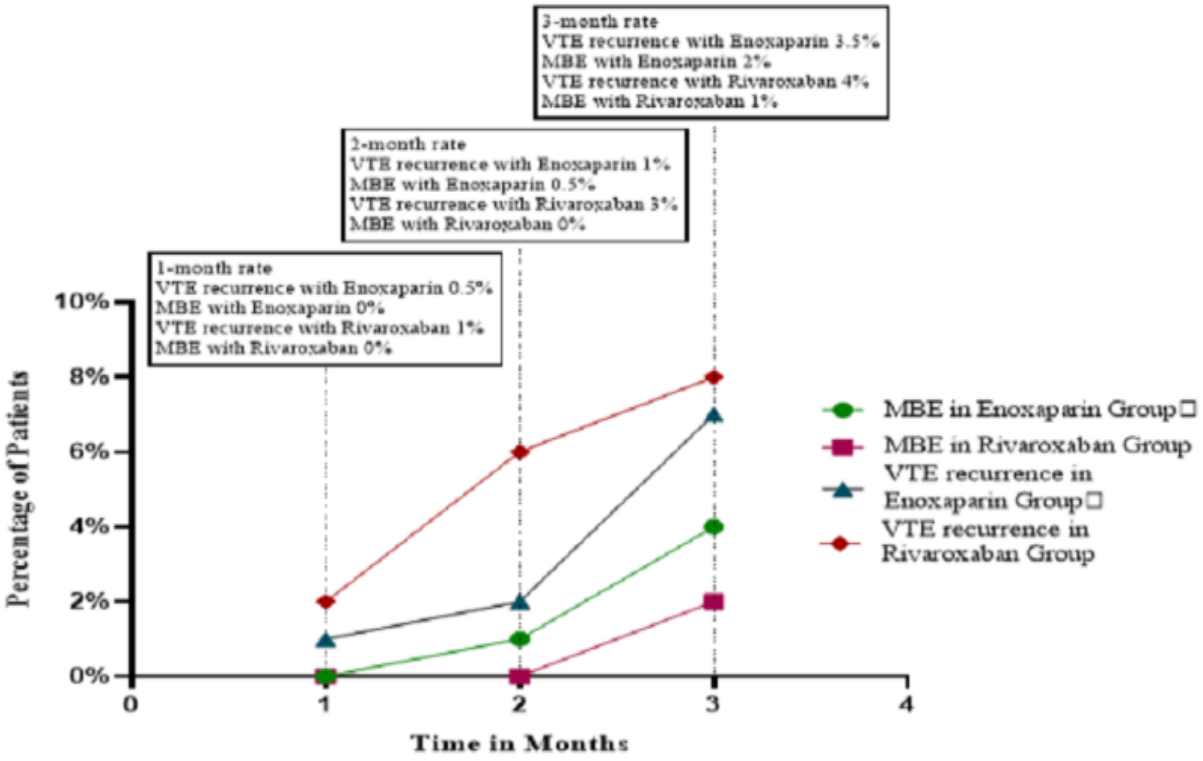


Figure 1. Pattern of indicative parameters used for assessment of clinical efficacy and safety over study time period (Kaplan-Meier estimate).

IIIc. Major Bleeding Events (MBEs)

The proportion of major bleeding events (MBEs) is 1% and 2.5% in rivaroxaban and enoxaparin treated groups, respectively showing non-inferiority of rivaroxaban. In rivaroxaban-treated renally impaired patients, 2% were reported with MBEs while no single case was reported in the normal renal function group. On the other hand, in the enoxaparin arm, 4 cases were reported in renal impairment and 1 in normal renal function patients (Figure 1). The respective *P-VALUES* are given in table 2. These incidences of MBEs were confirmed via results interpretation of several coagulation parameters (INR, aPTT, and PT) as shown in table 3 and figure 2.

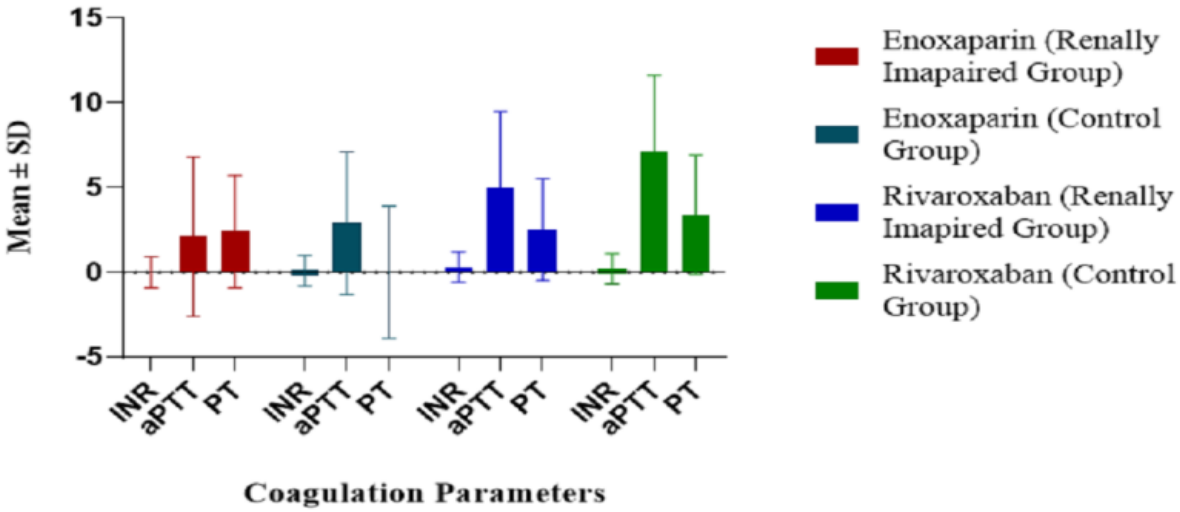


Figure 2. Coagulation Parameters by Class of Anticoagulants in Renally Impaired *vs.* Control Group.Data presented as Mean ± Standard Deviation.

IIId. Drug Dosage Adjustment

Results of renally impaired patients subjected to drug dose adjustment with subsequent effect in the form of safety are mentioned in percentage (Table 3). Based on the severity of renal impairment and drug used indication of enoxaparin as an anticoagulant, 40% of renally compromised patients in the enoxaparin treatment group were liable for drug dosage adjustment. Out of 40% of those patients, 24% were provided with the required dose adjustment in the form of dose reduction. However, in rest of the included patients, safety profile had been compromised and they were subjected to hemorrhagic complications.

Table 3. Effect of Dose Adjustment of Enoxaparin Required for Patients Suffering from Moderate and/or Severe Renal Impairment (n=10).

Enoxaparin Dose	**N**	**Safety Parameter (Mean value)**			**Outcome (Major Bleeding)**
		INR (2.0-3.0)	**aPTT (60-80 sec)**	**PT (26.1-39.2 sec)**	
Adjusted	6	2.33	65.23	26.68	Absent
Non-adjusted	4	3.52	88.67	45.82	Present

Abbreviations: INR, International Normalized Ratio; aPTT, Activated partial thromboplastin time; PT, Prothrombin Time; OD, Once Daily.

IV. DISCUSSION

Generally, findings of the study have revealed that therapeutic efficacy regarding the incidences of VTE recurrence by rivaroxaban is comparable to enoxaparin as shown in table 2 and figure 1. For instance, rivaroxaban at dosage regimen *i.e.*, 15 mg, twice daily for two weeks followed by 20 mg once daily had comparable efficacy to enoxaparin in treating Ca-VTE and preventing recurrence of VTE in said patients associated with and without renal impairment. According to studies conducted and reported in RCTs (SELECT D, Hokusai-VTE, and Hokusai VTE CANCER), their findings regarding the risk of VTE recurrence and therapeutic efficacy of rivaroxaban and enoxaparin were in accordance to our results.[21, 22] However, unlike to the outcomes of this study, few studies also have reported the higher risk of VTE with DOAC than parenteral anticoagulant in the treatment of Ca-VTE. Additionally, it has been demonstrated in the current study that a considerable percentage of GI cancer among the included patients contributed and identified as one of the risk factors for VTE recurrence. As DOAC (rivaroxaban) might have shown low absorption from the gut, subsequently results in sub-therapeutic effect, thereby increases the risk of recurrent VTE.[26] Furthermore, it has been revealed by this study that a greater number of recurrent VTE cases were associated in patients with renal impairment than subjects with normal/control renal function.

The episodes of major bleeding with rivaroxaban were less than the parenteral counterpart in both Ca-VTE patients with as well as without renal impairment. Our findings illustrated a high rate of MBEs in patients with renal impairment as compared to the control group, irrespective of the type of anticoagulant therapy given. There was an increased risk of bleeding events with an incremental decrease in renal function, especially in those with estimated glomerular filtration rate (eGFR) < 30 mL/min. In renally compromised patients, an anticoagulant, even at standard therapeutic dose may have an untoward effect due to increased plasma concentration and duration of action leading to a subsequent rise in toxic effects like major bleeding.[27] In comparison with the other studies, the outcomes of this study were consistent, except for the risk of MBEs that was higher with enoxaparin than rivaroxaban. When compared to RCTs like RECOVER/RECOVER-2, reported MBEs were comparable to the estimates of these findings. However, according to the findings of this study, the risk and episodes of bleeding in our results were comparatively highly associated with enoxaparin than rivaroxaban.[16, 28] Furthermore, HOKUSAI-VTE cancer study has reported that, not more than 7% of bleeding was associated with direct oral anticoagulants (DOACs), contrast to bleeding estimate of 16% and 9% found with enoxaparin as reported in the CANTHANOX and ONCENOX studies, respectively. As, only one-third of the administered dose of rivaroxaban is excreted via kidneys, while enoxaparin excretes mainly through renal pathway, therefore, a decline in the incidence(s) of MBEs can be obtained in patients on rivaroxaban (prescribed as an initial treatment) than enoxaparin.[13, 29-31] The potential justification could be its limited drug accumulation in case of renal impairment. As in severe renal impairment, the plasma concentration of rivaroxaban increases only by 30% with a subsequent increase in half-life by just 1 hour.[14]

It has been observed that those renally compromised cancer patients, where drug dosage adjustment for enoxaparin was required but not provided during the treating of Ca-VTE, resulted in the bleeding episode(s). The possible reason behind such un-towards effects included abnormal/altered renal functioning that ultimately led to altered pharmacokinetic properties of the drug. Reduced renal functioning in renal impairment may be due to one or combination of the risk factors included with lesser number of functioning nephrons, impaired renal blood flow, improper glomerular filtration rate, and/or tubular secretion rate which account for the reduced excretion capacity as kidney disease advances. Those anticoagulants which are primarily excreted or metabolized/transported by renal pathway are prone to alterations in their pharmacokinetics profile. If not excreted properly or in time, they may have untoward effects due to prolonged stay in the body. Therefore, drug dosage adjustment is of prime importance in patients with compromised renal function especially among subjects with older age.[32]

The clinical implications of the study were that it provided enough bases for practicing of rivaroxaban in symptomatic treatment of VTE especially with add-on renal impairment. It has been evident that rivaroxaban has a promising future in treating Ca-VTE due to its ease in administration and comparable efficacy to enoxaparin. Similarly, results of this have revealed a superior clinical safety profile with rivaroxaban when compared to its parenteral counterpart. Furthermore, in patients with mild-moderate renal impairment, rivaroxaban can be administered in fixed doses with no need for dose adjustment and routine monitoring for coagulation. In patients with long-term anticoagulation therapy, the use of rivaroxaban appeared to be a better choice in patients with a declining renal function because it can provide wider safety range. However, in severe renal impairment *i.e.*,CrCl 15-29 ml/min, it should be used with caution and in CrCl<15 ml/min, its use should be avoided due to insignificant reported data regarding its safety profile in those patients. Moreover, this study also revealed the

necessity of drug dosage adjustment in renally impaired subjects in prevention of drug adverse effect(s).

Findings of this study would have been more evident if this was a prospective database natured research, the selection was unbiased (selection of patients in a randomized fashion) that could have affected the validity of this study, and the information was well-defined on cancer staging which prevented us from describing Ca-VTE population in much detail. For these reasons, this data could not be generalized to the Pakistani population as a whole. Furthermore, it will be more beneficial to conduct this research for a longer time period (6-months) and the novel drug to assess in comparison with other anticoagulant drugs in-line.

V. CONCLUSION

It was concluded that the risk of recurrent venous thromboembolism (VTE), as well as major bleeding events (MBEs), correspondingly increases with severity of renal impairment in cancer-associated VTE (Ca-VTE) patients. The use of rivaroxaban is of superior safety and comparable efficacy to enoxaparin. Drug dosage adjustment can minimize the bleeding risk with the enoxaparin therapy. The results may be applied when managing Ca-VTE patients with/without renal impairment to minimize risk of MBE with enoxaparin and to adjust the enoxaparin dose in case of severe renal impairment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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