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

Majed S Al Yami,1,2 Mohammed Y Alzahrani,1,2 Abdalmajeed M Alshehri,1,2 Omar A Alshaya,1,2 Norah S Alsibiaie,1 Yazeed M Alharbi,1 Latifah K Albaiahy,1 Mounira Aldeiban,1 Haya A Alkuait,3 Wejdan Aloabidi,4 Anas Aldawarsi,5 Nouf M Almutairi,5,6 Mohannad Alshibani,1 Ghazwa B Korayem,6 Osamah M Alfayez,9 Abdulaa1 R Almutairi,10 Omar A Almohammed11

1Department of Pharmacy Practice, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; 2Sales Department, BAYER Pharmaceutical, Riyadh, Saudi Arabia; 3Sales Department, SPIMACO Addwaeih, Riyadh, Saudi Arabia; 4Sales Department, Novo Nordisk, Riyadh, Saudi Arabia; 5Sales Department, Sanofi, Riyadh, Saudi Arabia; 6Sales Department, BAYER Pharmaceutical, Riyadh, Saudi Arabia; 7Department of Pharmacy Practice, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia; 8Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia; 9Department of Pharmacy Practice, College of Pharmacy, Al Imam Abdullah Ibn Saud Ibn Abdul Aziz University, Riyadh, Saudi Arabia; 10Drug Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; 11Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Correspondence: Ghazwa B Korayem
Pharmacy Practice Department, College of Pharmacy, Princess Nourah bint Abdulrahman University, Al Imam Abdullah Ibn Saud Ibn Abdul Aziz University, Riyadh, Saudi Arabia
Tel +966 504161649
Email Gbkorayem@pnu.edu.sa

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 (≥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±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.1,2 The mainstay therapy for management of VTE is anticoagulation, which prevents clot embolization and reduces the risk of new clot formation.3 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.4,5 Other disadvantages of warfarin include increased risk of food–drug and drug–drug interactions.6
In 2010, the first direct oral anticoagulant (DOAC) agent, dabigatran, was approved by the US Food and Drug Administration (FDA), 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, leading to their preferential use for treatment of VTE. 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. 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.

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. DOAC activity is known to be affected by genetic variations among population groups. 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.
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. An α value of <0.05 was used for statistical significance. SAS® 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.

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 ± 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
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 MI 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; 95% CI 0.44–1.36), DVT with PE (AOR=1.12; 95% CI 0.21–6.03), and MI events (AOR=0.17; 95% CI 0.04–0.77). Data from multivariable analyses are presented in Table 3.

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/m²), 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) | <0.001   |
| ICU or CCU stay          | 95 (19.3) | 32 (15.1) | 63 (22.5) | 0.039    |
| 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) | <0.001   |
| 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) | 0.041    |
| 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.
VTE events

- Apixaban N=187
  - VTE events: 28 (15.0)
  - DVT: 17 (9.1)
  - PE: 9 (4.8)
  - DVT+PE: 2 (1.1)
  - Major bleeding: 2 (1.1)

- Warfarin N=239
  - VTE events: 35 (14.6)
  - DVT: 19 (8.0)
  - PE: 14 (5.9)
  - DVT+PE: 2 (0.8)
  - Major bleeding: 14 (5.9)

*p-values were from chi-squared test; and numbers in bold represent significant results. CORs are from the univariate logistic regression. AORs are from the multivariable logistic regression analyses; adjusted for significant baseline characteristics listed in Table 1.

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.

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)‡ | AOR (95% CI)‡ |
|------------------|----------------|----------------|----------|---------------|---------------|
| 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)       | 0.009    | 0.17 (0.04–0.77) | 0.18 (0.04–0.83) |

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,9 which is lower than the 82% reduction observed in our population group. The findings of Dawwas et al15 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,16 which was further confirmed in another study by Weycker et al.17

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.15 Furthermore, recent pharmacogenetic studies have identified new genetic loci and variants that can affect DOAC activity in some populations.11 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.19,20 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 al21 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.

**References**

1. Mahan CE, Borrego ME, Woersching AL, et al. Venous thromboembolism: annualised United States models for total, hospital-acquired and preventable costs utilising long-term attack rates. *Thromb Haemost*. 2012;108(08):291–302. doi:10.1160/TH12-03-0162
2. Stone J, Hangee P, AlBadawi H, et al. Deep vein thrombosis: pathogenesis, diagnosis, and medical management. *Cardiovasc Diagn Ther.* 2017;7(Suppl 3):S276–S284. doi:10.21037/cdt.2017.09.01

3. Oertel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv.* 2020;4(19):4693–4738. doi:10.1182/bloodadvances.2020001830

4. Quante M, Thate-Waschke I, Schofer M. [What are the reasons for patient preference? A comparison between oral and subcutaneous administration]. *Z Orthop Unfall.* 2012;150(4):397–403. (German). doi:10.1055/s-0031-1298347

5. Wong A, Kraus PS, Lau BD, et al. Patient preferences regarding pharmacologic venous thromboembolism prophylaxis. *J Hosp Med.* 2015;10(2):108–111. doi:10.1002/jhm.2282

6. Bishop L, Young S, Twells L, Dillon C, Hawboldt J. Patients’ and physicians’ satisfaction with a pharmacist managed anticoagulation program in a family medicine clinic. *BMC Res Notes.* 2015;8:233. doi:10.1186/s13104-015-1187-8

7. U.S. Food and Drug Administration (U.S. FDA). Pradaxa. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000TOC.cfm. Accessed April 20, 2021.

8. Julia S, James U. Direct oral anticoagulants: a quick guide. *BCJ.* 2013;725:2013. doi:10.1182/bcj.2013.725

9. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799–808. doi:10.1056/NEJMoai1302507

10. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br J Cancer.* 2014;110(3):551–555. doi:10.1038/bjc.2013.725

11. Cullell N, Carrera C, Muñoz E, Torres N, Krupinski J, Fernandez-Cadenas I. Pharmacogenetic studies with oral anticoagulants. Genome-wide association studies in vitamin K antagonist and direct oral anticoagulants. *Oncotarget.* 2018;9(49):29238–29258. doi:10.18632/oncotarget.25579

12. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005;3(4):692–694. doi:10.1111/j.1538-7836.2005.01204.x

13. Griffin BA, McCaffrey DF, Burgette LF, et al. Coffman, State-of-the-Art Strategies for Addressing Selection Bias When Comparing Two or More Treatment Groups. Santa Monica, CA: RAND Corporation; 2020. Available from: https://www.rand.org/pubs/conf_proceedings/CF421.html.

14. Griffin BA, Sanchez R, Cefalu M, et al. Toolkit for Weighting and Analysis of Nonequivalent Groups: A Tutorial on the TWANG Shiny App for Two Treatments. Santa Monica, CA: RAND Corporation; 2020. Available from: https://www.rand.org/pubs/tools/TLA570-2.html.

15. Dawdas GK, Smith SM, Dietrich E, Lo-Ciganic W-H, Park H. Comparative effectiveness and safety of apixaban versus warfarin in patients with venous thromboembolism. *Am J Health Syst Pharm.* 2020;77(3):188–195. doi:10.1093/ajhp/zzx307

16. Weycker D, Li X, Wygant GD, et al. Effectiveness and safety of apixaban versus warfarin as outpatient treatment of venous thromboembolism in U.S. clinical practice. *Thromb Haemost.* 2018;118(11):1951–1961. doi:10.1159/00038-1673689

17. Weycker D, Wygant GD, Guo JD, et al. Bleeding and recurrent VTE with apixaban vs warfarin as outpatient treatment: time-course and subgroup analyses. *Blood Adv.* 2020;4(2):432–439. doi:10.1182/bloodadvances.2019001081

18. AlAmmari M, AlBalwi M, Sultan K, et al. The effect of the VKORC1 promoter variant on warfarin responsiveness in the Saudi Warfarin Pharmacogenetic (SWAP) cohort. *Sci Rep.* 2020;10(1):11613. doi:10.1038/s41598-020-68519-9

19. Ireland R. Warfarin bleeding risk increased in CKD. *Nat Rev Nephrol.* 2009;5(6):306. doi:10.1038/nrneph.2009.58

20. Hazlewood KA, Fugate SE, Harrison DL. Effect of oral corticosteroids on chronic warfarin therapy. *Ann Pharmacother.* 2006;40(12):2101–2106. doi:10.1345/aph.1H418

21. Anouassi Z, Atallah B, Absoud LO, et al. Appropriateness of the direct oral anticoagulants dosing in the Middle East Gulf Region. *J Cardiovasc Pharmacol Ther.* 2021;77(2):182–188. doi:10.1097/fjc.0000000000000913