ABSTRACT

Background
Little is known about the effects of direct oral anticoagulants (DOACs) in cancer-related venous thromboembolism patients.

Methods
Data of patients with cancer-related venous thromboembolism (VTE) were retrieved from King Abdulaziz Medical City Database during 2016–2020. We excluded patients who were not using oral anticoagulants, used anticoagulants for <30 days, used 2 agents concomitantly or switched anticoagulants, were aged <65. The primary outcomes were recurrent VTE, major bleeding, and death from any cause.

Results
We identified 717 patients who received a diagnosis of cancer-related VTE. After the exclusion criteria were applied, 445 patients remained, 298 were used warfarin, and 147 were received NOACs. Both groups were followed up for 12±2 months. The mean age of the patients was 71 ± 8 in the DOACs group and 76 ±6 in the warfarin group (p > 0.05); 48.24% of patients in the DOAC group and 46.98% of patients in the warfarin group were men (p > 0.05). The mean HAS-BLED score was 3.7 ± 3.8 in the NOAC group and 3.8 ± 3.9 in the warfarin group (p > 0.05). Furthermore, among patients with cancer-related VTE, DOAC was associated with no difference in major bleeding or recurrence events (CRR = 0.91, 95% CI = 0.78–1.05; CRR = 0.63, 95% CI = 0.52–0.77, respectively), and significantly reduced death from any cause (aHR = 0.65, 95% CI = 0.52–0.80) compared with warfarin.

Conclusions
In elderly patients with cancer-related VTE, DOAC was associated with reduced death from any cause compared with warfarin, whereas no difference in major bleeding or recurrent VTE were observed between these treatment modalities.

Introduction:
Cancer-associated venous thromboembolism (VTE) is treated with anticoagulation for defined period based on international guidelines [1,2]. However, the risk of recurrence in these patients remains substantial despite the appropriate use of anticoagulation following the guideline recommendations. With regard to DOACs vs warfarin in recent years, one retrospective study [3] and two meta-analyses [4, 5] reported that DOACs were more efficacious in the treatment of cancer-associated VTE with similar bleeding risk compared to VKA, whereas another two meta-analyses [6,7] indicated that DOACs were more efficacious with a decrease of bleeding risk, compared to VKA. Besides, the Hokusai-VTE trial reported that DOAC was as effective as warfarin for the treatment of patients with cancer-associated VTE with less bleeding risk [8]. Therefore, we investigated the efficacy and safety profiles of DOAC and warfarin in patients with cancer-associated VTE.

Patients and Methods
In this retrospective cohort study, patient data were obtained from the King Abdulaziz Medical City (KAMC) Database which is the largest health care provider in Riyadh, Saudi Arabia. The hospital identification number of each patient was encrypted and deidentified to protect their privacy. Informed consent
was thus waived for this study. The diagnosis and laboratory data were linked and continuously monitored using consistent data encryption. The Institutional Review Board of King Abdullah International Medical Research Center (KAIMRC) approved the study protocol.

A search of the electronic medical records of the KAMC between the period of January 1, 2016 and December 31, 2020, yielded data from patients with a diagnosis of cancer-associated VTE. Patients who were not prescribed oral anticoagulants (e.g., warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) or had an anticoagulation use <30 days, had concomitant use of ≥2 agents, or had an anticoagulant used had missing LA diameter data had a history of valve surgery had mitral stenosis or had a history of cancer were excluded.

**Study outcomes and follow-up**

Primary outcomes were defined as recurrent VTE, major bleeding and death from any cause at the end of follow-up. Major bleeding was defined based on principal or secondary diagnosis at hospitalizations and emergency visits and any blood transfusion order including admission for any bleeding a need for a blood transfusion of >2 U and life-threatening bleeding or vital organ hemorrhage (e.g., intracerebral hemorrhage). The follow-up period was defined as the period from the index date until the first occurrence of any study outcome or the end date of the study period, whichever came first. We applied the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10 codes to categorize diseases. Covariates included age, sex HAS-BLED score, comorbidities and medications. The comorbidities included were diabetes mellitus, hypertension, heart failure, renal insufficiency, peptic ulcer disease, abnormal liver function, peripheral artery disease and old myocardial infarction. The medications included were antiplatelets, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, amiodarone/dronedarone, beta blockers, calcium channel blockers, diuretics, NSAIDs and antidiabetic drugs.

**Statistical Analysis**

The t test was used to assess continuous variables and the χ² test was used to assess categorical variables. The propensity score was included as a covariate based on the HAS-BLED scores. The risk of death from any cause was compared between groups using a Cox proportional hazards model. Competing risk regression (CRR) was performed with recurrent VTE and major bleeding. A p value <0.05 was considered statistically significant. No adjustments for multiple testing (multiplicity) were used in this study. Statistical analyses were performed using Stata® (Stata Corp LP, Texas, USA).

**Results**

We identified 717 patients who received a diagnosis of cancer-related VTE. After the exclusion criteria were applied, 445 patients remained 298 were used warfarin and 147 were received NOACs. Both groups were followed up for 12 ±2 months. The demographic characteristics are presented in Table 1. The mean age of the patients was 71 ± 8 in the DOACs group and 76 ± 6 in the warfarin group (p > 0.05); 48.24% of patients in the DOAC group and 46.98% of patients in the warfarin group were men (p > 0.05). The mean HAS-BLED score was 3.7 ± 3.8 in the NOAC group and 3.8 ± 3.9 in the warfarin group (p > 0.05). Furthermore, among patients with cancer-related VTE, DOAC was associated with no difference in major bleeding or recurrence events (CRR = 0.91, 95% CI = 0.78–1.05; CRR = 0.63, 95% CI = 0.52–0.77, respectively) and significantly reduced death from any cause (aHR = 0.65, 95% CI = 0.52–0.80) compared with warfarin. Based on our major findings, we calculated the observed (post hoc) power to be as follows: recurrent, 0.82; major bleeding, 0.08; and death from any cause, 0.84.

**Discussion**

The outcomes of DOAC compared with warfarin in elderly patients with cancer-related VTE aged ≥65 years; key findings are as follows: Patients with cancer-related VTE receiving DOAC were associated with significantly reduced deaths from any cause, without differences in recurrent VTE events and major bleeding compared with patients receiving warfarin. The risk of VTE in patients with cancer is a major concern, and treatment guidelines are continually updated to offer more precise approaches to predicting and preventing these events [20–22]. Epidemiologic data from the KAMC have several limitations. First, the use of ICD-9-CM and ICD-10 codes may lead to missing cases of patient conditions that were incorrectly coded. Second, we did not analyze individual DOACs to delineate the efficacy and safety of each drug compared with warfarin because the number of recently introduced apixaban users was relatively small.

**Conclusions**

In elderly patients with cancer-related VTE, DOAC was associated with reduced death from any cause compared with warfarin, whereas no difference in major bleeding or recurrent VTE were observed between these treatment modalities.

**Ethics approval and Consent to participate**

The study was approved by the Medical Ethics Research Board of King Abdullah International Medical Research Centre. All patients provided written consent for participating in the study.

**Consent for publication**

Not applicable.

**Availability of Data and Materials**

The datasets generated and/or analysed during the current study are not publicly available due to confidentiality reasons and institutional policies.

**Conflict of Interest**

None is declared.

**Authors’ Contributions**

Author conceptualized and designed the study, performed the statistical analysis and drafted the final manuscript and approved submission.

**Acknowledgment**

We would like to acknowledge the help of the Department of Data Management of King Abdullah International Medical Research Centre, King Saud bin Abdulaziz university for health Sciences, Health Affairs, Ministry of National Guard, in their assistance with data acquisition.
Table 1. Demographic characteristics of patients with cancer-related VTE

<table>
<thead>
<tr>
<th>Variables</th>
<th>DOAC n= 147</th>
<th>Warfarin n= 298</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (±SD)</td>
<td>71 ± 8</td>
<td>76 ± 6</td>
<td>.55</td>
</tr>
<tr>
<td>Sex, no (%)</td>
<td></td>
<td></td>
<td>.751</td>
</tr>
<tr>
<td>Male</td>
<td>95 (64.6)</td>
<td>188 (63.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52 (35.4)</td>
<td>110 (36.9)</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td>.461</td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td>25.9 (19.3-30.2)</td>
<td>25.3 (21.7-29.4)</td>
<td></td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td></td>
<td></td>
<td>.958</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>3.7 ± 3.8</td>
<td>3.8 ± 3.9</td>
<td></td>
</tr>
<tr>
<td>Concurrent illnesses, no (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>30 (20.4)</td>
<td>64 (21.5)</td>
<td>.795</td>
</tr>
<tr>
<td>Diabetes</td>
<td>71 (48.3)</td>
<td>132 (44.3)</td>
<td>.425</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>63 (42.9)</td>
<td>125 (41.9)</td>
<td>.854</td>
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<td>Renal insufficiency</td>
<td>11 (7.5)</td>
<td>28 (9.4)</td>
<td>.502</td>
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<td>Liver disease</td>
<td>7 (4.8)</td>
<td>16 (5.4)</td>
<td>.785</td>
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<td>Heart failure</td>
<td>9 (6.1)</td>
<td>20 (6.7)</td>
<td>.812</td>
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<td>Death, no (%)</td>
<td>25 (17.0)</td>
<td>88 (29.5)</td>
<td>.005</td>
</tr>
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</table>

References