

# Sex-specific effects of blood pressure-lowering pharmacotherapy for the prevention of cardiovascular disease: an individual participant-level data meta-analysis

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## Abstract

**Background:** Recent studies have shown that the relative effects of pharmacological blood pressure (BP)-lowering on cardiovascular outcomes are largely consistent across different BP levels. Whether such treatment effects differ by sex, particularly when BP is not substantially elevated, has been uncertain.

**Methods:** We conducted an individual participant-level data (IPD) meta-analysis of randomised controlled trials (RCT) of pharmacological BP-lowering versus placebo or other classes of BP-lowering medications, or between more versus less intensive treatment strategies, which had at least 1,000 person-years of follow-up in each treatment arm. We pooled the data and categorised participants by sex, systolic BP categories in 10-mmHg increments from <120 to  $\geq$ 170 mmHg, and age categories spanning from <55 to  $\geq$ 85 years old. We used fixed-effect one-stage IPD meta-analyses and applied Cox proportional hazard models, stratified by trial, to analyse the data. An IPD network meta-analysis was used to investigate the differential effects of the five major classes of antihypertensive drugs on major cardiovascular events by sex.

**Results:** We included data from 51 RCTs involving 358,635 (42% women) participants. Over 4.2 years of median follow-up, a 5-mmHg reduction in systolic BP decreased the risk of major cardiovascular events both in women and men (hazard ratio and 95% confidence interval 0.92 [0.89 to 0.95] for women and 0.90 [0.88 to 0.93] for men,  $p$  for interaction = 1). There was no evidence for heterogeneity of relative treatment effects by sex for the major cardiovascular disease, its components, or across the different baseline BP categories (all  $p$  for interaction  $\geq$ 0.57). The effects in women and men were consistent across age categories

and the types of antihypertensive medication used for treatment (all p for interaction  $\geq$  0.14).

**Conclusions:** The effects of pharmacological BP reduction were similar in women and men across all BP and age categories at randomisation, and with no evidence to suggest that major drug classes had differing effects by sex. This study does not substantiate sex-based differences in BP lowering treatment.

#### **Nonstandard abbreviations and acronyms**

BPLTTC: Blood Pressure Lowering Treatment Trialists' Collaborations

IPD: Individual participant data

OxTREC: Oxford Tropical Research Ethics Committee

## Background

The pathophysiology of cardiovascular disease (CVD) shows important differences between the sexes, partly because women and men experience different levels of physiological<sup>1-3</sup> and environmental risk factors.<sup>4,5</sup> While pharmacological treatments to lower blood pressure (BP) have been robustly shown to reduce cardiovascular morbidity and mortality,<sup>6,7</sup> there have been growing calls for research to better understand sex-specific effects of BP management and cardiovascular disease (CVD).<sup>8,9,10</sup> Clinically important questions exist concerning whether different BP-lowering approaches should be adopted to prevent CVD in women and men.

Several observational studies have shown that elevated BP is associated with an increased risk of cardiovascular disease and death; however, there is no general agreement about the existence of heterogeneity of risk by sex. For instance, some studies suggested that sex appears to be an important modifier of the effect of BP,<sup>11-13</sup> a finding that was not supported in a meta-analysis of observational studies.<sup>14</sup> These results from observational studies are subject to potential bias and confounding and might not provide answers to questions of relative pharmacological treatment effects. While some randomised clinical trials (RCTs) have found no sex-specific differences,<sup>15-18</sup> other RCTs and subsequent meta-analyses have revealed some sex-specific variations in effects (**Table S1**).<sup>19-23</sup> More importantly, conventional meta-analyses have been unable, and single RCTs too small, to investigate the heterogeneity of effects *simultaneously* stratified by sex, age, and the range of BP categories at the initiation of treatment. The third cycle of the BPLTTC now has access to individual participant data (IPD) of over 350,000 randomised patients, of whom 42% are

women.<sup>24,25</sup> This provides an opportunity to study the stratified effect of BP-lowering treatment.

We leveraged this resource to investigate the effects of BP-lowering treatment on the risk of major CVD events and all-cause death by sex, overall and across age and baseline systolic BP categories. As a secondary aim, we estimated the effect of each BP-lowering drug class on the risk of the outcomes to study the possible heterogeneity of drug effects between sexes.

## Methods

### Study setting and eligibility criteria

The BPLTTC dataset was used for the IPD meta-analysis ([www.bplttc.org](http://www.bplttc.org)). The BPLTTC is a global collaboration of investigators from major pharmacological BP-lowering trials and experts that began in 1995 and is now on its third cycle. Details of the current cycle can be found elsewhere.<sup>24,25</sup> All trials with a minimum of 1,000 person-years of follow-up in each randomly assigned group and shared information on sex, age, and BP levels at randomisation and during follow-up, as well as outcome data for cardiovascular events, were included in this analysis. Trials restricted to patients with heart failure or short-term therapies or conducted in patients with acute myocardial infarction or other acute circumstances were excluded. Before releasing a dataset for statistical analysis, a study protocol was developed and finalised with input from international collaborators and the

steering committee of the BPLTTC. The Oxford Tropical Research Ethics Committee has approved the BPLTTC (OxTREC Reference 545-14).

## Treatment and comparison groups

In each trial, treatment and comparator arms are determined by the trial design as in previous BPLTCC studies.<sup>6,26</sup> In summary, for placebo-controlled trials, the placebo arm was defined as the comparator and the active treatment arm as the intervention. In head-to-head trials comparing two or more classes of drugs, the arm with the greater systolic BP reduction was considered as treatment and the other treatment arm(s) as a comparator. In trials investigating two BP-lowering strategies, the intensive versus the standard, the intensive arm was defined as treatment and the standard arm as a comparator. Participants and trial characteristics, as well as the amount of BP reduction in each trial, have been reported previously.<sup>6,24-26</sup>

## Primary and secondary outcomes

The outcomes were defined using the diagnostic data provided for each trial. The primary outcome was defined as the first occurrence of a major CVD event, which includes fatal or non-fatal ischaemic heart disease, fatal or non-fatal stroke or cerebrovascular disease (ischaemic or haemorrhagic), or heart failure that requires hospitalisation or ends in death. Individual components of the primary outcome, as well as cardiovascular causes of death

(myocardial infarction, sudden cardiac death, coronary heart disease, stroke, heart failure) and all-cause mortality, were considered as secondary outcomes.

## Statistical analysis

We performed an intention-to-treat analysis and grouped individuals according to the initial random allocation in each trial. We used a fixed effect one-stage IPD meta-analysis that fits a single statistical model to the IPD from all trials simultaneously.<sup>27</sup> The hazard ratio (HR) was calculated using a Cox proportional hazard model stratified by trial. Kaplan-Meier estimates of cumulative incidence were used to compute event rates, plotted separately for women and men. The effect sizes were standardised for a 5-mm Hg systolic BP decrease, which was a near approximation to the achieved mean BP reduction across BP-lowering intensity and placebo-controlled trials.<sup>6,25</sup> To investigate the interaction of the treatment effect by sex, we included an interaction term for sex and treatment status in the model. Furthermore, we split the analysis by baseline categories of systolic BP in 10 mm Hg increments ranging from 120 to 170 mm Hg as well as age categories <55, 55-64, 65-74, 75-84, and ≥85 years old, and then examined the interaction between treatment and sex in each category. Additionally, each major CVD component (secondary outcomes) was assessed to determine the consistency of the treatment effects across these secondary outcomes. The likelihood-ratio test was used to assess for interaction between sex and treatment, and p values for interaction were adjusted for multiple comparisons using Hommel's method, to reduce the chances of false-positives results.<sup>28,29</sup> Risk reduction over the follow-up period was estimated using a Poisson regression model with an identity link to assess the treatment effect on the absolute risk scale.

Several complementary and sensitivity analyses were conducted. We investigated drug-class specific effects stratified by women and men to explore the possible differential effect of each drug class by sex. A stratified network meta-analysis framework was used to estimate the effect of each of the five major BP-lowering drug classes that is angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and thiazide diuretics, on the risk of the primary outcome.<sup>30</sup> We used logistic regression to estimate the relative risk (RR) for each available comparison of drug classes, separately for women and men, using IPD from each trial. The network meta-analysis model was fitted using a Markov chain Monte-Carlo simulation with four chains and 100,000 iterations after a 10,000 burn-in.<sup>30</sup> To test whether BP reduction standardisation might affect the estimated main effects, we also ran a sensitivity analysis without it.

## Results

Due to a lack of time-to-event information, we excluded one trial from the BPLTTC database (Efficacy of Candesartan on Outcome in Saitama Trial [E-COST]).<sup>31</sup> A total of 358,635 participants from 51 RCTs were included in the analysis. All trials enrolled both sexes, and overall 41.6 % (n=149,193) were women. Compared to men, women were two years older and had a ~5 mmHg higher systolic BP at baseline, with fewer individuals in the lower categories of BP (**Table 1**). Overall, the percentages of participants receiving non-study antihypertensive medication were 67.4 and 69.1 in women and men, respectively. Men were more likely to take alpha-blockers, beta-blockers, antiplatelets, anticoagulants, and lipid-lowering drugs, whereas women were more likely to take diuretics and ARBs. Other

medication use was similar (**Table 1**). Men had more comorbidities than women, except for diabetes, which did not differ between the two groups (**Table 1**).

During a median follow-up of 4.2 years, 43,350 major CVD events occurred. The total events for stroke, ischaemic heart disease, heart failure, cardiovascular deaths, and all-cause mortality were 14,843, 21,287, 8,086, 11,884, and 30,639, respectively. The primary outcome incidence rate was 8.7 (95% confidence interval [CI] 8.5 to 8.8) and 11.1 (95% CI 11.0 to 11.2) per 100,000 person-years in women and men, respectively. In women, the incidence rates of major CVD outcomes in treatment and comparator groups were 7.8 (95% CI 7.6 to 8.0) and 9.5 (95% CI 9.3 to 9.7) per 100,000 person-years, respectively; the corresponding incidence rates in men were 10.4 (95% CI 10.2 to 10.6) and 11.8 (95% CI 11.6 to 11.9) per 100,000 person-years, respectively. The HR associated with a 5 mm Hg reduction in systolic BP for risk of primary outcome was 0.92 (95% CI 0.89 to 0.95) in women and 0.90 (0.88 to 0.93) in men (**Figure 1**), with no statistically significant heterogeneity of relative effect between the sexes for the primary or any of the secondary outcomes (all p for interaction  $\geq 0.38$ ) (**Figure 2**).

We did not find any evidence for heterogeneity of relative treatment effects by sex for major CVD events in any of the age categories (all p for interaction  $\geq 0.54$ ) (**Figure 3**). Figure 4 shows the treatment effects for primary outcomes for women and men, according to categories of baseline systolic BP. Overall, the effect sizes across the systolic BP subgroups varied slightly, but there was no evidence that the relative effects differed between women and men by systolic BP at baseline (all p for interaction  $\geq 0.57$ ).

A complementary analysis incorporating a stratified network meta-analysis revealed no evidence of a difference in treatment effects between women and men for any of the drug

classes studied (**Figure 5, Figures S1- S2**). There was also no observable heterogeneity of absolute effects of BP lowering by sex on either primary or secondary outcomes (all  $p \geq 0.35$ ) (**Figure S3**). The sensitivity analysis findings were largely comparable to the main findings when we performed the analyses stratified by sex but without standardisation of systolic BP reduction across trials (**Figure S4**).

## Discussion

This IPD meta-analysis of major pharmacological BP-lowering trials, which included 149,193 women and 209,442 men, revealed that BP-lowering treatment reduced the risk of major cardiovascular events similarly in both sexes; within the wide range of baseline BP considered in this study, there was no apparent level of baseline systolic BP below which the relative treatment effect would be stronger or weaker in women or men. Our findings also show that the treatment effects across age categories and types of antihypertensive classes used for treatment were similar for women and men.

Previous observational studies have provided inconsistent findings on the relationship between increased BP and the risk of CVD in women and men. A pooled analysis of four community-based cohort studies including 27,542 participants (54% women) showed apparent sex differences, with a higher risk of CVD in women than men in all categories of systolic BP.<sup>13</sup> Similarly, another observational study showed that usual systolic BP was positively associated with risk of major CVD with greater risk in men than women in each age-specific group.<sup>32</sup> Nevertheless, a meta-analysis of prospective cohort studies involving

over a million individuals (44% women) found no evidence for sex-specific differences in the relationship between elevated BP and risk of stroke or coronary heart disease.<sup>14</sup> Likewise, no sex differences were found in a pooled analysis of Asia Pacific cohort studies, including half a million participants.<sup>33</sup> However, residual confounding could not be ruled out due to the observational nature of these studies.

Due to the low representation of women in trials and the insufficient sample sizes to efficiently analyse subgroups by sex, randomised trials are typically individually unable to rule out sex differences reliably.<sup>34</sup> For instance, in a post-hoc analysis of the SPRINT trial, targeting an intensive BP reduction in 9,361 participants showed no sex-treatment interaction for primary and secondary outcomes.<sup>35</sup> However, the total number of primary events in the treatment and control groups for women was 166, compared to 396 for men, with a relatively wide confidence interval.<sup>35</sup> In the ANBP-2 study, which examined ACEIs versus diuretics in a total of 6,083 participants (51% women), only a 17% reduction in risk of primary events was reported in men (HR 0.83; CI 0.71 to 0.97), with no beneficial effect in women (HR 1.00; CI 0.83 to 1.21).<sup>36</sup> Similarly, in a post-hoc analysis of the OSCAR trial, which included 1,164 participants (56% women), a beneficial effect for reducing the risk of primary events was only seen in men.<sup>23</sup> Furthermore, the majority of individual trials did not report sex-specific findings.<sup>37-39</sup>

A previous meta-analysis from the BPLTTC incorporating data from 31 trials with a total of 190,616 participants (45% women) found that all of the BP-lowering drug classes had similar preventative benefits against major CVD events in women and men.<sup>40</sup> Even though this meta-analysis has been one of the most reliable sources of evidence on this topic, it left many questions unanswered, which might explain the calls for a different threshold for

initiation of BP reduction treatment in men and women,<sup>11,41</sup> and more research into sex-specific effects.<sup>8,9,10</sup> The findings of our study contribute significantly to the existing body of evidence because we were able to standardise the relative effect sizes for a fixed magnitude of BP reduction in trials and investigate effects across a wide spectrum of BP categories and age at the baseline, all while using a sample size that was substantially larger than previous studies. Beyond evaluating the effects of BP reduction per se, we also investigated the individual effects of each BP-lowering drug class versus placebo for each sex separately. Overall, consistent with previous BPLTTC analyses, which demonstrated that the pattern of benefits accrued from BP-lowering is similar in people with or without CVD,<sup>6</sup> and across different age groups,<sup>26</sup> this analysis found that lowering BP is effective in preventing major CVD events in both women and men across baseline BP levels or age categories, and with no differential effects by BP-lowering medication class.

In recent years, there has been an increasing focus on the personalisation of treatment effects, as healthcare providers strive to maximise patient care based on each patient's unique traits and needs. Notably, recent research found that the efficiency of commonly used antihypertensive drugs varies across participants, with the possibility for larger blood pressure reductions with customised treatment targeting.<sup>42</sup> However, it is worth noting that other research, including the present one, has shown no significant changes in clinical outcomes when populations are stratified.<sup>6,26,43,44</sup> While this may seem to conflict with the concept of personalised treatment at first, it is critical not to dismiss the potential of more nuanced and subtle stratified effects. Multiple factors, including genetic variations, specific comorbidities, or unique physiological characteristics, may play a role in treatment responses that are not readily apparent in finite-factor stratified analyses. Further research

is warranted to explore these potential stratified effects, leveraging advancements in precision medicine and personalised treatment approaches.

Some limitations should be taken into account when interpreting the study findings. We were unable to include all eligible trials in our meta-analysis. This is an inherent limitation of IPD meta-analyses based on voluntary data contributions. However, the BPLTTC research group has examined the possibility of data acquisition bias using different approaches<sup>7</sup>, and as previously reported, there is no evidence to suggest that the findings are biased by trial selection.<sup>6,44,45</sup> Furthermore, some conditions, such as peripheral vascular diseases, show a strong sex-based difference in diagnosis and treatment.<sup>46</sup> Our study outcomes were defined based on a series of major CVD events and we did not include other important vascular conditions, such as peripheral vascular diseases, atrial fibrillation, microvascular diseases, and valvular heart diseases, which will be addressed in future studies. Furthermore, the burden of CVD in pre-menopausal women is high.<sup>10,47</sup> We did not have information on menopause status but given the age distribution of patients, we must assume that most were in postmenopausal stage and hence, direct extrapolation of effects to pre-menopausal women should be done cautiously. Finally, the purpose of the individual trials was not to examine treatment effects by sex but rather to assess the general effectiveness of the intervention. However, IPD meta-analyses allow for a more comprehensive and reliable assessment of the effect of interventions across various participant subgroups, including sex, and they can also increase the statistical power and precision of the estimates, especially when the assessment of stratified effects by individual trials is unreliable.

## **Conclusion**

This large-scale analysis of randomised evidence from trials found no evidence to support the hypothesis that BP-lowering strategies should be different for women and men, or that baseline BP values for initiating BP-lowering treatment should vary by sex or age, across all age groups and drug classes considered. Pharmacological BP-lowering treatment should become a basis of risk prevention for the adult population at risk of cardiovascular disease, regardless of sex or age at initiation.

### **Perspectives**

This extensive study affirms the efficacy of BP-lowering interventions in reducing CVD risk across both sexes. It advocates for an approach to BP management that prioritises individual cardiovascular risk profiles, challenging the reliance on a single determinant like age or sex. Moreover, this analysis opens avenues for additional research, emphasising the need to explore the subtle effects of factors such as genetic variations, individual physiological characteristics, or specific comorbidities on BP-lowering treatment responses. Lastly, our research underscores the urgent necessity for proportional representation of women in cardiovascular studies.

### **Contributors**

ZB, MN, EC, DC and KR have full access to the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. KR and ZB were responsible for

the study concept. ZB, MN, EC, DC and KR were responsible for data curation. All authors were responsible for protocol writing and investigation. ZB conducted data analysis. All authors interpreted the data. ZB drafted the original manuscript, which was reviewed and edited by all authors. ZB was responsible for data visualization. KR and DC acquired the funding for the study. KR supervised the project. KR was responsible for the decision to submit the manuscript. All authors gave final approval of the version to be published.

## **Data sharing**

The governance of the BPLTTC has been reported previously. The BPLTTC is governed by the University of Oxford's policies on research integrity and codes of practice and follows the university's policy on the management of research data and records. Scientific activities based on the BPLTTC dataset are overseen by the BPLTTC steering committee. All data shared with the BPLTTC will be considered confidential and will not be provided to any third party. Requests for data should be made directly to the data custodians of individual trials. Information about individual projects is posted on the [BPLTTC website](#).

## **Declaration of Interest**

KR reports personal fees from the BMJ Heart and PLOS Medicine outside the submitted work. MW reports personal funding from Amgen, Kyowa Kirin and Freeline outside the current work.

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## **Novelty and Relevance**

### **What is new?**

The individual participant data meta-analysis of major pharmacological blood pressure-lowering trials, which included a large sample of 149,193 women and 209,442 men, revealed that blood pressure-lowering treatment reduced the risk of major cardiovascular events similarly in both sexes. Importantly, there was no apparent level of baseline systolic blood pressure below which the treatment effect would be stronger or weaker in women or men. The findings also showed that the treatment effects were consistent across different age categories and types of antihypertensive classes used.

### **What is relevant?**

The pathophysiology of cardiovascular disease exhibits notable distinctions between sexes, attributed in part to differential levels of physiological and environmental risk factors. While pharmacological interventions for blood pressure reduction have demonstrated efficacy in mitigating cardiovascular morbidity and mortality, there is a growing need for research to elucidate the sex-specific effects of blood pressure management and cardiovascular disease.

### **Clinical Implications?**

The study supports the notion that blood pressure-lowering treatment should be a basis for risk prevention in the adult population at risk of cardiovascular disease, irrespective of sex

or age at initiation. The results suggest that there is no need for different blood pressure-lowering strategies for women and men or varying baseline blood pressure values for initiating treatment based on sex or age.

Table 1. Baseline characteristics of participants stratified by sex.

Characterise	Women (149193)	Men (209443)
Age (years), mean (SD)	66.2 (9.8)	64.2 (9.4)
Categories of age (years)		
<55	14944 (10.0)	27990 (13.4)
55 to 65	49760 (33.4)	78613 (37.5)
65 to 75	53685 (36.0)	74786 (35.7)
75 to 85	27835 (18.7)	26181 (12.5)
≥85	2938 (2.0)	1850 (0.9)
Systolic blood pressure [mmHg]	156 (21.6)	149.8 (20.6)
Diastolic blood pressure [mmHg]	87.7 (12.3)	87.1 (12.4)
Categories of systolic blood pressure [mmHg]		
<120	4980 (3.3)	11757 (5.6)
120 to 129	9743 (6.5)	20456 (9.8)
130 to 139	16839 (11.3)	31465 (15.0)
140 to 149	25448 (17.1)	40994 (19.6)
150 to 159	24911 (16.7)	36312 (17.4)
160 to 169	28418 (19.1)	32777 (15.7)
≥170	38717 (26.0)	35509 (17.0)
Categories of diastolic blood pressure [mmHg]		
<70	9565 (6.4)	13954 (6.7)

70 to 79	24891 (16.7)	37714 (18.0)
80 to 89	44172 (29.6)	64646 (30.9)
90 to 99	41842 (28.1)	56425 (27.0)
100 to 109	22302 (15.0)	28167 (13.5)
≥110	6272 (4.2)	8360 (4.0)
Body mass index [kg/m <sup>2</sup> ]	28.1 (5.8)	27.7 (8.2)
Comorbidity		
Peripheral vascular disease	4720 (8.7)	8177 (10.2)
Atrial fibrillation	3943 (2.6)	6547 (3.1)
Diabetes	43276 (29.0)	60049 (28.7)
Chronic kidney disease	7618 (12.4)	14732 (18.0)
Cerebrovascular disease	18745 (15.7)	32066 (18.9)
Ischaemic heart disease	37666 (25.4)	82503 (39.5)
Previous use of non-study medications		
Diuretic	15476 (26.1)	18945 (17.8)
Alpha-blocker	1343 (2.9)	3509 (4.9)
Beta-blocker	18580 (28.9)	41361 (37.3)
Angiotensin converting enzyme inhibitor	17525 (31.6)	30838 (32.6)
Angiotensin receptor blocker	4058 (10.3)	4520 (7.4)
Calcium channel blocker	20489 (31.9)	35553 (32.1)
Any BP-lowering drug	60585 (67.4)	92670 (69.1)
Anti-platelet	15407 (33.1)	35624 (49.8)
Anticoagulant	2151 (6.9)	4419 (8.2)
Lipid-lowering treatment	16724 (31.8)	37755 (39.6)

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Data are n (%) or mean (SD)

Figure 1. Cumulative incidence of major cardiovascular events per 5 mm Hg reduction in systolic blood pressure, stratified by treatment allocation and sex

Major cardiovascular events are defined as a composition of fatal or non-fatal stroke, fatal or non-fatal myocardial infarction or ischaemic heart disease, or heart failure causing death or requiring hospitalisation.

## Figure 2. Effects of blood pressure-lowering treatment on primary and secondary outcomes, by sex

Hazard ratios were standardised for blood pressure reduction across trials and rescaled to a 5 mmHg reduction in systolic blood pressure. *p*: *p*-value for interaction adjusted for multiple comparisons, CI: confidence interval

### Figure 3. Effects of systolic blood pressure-lowering treatment on major cardiovascular events stratified by age categories and sex

Hazard ratios were standardised for blood pressure reduction across trials and rescaled to a 5-mmHg reduction in systolic blood pressure. p: p-value for interaction adjusted for multiple comparisons, CI: confidence interval

## Figure 4. Effects of systolic blood pressure-lowering treatment on primary outcomes stratified by baseline systolic blood pressure and sex

Hazard ratios were standardised for blood pressure reduction across trials and rescaled to a 5-mmHg reduction in systolic blood pressure. p: p-value for interaction adjusted for multiple comparisons, CI: confidence interval

## Figure 5. Effect of major antihypertensive drug classes on the risk of major cardiovascular events stratified by sex

The estimated meta-regression coefficient for the effect of sex ratio (proportion of men) on the network meta-analysis model was 0.058 (95% CI -0.057 to 0.18,  $p=0.81$ ).

