Meta Analysis

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Efficacy and safety of nebivolol in hypertensive patients: a meta-analysis of randomized controlled trials

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Abstract

Purpose: Our meta-analysis was undertaken to evaluate the efficacy and safety of nebivolol compared with other second-generation β blockers for hypertensive patients.

Methods: We searched PubMed, the Cochrane Library, EMBASE, and Clinical Trials.gov databases for randomized controlled trials (RCTs). The efficacy endpoints included systolic blood pressure (SBP), diastolic blood pressure (DBP), reduction of SBP and DBP, heart rate (HR), and adverse events (AEs).

Findings: Eight RCTs with 1514 patients met the inclusion criteria. HR was significantly lower in patients receiving other second-generation β blockers compared with patients receiving nebivolol. There was no difference the reduction of blood pressure (SBP and DBP) or the reduction of SBP or DBP between the groups. The incidence of AEs was lower in patients taking nebivolol compared with patients taking other second-generation β blockers.

Conclusions: No significant difference was demonstrated between nebivolol and other second-generation β blockers in the reduction of blood pressure, SBP, and DBP. The tolerability of nebivolol was significantly better compared with other second-generation β blockers, and nebivolol was also associated with a stable HR and a lower risk of AEs compared with other second-generation β blockers.

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Introduction

As a globally prevalent disease, hypertension is a major risk factor for ischemic heart disease, heart failure, stroke, atrial fibrillation, chronic kidney disease, peripheral vascular disease, and cognitive decline. It is also the leading cause of premature death.[1] β blockers are effective for primary and secondary prevention of coronary artery disease; however, they may cause fatigue, depression, sexual dysfunction, and giddiness, and have an adverse effect on the lipid profile.[2] β blockers also have been used for many years to treat patients with hypertension, and they are still the first-line drugs for hypertension.[3,4] The 2018 ESC/ESH Guidelines for the management of arterial hypertension recommend β blocker as a first-line drug for the treatment of hypertension.[1] The common side effects of β blockers include dizziness, fatigue, cold extremities, gastrointestinal disorders, shortness of breath, dyslipidemia, and muscle cramps. Because of its high selectivity for β receptors, nebivolol will not produce adverse reactions such as bronchospasm, gastrointestinal symptoms, or Raynaud's phenomenon, which inhibit β receptors. Additionally, clinical use of third-generation β blockers such as nebivolol is expected. Nebivolol is a soluble selective β1 receptor blocker and its blockade of β1 receptors is 290 times stronger compared with that of β2 receptors.

Pharmacologically, β receptor blockers can be divided into three generations based on their receptor affinity. First-generation non-selective β-blockers such as propranolol, timolol, and nadolol have the same affinity for β1 and β2 receptors. Second-generation β receptor blockers such as metoprolol, atenolol, and bisoprolol are selective β1 blockers; their selectivity is dose-dependent, and they can block β2 receptors at high doses. Third-generation β receptor blockers can expand peripheral blood vessels in addition to competitive inhibition of β-receptor activity, such as nebivolol-mediated nitric oxide (NO) synthesis. Nebivolol is a third-generation β blocker, which has a β blocker effect and promotes NO generation and vasodilation. Currently, it is mainly used for mild and moderate essential hypertension or combined with standard therapeutic drugs, and it is used to treat patients over 70 years of age with mild and moderate stable chronic heart failure.[5]

This meta-analysis was undertaken to analyze the antihypertensive effect, HR reduction and adverse reactions of the third-generation β blocker nebivolol compared with second-generation β blockers to provide evidence for pharmacotherapy in hypertensive patients.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[6] statement for conducting a high-quality meta-analysis. Because animals and humans were not involved in

this study, ethics approval and informed consent were not necessary.

Literature search

A randomized comparison table was searched for literature in the Cochrane Library, EMBASE, PubMed, and Clinical Trials.gov databases. The search date was set from January 1990 to September 2016. The following keywords were used in the search strategy, and sensitive filters for randomized controlled trials (RCTs) were used: "β blocker"; "nebivolol"; "metoprolol"; "atenolol"; and "hypertension". Additionally, references listed in selected trials were reviewed for additional trials and information.

Study selection

Studies from the independently searched literature were screened by two investigators. When a disagreement arose, a third investigator was consulted. We included studies that met the following inclusion criteria: (1) clinical investigations were conducted in humans; (2) patients who had hypertension; (3) full-text articles of clinical trials examining nebivolol compared with second generation β blockers (including metoprolol, atenolol, hypertension); and (4) systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), reduction of blood pressure, and incidence of adverse events (AEs) were reported. When duplicate studies from the same trial and similar outcomes were reported, the most comprehensive and most recent data were included. Reviews, meta-analyses, editorials, observational studies, and studies in which it was not possible to assess the outcomes or studies that lacked a control group were excluded.

Data extraction and quality assessment

Clinical data were independently extracted by two investigators using a standardized extraction form. The following information was extracted from the included investigations: authors' name, publication year, participants' baseline characteristics, total number of individuals per arm, mean age, body mass index (BMI), and smoking history. The following endpoints were extracted: SBP, DBP, HR, reduction of SBP, reduction of DBP, and incidence of AEs. Information regarding blinding, random sequence generation, allocation concealment, indications for incomplete outcome data, indications for selective reporting, and other biases was also collected to evaluate the quality of the included investigations.

Statistical analysis

Data were analyzed in accordance with the intention-to-treat principle. Differences in dichotomous results were reported as risk ratio (RR) and 95% confidence interval (CI). Differences in consecutive results were reported as mean difference (WMD), including the 95%CI. Heterogeneity was assessed using the Cochrane Q test and I^2 statistics. Cochrane's $P < 0.10$ and $I^2 > 50$ indicated significant heterogeneity. Fixed-effects models were used for summary analysis, and the random-effects models were used if significant heterogeneity was present. The Berg test was used to assess publication bias. Data analysis was performed using Review Manager (RevMan) computer program (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The Begg test for assessing the symmetry of the funnel plot was performed using STATA software (version 11.1; StataCorp. LLC, College Station, TX, USA). Additionally, sensitivity

analyses were performed by excluding each individual study using STATA software.

Results

Search results

Based on the search strategy, 368 potentially relevant publications were identified, and 117 complete publications were reviewed. Eight of these studies met our selection criteria,[5,7–13] as shown in Figure 1. The baseline characteristics of the included studies are shown in Table 1. The quality assessment is detailed in the supplemental files (Supplemental Table 1 and Supplemental Figures 1 and 2).

Clinical results

We included 1154 participants in our meta-analysis (582 for nebivolol and 572 for other second-generation β blockers). The reduction of blood pressure was the primary efficacy endpoint and incidence of AEs was the safety endpoint. SBP, DBP, and HR served as secondary endpoints.

Blood pressure reduction. Three RCTs[7,10,11] involving 568 patients reported a reduction of blood pressure including reduction of SBP and DBP, with 288 patients randomized to nebivolol and 280 randomized to other second-generation β blockers. No significant difference was observed in SBP reduction (WMD, 0.54; 95%CI, −1.23 to 2.31; $I^2 = 0\%$; Figure 2) or DBP reduction (WMD, 0.35; 95%CI, −0.49 to 1.18; $I^2 = 0\%$; Figure 2) between the two groups after 12 weeks of treatment.

Systolic blood pressure. Seven RCTs[7–13] involving 881 patients reported the SBP, with 444 patients randomized to nebivolol and 437 randomized to other second-generation β blockers. No significant difference was observed in the SBP at week 8 (WMD, 0.56; 95%CI, −1.30 to 2.43; $I^2 = 0\%$; Figure 3a), week 12 (WMD, −0.88; 95%CI, −2.41 to 0.65; $I^2 = 0\%$; Figure 3a), and week 24 (WMD, 1.82; 95%CI, −4.28 to 0.50; Figure 3a) between the two groups.

Diastolic blood pressure. Seven RCTs[7–13] involving 881 patients reported the DBP, with 444 patients randomized to nebivolol and 437 randomized to other second-generation β blockers. No significant difference was observed in DBP at week 8 (WMD, −0.45; 95%CI, −1.28 to 0.38; $I^2 = 0\%$; Figure 3b), week 12 (WMD, −0.63; 95%CI, −1.48 to 0.21; $I^2 = 0\%$; Figure 3b), and week 24 (WMD, −2.67; 95%CI, −6.26 to 0.92; Figure 3b).

Heart rate. Six RCTs[7–10,12,13] involving 634 patients reported a reduction of blood pressure including reduction of the SBP and DBP, with 319 patients randomized to nebivolol and 315 randomized to other second-generation β blockers. The HR was significantly lower in patients taking other second-generation β blockers compared with patients taking nebivolol (WMD, 4.02; 95%CI, 1.35 to 6.68; $P = 0.003$; $I^2 = 86\%$; Figure 4a).

Adverse events. Common AEs that were associated with β blockers included vertigo, dizziness, headache, fatigue, hypotension, and fainting. Five RCTs[8–11,13] with 677 patients reported AEs. The incidence of AEs was lower in patients taking nebivolol compared with patients taking other second-generation β blockers (RR, 0.52; 95%CI, 0.34 to 0.79; $I^2 = 48\%$; Figure 4b).

Sensitivity and publication bias analysis. A sensitivity analysis was conducted, and no significantly different results were obtained by excluding each individual study, as shown in Figure 5. No significant evidence of a publication bias for the study endpoints

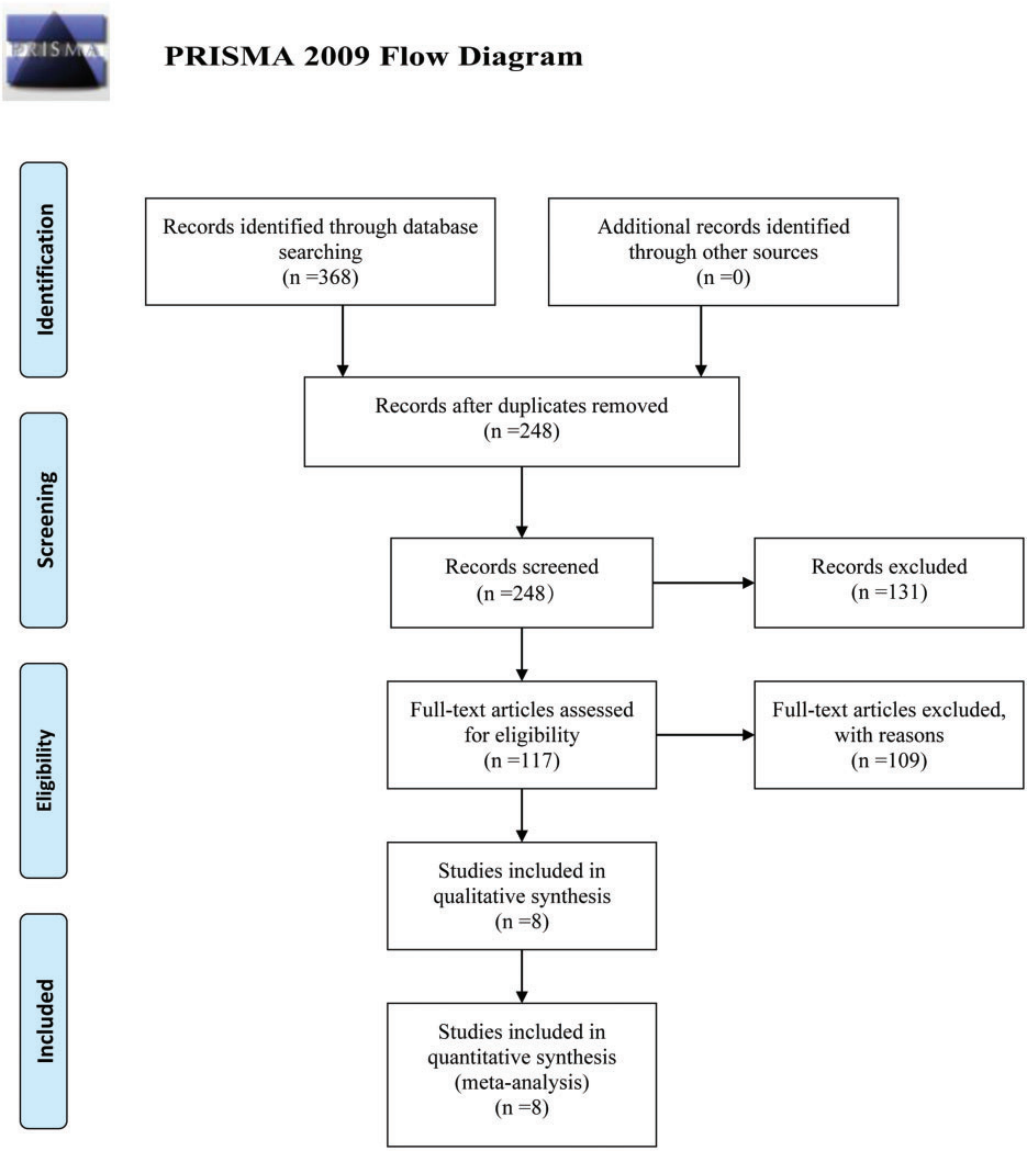

Figure 1. Flowchart of literature retrieval and selection.

was obtained using the Egger test, as shown in Table 2.

Discussion

This meta-analysis included 1154 patients with hypertension who were randomized to receive nebivolol or other second-generation β blockers in eight RCTs. Based on this meta-analysis, we found no significant difference between nebivolol and other second-generation β blockers in reducing blood pressure, SBP, and DBP. Nebivolol was associated with a lower risk of AEs compared with other second generation β blockers.

Table 1. Baseline characteristics of the included studies.

Study	Sample size		Female/Male		Dosage		Age (years)		SBP		DBP		BMI (kg/m^2)		Smoke (%)		Rate of side effects		Follow up (weeks)
	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	
Bhosale et al 2014	45	45	22/23	23/22	Nebivolol 5 mg/day	Atenolol 50 mg/day	51.32 ± 10.03	53 ± 8.61	151.53 ± 10.4	153.63 ± 8.4	97.53 ± 2.4	97.89 ± 3.47	/	/	15.55	13.33	/	/	12
Boydak et al 2004	43	44	0/43	0/44	Nebivolol 5 mg/day	Atenolol 50 mg/day	47.4 ± 4.4	46.8 ± 4.6	161.7 ± 9.9	163.6 ± 9.2	98.7 ± 4.9	97.8 ± 4.4	24.1 ± 1.8	24.2 ± 1.7	44.20	38.60	10/43	13/44	12
Chen et al 2013	26	26	15/11	14/12	Nebivolol 5–10 mg/day	Atenolol 5 mg/day	50.8 ± 9.2	50.1 ± 8.6	151 ± 21	149 ± 23	151 ± 11	108 ± 13	24.6 ± 1.4	24.2 ± 1. 5	/	/	4/26	4/26	8
Czuriga et al 2003	138	135	60/78	69/66	Nebivolol 5 mg/day	Bisoprolol 5 mg/day	50 ± 8.4	49 ± 8.2	153 ± 11.7	153 ± 11.5	99 ± 3.1	100 ± 3.1	/	/	21.00	24.40	8/138	12/135	12
Fici et al 2014	37	35	17/20	17/18	Nebivolol 5 mg/day	Metoprolo 100 mg/day	50.24 ± 6.10	52.48 ± 5.59	153.37 ± 5.78	155.00 ± 6.41	92.16 ± 6.61	94.85 ± 6.00	26.89 ± 3.64	26.77 ± 3.14	/	/	/	/	24
Grassi et al 2003	105	100	54/51	43/47	Nebivolol 5 mg/day	Atenolol 100 mg/day	50.1 ± 11.3	49.8 ± 10.9	157.3 ± 12.3	155.2 ± 13.5	100.4 ± 4.4	100.5 ± 4.6	/	/	18	21	6/105	24/100	12
Jin et al 2013	158	157	73/85	71/84	Nebivolol 5 mg/day	Bisoprolol 5 mg/day	55.6 ± 8.2	55.6 ± 7.2	150.4 ± 10.5	150.4 ± 10. 5	98.6 ± 2.6	98.2 ± 2.6	25.1 ± 2.5	25.1 ± 2.4	/	/	/	/	12
Yazici et al 2013	30	30	7/23	6/24	Nebivolol 5 mg/day	Metoprolol 50 mg/day	52.8 ± 9.5	55.7 ± 11.7	152.8 ± 5.9	151.3 ± 3.6	92.3 ± 4.1	91.1 ± 3.7	27.2 ± 3.7	27.6 ± 3.2	30	26.60	0/30	0/30	8

T, Treatment group (nebivolol group); C, Control group (other second-generation β blocker group); SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; /, no data.

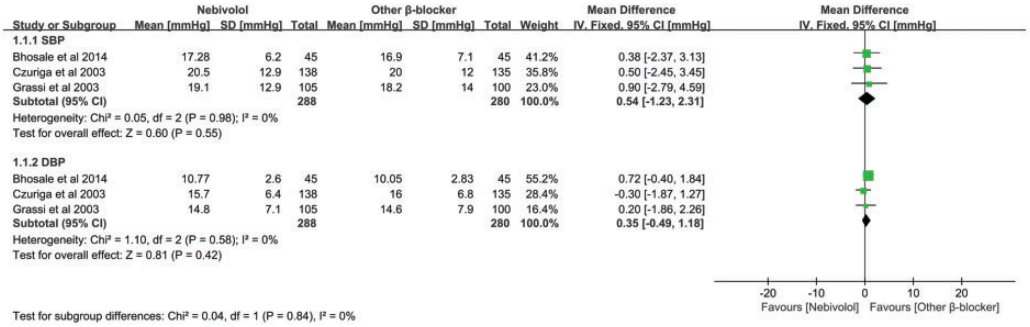

Figure 2. Forest plot of the reduction in blood pressure. WMD represents the difference between the reduction of blood pressure in nebivolol-treated patients and the control patients who were treated with other second-generation β blockers. The green squares represent the point estimation of WMD in each individual study and the size of the square reflects the weight of this study. The black squares represent the point estimation and 95%CI of overall WMD.
SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; IV, inverse-variance; 95% CI, 95% confidence interval; Fixed, fixed effects model; df, degrees of freedom; WMD, mean difference.

Nebivolol is a third-generation highly β_1-selective blocker with endothelium-dependent vasodilatory properties that are mediated by the *L*-arginine/NO pathway, which has not been observed in other β blockers (e.g. atenolol and metoprolol) that are used in clinical practice.[14–16] An early study showed that nebivolol and bisoprolol had similar effects on the mean change of DBP and SBP, but there was no difference in overall incidence of AEs.[10] Another study reported that the difference in the mean reduction in SBP and DBP was not statistically significant by nebivolol and atenolol, but the number of patients with AEs was higher in the atenolol group compared with the nebivolol group.[7] With more attention focused on the treatment of hypertension, several clinical trials of nebivolol and other β blockers have been conducted and meta-analyses are needed to evaluate the efficacy and safety of nebivolol.

The first meta-analysis of nebivolol for hypertension was conducted by Van et al.[17] Compared with this article, our analysis focuses on comparing nebivolol with other β blockers by including the latest clinical investigations on nebivolol. Additionally, we conducted a subgroup analysis based on the follow-up duration and analyzed more endpoints such as reduction of blood pressure and HR. Quality assessment, sensitivity, and publication bias analysis yielded high-quality evidence. This is the first meta-analysis that compared nebivolol with other β blockers, and we demonstrated no significant difference between nebivolol and other second-generation β blockers in the reduction of blood pressure, SBP, and DBP in all the subgroup and overall analysis. However, the HR was lower in patients who used other second-generation β blockers compared with those who used nebivolol. This finding is similar to the study by Bhosale et al.[7] Nebivolol reduced blood pressure via β1 receptor blockade as well as reducing peripheral resistance, but it caused less β1 blockade compared with atenolol. Nebivolol was observed in clinical studies to produce less bradycardia and tachycardia, which represents the advantage of nebivolol because changes in HR may have adverse effects on patient compliance. However, there were no clear

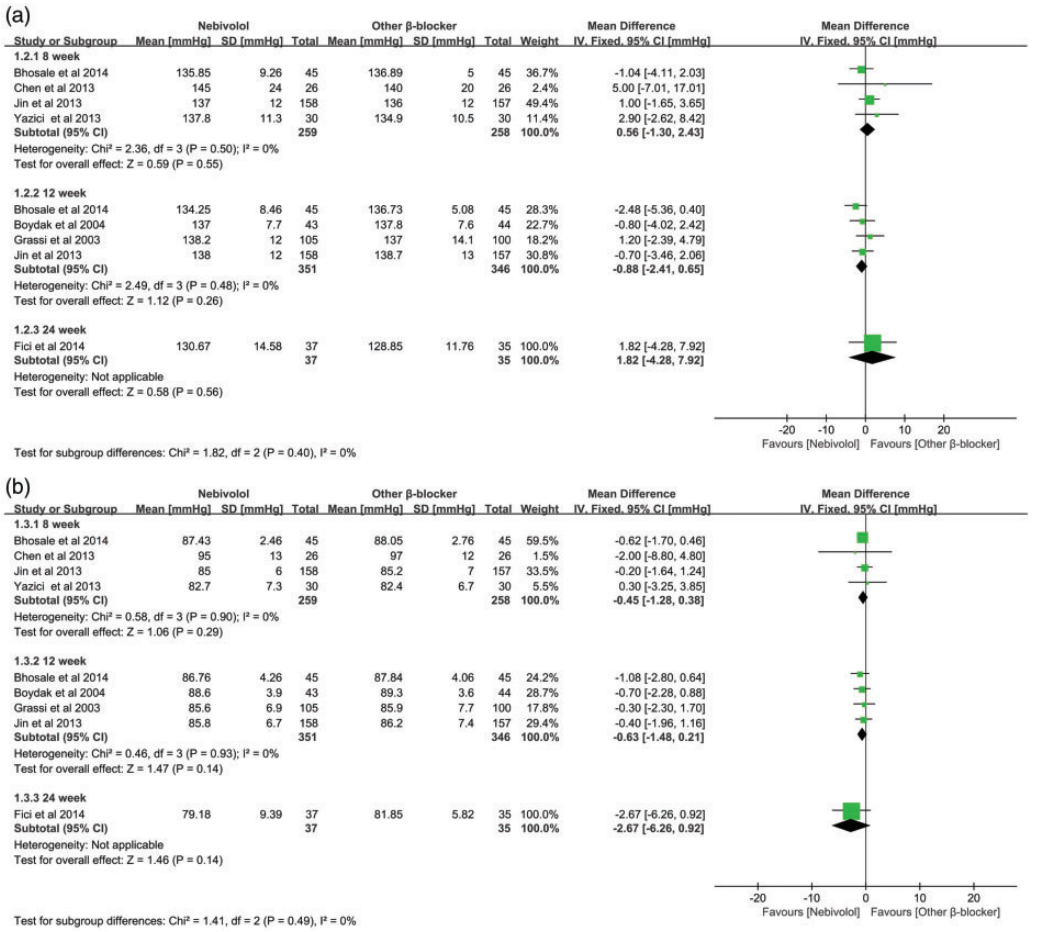

Figure 3. (a). Forest plot of systolic blood pressure. WMD represents the difference between the systolic blood pressure value in nebivolol treated patients and the control patients who were treated with other second generation β blockers. The green squares represent the point estimation of WMD in each individual study and the size of the square reflects the weight of this study. The black squares represent the point estimation and 95%CI of overall WMD. (b) Forest plot of diastolic blood pressure. WMD represents the difference between the diastolic blood pressure value in nebivolol treated patients and the control patients who were treated with other second-generation β blockers. The green squares represent the point estimation of WMD in each individual study and the size of the square reflects the weight of this study. The black squares represent the point estimation and 95%CI of the overall WMD.
DBP, diastolic blood pressure; SD, standard deviation; IV, inverse-variance; 95%CI, 95% confidence interval; Fixed, fixed effects model; df, degrees of freedom; WMD, mean difference.

pharmacological properties of nebivolol to demonstrate this result. Because of the high heterogeneity of this result and the small sample size, more clinical evidence is needed for confirmation, and it remains controversial whether the effect of nebivolol on patients' HR is lower compared with that of other β blockers. The tolerability of nebivolol was significantly better compared with that of other second-generation

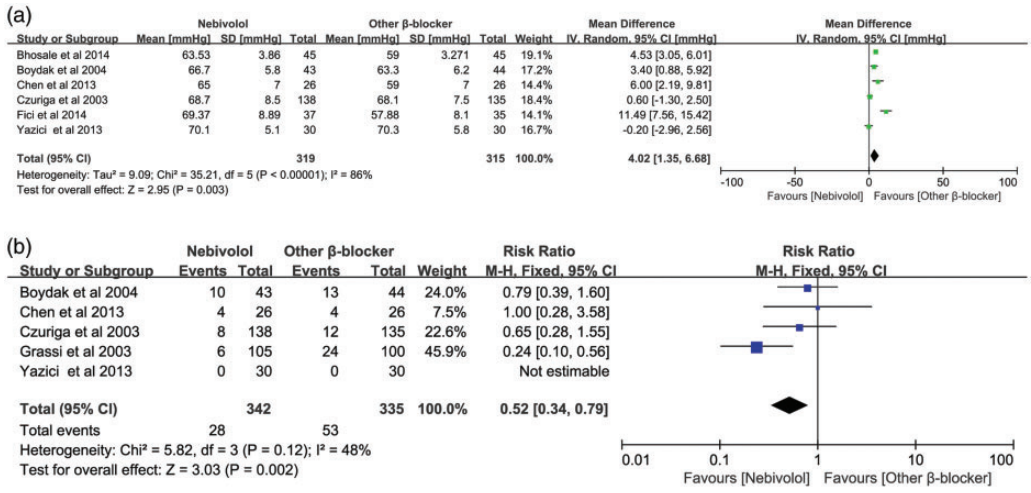

Figure 4. (a). Forest plot of HR. WMD represents the difference between the HR in nebivolol treated patients and the control patients who were treated with other second generation β blockers. The green squares represent the point estimation of WMD in each individual study and the size of the square reflects the weight of this study. The black squares represent the point estimation and 95%CI of overall WMD. (b) Forest plot of AEs. The RR represents the difference between the AE rate in nebivolol treated patients and the control patients who treated with other second generation β blockers. The green squares represent the point estimation of RR in each individual study and the size of the square reflects the weight of this study. The black squares represent the point estimation and 95%CI of overall RR.
SD, standard deviation; IV ,inverse-variance; 95%CI, 95% confidence interval; Fixed, fixed effects model; df, degrees of freedom; WMD, mean difference; RR, risk ratio; AEs, adverse events; M-H, Mantel–Haenszel; Events, number of the participant that experienced at least one adverse effect.

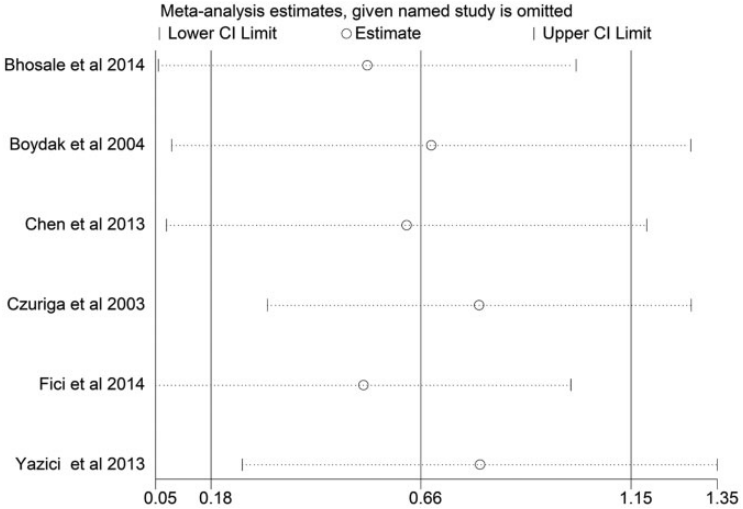

Figure 5. Sensitivity analysis.
Lower CI limit, lower limit of 95%CI; Upper CI limit, upper limit of 95%CI; 95%CI, 95% confidence interval.

Table 2. Egger Test of each endpoint.

Endpoints	P value of Egger test
Heart rate	0.425
Adverse events	1.000
SBP	0.348
DBP	0.175

SBP, systolic blood pressure; DBP, diastolic blood pressure.

β blockers, which was associated with a lower risk of AEs compared with other second-generation β blockers. Based on the above sensitivity analysis and Egger test, there was no significant heterogeneity or publication bias.

Although our study had some limitations, the meta-analysis included all available clinical data and met the inclusion criteria. Additionally, the quality of the included clinical trials is intermediate to excellent, and our meta-analysis results are reliable based on the results of the sensitivity and publication bias analysis. First, because of the limited number of clinical investigations and relatively small sample size, the power of our analysis was limited. Second, differences in patient clinical management, such as the kind of second-generation β blockers in the control group, may lead to some heterogeneity. Third, we have conducted subgroup analysis to compare SBP and DBP at weeks 8, 12, and 24. For other endpoints, such as AEs, more clinical evidence is needed to further explore medication doses and lengths of treatment. Fourth, less information is available about additional medications that were used together with nebivolol. Finally, large RCTs associated with the same medication doses and the same treatment duration of nebivolol and other medications are needed to further explore the efficacy and safety in clinical practice. A detailed subgroup analysis can be conducted when more clinical trials are published in the future.

Conclusion

No significant difference was observed between nebivolol and other second-generation β blockers in reduction of blood pressure, SBP, and DBP. The tolerability of nebivolol was significantly better compared with other second-generation β blockers, and nebivolol was associated with a stable HR and a lower risk of AEs.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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