

# Real-World Effectiveness and Safety of Apixaban versus Warfarin in Patients with Acute Venous Thromboembolism: Experience of a Large Tertiary Hospital in Saudi Arabia

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**Purpose:** The main objective of this study was to evaluate the effectiveness and safety of apixaban versus warfarin in patients with venous thromboembolism (VTE) in a “real-world” setting.

**Patients and Methods:** A retrospective cohort study was conducted using data from a large tertiary hospital in Saudi Arabia. Patients were included if they were adults ( $\geq 18$  years), diagnosed with VTE, and treated with either apixaban or warfarin between January 2016 and September 2018. Patients who had received anticoagulation therapy within three months of the date of the index event were excluded. The effectiveness outcomes were incidence of VTE recurrence (ie, deep vein thrombosis DVT or pulmonary embolism [PE]), while the safety outcome was incidence of any major bleeding (MB) event within 90 days of follow-up.

**Results:** Among the 492 patients included for study, 212 (43.1%) received apixaban and 280 (56.1%) received warfarin. The mean age of patients was  $53.6 \pm 19.1$  years and 62% of the cohort was female. Comparable rates of VTE recurrence were observed for apixaban and warfarin treatment groups during follow-up (adjusted odds ratio (AOR) = 0.95; 95% CI 0.53–1.68), including DVT (AOR=1.06; 95% CI 0.52–2.17) and PE (AOR=0.78; 95% CI 0.31–1.96). However, apixaban was associated with significantly fewer MB events than warfarin (AOR=0.18; 95% CI 0.04–0.83).

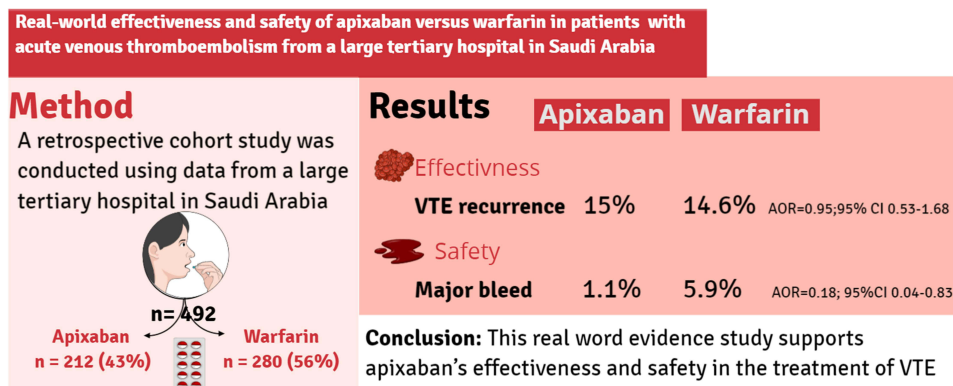
**Conclusion:** The use of apixaban for the treatment of Saudi patients with acute VTE is associated with a VTE recurrence rate comparable to that of warfarin, with significantly fewer MB events.

**Keywords:** venous thromboembolism, VTE, DVT, PE, bleeding, apixaban, DOACs, warfarin

## Introduction

Venous thromboembolism (VTE) is associated with a high mortality rate and significant healthcare expenditures.<sup>1,2</sup> The mainstay therapy for management of VTE is anticoagulation, which prevents clot embolization and reduces the risk of new clot formation.<sup>3</sup> For decades, VTE was managed using conventional anticoagulants, including low-molecular weight heparin (LMWH) and oral vitamin K antagonist (VKA). However, these agents have several limitations, such as requirement for multiple injections and frequent monitoring of the international normalized ratio (INR) levels of patients on warfarin therapy.<sup>4,5</sup> Other disadvantages of warfarin include increased risk of food–drug and drug–drug interactions.<sup>6</sup>

## Graphical Abstract



In 2010, the first direct oral anticoagulant (DOAC) agent, dabigatran, was approved by the US Food and Drug Administration (FDA),<sup>7</sup> followed by the development of several newer DOACs, such as rivaroxaban, apixaban, and edoxaban. Unlike warfarin, these agents have short half-lives and few drug–drug interactions and do not require routine drug monitoring,<sup>8</sup> leading to their preferential use for treatment of VTE.<sup>3</sup> The effectiveness and safety of apixaban have been validated in a large randomized controlled trial (RCT), designated AMPLIFY. In this study, apixaban was shown to be non-inferior to conventional therapy in reducing the risk of VTE-related death or recurrence while significantly lowering the risk of bleeding.<sup>9</sup> While RCTs have high internal validity, the findings of these studies may not be relevant to all real-world settings. RCTs have strict criteria for inclusion and exclusion to identify homogeneous populations that may not represent the heterogeneous populations in real-world settings. Patient genetics, medical practices, and healthcare systems from different countries worldwide may vary significantly in relation to those recruited for RCTs.<sup>10</sup>

To our knowledge, most RCTs assessing the effectiveness and safety of DOACs have not included patients from Saudi Arabia, and this population has been previously underrepresented.<sup>9</sup> DOAC activity is known to be affected by genetic variations among population groups.<sup>11</sup> Accordingly, in this study, we focused on evaluating the effectiveness and safety of apixaban compared to warfarin for VTE treatment using real-world data from a tertiary care center in Saudi Arabia.

## Materials and Methods

### Study Design, Setting, and Participants

This retrospective observational cohort study was conducted between January 2016 and September 2018 on patients treated for VTE at King Abdulaziz Medical City (KAMC (Riyadh, Saudi Arabia), a tertiary care center with a Level I trauma center). The study was approved by the Institutional Review Board at King Abdullah International Research Medical Centre (approval number: SP18/461/R) and included patients older than 18 years diagnosed with VTE and treated with either warfarin or apixaban. We excluded patients receiving anticoagulation therapy within three months of the date of the index event.

### Data Collection and Outcome Measures

The data obtained included demographic findings, anticoagulation type, comorbidities, other medications, VTE type, and documented bleeding while on anticoagulant therapy. We followed patients for 90 days after the date of the index event to assess the effectiveness and safety of apixaban. Effectiveness outcomes included VTE recurrence (DVT or PE or both) within 90 days of receiving anticoagulation therapy. VTE events were defined as any documented diagnosis of VTE on electronic health records (EHR) based on perfusion scanning, computed tomography, pulmonary angiography or Doppler ultrasonography. The safety outcome was documented major bleeding (MB) episodes in the EHR. MB events were identified using the International Society on Thrombosis and Haemostasis (ISTH) definition.<sup>12</sup>

## Statistical Analysis

Patient characteristics were described using descriptive statistics. Differences between the baseline characteristics of the two cohorts were determined using the *t*-test for continuous data and chi-squared test for categorical variables. Univariate logistic regression analyses were conducted to compare risk of VTE recurrence between apixaban and warfarin users, with effect sizes quantified using crude odds ratio (COR). Next, we conducted multivariable logistic regression analyses using baseline variables with significant differences between the two cohorts to adjust the results of univariate analyses for differences in baseline characteristics.

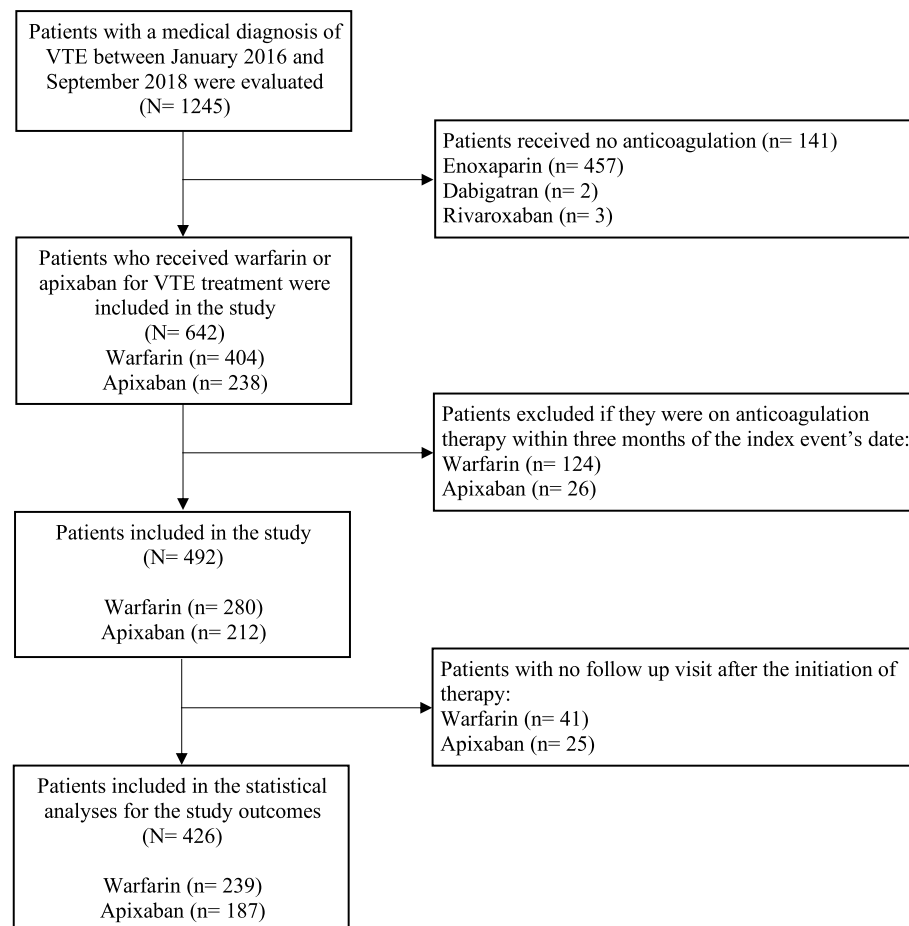
To ensure robustness of the results of multivariable logistic regression, we employed propensity score weighting (PSW) with doubly robust models for sensitivity analysis. PSW was used to create two cohorts with a balanced distribution of baseline characteristics. We further used data for the balanced cohorts from PSW with its associated weights in multivariable logistic regression analyses to produce

a doubly robust model.<sup>13</sup> An  $\alpha$  value of  $<0.05$  was used for statistical significance. SAS<sup>®</sup> version 9.4 (SAS institute, Cary, NC, USA) was applied for statistical analyses. PSW and the doubly robust model were facilitated through the TWANG Shiny Application from the RAND Corporation.<sup>14</sup>

## Results

### Patient Characteristics

A total of 492 patients with acute VTE were included for study over the data collection period (Figure 1). The mean age of patients was  $53.6 \pm 19.1$  years and 62% were female. Within our patient population, 14.4% had chronic kidney disease (CKD), 38% were on statins and 30.5% on aspirin. The proportions of patients with CKD, history of VTE, recent admittance to an intensive care unit (ICU) or coronary care unit (CCU) or recent use of systemic steroids were significantly higher for the warfarin cohort than the apixaban cohort ( $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.039$ , and  $p = 0.041$ , respectively). A difference between the groups in terms of history



**Figure 1** Patient selection criteria.

of bleeding at baseline was evident (3.3% in the apixaban group vs 6.4% in the warfarin group) but not statistically significant ( $p=0.117$ ). Both groups were comparable in terms of age, gender, body mass index (BMI), and comorbidities. Baseline characteristics for included patients are presented in Table 1. Among the 492 patients, only 187 from the apixaban cohort and 239 from the warfarin cohort were evaluated for study outcomes, while the rest were lost to follow-up at 90 days.

## Effectiveness and Safety Outcomes

In univariate analysis, the apixaban group showed comparable rates of VTE recurrence to the warfarin group within

90 days of follow-up (COR=1.02; 95% CI 0.59–1.76), including DVT (COR=1.16; 95% CI 0.58–2.30), PE (COR=0.81; 95% CI 0.34–1.92), and DVT with PE (COR=1.28; 95% CI 0.18–9.20). However, a significantly lower rate of MB events was observed with apixaban than warfarin (COR=0.17; 95% CI 0.04–0.77). Data from univariate analyses are presented in Table 2.

The results of multivariable logistic regression analyses were consistent with those of univariate analyses. With regard to effectiveness outcomes, no differences was observed between the two cohorts in VTE recurrence (adjusted odds ratio AOR=0.95; 95% CI 0.53–1.68), DVT (AOR=1.06; 95% CI 0.52–2.17), PE (AOR=0.78;

**Table 1** Characteristics of Patients Receiving Apixaban or Warfarin for VTE Treatment

Patients' Characteristics	Overall	Apixaban	Warfarin	p-value*
Number of patients	492 (100)	212 (43.1)	280 (56.1)	–
Age in years, mean (SD)	53.6 (19.1)	54.5 (18.9)	53.0 (19.3)	0.389
Female gender	305 (62.0)	130 (61.3)	175 (62.5)	0.789
BMI (kg/m <sup>2</sup> ), mean (SD)	31.5 (7.9)	31.4 (7.2)	31.5 (8.3)	0.809
Comorbidities				
Hypertension	217 (44.1)	88 (41.5)	129 (46.1)	0.313
Diabetes mellitus	188 (38.2)	74 (34.9)	114 (40.7)	0.189
History of VTE	145 (29.5)	41 (19.3)	104 (37.1)	<b>&lt;0.001</b>
ICU or CCU stay	95 (19.3)	32 (15.1)	63 (22.5)	<b>0.039</b>
Ongoing infection	83 (16.9)	35 (16.5)	48 (17.1)	0.852
Chronic kidney disease	71 (14.4)	8 (3.8)	63 (22.5)	<b>&lt;0.001</b>
Heart failure	54 (11.0)	25 (11.8)	29 (10.4)	0.614
History of stroke	47 (9.6)	20 (9.4)	27 (9.6)	0.937
Rheumatic disease	43 (8.7)	14 (6.6)	29 (10.4)	0.144
Active cancer	27 (5.5)	12 (5.7)	15 (5.4)	0.883
History of bleeding	25 (5.1)	7 (3.3)	18 (6.4)	0.117
Respiratory failure	17 (3.5)	7 (3.3)	10 (3.6)	0.871
Lower limb paralysis	13 (2.6)	3 (1.4)	10 (3.6)	0.140
Chronic obstructive pulmonary disease	12 (2.4)	3 (1.4)	9 (3.2)	0.200
Concurrent medications				
Statins	187 (38.0)	77 (36.3)	110 (39.3)	0.502
ASA	150 (30.5)	55 (25.9)	95 (33.9)	0.056
BB	136 (27.6)	61 (28.8)	75 (26.8)	0.625
ACEI/ARBs	129 (26.2)	57 (26.9)	72 (25.7)	0.769
CCB	126 (25.6)	52 (24.5)	74 (26.4)	0.632
NSAIDs	119 (24.2)	59 (27.8)	60 (21.4)	0.100
Diuretics	115 (23.4)	47 (22.2)	68 (24.3)	0.582
Systemic steroids	82 (16.7)	27 (12.7)	55 (19.6)	<b>0.041</b>
Clopidogrel	40 (8.1)	20 (9.4)	20 (7.1)	0.357

**Notes:** Results are presented as frequency (percentage) unless otherwise indicated. \*p-values were from t-test for continuous data and chi-Squared test for categorical data; and numbers in bold represent significant results.

**Abbreviations:** VTE, venous thromboembolism; SD, standard deviation; BMI, body mass index; ICU, intensive care unit; CCU, coronary care unit; ASA, aspirin; CCB, calcium channel blockers; BB, beta-blockers; ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; NSAIDs, non-steroidal anti-inflammatory agents.

**Table 2** Venous Thromboembolic and Major Bleeding Events in Patients Receiving Apixaban or Warfarin for VTE Treatment

Outcome	Apixaban N=187	Warfarin N=239	p-value*	COR (95% CI) <sup>†</sup>	AOR (95% CI) <sup>‡</sup>
VTE events	28 (15.0)	35 (14.6)	0.924	1.02 (0.59–1.76)	0.95 (0.53–1.68)
DVT	17 (9.1)	19 (8.0)	0.674	1.16 (0.58–2.30)	1.06 (0.52–2.17)
PE	9 (4.8)	14 (5.9)	0.636	0.81 (0.34–1.92)	0.78 (0.31–1.96)
DVT+PE	2 (1.1)	2 (0.8)	0.804	1.28 (0.18–9.20)	1.15 (0.14–9.46)
Major bleeding	2 (1.1)	14 (5.9)	<b>0.009</b>	<b>0.17 (0.04–0.77)</b>	<b>0.18 (0.04–0.83)</b>

**Notes:** Numbers are presented as number of patients with events (percentage). \*p-values were from chi-squared test; and numbers in bold represent significant results. <sup>†</sup>CORs are from the univariate logistic regression. <sup>‡</sup>AORs are from the multivariable logistic regression analyses; adjusted for significant baseline characteristics listed in Table 1.

**Abbreviations:** VTE, venous thromboembolism; COR: crude odds ratio; AOR: adjusted odds ratio; 95%CI: 95% confidence interval; DVT: deep vein thrombosis; PE: pulmonary embolism.

95% CI 0.31–1.96) or DVT with PE (AOR=1.15; 95% CI (0.14–9.46)). Moreover, the use of apixaban was associated with lower likelihood of MB events (AOR=0.18; 95% CI 0.04–0.83). The results of the sensitivity analyses using PSW and doubly robust models were consistent with those of multivariable logistic regression analyses. These results are presented in [Table S1](#) of [Supplementary Materials](#).

## Discussion

This retrospective cohort study in Saudi Arabia was conducted to assess the effectiveness and safety of apixaban versus warfarin for VTE, with a view to obtaining real-world evidence on the utility of apixaban. While VTE recurrence rates did not differ significantly between the apixaban and warfarin treatment groups, the risk of MB was 82% lower with apixaban, consistent with earlier literature on the utility of apixaban for VTE.

In the AMPLIFY trial, apixaban was non-inferior to warfarin in prevention of VTE recurrence. Earlier reports have shown a 69% lower risk of bleeding,<sup>9</sup> which is lower than the 82% reduction observed in our population group. The findings of Dawwas et al<sup>15</sup> are consistent with our results showing no differences in the efficacy of apixaban and warfarin in reducing risk of VTE recurrence, with lower risk of bleeding in the apixaban group (HR=0.67; 95% CI 0.54–0.84). Interestingly, Weycker et al reported a significantly lower rate of VTE recurrence (2.3% vs 2.9%) and MB (1.7% vs 2.3%) in patients using apixaban versus warfarin for VTE treatment,<sup>16</sup> which was further confirmed in another study by Weycker et al.<sup>17</sup>

The current findings present real-world evidence of the value of apixaban for VTE management within a Saudi population. To our knowledge, no previous RCTs have evaluated DOACs for management of VTE

in Saudi Arabia. Since the patient population of the AMPLIFY trial may be distinct from the Saudi population, we cannot confidently apply the results of international RCTs to our study group. Previous reports have disclosed alterations in responses of Saudi patients to warfarin due to genetic variations specific to that population.<sup>18</sup> Furthermore, recent pharmacogenetic studies have identified new genetic loci and variants that can affect DOAC activity in some populations.<sup>11</sup> Our research complements previous evidence supporting the effectiveness and safety of apixaban in the Saudi population. However, further large-scale studies are needed to confirm these findings.

No significant differences in baseline characteristics were observed between the two groups in the AMPLIFY trial. Although the warfarin treatment group in our study was mostly comparable to the apixaban group, a larger proportion of patients on warfarin used systemic steroids, had CKD or a history of VTE or had recently stayed in ICU or CCU. Any of these individual factors can increase the risk of VTE or bleeding, particularly in patients on anticoagulation medication.<sup>19,20</sup> In addition, the crude rate of history of bleeding was not significantly higher in the warfarin group but could contribute to our data on major bleeding. However, the rigorous analyses conducted in this study, including multivariable logistic regression and PSW with doubly robust models for sensitivity analysis, confirmed the findings of univariate analysis.

Our findings should be interpreted with caution. In addition to better safety outcomes with apixaban than warfarin, other factors should be considered before selection of anticoagulation agents, including drug–drug interactions, cost, and applicability of routine INR checks. In addition, apixaban dosing should follow the FDA recommendations, considering that Anouassi et al<sup>21</sup> reported

subtherapeutic dosing among prescribers practicing in the Gulf region. In our study, apixaban was dosed according to FDA recommendations for treatment of VTE, which could explain the lower rates of VTE recurrence.

This study has some limitations that should be considered, including the retrospective nature of data collected from EHR. Due to the lack of a unified integrated electronic health system in Saudi Arabia, a number of patients had no follow-up visits at our institution, and we were not informed of whether they had received care from other non-affiliated healthcare facilities. Another drawback is differences in anticoagulation follow-up practices between the two treatment groups. In our institution, patients initially treated with warfarin are referred to the pharmacy team, whereas patients on apixaban are monitored by medical doctors. Data on the cause of VTE and type of DVT (proximal vs distal) were not collected and thus differences between the cohorts based on cause of VTE or type of DVT were not assessed. In addition, data were collected between January 2016 and September 2018, which resulted in a relatively small sample size, since apixaban was added to the drug formulary of the institution in 2016 and prescribers have only gradually begun prescribing DOACs to VTE patients.

## Conclusion

Data from this study provide real-world clinical evidence that apixaban treatment is associated with comparable risk of VTE recurrence and significantly fewer MB events compared to warfarin in a patient population from Saudi Arabia. Our findings add value to the available data on the efficacy and safety of apixaban as a therapeutic agent for VTE. However, additional real-world studies are needed to evaluate the effectiveness and safety of apixaban for the treatment of VTE in other countries.

## Abbreviations

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low molecular-weight heparin; VKA, vitamin K antagonist; INR, international normalized ratio; DOACs, direct oral anticoagulants; FDA, Food and Drug Administration; US, United States; RCTs, Randomized controlled trials; MB, major bleeding; EHRs, electronic health records; COR, crude odds ratio; AOR, adjusted odds ratio; 95% CI, 95% confidence interval.

## Code Availability

Original code files are fully available if required upon request to corresponding author.

## Data Sharing Statement

Original data files are fully available if required upon request to corresponding author.

## Ethical Approval

The study was approved by the institutional review board at King Abdullah International Research Medical Centre (approval number: SP18/461/R)

## Consent to Participate

The institutional IRB required no informed consent from patients since this study was a retrospective study. Patient data were deidentified to protect the confidentiality of the included patients. This work was conducted in accordance with the Declaration of Helsinki.

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## Disclosure

Haya A Alkuait is an employee of SPIMACO Addwaeih. Wejdan Alobaidi is an employee of Novo Nordisk. Anas Aldawsari is an employee of Sanofi. Nouf M. Almutairi is an employee of BAYER pharmaceuticals. All authors report no other conflicts of interest in this work.

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