



Article

Real-World Analysis of the Safety and Effectiveness of Apixaban Therapy in Cancer Patients with Venous Thromboembolism in Saudi Arabia

Lolwa Alabdelmuhsin ¹, Metab Alwethairi ¹, Ohoud Almadani ², Turki A. Althunian ²
and Hisham A. Badreldin ^{1,*}

¹ Pharmaceutical Care Services, King Abdulaziz Medical Center, King Abdullah International Medical Research Center, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh 11426, Saudi Arabia

² Research Informatics Department, Saudi Food and Drug Authority, Riyadh 13513-7148, Saudi Arabia

* Correspondence: aldeenh@ksau-hs.edu.sa

Abstract: Purpose: This study was conducted to evaluate the effectiveness and safety of apixaban in patients with cancer for the treatment of venous thromboembolism (VTE) at a tertiary medical institution in Saudi Arabia. Methods: An observational retrospective cohort study was conducted on adult patients with cancer who were diagnosed with VTE and received apixaban therapy from August 2016 to October 2020. Results: A total of 478 patients were screened; 99 patients were included in the final analysis. Of those included, 38 (38%) were female, 74 (77.1%) had a solid tumor, and 36 (36.4%) were receiving apixaban therapy due to developing proximal deep vein thrombosis (DVT), and the mean age was 58.59 (± 14.77). At six months, thrombotic events occurred in 11 patients (11.1%), and bleeding events occurred in 14 (14.1%) of the included individuals. Mortality occurred in 9 (9.09%) of the included individuals. Close to 32% individuals discontinued apixaban therapy at six months. Conclusion: The prevalence of recurrent VTE and bleeding events in patients with cancer using apixaban for treating VTE is in line with many other real-world studies but slightly higher compared to the patients enrolled in the Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer (CARAVAGGIO) trial.

Keywords: cancer; venous thromboembolism; direct oral anticoagulants (DOACs); pulmonary embolism; deep vein thrombosis



Citation: Alabdelmuhsin, L.; Alwethairi, M.; Almadani, O.; Althunian, T.A.; Badreldin, H.A. Real-World Analysis of the Safety and Effectiveness of Apixaban Therapy in Cancer Patients with Venous Thromboembolism in Saudi Arabia. *J. Vasc. Dis.* **2023**, *2*, 102–111. <https://doi.org/10.3390/jvd2010008>

Received: 1 December 2022

Revised: 29 December 2022

Accepted: 3 January 2023

Published: 1 February 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Venous thromboembolism (VTE) is a common complication in patients with cancer. Globally, it increases mortality by two to six-fold and is considered the most prevalent cause of mortality in cancer patients [1]. A single-center retrospective study conducted in Saudi Arabia between 2006 and 2017 showed that the incidence of VTE in cancer patients was four-fold higher compared to non-cancer patients. The most common types of cancer were lymphoma, followed by breast, colorectal, pancreatic, and hepatocellular cancers [2]. According to the National Comprehensive Cancer Network Guidelines on Cancer-Associated Venous Thromboembolic Disease, pancreatic, brain, stomach, kidney, uterus, lung, and genitourinary cancers were associated with the highest risk for increasing the rates of VTE [1]. Trials have shown that low-molecular-weight heparin (LMWH) was superior to warfarin in the secondary prevention of VTE among patients with cancer. Ever since then, LMWH has become the gold standard for treating cancer-associated thrombosis (CAT). Direct oral anticoagulants (DOACs) might represent an efficient alternative to LMWH. Several trials were conducted to evaluate the safety and efficacy of DOACs versus LMWH, such as Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism (HOKUSAI VTE Cancer), Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight

Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D), Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial (ADAM-VTE), and Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer (CARAVAGGIO) trials [3–6].

A meta-analysis of these trials showed that the risk of recurrent VTE was 32% lower in patients who received DOACs. In contrast, there was a 36% increase in the risk of major bleeding and a 63% increase in clinically relevant non-major bleeding (CRNMB) in patients who received DOACs. Mortality was comparable in both groups (RR, 0.96; 95% CI, 0.68–1.36) [7]. As a result of these trials, treatment guidelines now recommend DOACs as the first-line treatment option for patients without gastrointestinal or genitourinary CAT who also have a low bleeding risk. For patients with gastrointestinal or genitourinary CAT, LMWH is the most reasonable option since there is an increased risk of bleeding with DOACs [1,8–10]. Although studies regarding the utilization of DOACs for the management of thrombosis in cancer patients are growing in number, there is a lack of real-world studies conducted in Saudi Arabia. Moreover, most of the landmark trials did not include patients from the Middle East. Therefore, this study aimed to evaluate the effectiveness and safety of apixaban therapy among patients with cancer and VTE in Saudi Arabia.

2. Materials and Methods

This was a single-center, retrospective cohort study conducted using the databases of all the Ministry of National Guard Health Affairs (MNG-HA) hospitals in Saudi Arabia. Institutional review board (IRB) approval was obtained from the King Abdullah International Medical Research Center (KAIMRC) (reference number: IRBC/0131/21). All cancer patients on apixaban from August 2016 through October 2020 were screened. We included all adult patients aged 18 years and above who had a regular follow-up in an inpatient or outpatient setting and were known to have an active or history of cancer (other than basal or squamous cell skin cancer) using the World Health Organization (WHO) International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), Chapter II: Neoplasms (C00–C97, Malignant neoplasms, and D00–D09, In situ neoplasms). We used the electronic hospital record system to extract detailed information for each patient.

We collected the following patient information: patient demographic, past medical history, indication of apixaban, dose of apixaban, initiation date of apixaban, interacting medications, prior use of anticoagulation therapy, and diagnosis of recurrent VTE or bleeding events. The list of interacting medications with apixaban was collected from the United States Food and Drug Administration (U.S. FDA) and the European Medicines Agency (EMA) package inserts. We excluded patients who were known to have documented adherence problems, could not be confirmed to have started the drug (despite the prescription), or had missing information. Patients who had undergone a thrombectomy, vena cava filter insertion, or thrombolysis, and those who had an unclear history of malignancy, creatinine clearance less than 30 mL/min based on the Cockcroft Gault equation or were receiving hemodialysis were also excluded from this study.

We also collected any documentation related to the clinical outcomes of a recurrent VTE event or bleeding event and recorded the type of event, onset of the event, death and discontinuation rate of apixaban, and reason for death and discontinuation. Patients were followed from the first prescription date until their discontinuation of apixaban, death, or the end of the study period. Bleeding events were included if they met the criteria for clinically relevant non-major or major bleeding according to the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Active cancer was defined as a diagnosis of new or recurrent or metastatic cancer within six months before the study inclusion or receiving treatment for cancer at the time of inclusion. History of cancer was defined as cancer diagnosis within two years before study inclusion.

The first endpoint of this study was to describe the effectiveness of apixaban therapy in cancer patients with VTE by estimating the recurrence of VTE within six months. The second endpoint was to describe the safety of apixaban therapy in cancer patients with VTE by estimating the incidence of bleeding events within six months. We also assessed the rate of deaths and discontinuation rate of apixaban and the reason for death and discontinuation.

All data collected were combined in an electronic data collection sheet using Excel version 16.58, 2019 (Microsoft, Redmond, WA, USA). The data were entered into the SPSS version 21 for Windows (SPSS) for analysis (IBM, Chicago, IL, USA). Descriptive analysis was used, categorical variables being reported as numbers and percentages, with continuous variables reported as mean (\pm standard deviation (SD) and 95% confidence interval (CI).

3. Results

3.1. Demographic and Clinical Characteristics

A total of 475 patients were screened for inclusion during the study period. A total of 99 individuals met the inclusion criteria and were included in the final analysis as shown in Figure 1. Of the 99 included patients, 38 (38.4%) were female, and the mean age was 58.59 (\pm 14.77). For most of the included patients, 85 (85.9%) had a baseline creatinine clearance of more than 50 mL/min as shown in Table 1. Regarding the type of cancer, 74 (74.7%) of the included individuals had a solid tumor as shown in Table 2. Of those included, 36 (36.4%) were receiving apixaban therapy due to developing proximal DVT. The most prevalent comorbid conditions in our cohort were hypertension and diabetes mellitus.

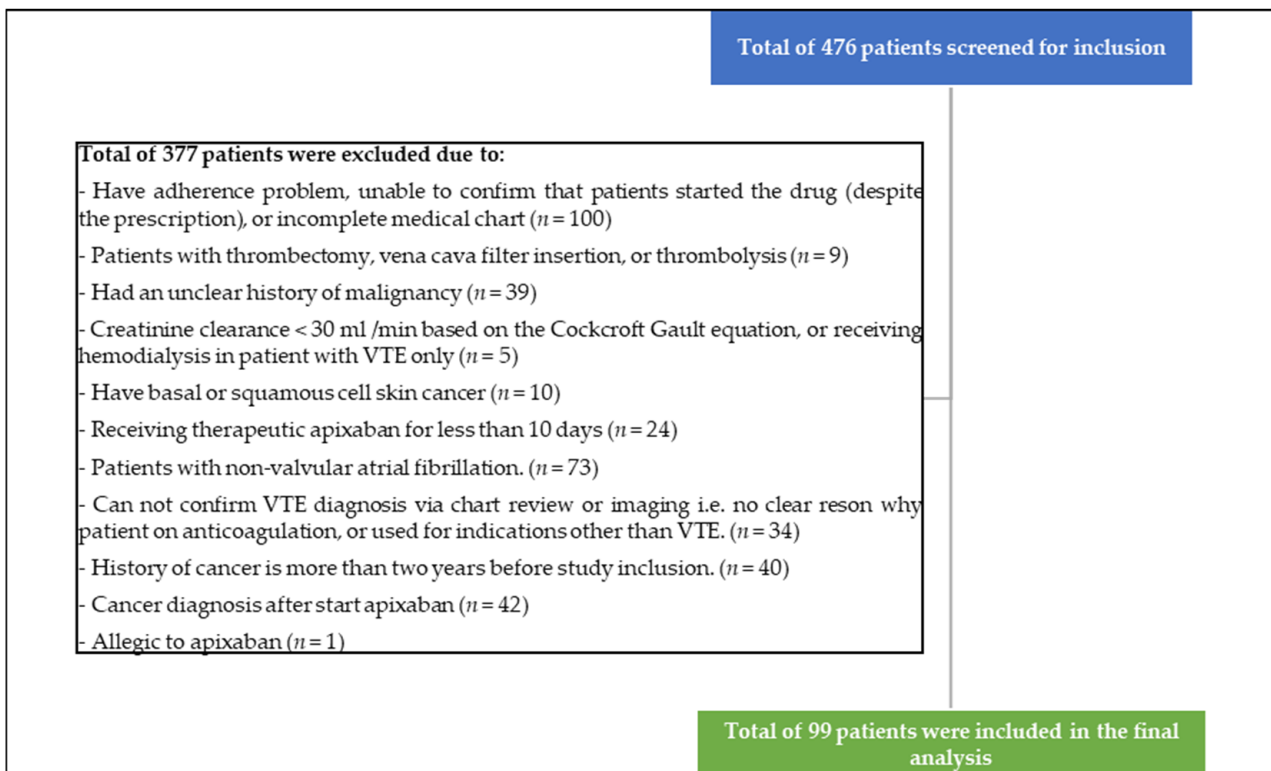


Figure 1. Patient Enrollment. VTE: venous thromboembolism.

Table 1. Patient demographics and clinical characteristics at the time of apixaban initiation.

Characteristic	
Age, years, (Mean, SD)	58.59 (14.77)
Female Sex, (n, %)	38 (38.4%)
Creatinine clearance category (n, %) *	
30–50 mL/min	14 (14.1%)
>50 mL/min	85 (85.9%)
Platelets count category, (n, %)	
<100 × 10 ⁹ /L	4 (4.0%)
100–349 × 10 ⁹ /L	67 (67.7%)
>349 × 10 ⁹ /L	28 (28.3%)
Hemoglobin < 10 g/dL, (n, %)	33 (33.3%)
Body Mass Index category, (n, %)	
<18.5 kg/m ²	5 (5.1%)
18.5–24.9 kg/m ²	32 (32.3%)
25–29.9 kg/m ²	22 (22.2%)
>29.9 kg/m ²	40 (40.4%)
Appropriate dose at baseline (n, %)	79 (79.8%)
ECOG performance status category (n, %)	
0	8 (8.33%)
1	11 (11.5%)
2	10 (10.4%)
≥ 3	12 (12.5%)
Unknown	55 (57.3%)
Active cancer (n, %)	96 (97.0%)
Type of cancer (n, %)	
Solid tumor	74 (77.1%)
Hematological malignancy	22 (22.9%)
Recurrent locally advance or metastatic Cancer (n, %)	69 (71.9%)
Qualifying diagnosis of venous thromboembolism (n, %)	
Proximal DVT	36 (36.4%)
Distal DVT	2 (2.0%)
Proximal and distal DVT	2 (2.0%)
Segmental PE	19 (19.2%)
Subsegmental PE	6 (6.1%)
Subsegmental & Segmental PE	10 (10.1%)
Proximal DVT & Segmental PE	5 (5.1%)
Splanchnic (SPVT)	9 (9.1%)
Superficial (SVT)	1 (1.0%)
Proximal DVT & Subsegmental PE	1 (1.0%)
RV thrombus	1 (1.0%)

Table 1. *Cont.*

Characteristic	
SVC thrombus	1 (1.0%)
Unknown	3 (3.0%)
Superficial (SVT) and unknown type of PE	1 (1.0%)
Proximal DVT and unknown type of PE	1 (1.0%)
Proximal DVT + SPVT + Segmental PE	1 (1.0%)
Medical history (n, %)	
Hypertension	37 (37.4%)
Diabetes mellitus	36 (36.4%)
Heart failure	6 (6.1%)
Prior ischemic stroke, TIA or MI	13 (13.1%)
History of myocardial infarction, peripheral artery disease, aortic plaque	2 (2.0%)
Prior gastrointestinal bleed	10 (10.1%)

* As per Cockcroft Gault equation. DVT: deep vein thrombosis; ECOG: Eastern Cooperative Oncology Group; MI: myocardial infarction; PE: pulmonary embolism; RV: right ventricular; SD: standard deviation; SCV: superior Vena Cava; TIA: transient ischemic attack.

Table 2. Type of cancer, and anticancer therapy while on apixaban.

Type of Cancer		
	Number	%
Solid tumor		
Colorectal	13	13.5%
Lung	3	3.1%
Breast	15	15.6%
Genitourinary	7	7.3%
Gynecological	15	15.6%
Pancreatic or hepatobiliary	10	10.4%
Upper gastrointestinal	3	3.1%
Head and neck	2	2.1%
Bone/Soft tissue	5	5.2%
Other solid tumor	1	1.0%
Hematological malignancy		
Multiple myeloma	7	7.3%
Non-Hodgkin lymphoma	9	9.4%
Hodgkin lymphoma	3	3.1%
Acute leukemia	1	1.0%
Chronic leukemia	1	1.0%
Other hematological	1	1.0%
Therapy while on apixaban		
Anti-Cancer Agents		
Alkylating agents	49	51.0%
Antimetabolites	37	38.5%
Monoclonal antibodies	32	33.3%

Table 2. *Cont.*

Type of Cancer		
Anti-Androgens	2	2.1%
Aromatase Inhibitor	4	4.2%
Cyclin-Dependent Kinase Inhibitor	1	1.0%
Taxanes	17	17.7%
Hormonal therapy	1	1.0%
Topoisomerase inhibitors	12	12.5%
PARP Inhibitor	1	1.0%
Anthracyclines	15	15.6%
Vinca alkaloids	11	11.5%
Kinase inhibitors	4	4.2%
Immunomodulating agents	6	6.3%
Proteasome inhibitors	2	2.1%
Antitumor antibiotics	4	4.2%
All-trans retinoic acid	1	1.0%
Arsenic Trioxide	1	1.0%
Radiation	14	14.6%
Radiation and Anti-cancer	11	11.5%
Other Therapy	Number	%
NSAID	17	17.2%
Clopidogrel	3	3.0%
Prior use of anticoagulation therapy	71	71.7%

3.2. Thrombotic and Bleeding Events

As shown in Table 3 and Figure 2, thrombotic events occurred in 11 (11.1%) individuals. Of these, four (36.4%) patients developed recurrent DVT, four (36.4%) patients developed recurrent Pulmonary embolism (PE), and one (9.1%) patient developed cerebrovascular events. All patients who developed recurrent DVT presented with proximal DVT. Three of the four patients who developed recurrent PE presented with segmental PE. In terms of the onset of VTE since apixaban initiation, seven (63.6%) patients developed recurrent thrombotic events within 0–3 months of apixaban initiation.

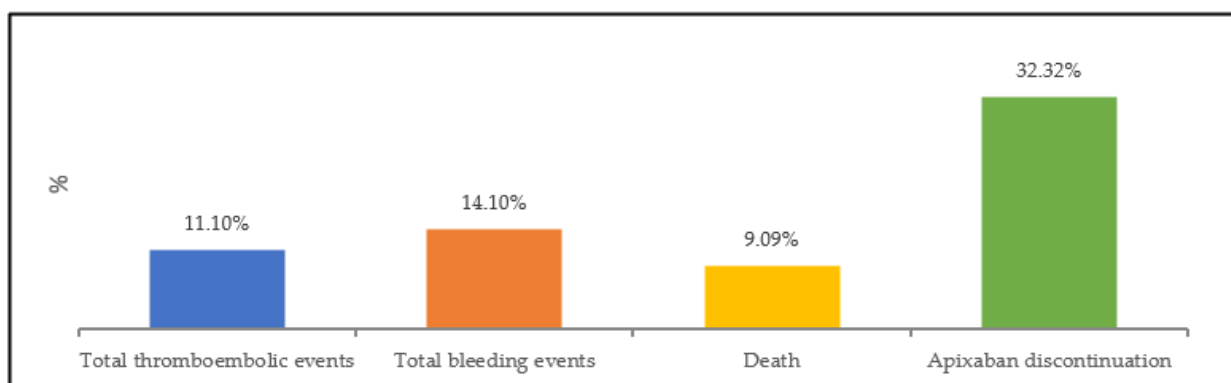


Figure 2. Efficacy and safety outcomes of apixaban use in cancer patients with VTE at six months.

Table 3. Efficacy and safety outcomes of apixaban use in cancer patients with VTE.

Outcome	Number	%
Primary efficacy outcome		
Total thromboembolic events	11	11.1%
Type of thromboembolic events		
Stroke	1	9.1%
PE	4	40.0%
DVT	4	40.0%
Other VTE	1	10.0%
Thromboembolic events Sub-Type		
Hemorrhagic stroke	1	9.1%
Segmental PE	3	27.3%
Subsegmental & Segmental PE	1	9.1%
Proximal DVT	4	36.4%
Superficial (SVT)	1	9.1%
Onset of VTE since apixaban initiation		
within 0–3 months	7	63.6%
3–6 months	3	27.3%
Primary safety outcome		
Total bleeding events	14	14.1%
Type of bleed events		
Major bleed	3	21.4%
Clinically relevant non major bleed	8	57.1%
Clinically NON relevant non major bleed	3	21.4%
Bleeding Location:		
Fatal	1	7.1%
Abdominal	1	7.1%
Cutaneous	1	7.1%
Hematuria	4	28.6%
Upper airways	1	7.1%
Upper GI	3	21.4%
Lower GI	1	7.1%
Undetermined site	1	7.1%
Stoma	1	7.1%
Mortality		
Death	9	9.09%
Reason of death:		
Cancer related	5	55.6%
Cardiovascular related	1	11.1%
Other	2	22.2%
Unknown reason	1	11.1%
Apixaban discontinuation	32	32.32%

Table 3. *Cont.*

Outcome	Number	%
Reasons of Apixaban discontinuation:		
Thrombosis or bleed event	12	12.1%
Death	7	7.1%
Thrombocytopenia	2	2.0%
High bleeding risk	1	1.0%
Unknown reason	4	4.0%
Completed VTE treatment duration	4	4.0%
Suspect thrombosis or bleed event	2	2.0%

GI: gastrointestinal tract.

As shown in Table 3 and Figure 2, bleeding events occurred in 14 (14.1%) individuals. Of these, three (21.4%) patients developed major bleeding events, eight (57.1%) developed clinically relevant non-major bleeding events, and three (21.4%) developed clinically non-relevant non-major bleeding events. Hematuria followed by upper gastrointestinal were the most commonly reported sites of bleeding.

3.3. Mortality and Apixaban Discontinuation

As shown in Table 3 and Figure 2, mortality occurred in 9 (9.09%) patients. Cancer-related mortality was the most common etiology of mortality. Of the included individuals, 32 (32.32%) discontinued apixaban therapy. The most prevalent reason for discontinuation was developing thrombosis or bleeding events.

4. Discussion

To the best of our knowledge, this is the first study to be conducted in Saudi Arabia to evaluate the real-world rates of recurrent VTE and bleeding events within six months while on apixaban in patients with cancer and VTE. Overall, we observed higher rates of recurrent VTE and major bleeding events in our cohort compared to the patients enrolled in the CARAVAGGIO trial—11.1% versus 5.6%, respectively, and 21.4% vs. 3.8%, respectively [6]. This might be due to the fact that we included patients with higher Eastern Cooperative Oncology Group (ECOG) performance status.

The current study showed that 11.1% of our cancer patients had recurrent VTE, which is consistent with previous retrospective studies that showed the prevalence range between 0 to 15.8% during a follow-up period of 6 months. Also, our study showed that 14.1% of our cancer patients had a bleeding event, which is consistent with previous retrospective studies that showed a prevalence that ranges between 11.1% to 13.91% during a follow-up period of six months [11,12]. One study reported that 2.5% of patients have major bleed, and 11.4% have CRNM bleed. However, the percentages were higher in our study (21.4% and 57.1%, respectively) [12]. The major and CRNM bleed events in this study were also more frequent than those reported in the CARAVAGGIO trial (21.4% vs. 3.8%, respectively, and 57.1% vs. 9%, respectively). On the other hand, the sites of bleeding events in this study were consistent with the CARAVAGGIO trial, which predominantly originated from the gastrointestinal and genitourinary systems. Death from any cause in this study was 9%, which is lower than that reported in the CARAVAGGIO trial, 23.4% [6]. The apixaban discontinuation rate in the current study was 32.3%, which is lower compared to 53.3% in another retrospective study [13].

Most of our patients were receiving alkylating agents (51%). Sixty-three percent of recurrent VTE events onset since apixaban initiation within 0–3 months, which is consistent with the recurrent VTE risk rate in non-cancer patients. This study is one of the few studies that evaluated the safety and efficacy of apixaban in patients with cancer in Saudi Arabia. Our results emphasize the importance of close monitoring for recurrent VTE within the first

six months, especially after VTE diagnosis, and to use apixaban with caution in patients with gastrointestinal and genitourinary cancer due to the high risk of bleeding events observed in the CARAVAGGIO trial. This could provide further guidance for clinicians whenever they prescribe this agent. However, our study has several limitations, including retrospective study design, single-center, and the possibility of documentation bias. We also only assessed the potential safety and efficacy of apixaban, and the results of this study should not be extrapolated to the other DOACs. Moreover, this study was designed to evaluate the safety and effectiveness of apixaban use in cancer patients with VTE and not to report the use of apixaban in cancer patients with atrial fibrillation or any other indication. In a future study, we plan to evaluate the safety and efficacy of apixaban use in cancer patients with atrial fibrillation and versus other anticoagulants.

5. Conclusions

The prevalence of recurrent VTE and bleeding events in patients with cancer using apixaban for treating VTE is in line with many other real-world studies but slightly higher compared to the patients enrolled in the CARAVAGGIO trial. The results of our study emphasize the importance of closely monitoring apixaban prescribed for patients with gastrointestinal and genitourinary cancer due to the higher incidence of bleeding events observed in the CARAVAGGIO trial.

Author Contributions: Conceptualization, H.A.B. and L.A.; methodology, H.A.B., L.A., O.A. and T.A.A.; writing—original draft preparation, H.A.B. and L.A.; writing—review and editing, H.A.B., L.A., O.A., M.A. and T.A.A.; visualization, H.A.B., L.A., O.A. and T.A.A.; supervision, H.A.B.; project administration, H.A.B. and T.A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board at King Abdullah International Medical Research Center (KAIMRC) (reference number: IRBC/0131/21).

Informed Consent Statement: Consent was waived due to the retrospective design of this study and due to the lack of patient identifiers utilization.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Streiff, M.B.; Holmstrom, B.; Angelini, D.; Ashrani, A.; Elshoury, A.; Fanikos, J.; Fertrin, K.Y.; Fogerty, A.E.; Gao, S.; Goldhaber, S.Z.; et al. Cancer-Associated Venous Thromboembolic Disease, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw. (JNCCN)* **2021**, *19*, 1181–1201. [[CrossRef](#)] [[PubMed](#)]
2. Alshahrani, S.; Alfawzan, A.; Alswaidan, A.; Alkharaan, A.; Alabduljabar, M.; Khan, A.; Alzahrani, M. Anatomical sites and clinical characteristics of venous thromboembolism in a tertiary hospital. *J. Appl. Hematol.* **2020**, *11*, 126. [[CrossRef](#)]
3. Raskob, G.E.; van Es, N.; Verhamme, P.; Carrier, M.; Di Nisio, M.; Garcia, D.; Grosso, M.A.; Kakkar, A.K.; Kovacs, M.J.; Mercuri, M.F.; et al. Cancer Investigators. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N. Engl. J. Med.* **2018**, *378*, 615–624. [[CrossRef](#)] [[PubMed](#)]
4. Young, A.M.; Marshall, A.; Thirlwall, J.; Chapman, O.; Lokare, A.; Hill, C.; Hale, D.; Dunn, J.A.; Lyman, G.H.; Hutchinson, C.; et al. Comparison of an Oral Factor Xa Inhibitor with Low Molecular Weight Heparin in Patients with Cancer with Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J. Clin. Oncol.* **2018**, *36*, 2017–2023. [[CrossRef](#)] [[PubMed](#)]
5. McBane, R.D., II; Wysokinski, W.E.; Le-Rademacher, J.G.; Zemla, T.; Ashrani, A.; Tafur, A.; Perepu, U.; Anderson, D.; Gundabolu, K.; Kuzma, C.; et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. *J. Thromb. Haemost. (JTH)* **2020**, *18*, 411–421. [[CrossRef](#)] [[PubMed](#)]
6. Agnelli, G.; Becattini, C.; Meyer, G.; Muñoz, A.; Huisman, M.V.; Connors, J.M.; Cohen, A.; Bauersachs, R.; Brenner, B.; Torbicki, A.; et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N. Engl. J. Med.* **2020**, *382*, 1599–1607. [[CrossRef](#)] [[PubMed](#)]
7. Mulder, F.I.; Bosch, F.; Young, A.M.; Marshall, A.; McBane, R.D.; Zemla, T.J.; Carrier, M.; Kamphuisen, P.W.; Bossuyt, P.; Büller, H.R.; et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: A systematic review and meta-analysis. *Blood* **2020**, *136*, 1433–1441. [[CrossRef](#)] [[PubMed](#)]

8. McCormack, T.; Harrisingh, M.C.; Horner, D.; Bewley, S.; Guideline Committee. Venous thromboembolism in adults: Summary of updated NICE guidance on diagnosis, management, and thrombophilia testing. *BMJ* **2020**, *369*, m1565. [[CrossRef](#)] [[PubMed](#)]
9. Farge, D.; Frere, C.; Connors, J.M.; Ay, C.; Khorana, A.A.; Munoz, A.; Brenner, B.; Kakkar, A.; Rafii, H.; Solymoss, S.; et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol.* **2019**, *20*, e566–e581. [[CrossRef](#)] [[PubMed](#)]
10. Lyman, G.H.; Carrier, M.; Ay, C.; Di Nisio, M.; Hicks, L.K.; Khorana, A.A.; Leavitt, A.D.; Lee, A.; Macbeth, F.; Morgan, R.L.; et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. *Blood Adv.* **2021**, *5*, 927–974. [[CrossRef](#)] [[PubMed](#)]
11. Davis, D.O.; Davis, K.A. Evaluation of Direct-Acting Oral Anticoagulant Use in Patients with Cancer. *J. Pharm. Pract.* **2018**, *31*, 441–444. [[CrossRef](#)] [[PubMed](#)]
12. Cohen, A.; Keshishian, A.; Lee, T.; Wygant, G.; Rosenblatt, L.; Hlavacek, P.; Mardekian, J.; Wiederkehr, D.; Sah, J.; Luo, X. Effectiveness and Safety of Apixaban, Low-Molecular-Weight Heparin, and Warfarin among Venous Thromboembolism Patients with Active Cancer: A U.S. Claims Data Analysis. *Thromb. Haemost.* **2021**, *121*, 383–395. [[CrossRef](#)] [[PubMed](#)]
13. Yamada, N.; Mo, M.; Ohsawa, A.; Sato, M.; Umeyama, M.; Shima, D.; Nakamura, M. Safety and Effectiveness of Apixaban in Japanese Patients with Venous Thromboembolism in Clinical Practice- A Post-Marketing Surveillance. *Circ. J. Off. J. Jpn. Circ. Soc.* **2021**, *85*, 2201–2207. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.