Breast Cancer: Targets and Therapy

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Assessing Thrombotic Risk in Patients with HR +/HER2- Breast Cancer Receiving CDK4/6 Inhibitors: Insights from Real-World Data from the Middle East

Nada Alsuhebany[1–3], Ahmed Alanazi[4], Mohammed Y Alzahrani[1–3], Saleh Alyousef[1], Bandar S Aldawish[1], Sultan Aljardan[1], Rawan Abu Alnasr[4], Ibtihal Mohammed Althumali[4], Maha AlDoughaim[1–3], Lama Alfehaid[1–3], Sadal Refae[2,5], Nafisa Abbas Abdelhafiez Jnr[2,5], Hatoon Bakhribah[6], Tariq Alqahtani[1,2]

[1]Department of Pharmacy Practice, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; [3]Department of Pharmaceutical Care Services, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; [4]Pharmacy Service Administration, King Fahad Medical City, Riyadh, Saudi Arabia; [5]Division of Adult Medical Oncology, Department of Oncology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; [6]Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia

Correspondence: Nada Alsuhebany, Department of Clinical Pharmacy, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, 2915 Al Haras Al Watani St, Ar Rimayah, Riyadh, 14611, Saudi Arabia, Tel +966500828585, Email nalsuhebany@gmail.com

Introduction: Hormone receptor-positive, HER2-negative (HR+/HER2-) is the most common subtype of breast cancer in women. Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, such as palbociclib, ribociclib, and abemaciclib play an important role in the treatment of advanced HR+/HER2- breast cancer. However, CDK4/6 inhibitors might be associated with an increased risk of thrombotic events, including venous thromboembolism (VTE).

Methods: We conducted a retrospective study at two centers in Saudi Arabia, analyzing data from 447 patients treated with CDK4/6 inhibitors for HR+/HER2- breast cancer between 2016 and 2023. Patients with early-stage, high-risk breast cancer receiving abemaciclib for at least one month were included. The primary outcomes were the incidence of VTE and arterial thrombosis.

Results: A total of 505 patients were screened in which 447 breast cancer patients receiving CDK4/6 inhibitors were included. Majority of patients were on palbociclib (70.4%), followed by abemaciclib (28.8%), and then ribociclib (0.67%). The thrombotic events were 11.8% (n=53), with 37.7% of these being pulmonary embolism (PE) and 18.8% symptomatic deep vein thrombosis (DVT). Patients with a prior history of VTE had a significantly higher risk of thrombosis (p=0.03). Abemaciclib was associated with a higher incidence of thrombosis (16.3%), followed by palbociclib (10.2%), and none of the three patients on ribociclib developed thrombosis. The median time to develop thrombosis while receiving CDK4/6 inhibitor therapy was 11.8 months. There was no significant difference in overall survival in breast cancer patients who developed thrombosis compared to patients without thrombosis (p=0.55).

Conclusion: This study shows a higher incidence of thrombotic events in real-world settings than clinical trials, emphasizing the need for risk assessment and possible thromboprophylaxis in patients receiving CDK4/6 inhibitors. Future risk assessment tools needed to be applied in breast cancer patients receiving CDK4/6 inhibitors and risk of developing thrombosis.

Keywords: thrombotic risk, venous thromboembolism, CDK4/6 inhibitors, breast cancer, hormone receptor-positive, real-world data, thrombosis risk assessment, deep vein thrombosis, DVT, pulmonary embolism, PE

Introduction

Breast cancer is the most commonly diagnosed type of cancer around the world and the second leading cause of cancer death globally in women.[1] There are four main subtypes of breast cancer, with the most common being Hormonal Receptor (HR) positive and Human Epidermal Growth Factor Receptor-2 (HER2) negative, which is commonly referred

https://doi.org/10.2147/BCTT.S554024
Received: 24 July 2025
Accepted: 3 December 2025
Published: 10 January 2026

to as HR+/HER2-.[2] The majority of HR+/HER2- breast cancer patients have an advanced stage, which requires the use of targeted therapy alongside hormonal medications.[2–4] Cyclin-dependent kinase (CDK) inhibitors have emerged as an essential first-line therapeutics in patients with recurrent unrespectable or stage IV disease.[4,5] There are three FDA-approved CDK4/6 inhibitors: palbociclib, ribociclib, and abemaciclib. These inhibitors have improved the outcomes for patients with HR+/HER2- advanced breast cancer when integrated into first-line treatment protocols. As research continues to refine and expand their use, these inhibitors are poised to further revolutionize breast cancer treatment strategies and potentially extend their benefits to other cancer types.[6]

CDK4/6 inhibitors work by inhibiting the activity of cyclin-dependent kinases 4 and 6, and act at the G1-to-S cell cycle checkpoint. This checkpoint is tightly controlled by the D-type cyclins and CDK4 and CDK6.[7] By blocking CDK4/6 the proliferation of cancer cells and tumor growth is stopped. In clinical practice, CDK4/6 inhibitors are commonly used in combination with hormone therapy, such as Aromatase Inhibitors (AI), eg letrozole, and Selective Estrogen Receptor Modulators, eg tamoxifen, to treat advanced or metastatic breast cancer. Resulting in prolonged progression-free survival as proven in pooled PFS curves showed a median PFS of 26.5 months in AI-sensitive patients treated with CDK4/6 inhibitors compared to 10.9 months of improvement over endocrine therapy alone.[8,9]

Despite their efficacy, CDK4/6 inhibitors can cause adverse events (AEs) such as neutropenia, fatigue, leukopenia, thrombocytopenia, and anemia which necessitate careful management during treatment.[10] One of the concerns is the occurrence of VTE which is under investigation.[11] Breast cancer accounts for 17% of cancer-related VTE cases, regardless of the fact that CDK4/6 inhibitors have an increased risk of developing VTE.[12,13] In the PALOMA clinical trial, palbociclib use with hormonal therapy resulted in a 5% risk of developing VTE compared with 0% in the control group.[14,15] Similarly, in the MONALESSA-7 trial, the risk of venous thromboembolism (VTE), pulmonary embolism (PE), was 2.7% in the treatment arm, compared to 0.9% in the control arm.[16–18] In the MONARCH trial, which led to the black box warning of abemaciclib,[19] the risk of developing VTE was 4.6% as compared to 0.6% the control group.[20,21] In a multi-center retrospective study of 266 patients with metastatic HR+/HER2- breast cancer on CDK 4/6 inhibitors, the risk of VTE was increased by 10.4%.[22]

In March 2023, the US FDA approved the use of abemaciclib with endocrine therapy for adjuvant treatment in early-stage, high-risk breast cancer patients based on monarchE trial, which expanded the use of abemaciclib beyond metastatic stage.[19,23] The published data have suggested that abemaciclib may be associated with a higher risk of venous thromboembolism compared with palbociclib or ribociclib; therefore, we explored whether similar patterns exist in our Middle Eastern cohort.

Although most of the published data on CDK4/6 inhibitors originate from Western clinical trials, there is a scarcity of real-world evidence from the Middle East. Population characteristics in the Middle East differ from those of Western cohorts, in which the prevalence of obesity and diabetes mellitus is high and may influence thrombotic risk.[24,25] Providing context-specific data is essential to ensure that treatment guidelines and risk assessment tools are applicable to our patient population. Based on that, our study aimed to investigate the real-world incidence of thrombotic events in advanced HR+/HER2- breast cancer patients receiving CDK 4/6 inhibitors or in early-stage, high-risk breast cancer patients receiving abemaciclib in Saudi Arabia. We also aimed to identify risk factors linked to thrombosis, we assess the effectiveness of the Khorana score as a predictive tool, and we describe the clinical outcomes associated with thrombosis.

Methods

Study Design and Setting

This is a retrospective study conducted at two tertiary hospitals in Saudi Arabia to assess the incidence of venous and arterial thrombosis among HR+/HER2- breast cancer patients receiving CDK4/6 inhibitors between January 2016 and June 2023. This study is approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center before initiation (Study #NRC23R/518/07) and IRB of King Fahad Medical City (Study # H-01-R-012). The study complies with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived by the IRB.

Participants

Inclusion criteria were adult patients (≥18 years) with a diagnosis of HR+/HER-2 advanced breast cancer who had received CDK4/6 inhibitor therapy for at least one month. The one month minimum exposure criterion was chosen to ensure sufficient drug exposure to capture early thrombotic events. Patients with early-stage, high-risk breast cancer who received abemaciclib were also included based on monarchE trial.[23] Patients were defined as high-risk if having either ≥4 pALN (pathologic axillary lymph nodes) or 1–3 pALN and either tumor grade 3 or a tumor size ≥50 mm. Exclusion criteria comprised patients without a breast cancer diagnosis, those on CDK4/6 inhibitors for less than one month, patients with superficial venous thrombosis, those with other primary cancers, and those lost to follow-up or with significant missing data. To reduce selection bias, all patients who met the inclusion criteria were included.

Variables and Data Collections

Data were gathered through chart reviews, and key variables included patient demographics, cancer stage, treatment duration, smoking status, and incidence of thrombosis. Thrombotic events were confirmed by diagnostic imaging studies (eg, Doppler ultrasound for DVT and computed tomography for PE). If a patient had been treated at an outside hospital, records were requested to ensure the accurate classification of events. The primary outcomes were the incidence of thrombotic events including VTE (symptomatic and asymptomatic DVT and PE) and arterial thrombosis. Venous thrombosis is defined as symptomatic or asymptomatic DVT and PE while arterial thrombosis is defined as stroke, transient ischemic attack, myocardial infarction or peripheral arterial thrombosis. Thrombosis events identified at outside hospitals were verified where possible. Thrombosis was deemed secondary to the treatment if it occurred during therapy or within 30 days post-discontinuation. Secondary outcomes included progression-free survival (PFS), overall survival (OS), and time to develop thrombosis. For clinical outcomes, PFS was defined as the time from CDK4/6 inhibitor initiation to disease progression, while OS was defined as the time from therapy initiation to death from any cause. Any adverse events (AEs) related to thrombosis were documented.

Potential predictors and confounders considered in the analysis included patient demographics (age, gender, body mass index [BMI]), comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation, chronic kidney disease), prior history of VTE or arterial thrombosis, and Eastern Cooperative Oncology Group (ECOG) performance status. The Khorana score was used to stratify patients into risk categories for VTE.

The Khorana score was calculated for each patient based on body mass index (BMI) ≥35 kg/m^2 (1 point), platelet count ≥350 $\times 10^9$/L (1 point), hemoglobin level <10 g/dL or use of erythropoiesis stimulating agents (1 point), leukocyte count >11 $\times 10^9$/L (1 point), and site of primary cancer (no points assigned for breast cancer). Patients with scores of 0 were classified as low risk, those with scores of 1–2 as intermediate risk and those with scores ≥3 as high risk.

Statistical Analysis

Descriptive statistics were used to summarize demographic characteristics and clinical variables. Continuous variables were presented as medians with interquartile ranges, while categorical variables were summarized as counts and percentage. The Mann–Whitney *U*-test was used to compare continuous variables between groups, and the chi-square or Fisher's exact test was employed for categorical variables as appropriate. Cumulative incidences of thrombosis were calculated and expressed as percentages with 95% confidence intervals (CIs). Overall survival was analyzed using Kaplan–Meier survival analysis to estimate the median time to event, and comparisons between groups were assessed using the Log rank test. A p-value <0.05 was considered statistically significant. Statistical analyses were conducted using R software version 4.3.3.

Results

Baseline Characteristics

A total of 505 patients were screened, of which 447 patients were included in the final analysis (Figure 1. Exclusion and Inclusion Flowchart). The patients were categorized into two groups: patients with thrombosis (11.9%), patients without thrombosis (88.1%). The median time to develop thrombosis while receiving CDK4/6 inhibitor therapy was 11.8 months.

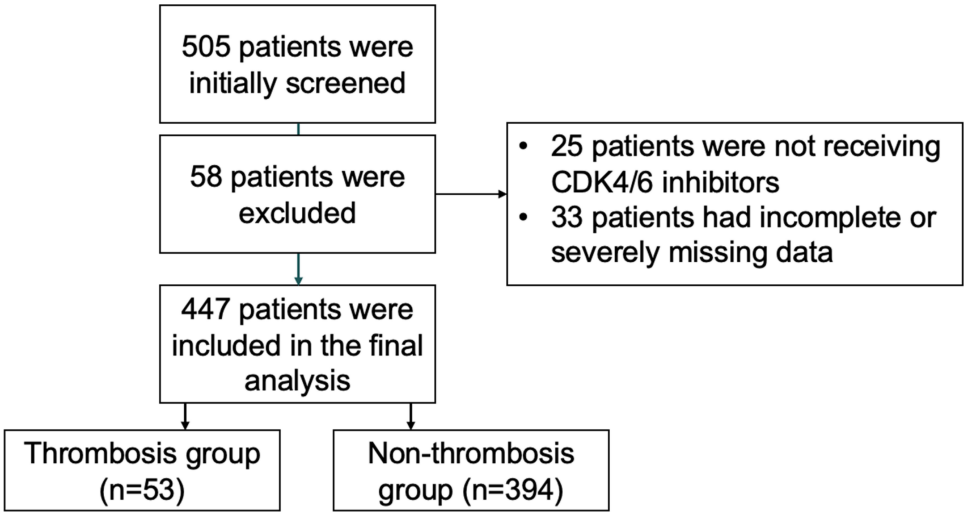

Figure 1 Exclusion and inclusion flowchart.

The majority of patients received palbociclib (70.4%), followed by abemaciclib (28.8%), and a small percentage received ribociclib (0.67%). Patient demographics are provided in Table 1, in which the majority of patients were female (97.3%) with a median age of 56 years (IQR 47–64). Common comorbidities included hypertension (39.3%) and diabetes (38.2%). A prior history of venous thromboembolism (VTE) was more common in the thrombosis group (9.4%)

Table 1 Baseline Characteristics for Breast Cancer Patients on CDK4/6 Inhibitors

Characteristic, n (%)	**Thrombosis (n= 53)**	**No Thrombosis (n=394)**	***P. value***
Gender, female	51 (96.2)	384 (97.4)	> 0.05
Age, median (IQR), yrs	56 (49–64)	56 (47–63)	> 0.05
BMI, median (IQR)	28.13 (23.1–33.3)	30.9 (25.1–38.2)	> 0.05
Hypertension	29 (45.28%)	147 (37.31%)	> 0.05
Hyperlipidemia	9 (16.98%)	78 (19.80%)	> 0.05
Atrial Fibrillation	2 (3.7%)	15 (3.81%)	> 0.05
History of VTE	5 (9.4%)	12 (3.05%)	0.03
Diabetes	23 (43.39%)	148 (37.56%)	> 0.05
Chronic Kidney Disease	1 (1.88%)	14 (3.55%)	> 0.05
Liver Disease	0	8 (2.03%)	> 0.05
Other co-morbidity	14 (26.4%)	58 (14.72%)	0.044
Smoking	2 (3.7%)	4 (1.02%)	> 0.05
ECOG			
Not assessed	8 (15.09%)	87 (22.08%)	> 0.05
0	4 (7.55%)	66 (16.75%)	> 0.05
1	14 (26.42%)	140 (35.53%)	> 0.05
2	16 (30.19%)	56 (14.21%)	0.005

(*Continued*)

Table 1 (Continued).

Characteristic, n (%)	Thrombosis (n= 53)	No Thrombosis (n=394)	*P. value*
3	5 (9.43%)	26 (6.60%)	> 0.05
4	6 (11.32%)	19 (4.82%)	> 0.05
On Hormone therapy	53 (100%)	394 (100%)	> 0.05
Early-stage, high-risk breast cancer patient	20 (37.7%)	106 (26.9%)	> 0.05
Stage IV	33 (62.2%)	288 (73.1%)	> 0.05
HER2 Status			
HER2-negative	50 (94%)	372 (94.41%)	> 0.05
Unknown Status	3 (5.6%)	22 (5.5%)	> 0.05
HR Status			
HR+	53 (100%)	394 (100%)	> 0.05
BRCA mutation	4 (7.54%)	45 (11.42%)	> 0.05
Khorana score			
0	23 (43.40%)	176 (44.67%)	> 0.05
1	19 (35.85%)	154 (39.09%)	> 0.05
2	10 (18.87%)	56 (14.21%)	> 0.05
>3	1 (1.89%)	8 (2.03%)	> 0.05
CDK 4/6 inhibitors			
Palbociclib	32 (60.3%)	283 (71.83%)	> 0.05
Abemaciclib	21 (39.6%)	108 (27.41%)	> 0.05
Ribociclib	0	3 (0.76%)	> 0.05

compared to the non-thrombosis group (3.05%), with a statistically significant difference (p=0.03). Notably, patients with thrombosis had a higher prevalence of other co-morbidities (26.4% vs 14.72%, p=0.044), and ECOG performance status of 2 (30.19% vs 14.21%, p=0.005).

Thrombotic Events and Risk Factors

Fifty-three thrombotic events (venous and arterial) were identified among the patients, during CDK4/6 inhibitor therapy. Of the thrombotic events, 35.85% were PE, and 15.1% were arterial thrombosis. Symptomatic DVT occurred in 18.8% of patients, while asymptomatic DVT occurred in 3.77% of cases. There were no cases of mesenteric thrombosis, and peripheral arterial ischemia was not observed in any patients. A total of 53 patients (11.8%) experienced at least one thrombotic event during CDK4/6 inhibitor therapy, with palbociclib having a 10.2% incidence of thrombosis and abemaciclib showing a slightly higher incidence of 16.3% (Tables 2 and 3). Thirty three of the VTE incidences in our study could not be classified as DVT or PE due to incomplete or unclear documentation. In terms of staging in patients who developed thrombosis, 37.7% of patients had an early-stage high-risk breast cancer, and 62.2% had stage IV breast cancer disease. A number of these events occurred at outside hospitals, and detailed records were not available for precise classification (Table 2).

Table 2 Incidence of Thrombotic Events Among Patients with Thrombosis

Incidence, n (%)	Thrombosis (n= 53)
All thrombotic events	53 (100%)
VTE	50 (94.3%)
Symptomatic DVT	10 (18.8%)
Asymptomatic DVT	2 (3.77%)
Central line-associated thrombosis	1 (1.89%)
PE	20 (37.7%)
Arterial Thrombosis	8 (15.1%)
Transient ischemic attack	2 (3.7%)
Myocardial infarction	2 (3.7%)

Table 3 Incidence of Thrombosis in Patients Receiving CDK4/6 Inhibitors

Thrombotic Events	Thrombosis (n= 53)
Incidence of thrombotic events during CDK4/6 inhibitor therapy	53 (11.8%)
Incidence of arterial thrombosis during CDK4/6 inhibitor therapy	8 (1.7%)
Cumulative incidence of thrombosis, by CDK4/6 inhibitor (95% CIs)	
Palbociclib	10.2% (6.8% to 13.5%)
Abemaciclib	16.3% (9.9% to 22.7%)
Ribociclib	0
Time to thrombosis while receiving CDK4/6 inhibitors, median in months (IQR)	11.8 (2.7–22.4)

Survival Analysis

The Kaplan–Meier survival analysis (Figure 2) did not show a statistically significant difference in OS between the thrombosis and non-thrombosis groups (p=0.55). The median OS was 16 months for patients who developed thrombosis and 18.5 months for patients without thrombosis.

Discussion

In our retrospective study, the thrombotic risk was evaluated in patients with HR+/HER2- receiving CDK4/6 inhibitors. Among 447 patients who were receiving CDK4/6 inhibitors, palbociclib (70.4%), and abemaciclib (28.8%). The incidence of thrombotic events was 11.8% including both venous and arterial thromboembolism. The median time to develop thrombosis while receiving CDK4/6 inhibitor therapy was 11.8 months. This real world revealed a higher incidence of VTE than reported in prior clinical trials of CDK4/6 inhibitor use. Specifically, in PALOMA-1 trial evaluating the safety of palbociclib for HR +/HER2- breast cancer, a 5% increase in VTE risk was reported.[26] Similarly, the MONARCH trials, which investigated abemaciclib, indicated a 4.6% increase in VTE risk.[21,27] These results suggest that real-world scenarios may introduce additional risk factors or patient characteristics that were not captured in clinical trial settings.

Importantly, this large real-world Middle Eastern cohort represents one of the most extensive regional datasets assessing CDK4/6 inhibitors associated thrombosis to date. The inclusion of such a substantial patient population enhances the robustness of our findings, supporting clinical decision-making and local guideline development based on regional experience and patient characteristics.

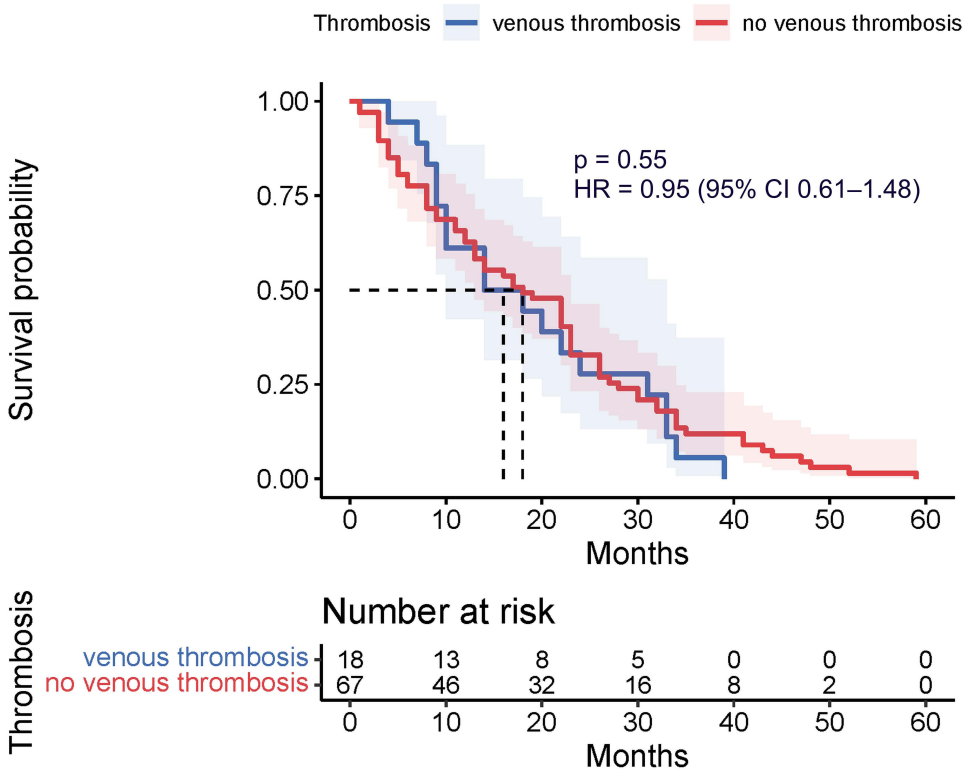

Figure 2 Overall Survival Kaplan–Meier curve (p-value = 0.55).

Two other real-world retrospective studies conducted in the United States have corroborated these findings.[22,28] In our study, the incidence of PE, a severe form of VTE exceeded that reported in similar studies. Specifically, West et al study documented PE in 13.8% of thrombosis events, while Gervaso et al reported an incidence of 18.4% for PE.[22,28] Moreover, our study revealed an arterial thrombosis risk comparable to that reported by West et al, highlighting a difference in arterial thrombosis incidences between what is reported in clinical trials as compared to real world data.[22]

The differences in the findings of this study in comparison to prior clinical trials and similar real-world analyses advocate potential inter-racial variations. Notably, none of the preceding trials assessing the efficacy and safety of CDK4/6 inhibitor therapy included the Middle Eastern population, thereby limiting the generalizability of the safety results.[26,27,29,30] In Saudi Arabia, around 25,000 patients are estimated to develop VTE annually.[31] This risk of VTE can be attributed to various factors including metabolic syndrome, obesity, diabetes and sedentary lifestyle.[24,25,32,33] Most of these factors were reflected in the clinical characteristics of the thrombosis group, where most patients who experienced thromboembolism were overweight, and over a third of the patients had a documented diagnosis of diabetes and hypertension. Furthermore, the study results indicated that having a history of VTE is a significant factor of risk to develop VTE. This aligns with the retrospective study by West et al, where a history of VTE was common among patients who experienced thromboembolism events.[22]

Treatment with CDK4/6 inhibitors appears to be an independent risk factor for VTE development in our study population. The precise underlying mechanisms leading to the heightened thrombosis risk are not comprehensively understood yet. However, emerging evidence from genomic profiling studies suggest an increased risk of VTE in tumors expressing CDKN2B mutations,[34] this mutation leads the overactivity of CDK4/6 and ultimately resulting in uncontrolled cellular proliferation.[35,36]

Majority of thrombotic events within our study were attributed to the utilization of abemaciclib, followed by palbociclib. This is different with the findings reported by West et al, who found a higher incidence of thrombosis cases in patients using palbociclib, followed by ribociclib, then abemaciclib.[22] It is important to underline in the black box warning issued in response to the increased risk of VTE associated with the use of abemaciclib, as observed in the

MONARCH trial, could be due to the less strict inclusion criteria compared to the Paloma-2 trial.[27,30] The Paloma-2 trial excluded individuals with a history of PE and those predisposed to thromboembolism, such as patients with inflammatory bowel disease, which likely reduced the heightened risk. In contrast, such limitation was taken in the MONARCH trial, leading to the issuance of the black box warning.

The findings of the survival analysis did not demonstrate a statistically significant difference in overall survival between the thrombosis and non-thrombosis groups. Nevertheless, it is widely acknowledged that VTE exerts a substantial impact on survival across all categories of cancers.[37,38] The absence of a notable difference in survival in this study may be attributed to inadequate documentation of mortality events. Notably, West et al study reported reduced survival in those with thrombosis compared to those without thrombosis of 35.7 months versus 7 months.[22] Moreover, emerging evidence from genomic profiling studies suggest an increased risk of thrombotic events in tumors expressing CDKN2B mutations,[34] however, there is still inconsistency in the risk of thrombosis with CDKN2B mutations and further studies are needed.[39]

Recognizing the potential risk of VTE associated with CDK4/6 inhibitors is crucial in the management of HR+/HER2 breast cancer patients. Khorana score is a predictive tool used to stratify patients with solid tumor cancer into risk groups based on clinical parameters, and pretreatment lab values, and it is adopted by several guidelines such as the NCCN Guidelines.[4] Patients with Khorana score of 2 or more can be considered for thromboprophylaxis prior to receiving cancer therapy. The Khorana score was evaluated in West et al study and showed that Khorana scores were between 0–2 in the majority of patients, and the thus tool was not predictive of VTE.[22] In our study, Khorana score was comparable between thrombosis and non-thrombosis thus confirming that the Khorana score might not anticipate VTE in our population. Hence, proactive measures include developing a tailored VTE risk assessment model that explicitly integrates the use of CDK4/6 inhibitor therapy and the patient's prior history of VTE are needed. It is important to note that, the Khorana score indicates any patients with breast cancer receives zero points, the predictive accuracy of the Khorana model for our population is uncertain. Evaluating its performance in patients receiving CDK4/6 inhibitors may help guide thromboprophylaxis decisions.

Limitations and Strengths

We acknowledge several limitations in our study. The lack of diversity in our patient population may limit the generalizability of our findings to broader groups. Additionally, only three patients received ribociclib and that were not included in the patient profile usually thus our ability to draw comprehensive conclusions regarding all CDK 4/6 inhibitors is somewhat constrained. The potential for incomplete documentation of mortality events may also influence the precision of our survival analysis. Moreover, some ambiguity in classifying the types of VTE may affect the interpretation of these outcomes. Despite these challenges, we consider our study makes a meaningful contribution to the post-approval literature by highlighting a higher real-world risk of thrombosis for the CDK4/6 inhibitors than previously observed in clinical trials. We hope our findings will encourage further multinational research to better understand the safety profiles of CDK 4/6 inhibitors across more diverse patient populations.

Conclusion

In this retrospective real-world study conducted in Saudi Arabia, we observed that patients with HR+/HER2- breast cancer taking CDK4/6 inhibitors have a significantly higher risk of developing VTE compared to those reported in clinical trials. Specifically, our study revealed that an 11.8% incidence of thrombotic events, with a notably high occurrence of PE. Patients receiving abemaciclib showed a higher incidence of VTE compared to those receiving palbociclib, aligning with the FDA black box warning for abemaciclib. Due to the increased risk of thrombotic events observed, it is vital to develop and implement individualized risk assessment tools for breast cancer patients starting on CDK4/6 inhibitors and specific for the Middle East population.

Abbreviations

VTE, Venous Thromboembolism; CDK4/6, Cyclin-Dependent Kinase 4/6; R+/HER2–, Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative; PE, Pulmonary Embolism; DVT, Deep Vein Thrombosis; PFS, Progression-

Free Survival; OS, Overall Survival; FDA, Food and Drug Administration; ECOG, Eastern Cooperative Oncology Group; AI, Aromatase Inhibitors; BRCA, Breast Cancer Gene; NCCN, National Comprehensive Cancer Network; SD, Standard Deviation; IQR, Interquartile Range; AF, Atrial Fibrillation; AE, Adverse Event.

Institutional Review Board Statement

This study was approved by the Institutional Review Board of King Abdullah International Medical Research Center before initiation (Study #NRC23R/518/07), and IRB of King Fahad Medical City (Study # H-01- R-012).

Funding

The preparation of this study was not supported by any external funding.

Disclosure

Authors declare no conflict of interest.

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