Research Article

Intensive versus Usual Control of Hypertension in the Prevention of Cardiovascular and Renal Outcomes: A Cumulative Meta-Analysis of Randomized Controlled Trials

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Keywords

Intensive blood pressure · Cardiovascular outcome · Renal outcome · Hypertension

Abstract

Background/Aims: Previous studies have reported inconsistent results regarding the treatment effects of intensive blood pressure (IBP) control in the prevention of cardiovascular and renal outcomes. We conducted this cumulative meta-analysis to evaluate the treatment effects of IBP control on cardiovascular and renal outcomes. **Methods:** We systematically searched PubMed, EMBASE, and the Cochrane Library databases from the date of their inception to October 2017, to identify randomized controlled trials (RCTs). The relative risks (RRs) with corresponding 95% confidence intervals (CIs) were used to evaluate the treatment effects of IBP control by using a random-effects model. **Results:** The final analysis included 20 RCTs involving 56,687 individuals. The summary RRs indicated that IBP control treatment significantly reduced the risk of major cardiovascular events (RR: 0.85; 95% CI: 0.77–0.94; $p = 0.001$), including myocardial infarction (RR: 0.87; 95% CI: 0.76–1.00; $p = 0.044$), stroke (RR: 0.77; 95% CI: 0.66–0.89; $p < 0.001$), and albuminuria (RR: 0.90; 95% CI: 0.84–0.97; $p = 0.007$). However, IBP control had no significant effect on heart failure (RR: 0.80; 95% CI: 0.62–1.03; $p = 0.077$), all-cause mortality (RR: 0.91; 95% CI: 0.81–1.02; $p = 0.112$), cardiac death (RR: 0.91; 95% CI: 0.75–1.12; $p = 0.390$), non-cardiac death (RR: 0.98; 95% CI: 0.86–1.12; $p = 0.773$), end-stage renal disease (RR: 0.90; 95% CI: 0.77–1.06; $p = 0.203$), and retinopathy (RR: 0.81; 95% CI: 0.66–1.00; $p = 0.052$). **Conclusion:** The findings of this study suggest that IBP control plays a beneficial role in the prevention of some major cardiovascular events, including myocardial infarction, stroke, and albuminuria.

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Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide and results in an overwhelming financial burden on healthcare systems [1, 2]. Currently, in the USA, the treatment of CVD occupies nearly 1/6 of the total healthcare budget [3, 4]. High blood pressure (BP) is a leading risk factor for the development of CVD [5, 6], and evidence from previous studies indicates that a reduction in systolic blood pressure (SBP) could significantly reduce CVD risk [7, 8]. However, it is unclear whether a substantial BP reduction is correlated to greater improvement in CVD risk.

Numerous studies have suggested a target SBP of <140 mm Hg and a target diastolic BP (DBP) of <90 mm Hg for the management of hypertension in elderly hypertensive patients. Although, the benefit of further BP reduction in diabetes mellitus (DM) and kidney disease patients has already been demonstrated, the treatment effect of further BP reduction in patients with other disease status remains unclear [9–11]. Xie et al. conducted a meta-analysis to evaluate the treatment effect of intensive BP (IBP) control on the risk of major cardiovascular events (MACEs), myocardial infarction (MI), stroke, albuminuria, and retinopathy and compared it with the treatment effect of standard BP control [12]. However, additional new randomized controlled trials (RCTs) have already been completed, and these studies should be re-evaluated and updated with the pooled results. Therefore, we conducted a meta-analysis to evaluate the treatment effect of IBP control in reducing cardiovascular and renal outcomes and determined the evidence base for IBP control in clinical practice using a cumulative meta-analytic approach.

Methods

Search Strategy and Inclusion Criteria

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [13]. RCTs that investigated the treatment effect of IBP control on cardiovascular and renal outcomes and were published in English were included in this study, regardless of the publication status. Outcomes including MACEs, MI, stroke, heart failure, all-cause mortality, cardiac death, non-cardiac death, end-stage renal disease (ESRD), retinopathy, and albuminuria were analyzed. PubMed, EMBASE, and the Cochrane Library databases were searched for studies from the time of database inception to October 2017, and the following core search terms were used: “target blood pressure” OR “intensive blood pressure treatment” OR “intensive blood pressure control” OR “strict blood pressure treatment” OR “strict blood pressure control” OR “tight blood pressure treatment” OR “tight blood pressure control” AND “randomized controlled trials.” We also conducted manual searches of reference lists from potentially relevant studies to identify additional eligible studies.

The literature search and study selection process were independently conducted by two authors, and any inconsistency was resolved by group discussion until a consensus was reached. Study inclusion criteria were as follows: (1) the study had to have a randomized controlled design; (2) the study investigated the treatment effect of IBP control compared with standard BP control; (3) the duration of follow-up period was greater than one year; and (4) the study reported at least 1 of following outcomes: MACEs, MI, stroke, heart failure, all-cause mortality, cardiac death, non-cardiac death, ESRD, retinopathy, or albuminuria. We excluded all observational studies due to confounding variables or bias.

Data Collection and Quality Assessment

Data extraction and quality assessment were conducted independently by two authors. Information was examined and adjudicated by an additional author to refer the original studies. The data abstracted included the first author or study group's name, publication year, country, sample size, mean age, percentage male, body mass index (BMI), baseline SBP, baseline DBP, BP achieved in IBP group, BP achieved in control group, difference in BP reduction, glomerular filtration rate, serum creatinine, disease status, target BP control, MACE definitions, percentage of smokers, and follow-up duration. In addition, the investigated outcome variables was abstracted including MACEs, MI, stroke, heart failure, all-cause mortality, cardiac death, non-cardiac death, ESRD, retinopathy, and albuminuria. The JADAD scale was employed to evaluate methodological quality, which has been validated by evaluating the quality of RCT in meta-analyses [14]. The JADAD was based on randomization (1 or 0), concealment of the treatment allocation (1 or 0), blinding (1 or 0), completeness of follow-up (1 or 0), and the use of intention-to-treat analysis with a total of 5 scores developed for assessment.

Statistical Analysis

We assigned the results from each study as dichotomous frequency data or effect estimates and corresponding 95% CIs. The fixed-effect model was first used to calculate the summary RR and 95% CI for the treatment effect of IBP control on MACEs, MI, stroke, heart failure, all-cause mortality, cardiac death, non-cardiac death, ESRD, retinopathy, and albuminuria [15]. We then combined the RRs of cardiovascular or renal outcomes in IBP control to usual BP control means by using a random-effects model due to the true underlying effect variability among the included trials [16]. The cumulative meta-analysis for MACEs, MI, stroke, heart failure, all-cause mortality, cardiac death, non-cardiac death, ESRD, retinopathy, and albuminuria were conducted sequentially according to the year in which they first published. Heterogeneity among the included studies was investigated using I-square and Q statistic, and a p value < 0.10 was considered significant heterogeneity [17, 18]. Sensitivity analyses were conducted by removing each study from the overall analysis [19]. Stratified analyses were conducted for MACEs and ESRD based on publication year, sample size, mean age, male inclusion percentage, BMI, the difference in SBP reduction, disease status, the smoker inclusion percentage, follow-up duration, and study quality. Funnel plot, Egger [20], and Begg [21] tests were used to evaluate publication bias for MACEs and ESRD. p values were two-sided, and if they were < 0.05 , they were considered statistically significant across the included studies. Statistical analyses were conducted using STATA software (version 10.0; Stata Corporation, College Station, TX, USA).

Results

Search of the Published Literature

A total of 597 studies were identified from our electronic search, of which 536 were excluded due to duplication, irrelevance, and issues related to study design. We retrieved the full text for the remaining 61 studies, and 20 RCTs (22 studies) were selected for the final analysis after detailed evaluations [12, 22–42]. The manual search of the reference lists of relevant reviews yielded no new eligible studies. The results of the study selection process are shown in Figure 1, and the general characteristics of the included studies are presented in Table 1 and online supplement 1 (see www.karger.com/doi/10.1159/000499009 for all online suppl. material).

Fig. 1. Flow diagram of the literature search and trials selection process.

Study Characteristics

Twenty RCTs involving 56,687 subjects were included in the final meta-analysis. The follow-up duration ranged from 1 to 10 years, whereas the number of subjects in an individual trial ranged from 75 to 18,790. Eight trials were conducted in the USA or Canada, five in Europe, five in Asia, and the remaining two in multiple countries. Four of the trials included in the final meta-analysis reported patients with type 2 DM, whereas the remaining reported patients without type 2 DM. The mean baseline SBP of subjects in the included trials ranged from 123.0 mm Hg to 171.6 mm Hg, and mean baseline DBP ranged from 76.0 mm Hg to 105.0 mm Hg. Study quality was evaluated by a JADAD scale, and a study with a score of 4 or higher was regarded as a high-quality study. Overall, 10 trials had a score of 4, and the remaining 10 had a score of 3.

Major Cardiovascular Events

A total of 15 trials reported a treatment effect of IBP control on the risk of MACEs. The summary RR indicated that relative to the standard BP control strategy, IBP control significantly reduced the risk of MACEs (RR: 0.85; 95% CI: 0.77–0.94; $p = 0.001$; online supplement 2 – Fig. S1), and unimportant heterogeneity across the included trials was observed ($I^2 = 28.1\%$; $p = 0.141$). Consequently, a sensitivity analysis was conducted, and the conclusion was not affected by the sequential exclusion of individual studies from the overall analysis (online supplement 3 – Table S1). Although there was a significant treatment effect of IBP control for the prevention MACEs in multiple subsets, we noted that IBP control has no significant impact on MACEs when the sample size was <1,000, the mean age of the included subjects was <60.0 years, the percentage of male $\geq 60.0\%$, BMI ≥ 30.0 kg/m², difference in SBP reduction <5.0 mm Hg, the percentage of smokers included was <20.0%, follow-up duration ≥ 5 years, and all included studies were high quality (Table 2). The findings of cumulative meta-analysis indicated a significant treatment effect for IBP control on MACEs by accumulative the trial to 2005 (Fig. 2A).

Myocardial Infarction

A total of 12 studies reported a treatment effect of IBP control on the risk of developing an MI. We noted that IBP control was associated with a reduced risk of MI as compared with standard BP control (RR: 0.87; 95% CI: 0.76–1.00; $p = 0.044$; with no evidence of heterogeneity; online supplement 2 – Fig. S2). The conclusion was variable after sequential exclusion of individual studies due to marginal significant effect (online supplement 3 – Table S2). The

Table 1. Baseline characteristic of studies included in the systematic review and meta-analysis

Study	Country	Sample size	Mean age, years	Percentage male, %	BMI, kg/m ²	Baseline SBP, mm Hg	Baseline DBP, mm Hg	BP achieved in active, mm Hg	BP achieved in control, mm Hg	Difference in BP reduction, mm Hg	Follow-up, duration, years	Follow-up Jadad score
Toto 1995 [22]	USA	77	55.7	62.3	28.7	123.0	76.0	133.0/81.0	138.0/87.0	-5.0/-6.0	3.4	3
HOT 1998 [23]	Multiple countries (26 sites)	18,790	61.5	53.0	28.4	170.0	105.0	139.7/81.1	142.6/82.2	-2.9/-3.1	3.8	4
UKPDS 38 1998 [24]	England, Scotland, and Northern Ireland	1,148	56.4	55.5	29.6	159.3	94.0	144.0/82.0	154.0/87.0	-10.0/-5.0	8.4	3
Estacio 2000 [25,26]	USA	470	57.9	67.4	31.8	155.0	98.0	132.0/78.0	138.0/86.0	-6.0/-8.0	5.3	3
Schrier 2002 [27]	USA	75	41.1	54.7	NA	142.5	95.5	NA	NA	NA	7.0	4
MDRD 2005 [28]	USA	840	51.7	60.5	NA	130.5	80.0	126.2/76.9	133.8/80.7	-7.6/-3.8	4.0	3
REIN-2 2005 [29]	Italy	335	53.8	74.9	NA	136.7	84.1	129.6/79.5	133.7/82.3	-4.1/2.8	4.0	4
Estacio 2006 [30]	USA	129	56.1	67.4	32.2	126.0	84.0	118.0/75.0	124.0/80.0	-6.0/-5.0	1.9	3
JATOS 2008 [31]	Japan	4,418	65.0–85.0	38.9	23.6	171.6	89.1	135.9/74.8	145.6/78.1	-9.7/-3.3	2.0	4
Cardio-Sis 2009 [32,33]	Italy	1,111	67.0	41.0	27.8	163.3	89.6	131.9/77.4	135.6/78.7	-3.8/-1.5	2.0	4
ESCAPE 2009 [34]	Germany	385	11.5	59.5	NA	NA	NA	NA	NA	NA	5.0	4
ACCORD 2010 [35]	USA and Canada	4,733	62.2	52.3	32.1	139.2	76.0	119.3/64.4	133.5/70.5	-14.2/-6.7	4.7	4
VALISH 2010 [36]	Japan	3,079	76.1	37.6	23.5	169.5	81.5	136.6/74.8	142.0/76.5	-5.4/-1.7	3.1	3
AASK 2010 [37]	USA	1,094	54.6	61.2	30.6	NA	NA	128.0/78.0	141.0/85.0	-13.0/-7.0	10.0	4
HOMED-BP 2012 [38]	Japan	3,518	59.6	50.0	24.4	151.6	90.0	128.8/76.1	130.4/76.8	-1.6/-0.7	5.3	4
Wei 2013 [39]	China	724	76.6	66.3	23.4	159.5	84.2	135.7/76.2	149.7/82.1	-14.0/-5.9	4.0	3
SPS3 2013 [40]	North America, Latin America, and Spain	3,020	63.0	63.0	29.1	143.0	78.5	NA	NA	NA	3.7	4
PAST-BP 2015 [12]	England	379	72.6	60.4	NA	142.8	79.8	127.4/72.0	129.4/74.4	-2.0/-2.4	1.0	3
COPE 2017 [41]	Japan	3,001	63.3	50.2	24.5	153.9	88.6	128.5/74.6	142.6/80.3	-14.1/-5.7	3.7	3
SPRINT 2017 [42]	USA	9,361	68.0	0.0	30.0	140.0	78.0	NA	NA	NA	3.3	3

BMI, body mass index; DBP, diastolic blood pressure; NA, not available; SBP, systolic blood pressure.

Table 2. Subgroup analysis for major cardiovascular events and end-stage renal disease

Outcomes	Factor	Subgroup	RR and 95% CI	p value	Heterogeneity, %	p value	p value between subgroups
Major cardiovascular events	Publication year	2010 or after Before 2010	0.85 (0.74–0.98) 0.85 (0.73–0.99)	0.029 0.033	39.3 24.9	0.117 0.230	0.905
	Sample size	≥1,000 <1,000	0.87 (0.78–0.97) 0.78 (0.61–1.01)	0.009 0.061	36.5 13.2	0.116 0.330	0.333
	Mean age, years	≥60.0 <60.0	0.83 (0.73–0.94) 0.90 (0.75–1.09)	0.003 0.287	33.8 30.2	0.147 0.198	0.665
	Percentage male, %	≥60.0 <60.0	0.88 (0.73–1.04) 0.84 (0.74–0.95)	0.140 0.005	30.6 33.0	0.184 0.165	0.559
	BMI, kg/m ²	≥30.0 <30.0	0.95 (0.84–1.08) 0.80 (0.70–0.92)	0.421 0.001	0.0 41.9	0.682 0.088	0.155
	Difference in SBP reduction, mm Hg	≥5.0 <5.0	0.85 (0.74–0.97) 0.83 (0.62–1.10)	0.017 0.199	39.7 28.2	0.093 0.233	0.833
	Disease status	Type 2 DM Without type 2 DM	0.83 (0.73–0.94) 0.86 (0.75–0.98)	0.004 0.026	3.7 37.6	0.386 0.099	0.402
	Percentage of smoker, %	≥20.0 <20.0	0.78 (0.65–0.94) 0.92 (0.82–1.02)	0.009 0.121	59.9 0.0	0.021 0.902	0.233
	Follow-up duration, years	≥5.0 <5.0	0.91 (0.73–1.12) 0.84 (0.75–0.94)	0.373 0.002	51.7 19.5	0.082 0.257	0.691
	Study quality	High Low	0.92 (0.84–1.00) 0.74 (0.64–0.85)	0.057 <0.001	0.1 0.0	0.428 0.438	0.008
End-stage renal disease	Publication year	2010 or after Before 2010	0.90 (0.70–1.15) 0.90 (0.73–1.11)	0.395 0.342	0.0 0.0	0.323 0.435	0.962
	Sample size	≥1,000 <1,000	0.88 (0.69–1.11) 0.94 (0.71–1.23)	0.273 0.635	0.0 22.9	0.662 0.269	0.754
	Mean age, years	≥60.0 <60.0	1.00 (0.72–1.40) 0.87 (0.72–1.06)	0.987 0.165	0.0 4.7	0.793 0.391	0.475
	Percentage male, %	≥60.0 <60.0	0.93 (0.73–1.19) 0.87 (0.67–1.14)	0.573 0.313	24.2 0.0	0.266 0.586	0.775
	BMI, kg/m ²	≥30.0 <30.0	0.90 (0.70–1.15) 0.99 (0.45–2.18)	0.395 0.974	0.0 33.3	0.323 0.223	0.995
	Difference in SBP reduction, mm Hg	≥5.0 <5.0	0.89 (0.74–1.08) 1.12 (0.74–1.69)	0.231 0.591	0.0 –	0.546 –	0.391
	Disease status	Type 2 DM Without type 2 DM	0.96 (0.68–1.35) 0.88 (0.74–1.06)	0.812 0.187	0.0 0.0	0.321 0.456	0.675
	Percentage of smoker, %	≥20.0 <20.0	0.77 (0.55–1.07) 1.00 (0.72–1.40)	0.118 0.987	0.0 0.0	0.596 0.793	0.512
	Follow-up duration, years	≥5.0 <5.0	0.75 (0.57–0.99) 0.99 (0.81–1.21)	0.041 0.944	0.0 0.0	0.734 0.554	0.109
	Study quality	High Low	0.91 (0.75–1.10) 0.93 (0.52–1.65)	0.320 0.792	0.0 34.2	0.577 0.219	0.880

Fig. 2. Cumulative meta-analysis of the IBP control for major cardiovascular events (MACEs) **(A)** and end-stage renal disease (ESRD) **(B)**.

non-significant result persisted when cumulative trials published up to 2013 (online supplement 4 – Fig. S1).

Stroke

A total of 12 studies reported a treatment effect of IBP control on the risk of stroke. In the pooled analysis, IBP control showed a beneficial effect on stroke risk as compared with standard BP control (RR: 0.77; 95% CI: 0.66–0.89; $p < 0.001$; online supplement 2 – Fig. S3), and unimportant heterogeneity was detected ($I^2 = 20.6\%$; $p = 0.229$). The sensitivity analysis suggested that the conclusion was not affected by the exclusion of any specific study (online supplement 3 – Table S3). A significant treatment effect of IBP control for stroke was observed when accumulative the trial published by 2009 (online supplement 4 – Fig. S2).

Heart Failure

A total of 10 studies reported a treatment effect of IBP control on the risk of heart failure. There was no significant difference between IBP control and standard BP control on the risk of heart failure (RR: 0.80; 95% CI: 0.62–1.03; $p = 0.077$; online supplement 2 – Fig. S4). Substantial heterogeneity was detected among the included studies, and the results were changed after excluding the study conducted by the HOT or AASK group (online supplement 3 – Table S4). The non-significant result persisted when cumulative meta-analyses for heart failure online supplement 4 – Fig. S3).

All-Cause Mortality

A total of 19 studies reported a treatment effect of IBP control on the risk of all-cause mortality. We noted IBP control does not affect all-cause mortality as compared with standard BP control (RR: 0.91; 95% CI: 0.81–1.02; $p = 0.112$; online supplement 2 – Fig. S5). Unimportant heterogeneity was observed across included studies ($I^2 = 17.3\%$; $p = 0.239$). A sensitivity analysis was conducted and after excluding the trial conducted by the HOT group, which specifically included a large sample size and greater baseline BP. We noted IBP control significantly reduced the risk of all-cause mortality (RR: 0.88; 95% CI: 0.78–0.99; $p = 0.028$; online supplement 3 – Fig. S5). The non-significant result persisted when cumulative meta-analyses were performed for all-cause mortality (online supplement 4 – Fig. S4).

Cardiac Death and Non-Cardiac Death

Eleven RCTs reported a significant effect of IBP control on the risk of cardiac death and non-cardiac death, respectively. We noted that IBP control has no effect on cardiac death (RR: 0.91; 95% CI: 0.75–1.12; $p = 0.390$; with significant heterogeneity; online supplement 2 – Fig. S6), and non-cardiac death (RR: 0.98; 95% CI: 0.86–1.12; $p = 0.773$; with no evidence of heterogeneity; online supplement 2 – Fig. S7). The results of the sensitivity analysis were consistent with those of the overall analysis and are shown in online supplement 3 – Tables S6 and S7. Lack of statistical significance persisted when cumulative meta-analyses were conducted for cardiac death (online supplement 4 – Fig. S5) and non-cardiac death (online supplement 4 – Fig. S6).

End-Stage Renal Disease

A total of 9 studies reported a treatment effect of IBP control on the risk of ESRD. There was no significant difference between IBP control and standard BP control on ESRD risk (RR: 0.90; 95% CI: 0.77–1.06; $p = 0.203$; with no evidence of heterogeneity; online supplement 2 – Fig. S8). Although each study was sequentially excluded from the pooled analysis, the conclusion was not affected by the exclusion of any specific study (online supplement 3 – Table S8). The non-significant result persisted when a cumulative meta-analysis for ESRD was performed (Fig. 2B). Subgroup analysis indicated IBP control significantly reduced the risk of ESRD if the duration of follow-up was ≥ 5 years (RR: 0.75; 95% CI: 0.57–0.99; $p = 0.041$; Table 2).

Retinopathy and Albuminuria

Three RCTs reported a significant effect of IBP control on the risk of retinopathy and albuminuria, respectively. We noted that IBP control has no effect on the risk of retinopathy (RR: 0.81; 95% CI: 0.66–1.00; $p = 0.052$; with significant heterogeneity; online supplement 2 – Fig. S9), whereas it significantly reduced the risk of albuminuria (RR: 0.90; 95% CI: 0.84–0.97; $p = 0.007$; with no evidence of heterogeneity; online supplement 2 – Fig. S10). The sensitivity analysis indicated the results varied possibly due to the smaller number of included studies (online supplement 3 – Tables S9 and S10). The findings of cumulative meta-analyses indicated the results were altered and presented in online supplement 4 – Figs. S7 and S8.

Publication Bias

Review of the funnel plots could not rule out a publication bias for MACEs and ESRD (online supplement 5 – Fig. S1). Further, the Egger and Begg test results showed no evidence of publication bias for MACEs (p value for Egger: 0.379; p value for Begg: 0.558) and ESRD (p value for Egger: 0.494; p value for Begg: 0.466).

Discussion

Due to the characteristics of hypertension that impact the progression of cardiovascular and renal outcomes, the included RCTs evaluated the treatment effect of IBP control on cardiovascular and renal outcomes according to publication year, sample size, mean age, percentage male, BMI, difference in SBP reduction, disease status, percentage of smokers, follow-up duration, and took into consideration the quality of the investigation. The meta-analysis included 56,687 subjects from 20 RCTs with a broad range of individual characteristics. The findings of this study indicated that IBP control approaches significantly reduce the risk of MACEs, MI, stroke, and albuminuria. However, IBP control does not affect heart failure, all-cause mortality, cardiac death, non-cardiac death, ESRD, and retinopathy. Subgroup analysis suggests that long-term IBP control could play a beneficial role in the prevention of ESRD.

A previous meta-analysis based on 9 investigations in chronic kidney disease patients found that IBP control did not provide additional benefits for renal outcomes when compared with standard BP control during the follow-up period of 3.3 years, whereas this effect was not observed in diabetic patients [43]. However, the authors did not investigate the treatment effects of IBP control on cardiovascular outcomes. Further, Weiss et al. included 21 RCTs indicates IBP was associated with lower risk of all-cause mortality, MACEs, and stroke, whereas other specific outcomes were not evaluated [44]. Reboldi et al. conducted a meta-analysis in 31 studies and including 73,913 diabetic patients and indicated the protected effect of stroke was increases with the magnitude of BP reduction, whereas this effect was not observed for MI [45]. The results of previous investigations had inconsistent conclusions due to marginal significant results and the potential impact of the inclusion of additional studies. The major strengths of this study included the comprehensive inclusion of RCTs with large sample sizes and a broad selection of subjects. The large sample sizes ensured the stability of our conclusions, and the general characteristics of the subjects ensured the applicability of the summary results. Further, the treatment effects of IBP control for preventing MACEs and ESRD in specific characteristics of subjects were conducted.

The pooled results showed a significantly reduced risk of MACEs, MI, and stroke for IBP control when compared with standard BP control, but this did not impact the risk of heart failure, all-cause mortality, cardiac death, and non-cardiac death. Several previous investigations have suggested that IBP control achieves a clinically relevant reduction in the complications related to CVD. However, several reasons could affect the treatment effects of IBP control, including (1) the sensitivity of diagnosis of MACEs were different among the included trials [46]; (2) differing inclusion criteria and blindness to the analysis could have affected the clinical decisions; (3) the incidence of MACEs was different according to ethnicity; (4) disease status was associated with different risk level of included subjects; and (5) different baseline BP and target of BP reduction was introduced potential confounder factors. Subgroup analyses indicated the treatment effects of IBP was greater in subjects >60.0 years, the percentage of male <60.0%, BMI <30.0 kg/m², the difference in SBP reduction ≥5.0 mm Hg, and the inclusion of ≥20.0% smokers. These findings suggest that IBP control plays a beneficial role in the development of MACEs in high-risk subjects.

The results from this analysis suggest that IBP control is not associated with the progression of ESRD, but it might play a beneficial effect on retinopathy and albuminuria. These results were focused on DM and chronic kidney disease patients. Further, subgroup analysis indicated that IBP control is associated with lower risk of ESRD when the follow-up duration is >5 years. All the included trials reported herein showed no significant effect of IBP control on ESRD, the reason for this could be the incidence of ESRD being lower than expected, which was associated with lower statistical power and acquired broad 95% CI. Finally, the summary results for retinopathy and albuminuria might be varied due to the few studies included and potential confounding factors that could be explored.

This meta-analysis has several limitations. The ascertainment of the endpoints in individual studies was inconsistent, which may have introduced confounders into the final analysis. In addition, heterogeneity could not be explored fully due to the unavailability of several essential factors. Finally, the inherent limitation in any meta-analysis, including publication bias, and individual data were not available.

Conclusions

Relative to standard BP control, IBP control was associated with a reduced risk of MACEs, MI, stroke, and albuminuria. However, IBP control has no significant effect on the risk of heart failure, all-cause mortality, cardiac death, non-cardiac death, ESRD, and retinopathy. Future investigations should clarify the correlation between cardiovascular and renal outcomes and the extent of BP reduction.

Disclosure Statement

The authors declare no conflicts of interest in this work.

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