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BRIEF REPORT

Venous thromboembolism risk in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with combined CDK 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Purpose Approximately 70% of patients with metastatic breast cancer (MBC) are hormone receptor (HR)-positive. Recent studies have shown that CDK4/6 inhibitors (CDKI) improve survival in combination with ET in HR-positive, HER2-negative MBC. The risk of venous thromboembolism (VTE) is 3–4 times higher in patients with breast cancer (BC) than in patients without cancer. The risk is even higher in BC patients receiving ET and chemotherapy. The aim of the study was to determine the VTE risk of CDKIs plus ET versus ET alone in patients with HR-positive, HER2-negative MBC.

Methods We performed a systematic review and meta-analysis to demonstrate the risk of VTE in patients with HR-positive HER2-negative MBC treated with combined CDKIs and ET versus ET alone.

Results Eight randomized controlled trials (RCT) with a total of 4,557 patients were eligible. The study arms comprised of palbociclib or ribociclib or abemaciclib plus ET while the control arms utilized placebo plus ET. The VTE events were 56 (2%) in the CDKIs plus ET group compared to 10 (0.5%) in the control group. Pooled relative risk (RR) for VTE was 2.62 (95% CI 1.21–5.65; $P=0.01$) and the risk difference (RD) was 0.01 (95% CI 0.00–0.03; $P=0.02$). Over a median follow-up of up to 36 months, RR was 3.18 (95% CI 1.22–8.24; $P=0.02$) and RD was 0.03 (95% CI 0.01–0.06, $P=0.008$).

Conclusions Our meta-analyses demonstrated that the addition of CDKIs to ET in patients with HR-positive HER 2-negative MBC contribute to a higher incidence of VTE. Further trials are required to define the actual relation and definitive incidence of VTE with different CDKIs.

Keywords Metastatic breast cancer · Venous thromboembolism · Hormone receptor-positive HER2-negative · Meta-analysis

Introduction

BC is the most common type of cancer in women worldwide and represents tremendous impact on public health [1]. The BC cells may be associated with overexpression of specific

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hormone receptors which favor the proliferation of cancer cells and stimulate other signaling cell cycle pathways [1]. From the therapeutic perspective, the BC is categorized into three subtypes depending on the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) positivity status [2]. Hormone receptor positivity is important in evaluating the patient's response to ET and prognosis [2]. Generally, women diagnosed with BC with expression of ER/PR have a better prognosis than those without [2]. Expression of the ER is found in 70–75% all BC especially in postmenopausal women and is associated with higher survival rate as a result of targeted ET [1]. Nonetheless, the BC cells can develop resistance to ET which poses a major therapeutic challenge to physicians. Cell cycle dysregulation has a crucial role in carcinogenesis through induction of proliferative potential and genomic instability in cancer cells [3]. Cyclin dependent kinases phosphorylate retinoblastoma (Rb) protein resulting in initiation of G1-S phase transition in the cell cycle. Overexpression of cyclin D1 and activation of CDK4 and CKD6 in the HR-positive BC favor proliferation of BC cells [4]. The studies have shown that CDKIs improve survival in combination with ET in HR-positive and HER 2 negative MBC. Recently, CDKIs such as palbociclib, ribociclib and abemaciclib, have been approved by the FDA to be used in combination with ET not only as a firstline option, but also in patients who progressed after ET in HR-positive and HER2-negative MBC [5]. The risk of VTE is 3–4 times higher in patients with cancer than in patients without cancer [6, 7]. This risk is even 5–10 times higher in BC patients receiving tamoxifen and chemotherapy [8–11]. We performed a systematic review and meta-analysis of RCTs to demonstrate the incidence of VTE in patients with HR-positive HER2-negative MBC, who are treated with CDKIs plus ET versus ET alone.

Methods

We performed the systematic review per Cochrane Handbook for Systematic Reviews [12] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

Literature search

We conducted a comprehensive literature search in MEDLINE and EMBASE databases, from inception until 31 August 2019, using the following terms 'palbociclib OR ribociclib OR abemaciclib OR CDK 4/6 inhibitors' AND 'breast cancer'. We also hand searched major oncology conferences, especially the American Society of Clinical Oncology and the European Society of Medical Oncology. RCTs written in English were retrieved. We reviewed the references of appropriate studies for any further relevant studies. All potential studies were reviewed to assess eligibility.

Eligibility criteria

The studies that were eligible to be included in the meta-analysis had to conform with the following characteristics: RCTs comparing the CDKIs-based regimen and a control group; RCTs of patients who were hormone receptor positive HER-2 negative metastatic BC; and RCTs which mentioned VTE as adverse effects.

Data extraction, and quality assessment

Four authors (TWH, SS, AS, and S.B) independently conducted data extraction from the eligible studies. We collected the following data: first author's last name, publication year, the study title and type, its primary and secondary outcomes, number of VTE events, study drug and dosage and duration, types of hormonal therapies, and number of patients included in each arm. Disagreements were resolved by consensus, in conjunction with the senior investigators (KZT and THO). Biases in each study were identified by using the tool recommended by the Cochrane Collaboration. Potential biases were categorized into mainly five types, such as selection bias, performance bias, detection bias, attrition bias, reporting bias and others and they were rated as low, high or unclear risk [12].

Data synthesis and analysis

All analyses were performed using the Review Manager, version 5.3 (Nordic Cochrane Centre; Copenhagen, Denmark). The significance of the data was defined as p value of less than 0.05. I^2 statistic and Cochran's Q statistic were used to assess heterogeneity among the studies [14]. The pooled RR and RD with 95% confidence interval (CI) were calculated by using the random effects model with Mantel–Haenszel (MH) method as our primary meta-analytic approach. The primary objective of our analysis was to determine the risk of VTE with the use of CDKIs plus ET versus ET alone in patients with MBC. Subgroup analyses for RRs for VTE risk were conducted based on different CDKIs; types of ET, or whether CDKIs containing regimen were used as firstline or secondline treatment, in the HR-positive, HER2-negative MBC. Publication bias was assessed by the funnel plots.

Results

Search results

We identified 751 potential references and 193 duplicates were removed. After exclusion, a total of 12 records

identified from the databases were assessed for eligibility for inclusion in our study. Four studies were excluded due to ineligibility of inclusion criteria [15–18]. Eight randomized controlled trials (PALOMA-1, PALOMA-2, PALOMA-3, MONARCH-2, MONARCH-3, MONALEESA-2, MONALEESA-3, and MONALEESA-7) with 4557 patients were included in the final analysis [19–28]. Steps of the systematic review process in accordance with PRISMA have been shown in Fig. 1.

Characteristics of the studies

The characteristics of included studies have been summarized in Table 1. Patients in the study arms received palbociclib-letrozole, palbociclib-fulvestrant, ribociclib-letrozole, abemaciclib-fulvestrant, ribociclib-fulvestrant, ribociclib-hormone therapy combination, while those in the control arms had a placebo in combination with letrozole or fulvestrant or hormone therapy. The randomization ratio was 2–1 in PALOMA-2, PALOMA-3, MONARCH-2, MONARCH-3, MONALEESA-3 studies and 1–1 in PALOMA-1, MONALEESA-2, MONALEESA-7 studies.

Study quality, risk bias and publication bias

Risk of bias for each study was evaluated by Cochrane RevMan 5.3 software and is depicted in Table 2. All studies used computer-generated randomization schedule and only PALOMA 2 study lacked blinding between investigators and participants. Other biases remain uncertain since they are pharmaceutical sponsored studies. Publication bias was not detected in the study.

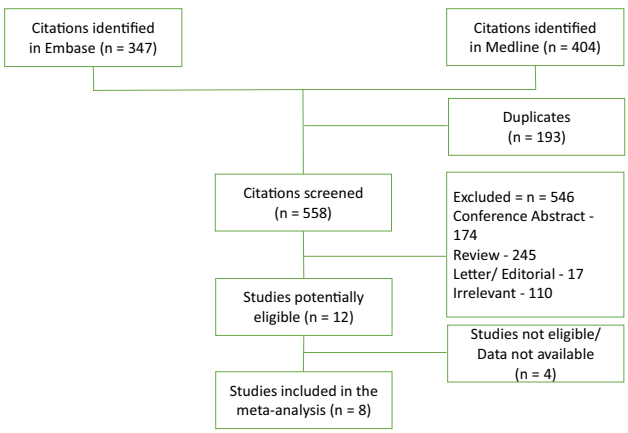

Fig. 1 Study flow diagram in accordance with preferred reporting items for systematic reviews and meta-analyses statement (PRISMA)

Meta-analysis results

The total number of VTE events occurred in 56 (2%) in the CDKIs group compared to 10 (0.5%) in the control group. The pooled RR for VTE was 2.62 (95% CI 1.21–5.65; $P=0.01$) and the absolute RD was 0.01 (95% CI 0.00–0.03; $P=0.02$) (Figs. 2, 3). Over a median follow-up of up to 36 months, the pooled RR of VTE was 3.18 (95% CI 1.22–8.24; $P=0.02$) and RD was 0.03 (95% CI 0.01–0.06, $P=0.008$).

We performed subgroup analyses of the included 8 studies for the occurrence of VTE in HR-positive, HER-2 negative MBC treated with different CDKIs and ET. In PALOMA-1, PALOMA-2 and PALOMA-3 studies including total number of 1343 patients, palbociclib was given together with ET (letrozole or fulvestrant) to 872 patients in the study arm while 471 patients in the control arm had ET. VTE events occurred in 14 patients (1.6%) in the study arm and in 3 patients (0.6) in the control arm with RR of 2.33 (95% CI 0.36–15.19; $P=0.38$). Among 1152 patients in MONARCH-2 and MONARCH-3 trials, 768 patients received abemaciclib with ET in the study arm whereas 384 patients in the control arm had placebo and ET. The VTE incidence was 29 patients (3.77%) in the abemaciclib arm vs 2 patients (0.5%) in the control arm. The pooled RR for VTE was statistically significant at 6.77 (95% CI 1.61–28.43; $P=0.009$). Out of total 2062 patients in MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials, VTE incidence was 13 patients (1.12%) out of 1153 patients in the study arm compared with 5 patients (0.55%) out of 909 patients in the control arm (RR 2.19; 95% CI 0.80–5.97; $P=0.13$).

In the subsets of studies with CDKIs as first-line or subsequent-line treatment, the pooled RR was 2.75 (95% CI 0.98–7.75, $P=0.06$) for first-line subgroup, and 5.14 (95% CI 0.96–27.38, P value $=0.06$), for subsequent-line subgroup. In different hormonal therapies with fulvestrant or non-fulvestrant, the pooled RR was 2.73 (95% CI 0.63–11.91; $P=0.18$) in fulvestrant subgroup and 2.75 (95% CI 0.9–7.75; $P=0.06$) in non-fulvestrant subgroup. Detailed subgroup analyses were shown in the Table 3.

Discussion

VTE is associated with increased mortality and worse survival in BC patients [29, 30]. ET has been a cornerstone treatment for HR-positive and HER2-negative MBC but resistance to ET poses a therapeutic challenge to physicians. Novel therapeutic agents have recently been explored to overcome such endocrine resistance in the MBC treatment [31]. In the last few years, combined treatment of CDKIs such as palbociclib, abemaciclib, or ribociclib with ET have

Table 1 Characteristics of the studies included in the meta-analysis

Study	Author (year)	Study type	Study phase	Type of cancer	Line of treatment	Number of patients		Treatments rendered		Number of VTE events	
						CDK 4/6 inhibitor	Control			CDK 4/6 inhibitor	Control
PALOMA 1 [19]	Finn (2015)	Open label, randomized	Phase 2	ER + ve, HER2-ve advanced breast cancer	First line	83	77	Palbociclib + letrozole	Letrozole	4	0
PALOMA 2 [20]	Finn (2016)	Randomized, multicenter, double-blind	Phase 3	ER + ve, HER2-ve advanced breast cancer	First line	444	222	Palbociclib + letrozole	Letrozole	4	3
PALOMA 3 [26]	Cristofanilli (2016)	Multicenter, randomized, double-blind, placebo-controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	Second line	345	172	Palbociclib + fulvestrant	+ fulvestrant	6	0
MONARCH 2 [21]	Sledge (2017)	Randomized, Double-Blind, Placebo-Controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	Second line	441	223	Abemaciclib + fulvestrant	+ fulvestrant	9	1
MONARCH 3 [22, 27]	Goetz (2017)	Randomized, double blind	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line	327	161	Abemaciclib + Aromatase Inhibitor[a]		20	1
MONALEESA 2 [23]	Hortobagyi (2016)	Randomized double-blind, placebo-controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line	334	330	Ribociclib + letrozole	+ letrozole	2	0
MONALESSA 3 [24]	Slamon (2018)	Randomized double-blind, placebo-controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line or Second line	484	242	Ribociclib + fulvestrant	Fulvestrant	1	1
MONALESSA 7 [25, 28]	Tripathy (2018)	Randomized, double blind	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line	335	337	Ribociclib + hormone therapy[b]	Hormone therapy[b]	10	4

HR + ve, hormone receptor positive; HER2 − ve, HER2 negative; CDK 4/6 inhibitor, cyclin dependent kinase 4 and 6 inhibitor; VTE, venous thromboembolism

[a]Includes a nonsteroidal aromatase inhibitor: anastrozole or letrozole

[b]Includes goserelin and either a nonsteroidal aromatase inhibitor or tamoxifen

Table 2 Risk of bias summary

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Free of selective reporting (reporting bias)
PALOMA 1 (Finn et al., 2015)	+	+	−	+	+	+
PALOMA 2 (Finn et al., 2016)	+	+	+	+	+	+
PALOMA 3 (Cristofanilli et al., 2016)	+	+	+	+	+	+
MONARCH 2 (Sledge et al., 2017)	+	+	+	+	+	+
MONARCH 3 (Goetz et al., 2017)	+	+	+	+	+	+
MONALEESA 2 (Hortobagyi et al., 2016)	+	+	+	+	+	+
MONALEESA 3 (Slamon et al., 2018)	+	+	+	+	+	+
MONALEESA 7 (Tripathy et al., 2018)	+	+	+	+	+	+

Abbreviations: +, low risk of bias; −, high risk of bias; ?, unclear risk of bias

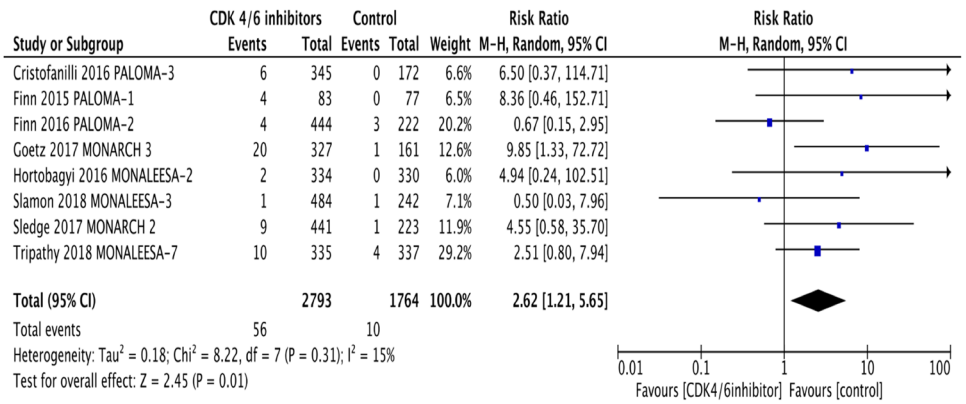

Fig. 2 Pooled relative risk for venous thromboembolism in patients with HR-positive HER2-negative metastatic breast cancer receiving CDK 4/6 inhibitors containing regimen vs control

improved survival in first line and second line settings in HR-positive/HER2-negative MBC [31]. The most common toxicities reported with these drugs include hematological adverse effects in palbociclib, mild elevation of liver enzymes in ribociclib, and gastrointestinal adverse effects in abemaciclib treated patients, respectively [21, 23, 26].

Studies have shown that women with BC where VTE occurred within approximately two years in such population,

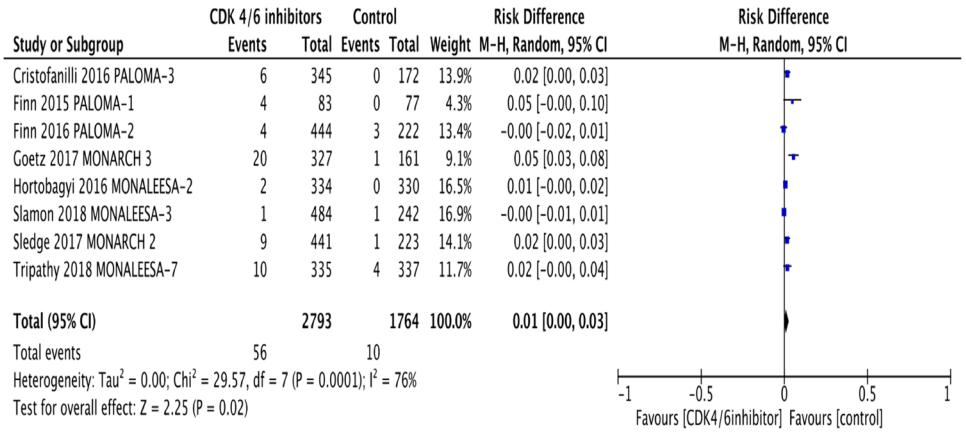

Fig. 3 Pooled risk difference for venous thromboembolism in patients with HR-positive HER2-negative metastatic breast cancer receiving CDK 4/6 inhibitors containing regimen vs control

Table 3 Subgroup analyses of pooled RR for venous thromboembolism in patients with metastatic HR-positive HER2-negative breast cancer receiving CDK 4/6 inhibitors containing regimen vs control

Subgroup	Number of studies (number of patients)	VTE events/number of patients (CDKI arm)	VTE events/number of patients (control arm)	Pooled RR (95% CI)	I^2 (%), *P* value
Palbociclib containing regimen	3 (1343)	14/872	3/471	2.33 (0.36, 15.19)	48%, 0.38
Abemaciclib containing regimen	2 (1152)	29/768	2/384	6.77 (1.61, 28.43)	0%, 0.009*
Ribociclib containing regimen	3 (2062)	13/1153	5/909	2.19 (0.80, 5.97)	0%, 0.13
First line treatment	5 (2650)	40/1523	8/1127	2.75 (0.98, 7.75)	34%, 0.06
Second line treatment	2 (1181)	15/786	1/395	5.14 (0.96, 27.38)	0%, 0.06
Fulvestrant ET	3 (1907)	16/1270	2/637	2.73 (0.63, 11.91)	5%, 0.18
Non-fulvestrant ET	5 (2650)	40/1523	8/ 1127	2.75 (0.98, 7.75)	34%, 0.06

CDKI, CDK 4/6 inhibitors, RR, relative risk; ET, endocrine therapy; VTE, venous thromboembolism; CI, confidence interval

carried a 3.5-fold increased risk of VTE than in normal population [8, 29]. In English health care data cohort containing ~ 13,000 patients, the risk of VTE was notably high (absolute rate of 23.5 per 1000 person years) in the first month after surgery [8]. Chemotherapy further heightened the risk of VTE (~ 10-fold higher compared to who did not receive chemotherapy) in patients with metastatic BC [8, 30]. Among hormonal therapies, tamoxifen carried the highest risk which could increase the risk of VTE up to sevenfold, followed by aromatase inhibitors [32]. In the ATAC trial which included more than 9000 patients, the VTE incidence was 2.8% in anastrozole arm compared to 4.5% in tamoxifen arm whereas the VTE rate was noted in 1.5% in letrozole group vs 3.5% in tamoxifen group in the BIG 1–98 trial where ~ 8000 patients were examined [33, 34]. In combined analysis of two randomized trials of 0021 and 0021, the VTE incidence was observed in 4.5% in anastrozole and 3.5% in letrozole ($P = 0.46$) and suggested that fulvestrant which is a pure estrogen receptor antagonist, might have a slightly lower risk of VTE among hormonal therapies employed in breast cancer [35].

The introduction of newer novel class agents such as CDKI has made significant paradigm shift in the treatment landscape in patients with HR- positive breast cancer where they significantly confer improvement in both progression free survival and overall survival. Yet there is some concern of the impact of CDKI on the VTE. Recent retrospective study by Gervaso et al. showed that VTE was occurred in nearly 10% BC patients who are receiving CDKIs and among those patients, deep vein thrombosis alone was found to be, the most common presentation (47.4%) followed by pulmonary embolism (18.4%) and visceral vein thrombosis (21.1%) [30]. Gervaso and colleagues pointed out that the cumulative incidence of VTE was 6.3% in BC patients treated with CDKIs at 1 year, which was more than the registrational trials (range from 0.6 to ~ 5%), and the randomized trials might underestimate the real world incidence [30]. Furthermore, Olson et al. claimed relationship between VTE and CDKIs, and among the three FDA approved CDKIs, abemaciclib is more potent in inhibiting CDK4, compared with palbociclib and ribociclib. Abemaciclib was also associated with visceral vein thromboses and unusual site thromboses [36].

According to our meta-analysis, combined treatment of CDKIs and ET significantly increases the risk of VTE in patients with HR-positive HER2-negative MBC compared

to ET alone. Among different CDKIs, abemaciclib was noted to be statistically significantly associated with VTE with RR of 6.77 ($P=0.009$). MONARCH-2 trial pointed out that nine patients developed thromboembolism in the abemaciclib arm with four cases of pulmonary embolism reported among them, compared with one case of VTE in the placebo arm although none of which caused death [21]. On the other hand, MONARCH-3 trial described that VTE or PE contributed to two reported deaths in the study arm of abemaciclib [22]. Furthermore, our meta-analysis depicted that there was no statistical difference in the incidence of VTE between subset of first line treatment of CDKIs and that of second line treatment in HR-positive and HER2-negative MBC. Albeit, the occurrence of VTE was not statistically different for subgroups of fulvestrant and non-fulvestrant therapy, there was a trend toward increased risk of VTE with a RR of 2.75 (95% CI 0.98–7.75; $P=0.06$) in non-fulvestrant subgroup.

Antithrombotic prophylaxis in cancer patients remains debatable. According to Khorana Score prediction model, BC is not considered high risk type of cancer [37]. Although multiple studies have shown that there is estimate monthly VTE rate of 0.7% in metastatic breast cancer, routine outpatient thromboprophylaxis is not recommended [38]. In contrast to the Khorana Score which is used for outpatient setting, the COMPASS-CAT predictive score where the derivation cohort was conducted in the patients with BC majority (61%), patients with BC could even further increased the VTE rate up to 13.3% if the score was 7 and above [39]. The fact that our study population receiving anti-hormonal therapy (score of 6) and metastatic stage (score of 2) already put them in the high risk group.

The major strength of our study was that we set a strict, predefined inclusion criteria and included only RCTs in our analysis leaving out the retrospective and other prospective cohort studies. The calculated measures showed that the heterogeneity among selected studies was low. One of the limitations of our study was that we included studies with different CDKIs along with different ET, such as fulvestrant, or letrozole or aromatase inhibitors in our meta-analyses which might lead to confounding variables. Another limitation is that combined treatment of CDKIs plus ET was given as second line treatment in PALOMA-3 and MONARCH-2 and the VTE outcome might be overestimated by preceding first-line therapies. Lastly, there were limitations on the data and inconsistencies in the reporting of deaths which occurred due to anticoagulant-associated bleeding in the studies which would guide us in predicting the CDKI-associated VTE attributable deaths, balancing the pros and cons of anticoagulation in such population and ultimately outweighing the survival benefit vs risk from CDKI. Future well designed larger prospective trials will hopefully better define the association of VTE with this new promising drug class of CDK 4/6 inhibitors and determine the actual incidence of VTE events, which are a major cause of morbidity and mortality in BC patients.

Conclusion

Our meta-analyses clearly demonstrated that the addition of CDKIs to endocrine therapies in patients with HR-positive HER 2- negative MBC contribute to a higher incidence of VTE, compared to ET alone. VTE remains the second leading cause of death in cancer patients receiving antineoplastic therapy in general. BC patients account for the vast majority of cancer patients in the world. Future well designed randomized controlled trials are required to define the actual relation and definitive incidence of VTE with different CDKIs, and their risk factors.

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Compliance with ethical standards

Conflict of interest Kyaw Z. Thein, Thura W. Htut, Somedeb Ball, Sriman Swarup, and Anita Sultan declare no conflict of interest. Thein H. Oo received honoraria from Medical Education Speakers Network, served as a co-investigator for Janssen and Janssen and on Advisory Board for Bristol-Myers Squibb, not related to this manuscript.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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