Systematic Review

Risk of Cardiovascular Events with Cyclin-Dependent Kinases 4 and 6 (CDK 4/6) Inhibitors among Patients with Advanced Breast Cancer: A Systematic Review and Network Meta-Analysis

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Abstract

Background: Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors have shown promising survival outcomes with additional treatments to the traditional endocrine therapy (ET) in patients with hormone receptor-positive (HR-positive) and human epidermal growth factor receptor type 2 negative (HER2–negative) advanced breast cancer (aBC). However, the head-to-head cardiovascular safety profile of these three agents (palbociclib, ribociclib, and abemaciclib) remains unclear. We summarized the incidence of major adverse cardiovascular events (MACE) and hypertension associated with the use of CDK4/6 inhibitor in randomized control trials (RCTs) and compared the risks of MACE and hypertension through network-meta analysis (NMA).

Methods: A systematic search through PubMed and Cochrane Library was performed to identify phase III RCTs reporting cardiovascular safety data of CDK4/6 inhibitors in patients with aBC. We qualitatively synthesized the incidence of MACE and hypertension associated with CDK4/6 inhibitor use within on-treatment or placebo-controlled duration. A Bayesian NMA with random-effects models was performed, and pairwise comparisons between treatment options were presented by odds ratio (OR). The probability of each treatment arm’s relative ranking was reported using surface under the cumulative ranking curve (SUCRA) scores. A sensitivity analysis was conducted using the Mantel–Haenszel (MH) method.

Results: Nine RCTs with four unique treatment arms and event(s) in at least one arm were included in the NMA. A total of 5218 patients were analyzed for MACE outcomes. The overall incidence of MACE in the CDK4/6 inhibitors+ET arm was 0.8%, while the endocrine therapy alone group was 0.4%. Abemaciclib+ET ranked the best in reducing the risk of MACE (SUCRA = 0.90) as compared to ET alone (SUCRA = 0.67, OR = 0.45, 95% credible interval (CI) = 0.07–2.82), palbociclib+ET (SUCRA = 0.25, OR = 0.09, 95% CI = 0.00–2.39) and ribociclib+ET (SUCRA = 0.17, OR = 0.08, 95% CI = 0.00–1.18). The findings were similar in the MH network. However, abemaciclib+ET (OR = 0.11; 95% CI = 0.02–0.81) had a significantly lower risk of MACE than ribociclib+ET in the MH network. No statistically significant differences in hypertension were shown among all comparisons. Conclusions: Abemaciclib+ET may have a lower risk of MACE for the treatment of aBC, while palbociclib+ET may reduce the risk of hypertension in this population. Our findings suggest a comparative cardiovascular safety trend among the three CDK4/6 inhibitors, but further research on direct comparisons is needed to guide treatment choice.

Keywords: CDK 4/6 inhibitors; endocrine therapy; advanced breast cancer; network meta-analysis; major adverse cardiovascular events (MACE); hypertension

1. Introduction

Breast cancer is the most frequently diagnosed cancer in the United States (US) and worldwide with an increasing incidence rate of 0.5% each year [1,2]. Hormone receptor-positive and human epidermal growth factor receptor type 2 negative (HR+/HER2–) is the most common subtype, with an approximate five-year survival rate of 90%. However, when diagnosed in late stages as advanced breast cancer (aBC), the five-year survival rate significantly decreases [3].

The cornerstone of treatment of aBC constitutes of endocrine therapy (ET): including aromatase inhibitors (such as letrozole, anastrozole, and exemestane), selective estrogen receptor (ER) modulators (such as tamoxifen), and ER down-regulators (such as fulvestrant). Unfortunately, the efficacy of these agents is limited by the presence of primary or acquired resistance [4,5]. However, in recent years, it has been demonstrated that several solid tumors have direct modifications of genes that encode various proteins involved in cyclin-dependent kinases (CDK) and D-type cyclins activity and regulation [6]. As a result, small molecule inhibitors have been developed that target this mitogenic pathway, and three of them, known as cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors (palbociclib, ribociclib, and abemaciclib), are currently available for the treatment of aBC in combination with aromatase inhibitors or fulvestrant [6]. Three CDK4/6 inhibitors have been approved by the US Food and Drug Administration since 2015 as treatments in combination with ET for patients with HR+/HER–aBC, as informed by numerous randomized controlled trials (RCTs) [7–13]. In addition, several meta-analyses support
Fig. 1. Diagram flow of the study selection. MACE, major adverse cardiovascular events.

this combined treatment which improves progression-free and overall survival of patients with aBC as compared to ET treatment alone [14–17]. The American Society of Clinical Oncology guideline also recommends combined CDK4/6 and ET use [18,19].

The use of CDK4/6 inhibitors, while providing clinical benefits, has raised concerns regarding cardiovascular events and cardiac toxicity [20,21]. Significant QT prolongation was observed with ribociclib in the Mammary Oncology Assessment of LEE011’s (Ribociclib’s) Efficacy and Safety (MONALEESA) trials [9,11,13]. Furthermore, an updated review has reported that the use of palbociclib and ribociclib may be associated with an increased risk of thromboembolic events, based on data extracted from various clinical trials [22]. In addition, a prospective study has suggested that CDK4/6 inhibitors activate the inflammatory pathway, which may potentially lead to cardiovascular impairment [20].

Due to the heterogeneous safety profiles of different CDK4/6 inhibitors in relation to cardiovascular events, coupled with a lack of head-to-head trials comparing these drugs, we aimed to qualitatively synthesize the incidence of major adverse cardiovascular events (MACE) and hypertension associated with the use of CDK4/6 inhibitors reported in RCTs. Furthermore, this study conducted a network meta-analysis (NMA) to compare the MACE and hypertension risks associated with the use of CDK4/6 inhibitors.
Fig. 2. Network geometry for (A) major adverse cardiovascular events and (B) hypertension. The thickness of the lines corresponds to the number of trials comparing each treatment pair. ET, endocrine therapy; Abemaciclib, Abemaciclib + ET; Ribociclib, Ribociclib + ET; Palbociclib, Palbociclib + ET.

Fig. 3. Revised cochrane risk of bias for risk assessment on included randomized controlled trials.

Fig. 4. Network meta-analysis plot for major adverse cardiovascular events of endocrine therapy and different CDK4/6 inhibitors. Values are expressed as OR with 95% credible intervals. CI, credible intervals; ET, endocrine therapy; OR, odds ratio; CDK4/6, cyclin-dependent kinases 4 and 6.
2. Materials and Methods

This systematic review and network meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for systematic reviews, incorporating network meta-analyses for healthcare interventions.

2.1 Search Strategy

A systematic search through PubMed and Cochrane Library was performed up until December 31, 2021 to identify phase III RCTs of CDK4/6 inhibitors with reported cardiac safety outcomes in aBC. In addition, each reference in the RCTs were manually reviewed to fully capture all the relevant studies that were not included in the above databases. The search strategy used key terms including breast cancer, cyclin-dependent kinase 4, CDK4, cyclin-dependent kinase 6, CDK6, ribociclib, palbociclib, and abemaciclib.

2.2 Study Selection and Evaluation

The initial screening of title/abstracts was conducted independently by two reviewers (KD and YL) based on the inclusion and exclusion criteria. In the second screening, full-text articles were selected based on a full-text review. RCTs were eligible for inclusion based on the following criteria: (1) phase III RCTs of HR+/HER– aBC, (2) patients receiving either CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) plus ET or ET monotherapy, (3) with safety data of hypertension or MACE, which was defined as the composite endpoint of heart failure, myocardial infarction, cardiac arrest, cardiac failure, and stroke in our study [23], and (4) a restriction on English studies. Certain exclusion criteria were applied in our study. Firstly, studies that solely reported subgroup analyses derived from the main findings were excluded. Secondly, open-label studies with extended follow-up from the primary RCTs were also excluded. Additionally, studies that were not available in full-text format, including conference abstracts or reports,
Table 1. Main characteristics of the studies included in the qualitative synthesis.

<table>
<thead>
<tr>
<th>Source [reference]</th>
<th>Journal</th>
<th>Country (region)</th>
<th>Menopause Status</th>
<th>NCT Number</th>
<th>Line of Therapy</th>
<th>Drug treatment</th>
<th>Age[^a^]</th>
<th>No. of patients[^a^]</th>
<th>No. of MACE[^b^]</th>
<th>No. of Hypertension[^b^]</th>
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<tr>
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<td>222</td>
<td>0</td>
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<tr>
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<td></td>
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<td></td>
<td>Fulvestrant</td>
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<td>5 countries (Asia)</td>
<td>Post</td>
<td>NCT 2297438</td>
<td>Palbociclib + Letrozole</td>
<td>53.8[^d^]</td>
<td>169</td>
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<td>MONALEESA-7, [13]</td>
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<td>Pre and Peri</td>
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<td>Ribociclib + Endocrine Treatment (AI/TAM)</td>
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<td>Tripathy et al., 2018</td>
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<td></td>
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<td></td>
<td>Endocrine Treatment (AI/TAM)</td>
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<td>MONARCH-2, [12]</td>
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<td>20 countries (EU, NA, Asia, SA, Australia)</td>
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<td>NCT 2107703</td>
<td>Abemaciclib + Fulvestrant</td>
<td>59[^c^]</td>
<td>446</td>
<td>3</td>
<td>-</td>
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<tr>
<td>Sledge et al., 2017</td>
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<td></td>
<td></td>
<td></td>
<td>Fulvestrant</td>
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<td>62</td>
<td>223</td>
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<td>Goetz et al., 2017</td>
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<td>NSAI (Anastrazole/Letrozole)</td>
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<td>165</td>
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<td>24</td>
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</tr>
<tr>
<td>MONARCH Plus, [30]</td>
<td>Therapeutic Advances in Medical Oncology</td>
<td>4 countries (China, Brazil, India and South Africa)</td>
<td>Post</td>
<td>NCT 2763566</td>
<td>A: Abemaciclib + AI; AI</td>
<td>A: 56.4, 55.5[^c^]</td>
<td>A: 207, 99</td>
<td>A: 2, 0</td>
<td>A: 14, 9</td>
<td></td>
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<tr>
<td>Zhang et al., 2020</td>
<td></td>
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<td></td>
<td></td>
<td>B: Abemaciclib + Fulvestrant; Fulvestrant</td>
<td>B: 59.7, 58.2[^b^]</td>
<td>B: 104, 53b</td>
<td>B: 0, 0</td>
<td>B: 4, 0</td>
<td></td>
</tr>
</tbody>
</table>

[^a^] Values are given for treatment group first and control group second.  
[^b^] There was more than 1 treatment group. The control group is second.  
[^c^] Median age.  
[^d^] Mean age.  

Abbreviations: AI, aromatase inhibitor; EU, Europe; MACE, major adverse cardiovascular events; NA, North America; NCT, National Clinical Trial; NSAI, nonsteroidal aromatase inhibitor; SA, South America; TAM, tamoxifen.
were not included in our analysis. Lastly, we excluded studies published prior to 2015 or those that contained investigation drug names.

2.3 Data Extraction and Quality Assessment

Articles of interest were advanced to the data extraction stage after the two-stage screening process where two independent reviewers (KD and YL) identified the following key elements: author, year of publication, RCT name, journal of publication, countries, menopause status, the National Clinical Trial (NCT) number, line of therapy, drug treatment and comparator, age, number of patients (total and in each intervention), number of hypertension events, and number of major adverse cardiovascular events. Any discrepancies between the two reviewers were resolved by consensus and input from a third reviewer (CP). Moreover, the quality of the included studies was assessed by two reviewers (KD and YL) independently using the revised Cochrane risk of bias version 2 (RoB2) for RCTs [24].

2.4 Statistical Analysis

A Bayesian network meta-analysis with random-effects models was performed using NetMetaXL (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada), which is a worksheet linked to WinBUGS 1.4.3 (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom) [25]. In our network, we included RCTs that reported MACE or hypertension events in at least one treatment arm. Conversely, trials that reported zero events in all arms or did not report any MACE or hypertension events were excluded from the network analysis. Random-effects model was chosen due to the assumption of equal between-study heterogeneity variances across comparisons. Effect sizes were pooled using the Markov chain Monte Carlo approach with 10,000 iterations, and pairwise comparisons between treatment options were presented by odds ratio (OR) and 95% credible intervals (CIs). The intervention with the worst cardiovascular safety outcomes as determined by the NMA results was designated as the reference for the pairwise comparison. To compare the comparative safety of different treatment options regarding the risk of MACE or hypertension, we reported the probability of each treatment’s relative ranking using surface under the cumulative ranking curve (SUCRA) with a rankogram [26]. A SUCRA value approaching one indicates that a given treatment option has a higher likelihood of being ranked as the best. NetMetaXL also generated a plot that compares the posterior mean deviance of individual intervention pairs in the consistency and inconsistency models to detect loops in the treatment network where inconsistency may exist [25]. The Mantel–Haenszel (MH) approach was used in the R (Version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) software as a sensitivity analysis due to the sparse outcomes in our study [27].

3. Results

3.1 Characteristics of the Included Studies

Our network meta-analysis included a total of nine RCTs for MACE outcomes [7–9,11–13,28–30] and six RCTs for hypertension [7–9,11,13,30], which involved 5218 and 3688 patients, respectively. The process of study selection was outlined in Fig. 1. Four eligible comparisons for the MACE and hypertension outcomes were presented in Fig. 2. Table 1 (Ref. [7–9,11–13,28–30]) provides a description of the baseline characteristics of the study population and the outcomes related to MACE and hypertension. A full list of excluded studies through the full-text review are provided in Appendix Table 2. Within the selected patients with HR+/HER− aBC, 3198 (61.0%) were administered CDK4/6 inhibitors in combination with ET, while 2020 (39.0%) received ET alone. Among those treated with CDK4/6 + ET, 960 (30.0%) were prescribed palbociclib, 1153 (36.1%) received ribociclib, and 1085 (33.9%) were given abemaciclib (Appendix Fig. 6).

3.2 Risk of Bias in Included Studies

The RoB2 tool was used to assess the risk of bias in RCTs. While there were concerns about missing outcome data across all included studies in this systematic review [7–9,11–13,28–30], all RCTs were evaluated as having an overall low risk of bias based on the judgments of two assessors, as shown in Fig. 3.
<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>Study</th>
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Table 2. Continued.

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<tr>
<th>Reasons for exclusion</th>
<th>Study</th>
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HER2−, human epidermal growth factor receptor type 2 negative; HR, hormone receptor; PALOMA, Palbociclib: Ongoing Trials in the Management of Breast Cancer; MONALEESA, Mammary Oncology Assessment of LEE011’s (Ribociclib’s) Efficacy and Safety; TAM, tamoxifen; MONARCH, a series of clinical trials conducted to evaluate the efficacy and safety of the drug Abemaciclib in the treatment of various types of cancer.
Table 3. League table of pair-wised comparisons among endocrine therapy and different CDK4/6 inhibitors in major adverse cardiovascular events using the Bayesian framework (with odds ratios and 95% credible intervals).

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib+ET</th>
<th>ET</th>
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<tbody>
<tr>
<td>Abemaciclib+ET</td>
<td>0.45 [0.07–2.82]</td>
<td>ET</td>
</tr>
<tr>
<td>Palbociclib+ET</td>
<td>0.09 [0.00–2.39]</td>
<td>0.22 [0.00–2.97]</td>
</tr>
<tr>
<td>Ribociclib+ET</td>
<td>0.08 [0.00–1.18]</td>
<td>0.18 [0.01–1.25]</td>
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Table 4. League table of pair-wised comparisons among endocrine therapy and different CDK4/6 inhibitors in major adverse cardiovascular events using the Mantel-Haenszel method (with odds ratios and 95% credible intervals).

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib+ET</th>
<th>ET</th>
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</thead>
<tbody>
<tr>
<td>Abemaciclib+ET</td>
<td>0.50 [0.14–1.72]</td>
<td>ET</td>
</tr>
<tr>
<td>Palbociclib+ET</td>
<td>0.15 [0.01–1.72]</td>
<td>0.31 [0.04–2.47]</td>
</tr>
<tr>
<td>Ribociclib+ET</td>
<td>0.11 [0.02–0.81]</td>
<td>0.23 [0.05–1.05]</td>
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Table 5. League table of pair-wised comparisons among endocrine therapy and different CDK4/6 inhibitors in hypertension outcomes using the Bayesian framework (with odds ratios and 95% credible intervals).

<table>
<thead>
<tr>
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<th>Abemaciclib+ET</th>
<th>ET</th>
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<tbody>
<tr>
<td>Abemaciclib+ET</td>
<td>0.97 [0.62–1.54]</td>
<td>ET</td>
</tr>
<tr>
<td>Palbociclib+ET</td>
<td>1.52 [0.71–3.22]</td>
<td>1.54 [0.84–2.78]</td>
</tr>
<tr>
<td>Ribociclib+ET</td>
<td>0.92 [0.54–1.57]</td>
<td>0.95 [0.71–1.26]</td>
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</table>

Table 6. League table of pair-wised comparisons among endocrine therapy and different CDK4/6 inhibitors in hypertension outcomes using Mantel-Haenszel method (with odds ratios and 95% credible intervals).

<table>
<thead>
<tr>
<th></th>
<th>Abemaciclib+ET</th>
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<tbody>
<tr>
<td>Abemaciclib+ET</td>
<td>0.96 [0.62–1.51]</td>
<td>ET</td>
</tr>
<tr>
<td>Palbociclib+ET</td>
<td>1.50 [0.71–3.14]</td>
<td>1.55 [0.86–2.80]</td>
</tr>
<tr>
<td>Ribociclib+ET</td>
<td>0.91 [0.54–1.55]</td>
<td>0.95 [0.71–1.26]</td>
</tr>
</tbody>
</table>

3.3 Inconsistency Assessment

In the Appendix Fig. 7, most points were located in the upper left of the plots. Thus, the assessment of inconsistency plots between direct and indirect estimates for both outcomes suggests a low likelihood of inconsistencies impacting the results of the network meta-analysis.

3.4 Outcomes (MACE)

The overall incidence of MACE in the CDK4/6 + ET group was 0.8%, whereas in the ET alone group, it was 0.4%. Based on our mixed comparisons among four intervention arms, no statistically significant differences were found in the occurrence of MACE among abemaciclib+ET (OR = 0.08; 95% CI = 0.00–1.18), ET alone (OR = 0.18; 95% CI = 0.01–1.25), and palbociclib+ET (OR = 0.83; 95% CI = 0.02–59.42), when compared to ribociclib+ET (Fig. 4).

However, based on the relative ranking SUCRA, abemaciclib+ET (SUCRA = 0.90) was ranked as the best treatment with the least risk of MACE, followed by ET alone (SUCRA = 0.67), palbociclib+ET (SUCRA = 0.25); while ribociclib+ET (SUCRA = 0.17) was ranked the worst. Pairwise comparisons for MACE were displayed in a league table (Appendix Table 3).

In our sensitivity analysis using MH approach as shown in the forest plot (Fig. 4), abemaciclib+ET (OR = 0.11; 95% CI = 0.02–0.81) had a significantly lower risk of MACE as compared to ribociclib+ET. However, there were no statistically significant differences in the risk of MACE between the other two intervention arms as compared to ribociclib+ET: ET alone (OR = 0.23; 95% CI = 0.05–1.05) and palbociclib+ET (OR = 0.75, 95% CI = 0.06–9.88). Pairwise comparisons for MACE were displayed in a league table (Appendix Table 4), and the trend of the results was consistent to the Bayesian NMA.

3.5 Outcomes (Hypertension)

Hypertension risk was evaluated in six RCTs with 3688 aBC patients. As Fig. 5 showed, no statistically significant differences in the risk of hypertension were shown between different treatment arms and ribociclib+ET: palbociclib+ET (OR = 0.60, 95% CI = 0.20–1.84), abemaciclib+ET (OR = 0.91, 95% CI = 0.37–2.26), and ET alone (OR = 0.93, 95% CI = 0.54–1.60). According to SUCRA scores, palbociclib+ET (SUCRA = 0.83) was ranked the best treatment with the least risk of hypertension, followed by abemaciclib+ET (SUCRA = 0.45), ET alone (SUCRA = 0.25); while ribociclib+ET (SUCRA = 0.30) was the worst treatment with the highest risk of developing hypertension. Pairwise comparisons for MACE in the Bayesian framework were displayed in the Appendix Table 5. The sensitivity analysis using MH method also confirmed these results (Fig. 5 and Appendix Table 6).

4. Discussion

The combination of CDK4/6 inhibitors and ET has been deemed an optimal treatment to prolong the survival outcomes of patients living with HR+/HER– aBC [15]. However, the negative impact of CDK4/6 inhibitors on the cardiovascular system has been investigated in some molecular studies [20,31]. These studies have highlighted potential pathophysiological mechanisms such as increased vascular inflammation, left ventricular remodeling, and down-
Our NMA indicated that ribociclib had a relatively higher risk of MACE compared to other agents. This may be attributed to its significantly higher likelihood of inducing QTc prolongation compared to the other two agents [9,39]. Prolongation of the QTc interval is associated with sudden cardiac death and other heart-related adverse events [40]. Hence, the use of ribociclib in cancer patients with concurrent cardiovascular dysfunction should be carefully monitored and ribociclib should be avoided in patients with a QTc prolongation prior to initiating treatment.

In our study, the MH method was used as an alternative approach to testing the robustness of our findings, and the results were consistent with the trends of cardiac safety identified through the Bayesian NMA. However, the Bayesian approach exhibited wider CI than the MH method, although the point estimates were similar. Notably, a growing number of recent studies have discussed the use of Bayesian framework in the analysis of sparse outcomes, such as mortality and serious adverse events [41,42]. The Bayesian model might be a concern as the prior distributions for the models’ parameters can strongly influence the results. In our study, a non-informative prior distribution was used in the random-effects Bayesian NMA, as there was no other external information established for our outcomes of interest. However, the impact of prior distributions on the posterior estimates of the model was believed to be more significant when dealing with sparse data [27]. Therefore, the utilization of both the Bayesian and MH methods for our network in this study adds further credibility to our findings.

Unfortunately, the RCTs analyzed in this network meta-analysis were underpowered to detect statistically significant differences in MACE and hypertension events among patients with aBC. This might result from a limited follow-up period and infrequent reporting of outcomes. For example, three RCTs were excluded due to a lack of reported hypertension events. More RCTs with a longer follow-up period and real-world studies involving a larger population are needed to validate the findings of our study. Furthermore, a future examination of patient subgroups with different comorbidities and age ranges would be valuable in helping clinicians determine which CKD4/6 inhibitors offer the most cardiovascular protection for patients with aBC.

**Study Limitations**

The present network meta-analysis has some limitations to be considered. First, the analysis was limited by a relatively small number of studies and events of interest, which might lack the statistical power to detect differences in cardiovascular risks between intervention arms, thus potentially skewing the conclusions. Second, the lack of individual patient data represented another limitation. While the use of individual patient data in network meta-analysis would have led to more accurate estimates, such data were...
5. Conclusions

Our study demonstrates that the combination of abemaciclib and ET led to a reduced risk of MACE in patients with HR+/HER2− aBC, while ribociclib plus ET was associated with a higher risk of cardiovascular events. Furthermore, the use of palbociclib+ET appeared to have a favorable safety profile with respect to hypertension. While most of the results in our analyses did not reach statistical significance, both Bayesian and MH network meta-analyses in our study supported the trend of comparative cardiovascular safety among the three CDK4/6 inhibitors. Given the growing importance of cardio-oncology, our findings could serve as a foundation for future research to further explore direct comparisons and aid in determining the optimal treatment choice.

Abbreviations

aBC, advanced breast cancer; CDK4/6, cyclin-dependent kinases 4 and 6; CIs, credible intervals; ET, endocrine therapy; HR+/HER2−, hormone receptor-positive and human epidermal growth factor receptor type negative; MACE, major adverse cardiovascular events; MH, Mantel–Haenszel; NMA, network meta-analysis; OR, odds ratios; RCTs, randomized controlled trials; SUCRA, the surface under the cumulative ranking curve.

Author Contributions

YL and CP designed the study design. YL developed the literature search. YL and KD conducted the literature research and performed the study selection. YL and KD extracted the data while YL handled the statistical part. YL and KD interpreted the results and wrote the manuscript. CP provided help and advice on the manuscript write-up.

All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

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Conflict of Interest

Yi-Shao Liu: YL is a current student assistant (co-op) at Novo Nordisk Inc. and a graduate student at the University of Texas at Austin. The work was completed without any involvement with Novo Nordisk Inc.

The rest of two authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.rcm2411309.

Appendix

See Tables 2,3,4,5,6 and Figs. 6,7.

References


