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ORIGINAL RESEARCH

Comparative study on individual aromatase inhibitors on cardiovascular safety profile: a network meta-analysis

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Xihe Zhao[1]
Lei Liu[2]
Kai Li[1]
Wusheng Li[1]
Li Zhao[1]
Huawei Zou[1]

[1]Department of Oncology, [2]Department of General Surgery, Shengjing Hospital of China Medical University, Shenyang, People's Republic of China

Abstract: The third-generation aromatase inhibitors (AIs: anastrozole, letrozole, and exemestane) have now become standard adjuvant endocrine treatment for postmenopausal estrogen receptor-positive breast cancer complementing chemotherapy and surgery. Because of the absence of direct head-to-head comparisons of these AIs, an indirect comparison is needed for individual treatment choice. In this network systemic assessment, the cardiovascular (CV) side effects in using anastrozole, letrozole, and exemestane based on original studies on AIs vs placebo or tamoxifen were compared. We integrated all available direct and indirect evidences. The odds ratio (OR) of severe CV events for indirect comparisons between exemestane and anastrozole was 1.41 (95% confidence interval [CI] =0.49–2.78), letrozole and anastrozole was 1.80 (95% CI =0.40–3.92), and letrozole and exemestane was 1.46 (95% CI =0.34–3.4). OR of subgroup risk for AIs and tamoxifen were all >1 except for thrombolism risk subgroup. The results showed that the total and severe CV risk ranking is letrozole, exemestane, and anastrozole in descending order. None of the AIs showed advantages in CV events than tamoxifen except for thromboembolism event incidence.

Keywords: CV risk, breast cancer, AI, network meta-analysis

Introduction

Hormonal therapy remains a standard form of therapy in the treatment of endocrine-positive breast cancer. Large-scale clinical trials have proved that 5 years of endocrine therapy significantly reduced the recurrence rate and mortality in adjuvant setting.[1–3] The results of trials carried out with the third generation of aromatase inhibitors (AIs) indicated better disease-free survival (DFS) among patients with postmenopausal endocrine-responsive breast cancer than those given tamoxifen in the neoadjuvant,[4,5] adjuvant,[6,7] and metastatic[8] settings. AIs are currently part of the standard treatment for patients, including men, with postmenopausal endocrine-responsive breast cancer. Recently, it has been proved that no difference is noted in antitumor efficacy among these three compounds.[9] A significant overall survival benefit was expected comparing AIs with tamoxifen; however, in most published literatures, the effect was not significant in randomized controlled trials (RCTs). Some experts believe that the only limitations in using AIs are their tendency to cause side effects. Potential adverse events, including cardiovascular (CV) side effects, should be considered in long-term management of patients taking AIs. AIs reduce estrogen levels by inhibiting the aromatase enzyme and reducing the level of circulating estrogen; thus, further reduction in estrogen level may potentially increase the risk of developing CV disease. The recent meta-analysis by Aydiner[9] concludes that there is a greater risk of CV events

Correspondence: Huawei Zou
Department of Oncology, Shengjing Hospital of China Medical University, Shenyang 110004, People's Republic of China
Tel +86 24 96 6156 3115
Email zhw8880310@163.com

(odds ratio [OR] =1.20; *P*=0.030) in AI monotherapy than tamoxifen. We first proceeded to a literature-based network meta-analysis of RCTs to evaluate and compare serious and/or life-threatening CV risk reported comparing different AIs in postmenopausal women.

This systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[10]

Materials and methods

The authors advise that ethics approval was not applicable for this study as it is a recombination and statistical analysis upon the published studies, all the data were obtained from published data, and all the studies included in this study had ethics approval.

Search strategy

Our systematic review protocol was compiled and reviewed by the team. We searched PubMed, Embase, CENTRAL, CDSR, and DARE databases using the keywords "aromatase inhibitors", "anastrozole", "letrozole", "exemestane", "tamoxifen", "breast neoplasm", "randomized controlled trial", and similar terms were cross-searched from RCTs. We complemented searches by perusing the reference lists of previous meta-analyses and set no geographical restrictions. Two investigators (XHZ and LL) independently assessed trials for eligibility and extracted data. The Quality of Reporting of Meta-analyses guidelines has been followed throughout the design, implementation, analysis, and reporting of this meta-analysis. All statistical tests were two-sided.

Inclusion and exclusion criteria

Inclusion criteria were drawn according to Participants, Intervention, Comparison, Outcome, Study design (PICOS)[11] approach. RCTs that enrolled postmenopausal patients with hormonal receptor positive were eligible. The intervention is one AI regime including anastrozole, exemestane, letrozole monotherapy, or following tamoxifen, and the control group is tamoxifen in monotherapy or placebo following initial tamoxifen in sequential therapy. The prespecified primary outcome was fatal or nonfatal myocardial infarction. Secondary outcomes were hemorrhagic or ischemic stroke, CV death, death of unknown

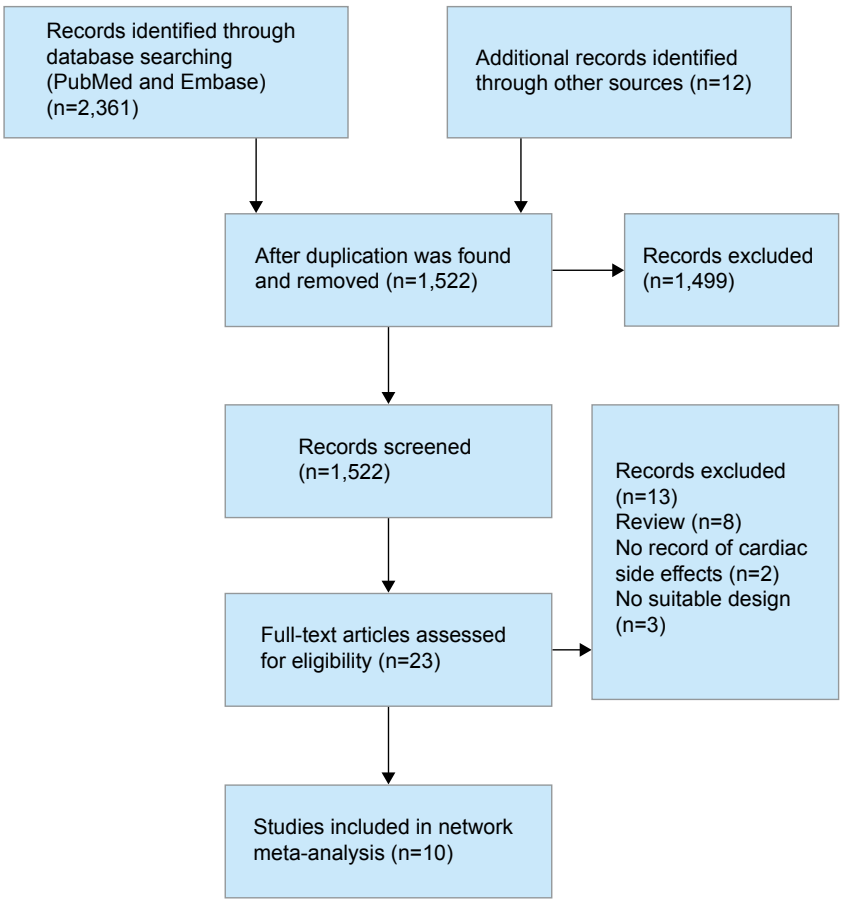

Figure 1 Study selection flow diagram.

cause, and death from any cause. We attempted to avoid duplication of information from multiple reports on the same trial by considering only the data from the report containing detailed events with the longest follow-up. The flowchart is shown in Figure 1. Accordingly, the present meta-analysis incorporates more recent results and covers a larger patient population.

Data extraction

Data abstraction was performed by two independent observers who extracted the data from the respective trials and verified the results by comparison. Data of only severe side effects (3–5 grade or death) were extracted.

Statistical analysis

Whenever possible, we used data from studies with the longest follow-up available. We excluded comparisons with zero events in both groups from the relevant analysis since such comparisons provide no information on the magnitude of the treatment effect. In main analysis, all trials with available quantitative information were utilized. For all calculations, we undertook subgroup analyses according to the type of CV events (myocardial infarction, cerebrovascular events, thromboembolism, CV death, non-breast cancer-related death, and breast cancer-related death). We used a Bayesian random effects model, which fully preserved randomized treatment comparisons within trials. Analysis was done using Markov chain Monte Carlo methods with minimally informative prior distributions. We did separate random effects meta-analyses for all available direct comparisons (head-to-head comparisons of two treatments in the same RCT). The extent was quantified to study heterogeneity with I^2 (ranging between 0% and 100%). To check the robustness of our analyses, we calculated Bayesian random effects meta-analysis for all accessible direct comparisons. For all analyses, we used Stata release 12.0 with the metan routine (a Stata routine for fixed and random effects meta-analysis), and WinBUGS version 1.4 (MRC Biostatistics Unit, Cambridge, UK). The difference in ORs derived from direct and indirect comparisons was plotted.

Table 1 The characteristics of the included trials

RCTs	Participants (n)	Median follow-up (months)	Serious cardiac side effects definition	Number of serious cardiac side effects	
Monotherapy ATAC (2006)[24]					
Tamoxifen for 5 years	3,116	120	Ischemic	Tamoxifen	95
Anastrozole for 5 years	3,125		cardiovascular	Anastrozole	91
Monotherapy BIG 1-98 (2011)[12]					
Tamoxifen for 5 years	2,459	97	Cardiac events	Tamoxifen	51
Letrozole for 5 years	2,463		including ischemic	Letrozole	93
Monotherapy EORTC (2008)[34]					
Tamoxifen for 5 years	2,372	49	Cardiovascular disease	Tamoxifen	3
Exemestane for 5 years				Exemestane	4
Sequenced therapy TEAM (2007)[33]					
Tamoxifen for 2 years followed by exemestane for 3 years	4,868	31	Cardiac disorders	Tamoxifen	98
Exemestane for 5 years	4,898			Exemestane	154
Sequenced therapy ABCSG 8/ARNO 95 (2005)[25]					
Tamoxifen for 5 years	1,606	72	Myocardial infarction	Tamoxifen	2
Tamoxifen for 2 years followed by anastrozole for 3 years	1,618			Anastrozole	3
Sequenced therapy ITA (2006)[26]					
Tamoxifen for 5 years	225	64	Cardiovascular disease	Tamoxifen	14
Tamoxifen for 2 years followed by anastrozole for 3 years	223			Anastrozole	17
Sequenced therapy N-SAS BC03 (2010)[27]					
Tamoxifen for 5 years	469	42	Cardiovascular disease	Tamoxifen	3
Tamoxifen for 2 years followed by anastrozole for 3 years	387			Anastrozole	2
Sequenced therapy IES (2007)[28]					
Tamoxifen for 5 years	2,372	56	Cardiovascular events	Tamoxifen	39
Tamoxifen for 2 years followed by exemestane for 3 years	2,352			Exemestane	41
Extended therapy ABCSG6 (2007)[29]					
Tamoxifen for 5 years	469	62	Myocardial infarction	Placebo	0
Tamoxifen for 5 years followed by anastrozole for 3 years	387			Anastrozole	1
Extended therapy MA.17 (2003)[30]					
Tamoxifen for 5 years	2,594	64	Cardiovascular events	Placebo	144
Tamoxifen for 5 years followed by letrozole for 5 years	2,593			Letrozole	149

Abbreviation: RCTs, randomized controlled trials.

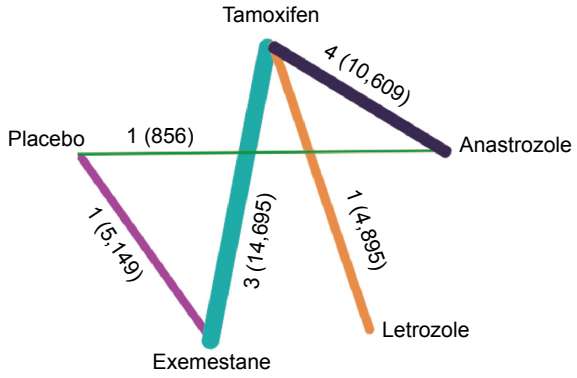

Figure 2 Network relationship diagram.
Notes: The direct comparison included in this study is represented. There are five interventions in this study (anastrozole, exemestane, letrozole, tamoxifen, and placebo). The lines connecting them represent direct comparison and the number of patients included in this study. The thickness of lines is according to the number of patients included in this study. For example, blue line between tamoxifen and exemestane represents the RCTs that directly compare exemestane with tamoxifen (EORTC,[34] TEAM,[33] etc), 3 (14,695) means there are 3 RCTs, and 14,695 patients are included in this study.
Abbreviation: RCTs, randomized controlled trials.

Results

Of the 1,522 studies screened, full text of 23 studies had been assessed and ten trials consisting of a total number of 36,204 patients were included in this meta-analysis. Three studies without suitable design, eight reviews, and two trial publications without cardiac side effect records were excluded. The flow chart is shown in Figure 1, and characteristics of the included trials are presented in Table 1. The network relationship among the five strategies and the number of patients involved are shown in Figure 2. In addition, the direct comparisons included in this study are represented. There are five interventions in this study (anastrozole, exemestane, letrozole, tamoxifen, and placebo), and the lines connecting them represent the direct comparisons and the number of patients included in this study. According to the number of patients, the thickness of lines varies.

We extracted the data from ten trials and calculated the CV risk incidence. The onset distribution and OR of the direct comparisons are listed in Table 2. The OR density diagram is shown in Figure 4. After 30,000 times of iteration, the Markov Chain Monte Carlo values of each comparison were fluctuated and finally stable at 1, which meant the sampling error was too small to effect the results. In indirect comparisons, the onset distribution of CV risk was not significant (ORs were beyond 95% confidence intervals [CI]) and hence not listed. In direct comparisons of CV side effect, anastrozole (OR =1.0, 95% CI =0.994–1.005, P=0.815) and exemestane (OR =1.007, 95% CI =0.998–0.015, P=0.103) showed no significant effect compared with tamoxifen, whereas the effect of letrozole was less, as only one selected experiment (BIG1-98)[12,13] directly compared letrozole and tamoxifen and carried out χ^2 test (χ^2=13.211, P=0.0003). According to the subgroup analyses, all three AIs showed OR >1 compared with tamoxifen in myocardial infarction (anastrozole: OR =1.489, 95% CI =0.249–8.898; exemestane: OR =1.389, 95% CI =0.871–2.215; letrozole: OR =1.919, 95% CI =1.187–3.102). Among the AIs, anastrozole related with the lowest CV risk generally speaking. Anastrozole showed as superior to tamoxifen in severe CV risk incidence except for myocardial infarction and non-breast cancer related death (OR =1.489, 95% CI =0.249–8.898; OR =1.074, 95% CI =0.933–1.238). The risk of non-breast cancer-related mortality appeared to be increased with anastrozole, exemestane, and letrozole (anastrozole: OR =1.074, 95% CI =0.933–1.238; exemestane: OR =1.151, 95% CI =0.954–1.389; letrozole: OR =1.010, 95% CI =0.754–1.353; Table 2) and the breast cancer-related mortality appeared to be decreased (anastrozole: OR =0.885, 95% CI =0.788–1.081; exemestane: OR =0.932, 95% CI =0.822–1.062; letrozole: OR =0.985, 95% CI =0.774–1.034).

The rank of cardiac side effect is listed in Figure 3. Among the three AIs, anastrozole was found to be less hazardous. OR value was 1.36 (95% CI =0.47–2.82) compared

Table 2 Characteristics of trials across different direct comparisons

	Anastrozole vs tamoxifen[24–27]	Letrozole vs tamoxifen[12,13]	Exemestane vs tamoxifen[28,33,34]	Anastrozole vs placebo[29]	Letrozole vs placebo[30]
Number of trials	4	1	3	1	1
Number of patients	10,609	4,895	14,695	883	5,187
Year of publication	2008 (2005–2010)	2010–2011	2007 (2007–2008)	2007	2003
Myocardial infarction (‰)	1.45 vs 1.46	19.61 vs 10.22	8.65 vs 6.23	25 vs 0	NA
Cerebrovascular disease (‰)	10.08 vs 10.10	18.38 vs 15.53	12.57 vs 10.18	NA	6.4 vs 6.1
Thromboembolism (‰)	2.49 vs 11.22	12.66 vs 21.66	7.48 vs 19.70	2.1 vs 7.6	NA
Cardiovascular death (‰)	29.12 vs 30.49	NA	8.51 vs 5.31	NA	NA
Non-breast cancer-related death (‰)	71.51 vs 67.65	35.32 vs 34.97	31.51 vs 27.27	NA	8.2 vs 9.7
Breast cancer-related death (‰)	81.53 vs 93.35	87.70 vs 102.48	63.90 vs 67.21	NA	3.5 vs 6.6

Abbreviation: NA, not available.

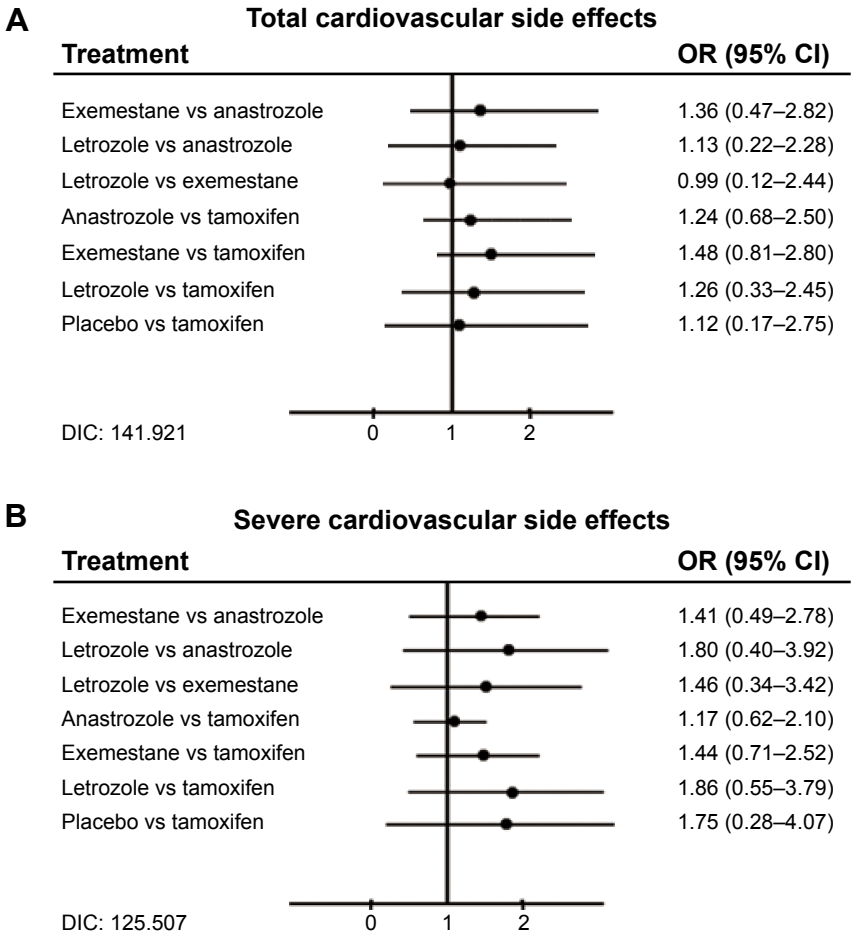

Figure 3 The calculated results of the network meta-analysis.
Notes: (**A**) Total cardiovascular side effects. (**B**) Severe cardiovascular side effects. Among the three AIs, anastrozole was found to be less hazardous. OR value was 1.36 (95% CI =0.47–2.82) compared with exemestane and 1.13 compared with letrozole (95% CI =0.22–2.28). Letrozole and exemestane were almost the same in total CV risk. Both severe and total CV risk deviance information criterion (DIC) values were <200, which meant the calculated results were convincible.
Abbreviations: AIs, aromatase inhibitors; OR, odds ratio; CV, cardiovascular; CI, confidence interval.

with exemestane and 1.13 compared with letrozole (95% CI =0.22–2.28). Letrozole and exemestane were almost the same in total CV risk.

All the trials reported severe CV events constituting a total number of 1,004 patients. The onset incidence was 2.02% (305/15,084) in tamoxifen strategy and 3.07% (555/18,074) in AI strategy, just corresponding to a recent report about endocrine treatment side effect.[14] According to the result of network meta-analysis, the OR values of AI to tamoxifen were all greater than 1. OR of anastrozole vs tamoxifen was 1.17 (95% CI =0.62–2.10), exemestane vs tamoxifen was 1.44 (95% CI =0.71–2.52), and letrozole vs tamoxifen was 1.86 (95% CI =0.55–3.79). Among the three AIs, letrozole represented a higher OR value than the other two and anastrozole represented the lowest OR (OR of letrozole vs anastrozole =1.80, 95% CI =0.40–3.92; OR of letrozole vs exemestane =1.46, 95% CI =0.34–3.42; OR of exemestane vs anastrozole =1.41, 95% CI =0.49–2.78; Figure 3). In the subanalysis of indirect comparison of AIs for each CV disease such as myocardial infarction, the I^2s were >50%, which meant the heterogeneities of subgroups were too obvious to analyze.

As for tamoxifen, it showed no more CV risks in subgroup analysis compared with exemestane and letrozole; however, the thromboembolism risk was greater than three AIs (anastrozole vs tamoxifen: OR =0.393, 95% CI =0.178–0.868, P=0.03; exemestane vs tamoxifen: OR =0.579, 95% CI =0.418–0.801, P=0.508; letrozole vs tamoxifen: OR =0.585, 95% CI =0.377–0.907, P=0.508; Figure 5).

Discussion

Albeit reduced cancer-related mortality necessitates AI intake, the compliance remains relatively low due to side effects, especially CV events, fractures, and menopausal symptoms.

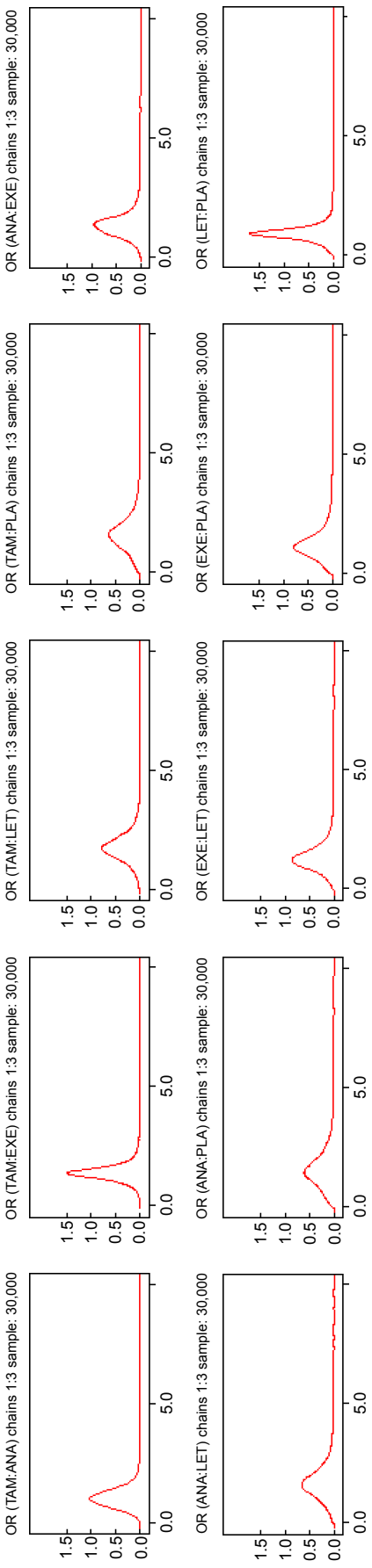

Figure 4 OR density diagram after 30,000 times of iteration, MCMC =1.
Notes: After 30,000 times of iteration of Winbugs software, the MCMC values of each comparison were fluctuated and stable at 1, which meant the sampling error was too small to affect the results.
Abbreviations: ANA, anastrozole; EXE, exemestane; LET, letrozole; MCMC, Markov Chain Monte Carlo; OR, odds ratio; PLA, placebo; TAM, tamoxifen.

AIs block estradiol biosynthesis from androgens by inhibiting aromatase, which are expected to induce extensive alterations in human body. Functional estrogen receptors are detected in vascular endothelial cells and smooth muscle cells.[15,16] Estrogen receptor β (ERβ) plays a dominant role in protecting myocardial cells from afterload pressure. Similar phenotypes with hypertension cardiac hypertrophy can be seen in ERβ knockout mice. Increase in ERα gene expression can improve the stability of intercalated discs of the myocardial cells.[17]

Reducing circulating estrogen in plasma can also lead to lipid metabolism interruption. High-density lipoprotein cholesterol (HDL) was likely to decline after 3 months after initiation of AI therapy in women and generally remained stable throughout the studies.[17,18] Exemestane can induce androgen-like effects that are still controversial in CV system.[19,20] Tamoxifen lowers serum cholesterol after 2 weeks of administration, and this may contribute to cardiac protection.

Theoretically speaking, Letrozole, also called the fourth-generation AI, as well as exemestane demonstrate a better inhibition to aromatase activity. Compared with anastrozole, letrozole and exemestane may represent weaker protection to myocardium due to the strong inhibition of estrogen.

Aydiner conducted a meta-analysis on breast cancer outcome of several adjuvant hormonal therapy regimes. He announced no difference between monotherapy and sequenced therapy in CV risk (OR =1.20 and 1.15; P=0.030 and 0.003, respectively), whereas both of them are of high risk in myocardial disease.[21] In the study of Josefsson and Leinster, no differences were observed for CV disease of different regimes.[22]

Cardiac complications arise from complex interactions of multiple factors. The prime issues can be summarized as pre-existing patient factors, cancer-related factors, toxic effects of the drugs, and radiation dose of heart. The snowball effect of the consolidated result will finally turn to increased risk. The incidence of late-onset ventricular dysfunction appears to increase in conjunction with the length of the follow-up.[3] An unanswered question is that no data are available regarding the timing of onset. It questions the patient's vulnerability of long-term AI regime. AIs have a somewhat different adverse-effect profile. Individualized treatment should provide more survival benefits with less serious events considering the biological type, grade of disease, and antecedent history of CV disease.

Till now, far less is known about head-to-head comparison among AIs. Although FACE[23] and MA.27[24] trials are ongoing, cardiac details are still under investigation.

In this network meta-analysis, we found a significant superiority of anastrozole to letrozole and exemestane.

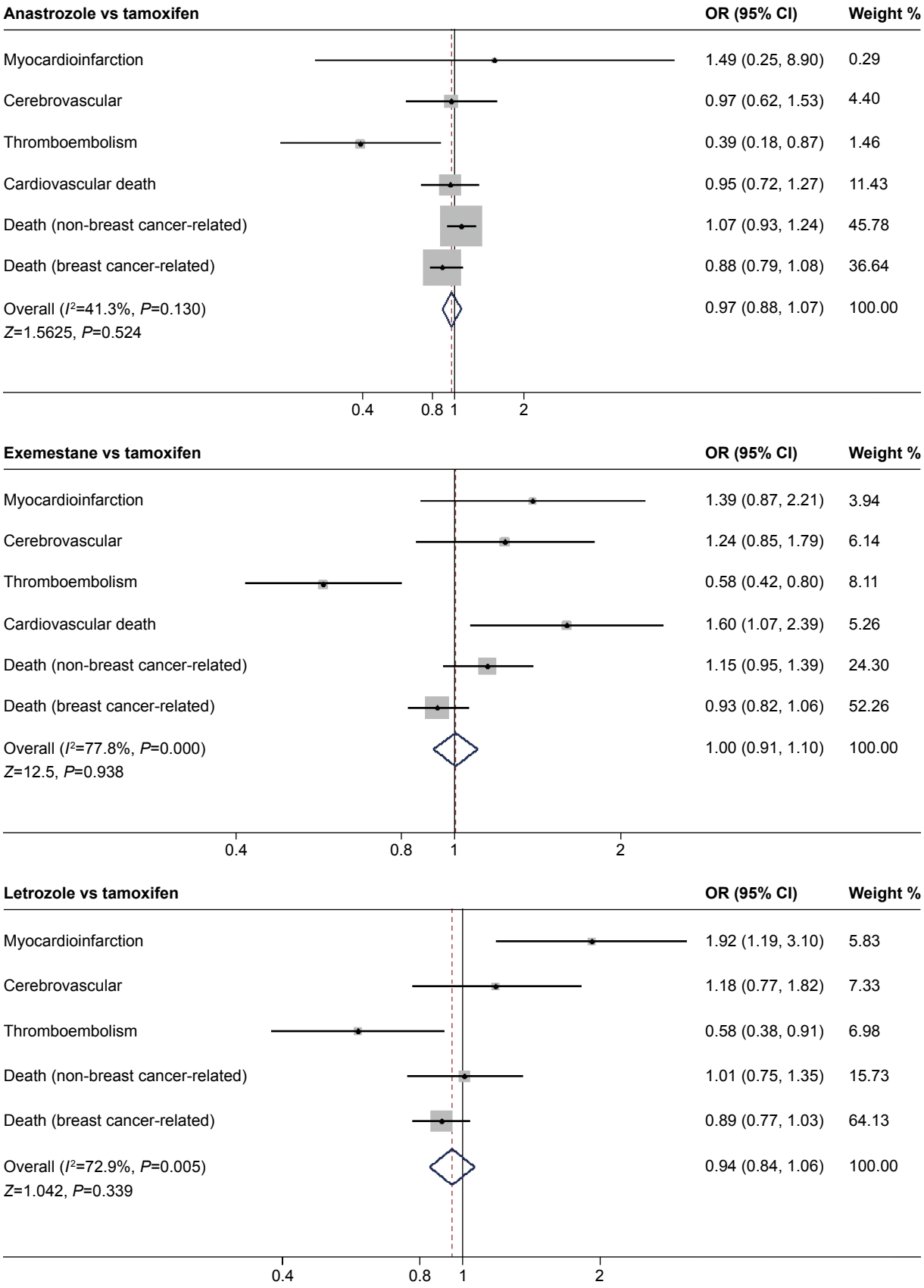

Figure 5 Forest plot of comparison of cardiovascular side effects between AIs and tamoxifen.
Notes: Trials with no events in both groups have been left out of these calculations. Their inclusion with continuity corrections does not alter these results appreciably.
Abbreviations: OR, odds ratio; CI, confidence interval; AIs, aromatase inhibitors.

The hazard is almost reduced to half when compared with letrozole (Figure 3). In subgroup analysis, the result was still pronounced. Letrozole is shown to provide lower non-breast cancer-related death (letrozole vs tamoxifen: 35.32‰ vs 34.97‰, anastrozole vs tamoxifen: 71.51‰ vs 67.65‰, exemestane vs tamoxifen: 31.51‰ vs 27.27‰), while anastrozole has decreased rate of causing myocardial infarction, cerebral disease, thromboembolism, and CV death (Table 2). It confirms that anastrozole is more suitable for the continuous endocrine therapy for longer duration when basal CV disease exists.

Network meta-analysis not only increases statistical power by incorporating evidence from both direct (head-to-head) and indirect comparisons across all five interventions but can also provide insights into the relative effectiveness of interventions that have never been directly compared, such as anastrozole therapy and letrozole therapy. It combines direct and indirect evidences on the relative effectiveness of several interventions with respect to randomization. An important feature of this methodology is that heterogeneity between trials is set to zero. Thus, the underlying true treatment effects are assumed homogeneous. Network meta-analysis concerns more about the fitness of models and model consistency than the heterogeneity of the data. In this analysis, the heterogeneity is difficult to avoid because the drug administration regimes are not same, and they can include monotherapy and sequenced therapy,[25–28] or even extended therapy.[29,30] The population in each trial differs and the average age differs in trials. In the network diagram, we can see that the number of people assigned in exemestane trial are 14,695, which is >10,609 in anastrozole and 4,895 in letrozole; thus, data in the analysis can be biased. In data selection and processing, for example in BIG-198, we chose patients getting monotherapy rather than sequenced therapy groups among the four groups. In ABCSG 6a,[29] although the result is the comparison between placebo and anastrozole, it indeed represents tamoxifen for 5 years compared with tamoxifen for 5 years followed by anastrozole for 3 years. As for patients' age, trials of anastrozole (ABCSG-6a and ATAC) included more elderly patients (average age =67.8 and median age =65, respectively), which contributed to non-breast cancer-related deaths. Despite the fact that random effect model was chosen to reduce the effect caused by heterogeneity, the effect is difficult to eliminate. In some subgroup analysis, the data cannot be analyzed due to the excessive heterogeneity.

This analysis is the first network meta-analysis about comparison of three AIs on CV toxicity. Experts had done lot of studies on direct comparison between AI and tamoxifen, while there is no direct evidence about head-to-head comparison between AIs. In this article, indirect comparison will provide some guidance for patients' choices on drug. This study has certain limitations. First, for the ATAC study, the earlier published edition[31] rather than the latter one reported the detailed CV events, although the latter one had a longer follow-up.[3] In ABCSG-6a trial, only myocardial infarction rate was recorded.[32] In TEAM trial,[33] some patients were not graded. This may have influence on the statistical result. Second, the criteria of CV toxicity in different trials may be different, and the patient's baseline varied among trials. The results of the present meta-analysis should be cautiously interpreted in addition to the risk of publication bias that exists in any meta-analysis. Third, in network analysis, results calculated through WinBUGs are represented as OR value without *P*-value; thus, it is difficult to explain the significance of differences between three AIs.

Implications and conclusion

From our study, anastrozole was found to be less toxic compared with exemestane and letrozole, while letrozole was found to be the most toxic. Similar to previous reports, AIs are associated with more CV risk than tamoxifen. In the treatment with anastrozole and exemestane, the risk of non-breast cancer-related mortality appeared to increase (Letrozole showed almost the same effect with tamoxifen), while the breast cancer-related mortality appeared to decrease. Ultimately, AI represents the standard adjuvant endocrine regime for postmenopausal women with endocrine-responsive disease. Because of the reduction of estrogen, avoiding the side effects is difficult. Their benefit appeared to be always balanced with a potential increase in non-breast cancer-related hazard, especially in long-term follow-up. It is wise and necessary to select an appropriate endocrine therapy drug and make specific periodic examination according to an individual's condition and underlying disease.

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Disclosure

The authors report no conflicts of interest in this work.

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