Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials

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Background: Antihypertensive treatment is based on randomized controlled trials (RCTs) started since 1966. Meta-analyses comprehensive of all RCTs but limited to RCTs investigating blood pressure (BP) lowering in hypertensive patients are lacking.

Objectives: Two clinical questions were investigated: the extent of different outcome reductions by BP lowering in hypertensive patients, and the proportionality of outcome reductions to SBP, DBP, and pulse pressure (PP) reductions.

Methods: PubMed between 1966 and December 2013 (any language), Cochrane Collaboration Library and previous overviews were used as data sources for identifying and selecting all RCTs comparing the antihypertensive drugs with placebo or less intense BP lowering (intentional BP-lowering RCTs); comparing BP-lowering drugs with placebo without BP-lowering intention, but with BP difference (nonintentional BP-lowering RCTs); and enrolling at least 40% hypertensive patients. RCTs on acute myocardial infarction, heart failure, acute stroke, and dialysis were excluded. RCT quality was assessed by scoring. Risk ratios and 95% confidence interval (CI), standardized to 10/5 mmHg SBP/DBP reduction, of seven fatal and nonfatal outcomes were calculated (random-effects model). The relationships of different outcome reductions to SBP, DBP, and PP reductions were investigated by meta-regressions.

Results: A total of 68 RCTs (245 885 individuals) were eligible, of which 47 (153 825 individuals) were 'intentional' RCTs. All outcomes were reduced ($P < 0.001$) by BP lowering, stroke [−36% (−29, −42)], and heart failure [−43% (−28, −54)] to a greater extent, with smaller reductions for coronary events [coronary heart disease (CHD): −16% (−10, −22)], cardiovascular [−18% (−11, −24)], and all-cause mortality [−11% (−5, −16)]. Absolute risk reductions were 17 (14, 20) strokes, 28 (19, 35) cardiovascular events, and 8 (4, 12) deaths prevented every 1000 patients treated for 5 years. Logarithmic risk ratios were related to SBP, DBP, and PP reductions ($P = 0.001–0.003$) for stroke and composite cardiovascular events, but not for CHD.

Conclusion: Meta-analyses of all BP-lowering RCTs involving hypertensive patients provide precise estimates of benefits (larger for stroke and heart failure, but also significant for CHD and mortality). Absolute risk reductions are substantial. Relationships of logarithmic risk ratios with BP reductions imply risk reduction increases progressively to a smaller extent the larger the BP reduction.

Keywords: blood-pressure-lowering trials, cardiovascular death, coronary heart disease, hypertension, meta-analysis, randomized controlled trials, stroke

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; HF, heart failure; JNC, Joint National Committee; NNT, number needed to treat; PP, pulse pressure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; RR, relative risk

INTRODUCTION

Hypertension is an area of cardiovascular medicine, in which evidence in favor of therapeutic intervention was searched by randomized controlled trials (RCTs) long before the same methodology was applied to the treatment of other cardiovascular illnesses, such as myocardial infarction and heart failure [1]. Consequently, there have been a number of overviews and meta-analyses of antihypertensive drug trials, starting from the seminal meta-analysis by Collins *et al.* [2], which have been instrumental to confirm and help quantifying the cardiovascular-disease-preventing effects of blood pressure (BP)-lowering treatment [3–6].

Evidence on the effects of BP lowering on different types of fatal and nonfatal cardiovascular outcomes largely relies upon the placebo-controlled trials, many of which were completed before 2000 and were included in the earlier meta-analyses [2–4]. A considerable number of

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placebo-controlled trials and trials of more or less intense BP lowering have been added recently and have not been covered by the existing overviews. Furthermore, meta-analyses of antihypertensive treatment RCTs have included all trials that have used antihypertensive agents even in individuals without hypertension [4,5] and in cardiovascular conditions, such as acute myocardial infarction and heart failure [6], in which drugs with antihypertensive activity were used to investigate the mechanisms of their potential benefits and in which benefits of antihypertensive drugs may be independent of BP lowering. The importance of restricting the analyses to RCTs on hypertensive individuals has been recently underlined by the panel members appointed to the Eighth Joint National Committee (JNC 8) [7], who have done a critical overview but no meta-analyses.

We have done a comprehensive overview of antihypertensive treatment RCTs from their inception in 1966–2013, and carried out a series of meta-analyses and meta-regression analyses to approach the problems listed above. This article reports the results of analyses quantifying the relative and absolute effects of BP lowering on different types of cardiovascular outcomes, and investigating the effects of BP reductions of different extent.

METHODS

Trial eligibility

The present overview intended to include all RCTs of BP-lowering drugs, in which active drugs were compared with placebo or no treatment with the intention to investigate the consequences of BP differences (intentional BP-lowering trials, placebo controlled); a more intense BP lowering was compared with a less intense one (intentional BP-lowering trials, more or less intense); or BP-lowering drugs were compared with placebo and a between-group difference of at least 2 mmHg in either SBP or DBP occurred, though the design of the trials was not that of investigating the effects of BP differences (nonintentional BP-lowering trials).

In addition, trials had to meet the following predetermined criteria: enrolling individuals with hypertension (SBP $\geq$140 or DBP $\geq$90 mmHg or current antihypertensive drugs) or a proportion of at least 40% hypertensive individuals among those randomized, with exclusion of trials investigating acute myocardial infarction, heart failure, acute stroke and patients on dialysis; protocol including measurement of at least one type of cardiovascular events as primary or secondary endpoints; BP values measured at baseline and follow-up; follow-up of at least 6 months; a minimum of five events during follow-up; randomized allocation to treatments; and publication within 31 December 2013. In order to make the overview as comprehensive as possible, no other inclusion criteria were prespecified.

The database search was done by two of the authors (C.T. and A.Z.) by consulting PubMed between 1966 and end of December 2013 (any language), the Cochrane Collaboration Library database, and the reference lists of all major previous meta-analyses and overviews of antihypertensive treatment trials [3–6]. Whenever possible, in case of doubt or missing information, the trial authors were consulted. Recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [8] were adhered to.

Outcomes

Data on seven predetermined outcomes were extracted: stroke (fatal and nonfatal); coronary heart disease (CHD) events (coronary death and nonfatal myocardial infarction); hospitalized heart failure; major cardiovascular events, composite of stroke and CHD; major cardiovascular events, composite of stroke, CHD, and heart failure; cardiovascular death; and all-cause death. The definition of outcomes reported in the original article was retained, but whenever possible transient ischemic attacks, angina, revascularization procedures, and nonhospitalized nonfatal heart failure were excluded. Two authors (C.T. and A.Z.) independently extracted the data, with differences resolved by discussion.

Quality assessment

Selection, detection, and attrition bias were assessed based on the randomization procedure, method of blinding, and combined evaluation of lost to follow-up and therapy discontinuation ratio. Studies of higher quality were those reporting randomization generation sequence, with double blinding, and lost to follow-up ratio less than 10%, accompanied by therapy discontinuation less than 10% per year of follow-up. We also arbitrarily assigned higher quality to studies with at least 60% of hypertensive individuals prevalence at baseline and to studies with at least 5000 patient-years. Moreover, we evaluated the number of outcomes reported in each individual trial, with those reporting four or more types of outcome being of higher quality compared with those reporting less than 4. The evaluation and scoring of the above six criteria were based on a binomial integer scale ranging from 0 to 1, with 1 being better. These scores were summed-up and reflected the overall study quality, with six being the best. Our quality assessment was not substantially different from that proposed by the Cochrane Collaboration's tool to assess the risk of bias; however, our modified procedure further aims at evaluating the extent of hypertension prevalence among studies, integrates specific additional criteria of bias beyond randomization and blindness, and finally takes into account the magnitude of the product 'patient-years'.

Statistical analyses

We did separate analyses of different groups of RCTs: placebo-controlled trials of intentional BP lowering; intentional BP-lowering trials comparing more with less intense treatment; and nonintentional BP-lowering trials. We also analyzed groups 1 and 2 together, both being of intentional BP lowering. This joint analysis was predetermined as the primary objective of the meta-analyses. In a secondary type of analyses, the three groups of trials were meta-analyzed together.

All analyses were done using the data as tabulated in the original publications. In each group, baseline patient characteristics and SBP/DBP differences between randomized treatments were the means of every individual trial values weighted by patients' number and follow-up duration. For every group of comparison, the null hypothesis of no

difference between randomized treatments (active or more active versus placebo or less active) was tested for each of the outcomes. Relative risk (RR) estimates [with 95% confidence interval (CI)] were combined using a random-effect model, in which the log RR for every trial was weighted by the reciprocal of the variance of the log RR. The proportion of inconsistency across the studies not explained by chance was quantified with the I^2 statistics. Whenever no significant heterogeneity was detected by the X^2 Q statistics ($P > 0.05$), a fixed-effect model was also implemented.

Risk ratios and their 95% CI were reported using the Mantel–Haenszel method, and the effects of BP lowering on each outcome were illustrated with the forest plots under the random-effects model. Risk estimates were standardized to a difference of 10 mmHg SBP and 5 mmHg DBP by multiplying the RR estimate in each trial by the appropriate factor after having considered the effect of the inverse variance of individual trials. Five-year absolute risk reductions (weighted for follow-up period inverse variance and sample size) of standardized BP-lowering treatment were also calculated as well as the number of patients needed to treat (NNT) for 5 years to prevent one outcome. Random-effect meta-regression models with inverse variance weighting were constructed to explore whether the achieved BP difference (independent variable) between the randomized groups explained the variance of RR estimates for various outcomes. Meta-regressions versus SBP reductions were also calculated after adjustment for DBP reductions and vice versa. In order to correct for the different levels of control BP, meta-regressions were also calculated by expressing SBP, DBP, and pulse pressure (PP) reductions as percentages of respective values in the control groups.

The presence of publication bias was investigated graphically by the funnel plots of precision (random effect plotting) and the Duval and Tweedie trim-and-fill method.

All statistical analyses were done using the Comprehensive Meta Analysis version 2 (Biostat, Englewood, New Jersey, USA). In each individual analysis, a P value less than 0.05 was considered to indicate statistical significance; however, this statistical threshold should be interpreted with caution because multiple comparisons were performed.

RESULTS

Trials and patients

Figure 1 illustrates the investigational steps to identify trials to be included. Searching strategy is indicated in online Supplemental Table S1, http://links.lww.com/HJH/A412, and trials excluded are listed in online Supplemental Table S2, http://links.lww.com/HJH/A412.

This procedure identified 68 eligible trials. All trials were randomized, with the only exception of the Systolic Hypertension in China (SystChina) trial, in which treatment assignment was by alternate allocation. This trial was included because its design was parallel to the randomized Systolic Hypertension in Europe (SystEur) trial and the results very similar; what makes bias because of alternate allocation unlikely. The SystChina trial was excluded in the sensitivity analyses excluding low-quality trials.

Table 1 shows the characteristics of the 68 trials [9–79], with a total of 245 885 participants followed up for a mean of 4.3 years, that is, 1 058 177 patient-years. About 81% of RCTs (55 of 68) were of higher quality (scoring from 4 to 6), with only 19% (13 of 68) of lower quality. Thirty-three trials [9–43] (111 471 participants, 4362 strokes, and 4167 CHD) were of intentional BP lowering versus placebo; 14 trials [44–57] (42 354 participants, 896 strokes, and 842 CHD) were of intentional more versus less intense BP lowering; and 21 trials [58–79] (92 060 participants, 4254 strokes, and 3457 CHD) were classified as nonintentional BP-lowering trials. Data on heart failure were available from only 36 trials.

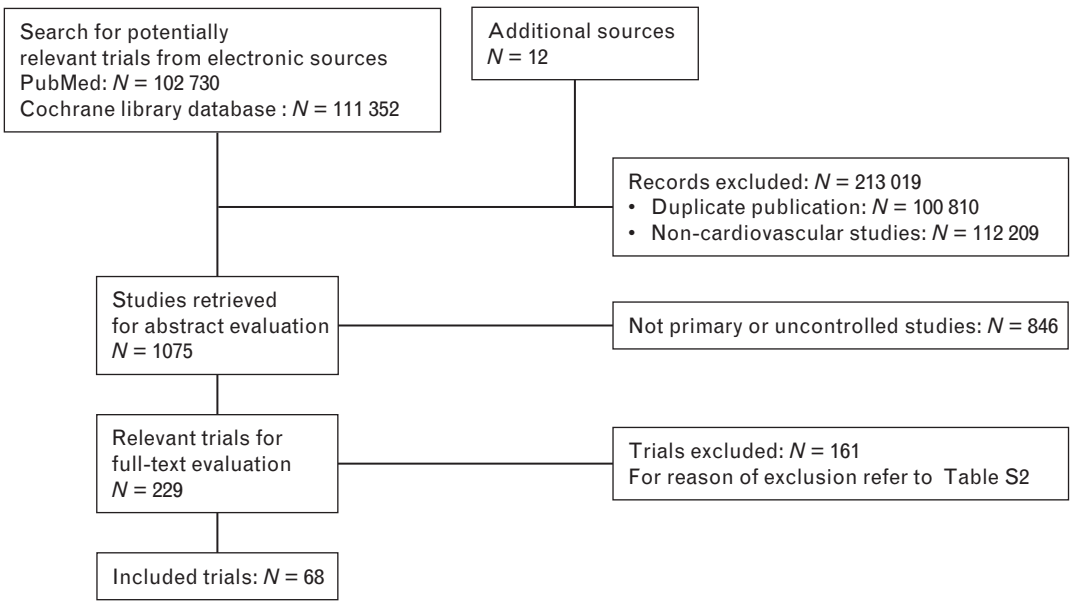

FIGURE 1 Identification process for eligible randomized controlled trials.

TABLE 1. Characteristics of all BP-lowering treatment trials included

Trial acronym	Patient number	Follow-up (years)	Hypertensive patients (%)	SBP/DBP difference (mmHg)	Baseline BP-lowering drugs	Quality assessment score
Intentional, placebo (or no-treatment) controlled trials						
ACTION [9]	7665	4.9	52	−5.4/−3	Yes	5/6
ADVANCE [10]	11140	4.3	>75	−5.6/−4.2	Yes	6/6
AUSTRALIAN-Mild [11]	3427	4.0	100	NR/−5.6	No	5/6
Barraclough [12]	116	2.0	100	NR/−14.4	No	4/6
CAMELOT [13]	1991	2.0	60	−4.9/−3.2	Yes	4/6
CARTER [14]	99	4.0	100	−17/−9	No	4/6
EWPHE [15]	840	4.7	100	−21.7/−8.3	No	4/6
FEVER						6/6
All [16]	9711	3.3	100	−4.7/−2.3	Yes, low	
<153 mmHg [17]	4855	3.3	100	−3.7/−2.2	Yes, low	
HDFP						5/6
All [18]	10940	5.0	100	−10/−5.3	No	
Stratum 90–94 [19]	2043	5.0	100	−10/−7	No	
Stratum 1 [18,19]	7825	5.0	100	−10/−5	No	
Stratum 2–3 [18]	3115	5.0	100	−10/−7	No	
HEP [20]	884	4.4	100	−18/−11	No	4/6
HSCSG [21]	452	2.3	100	−15/−12	No	5/6
Hunan Province [22]	2080	4.7	100	−8.2/−5.3	No	3/6
HYVET pilot [23]	1283	1.1	100	−22.2/−10.9	No	4/6
HYVET [24]	3845	2.1	100	−13.3/−4.9	No	5/6
MRC-mild [25]	17354	5.0	100	−11.5/−6	No	4/6
MRC-old [26]	4396	5.8	100	−14/−7.8	No	4/6
OSLO [27]	785	5	100	−16.7/−9.8	No	4/6
PATS [28]	5665	1.8	84	−5.3/−3.4	No	3/6
PROGRESS [29]	6105	3.9	>48	−9/−4	Yes	5/6
SCOPE [30]	4937	3.7	100	−3.3/−1.7	Yes, low	6/6
SHEP pilot [31]	551	2.8	100	−16.9/−3.9	No	4/6
SHEP [32]	4736	4.5	100	−13/−3.9	No	6/6
Sprackling [33]	120	5.0	100	−16.5/−4.3	No	2/6
STOP [34]	1627	2.1	100	−22.3/−9.5	No	5/6
SystChina [35]	2394	3.0	100	−7.8/−4	No	4/6
SystEur [36]	4695	2.6	100	−8.8/−5.6	No	5/6
TEST [37]	720	2.3	100	−4/−4	No	5/6
TOMHS [38]	902	4.4	100	−6.8/−3.6	No	4/6
USPHS [39]	389	7.0	100	−15.9/−10	No	4/6
VA1 [40]	143	1.5	100	−39.4/−26.9	No	5/6
VA2 [41]	380	3.8	100	−34.4/−18.3	No	5/6
VA-NHLBI [42]	1012	1.5	100	NR/−5.9	No	4/6
Wolff [43]	87	1.4	100	−32.9/−19.8	No	5/6
Intentional, more versus less intense BP-lowering trials						
AASK [44]	1094	4.0	100	−13/−7	Yes	3/6
ABCD-HT [45]	470	5.0	100	−6/−8	No	3/6
ACCORD [46]	4733	4.7	87	−14.2/−6.4	Yes	6/6
BBB [47]	2127	4.9	100	−11/−8	Yes	5/6
Cardio-SIS [48]	1111	2.0	100	−3.8/−1.5	Yes	3/6
Fogari [49]	309	4.0	100	−8.9/−4.6	No	4/6
HOT [50]	18990	3.8	100	−2.8/−3.1	No	5/6
JATOS [51]	4418	2.0	100	−9.6/−3.3	Yes	5/6
MDRD [52]	840	2.2	86	−10.7/−6.9	Yes	3/6
REIN-2 [53]	335	1.6	60	−4/−2	Yes	2/6
SANDS [54]	499	3.0	100	−7/−6	Yes	4/6
SPS-3 [55]	3020	3.7	75	−12.1/NR	Yes	5/6
UKPDS [56]	1148	8.4	100	−10/−5	Yes, low	5/6
VALISH [57]	3260	2.9	100	−5.4/−1.7	Yes	5/6
Nonintentional BP-lowering trials						
ACTIVE-I [58]	9016	4.1	88	−2.9/−1.9	Yes	6/6
AIPRI [59]	583	3.0	82	−10.1/−6.2	Yes	4/6
BENEDICT-A [60]	1204	3.6	57	−2.3/−2	Yes	3/6
DEMAND [61]	380	3.8	44.2	−1.4/−2.0	Yes	3/6
DIABHYCAR [62]	4912	3.9	56	−2/−0.7	Yes	5/6
DIRECT-2 [63]	1905	4.7	62	−3.9/−2	Yes	5/6
DREAM [64]	5269	3.0	43.5	−4.2/−2.4	Yes	5/6
GISSI-AF [65]	1442	1.0	85.4	−3/NR	Yes	3/6

TABLE 1 (*Continued*)

Trial acronym	Patient number	Follow-up (years)	Hypertensive patients (%)	SBP/DBP difference (mmHg)	Baseline BP-lowering drugs	Quality assessment score
HOPE [66]	9297	5.0	46.9	−4.4/−1.7	Yes	5/6
MICROHOPE [67]	3577	4.5	56	−3.3/−1.6	Yes	
IDNT [68]	1715	2.6	100	−3.5/−3	Yes	5/6
IRMA-2 [69]	590	2.0	100	−2/0	No	4/6
I-PRESERVE [70]	4128	4.1	88	−2.6/−2	Yes	6/6
LEWIS [71]	409	3.0	75.5	−2/−2.5	Yes	3/6
NAVIGATOR [72]	9306	6.5	77.5	−3/−2	Yes	6/6
NICOLE [73]	819	3.0	40	−8/−3	No	3/6
ORIENT [74]	577	3.2	93	−4.5/−1	Yes	5/6
PEACE [75]	8290	4.8	45.5	−2/−1.2	Yes	5/6
PROFESS [76]	20332	2.5	74	−4.6/−2.2	Yes	6/6
RENAAL [77]	1513	3.4	93	−2.7/−1	Yes	5/6
ROADMAP [78]	4447	3.2	82	−3/−1.9	Yes	6/6
TRANSCEND [79]	5926	4.7	76.4	−4.6/−2.2	Yes	6/6

In all RCTs in which randomization was to more than two groups, comparisons are between the average of all active treatment groups and placebo [13,25,26,38,60,61,68] or between combination therapy and average of monotherapies [49]. In HOT [50], comparison is between the groups randomized to DBP target less than 80 versus DBP targets less than 85 and less than 90 mmHg together. BP, blood pressure; NR, not reported.

Effects of blood-pressure-lowering treatment on various outcomes in hypertensive individuals

BP differences between treatments were larger in placebo controlled than in more versus less intense BP-lowering trials and nonintentional BP-lowering trials. The risk of each of the seven outcomes was significantly reduced in the first group of trials (Fig. 2a), whereas only risks of stroke, CHD, and heart failure (limited to the nonintentional group) were significantly reduced in the other two groups of BP-lowering trials (Fig. 2b and c). When all intentional BP-lowering trials (primary analysis; Fig. 2d) and all intentional and nonintentional ones (secondary analysis; Fig. 2e) were analyzed together, the risk of all outcomes was significantly reduced. In the primary analysis (Fig. 2d), a standardized lowering of 10 mmHg SBP and 5 mmHg DBP was found to reduce the risk of stroke and heart failure to the greatest

Outcome	Trials (*n*)	Difference SBP/DBP (mmHg)	Events (*n*/patients) Treated	Events (*n*/patients) Controls	RR (95% CI)	Standardized RR (95% CI)	Absolute Risk Reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
(a) Intentional trials vs placebo (or no treatment)								
Stroke	29	−9.3/−4.7	1842/55523	2520/53798	0.70 (0.64–0.76)	0.67 (0.61–0.73)	−17 (−20, −13)	59 (50, 72)
CHD	30	−9.4/−4.7	1949/52876	2218/50730	0.86 (0.80–0.92)	0.84 (0.77–0.91)	−8 (−11, −4)	131 (91, 233)
HF	19	−8.8/−4.2	542/28467	770/27275	0.62 (0.50–0.76)	0.52 (0.39–0.69)	−16 (−19, −10)	63 (51, 94)
Stroke + CHD	29	−9.6/−4.8	3579/52208	4413/50496	0.79 (0.74–0.84)	0.76 (0.70–0.82)	−24 (−29, −17)	42 (34, 56)
Stroke + CHD + HF	22	−9.7/−4.8	3001/39410	3679/38202	0.76 (0.69–0.83)	0.74 (0.66–0.81)	−29 (−37, −21)	35 (27, 48)
CV death	30	−9.3/−4.7	1898/55049	2208/53320	0.84 (0.78–0.90)	0.82 (0.75–0.89)	−9 (−12, −5)	115 (86, 192)
All-cause death	32	−9.3/−4.7	3612/56149	3955/54420	0.90 (0.85–0.95)	0.89 (0.83–0.94)	−9 (−14, −5)	108 (70, 198)
(b) Intentional trials: more vs less active								
Stroke	9	−6.8/−3.8	358/16141	538/22362	0.78 (0.68–0.90)	0.66 (0.53–0.84)	−10 (−14, −5)	98 (74, 203)
CHD	11	−6.7/−3.8	384/16936	458/23148	0.86 (0.76–0.99)	0.81 (0.69–0.99)	−4 (−7, −1)	227 (141, 4246)
HF	5	−11.0/−4.6	116/ 6142	129/ 5767	0.73 (0.48–1.11)	0.76 (0.53–1.09)	−6 (−11, +2)	89 (73, −452)
Stroke + CHD	9	−6.7/−3.8	722/16141	946/22362	0.84 (0.77–0.93)	0.77 (0.67–0.90)	−12 (−17, −5)	85 (60, 192)
Stroke + CHD + HF	4	−11.8/−5.0	478/ 5584	459/ 5214	0.84 (0.67–1.07)	0.86 (0.70–1.06)	−14 (−30, +6)	71 (34, −162)
CV death	12	−7.0/−4.0	324/17279	387/23490	0.95 (0.82–1.11)	0.91 (0.70–1.20)	−2 (−6, +4)	545 (169, −238)
All-cause death	14	−6.9/−3.9	759/18074	888/24276	0.99 (0.90–1.11)	0.98 (0.82–1.20)	−1 (−8, +9)	1057 (120, −103)
(c) Non-intentional trials								
Stroke	16	−3.6/−1.9	2015/44026	2239/43535	0.88 (0.82–0.95)	0.73 (0.61–0.88)	−19 (−26, −9)	54 (38, 116)
CHD	16	−3.5/−1.6	1656/43693	1801/43016	0.90 (0.83–0.98)	0.72 (0.56–0.94)	−14 (−21, −3)	74 (47, 336)
HF	12	−3.6/−1.9	2008/40364	2222/39906	0.88 (0.81–0.96)	0.70 (0.55–0.89)	−19 (−28, −7)	52 (35, 138)
Stroke + CHD	17	−3.6/−1.9	3708/44461	4070/43242	0.89 (0.84–0.93)	0.74 (0.64–0.83)	−31 (−42, −20)	33 (24, 48)
Stroke + CHD + HF	12	−3.6/−1.9	5628/40364	6226/39906	0.89 (0.84–0.94)	0.73 (0.62–0.84)	−51 (−70, −30)	20 (14, 33)
CV death	16	−3.5/−1.9	2355/44053	2371/42831	0.99 (0.90–1.11)	0.98 (0.80–1.25)	−1 (−10, +13)	963 (96, −78)
All-cause death	20	−3.6/−1.9	4414/45826	4402/45019	0.98 (0.94–1.03)	0.95 (0.85–1.08)	−6 (−18, +10)	160 (54, −98)
(d) All intentional trials (vs placebo + more vs less active)								
Stroke	38	−8.4/−4.4	2200/71664	3058/76160	0.71 (0.66–0.77)	0.64 (0.58–0.71)	−17 (−20, −14)	58 (51, 72)
CHD	41	−8.7/−4.4	2333/69812	2676/73878	0.86 (0.81–0.91)	0.84 (0.78–0.90)	−6 (−9, −4)	160 (116, 254)
HF	24	−9.2/−4.3	658/34609	899/33042	0.64 (0.54–0.77)	0.57 (0.46–0.72)	−14 (−17, −9)	73(59, 109)
Stroke + CHD	38	−8.7/−4.4	4301/68349	5359/72858	0.80 (0.76–0.84)	0.76 (0.71–0.81)	−20 (−24, −16)	49 (41, 62)
Stroke + CHD + HF	26	−10.0/−4.8	3479/44994	4138/43416	0.77 (0.71–0.84)	0.75 (0.69–0.83)	−28 (−35, −19)	36 (29, 52)
CV death	42	−8.6/−4.4	2222/72328	2595/76810	0.85 (0.80–0.91)	0.82 (0.76–0.89)	−7 (−9, −4)	141 (106, 228)
All-cause death	46	−8.6/−4.4	4371/74223	4843/78696	0.91 (0.87–0.96)	0.89 (0.84–0.95)	−8 (−12, −4)	125 (87, 274)
(e) All intentional and non-intentional trials								
Stroke	54	−6.6/−3.5	4215/115690	5297/119695	0.76 (0.71–0.81)	0.64 (0.57–0.71)	−19 (−22, −15)	53 (45, 65)
CHD	57	−6.7/−3.4	3989/113505	4477/116894	0.87 (0.84–0.91)	0.80 (0.76–0.86)	−8 (−10, −6)	119 (99, 169)
HF	36	−6.0/−2.9	2666/ 74973	3121/ 72948	0.79 (0.72–0.87)	0.62 (0.51–0.75)	−19 (−24, −13)	53 (42, 79)
Stroke + CHD	55	−6.7/−3.4	8001/112810	9429/116100	0.83 (0.80–0.87)	0.74 (0.70–0.80)	−24 (−29, −19)	40 (35, 52)
Stroke + CHD + HF	38	−6.9/−3.4	9107/ 85358	10364/ 83322	0.83 (0.79–0.87)	0.73 (0.68–0.79)	−39 (−46, −30)	26 (22, 33)
CV death	58	−6.8/−3.4	4577/116381	4966/119641	0.90 (0.85–0.95)	0.84 (0.77–0.92)	−8 (−11, −4)	125 (88, 249)
All-cause death	66	−6.7/−3.5	8785/120049	9245/123715	0.94 (0.91–0.97)	0.90 (0.85–0.95)	−9 (−13, −5)	111 (74, 220)

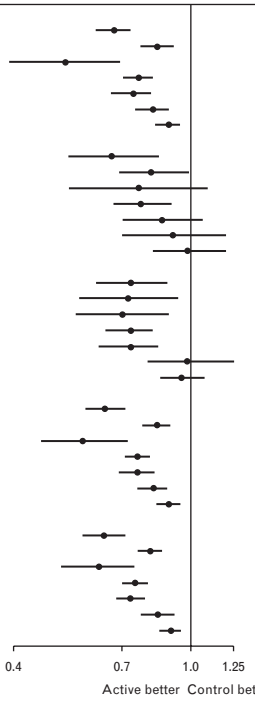

FIGURE 2 Relative and absolute risk reduction of various outcomes in the blood-pressure-lowering trials. Standardized RR is to a SBP/DBP reduction of 10/5 mmHg. The column absolute risk reduction reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with a standardized RR. NNT is the number (and 95% CI) of patients needed to treat for 5 years to prevent one event. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number needed to treat; pts, patients; RR, Mantel–Haenszel risk ratios; vs., versus.

extent (36 and 43%, respectively), and to a lesser extent the risk of CHD, cardiovascular and all-cause mortality (16, 18 and 11%), respectively. In terms of absolute risk, a SBP/DBP lowering of 10/5 mmHg could prevent 17 strokes, 28 cardiovascular events (composite of stroke, CHD, and heart failure), and seven cardiovascular deaths for every 1000 patients treated for 5 years (NNT 58, 36 and 141). Inclusion of nonintentional BP-lowering trials (secondary analysis) did not change the risk reductions substantially (Fig. 2e). A sensitivity analysis of the intentional trials excluding nine in which not all patients were hypertensive [9,10,13,28,29,46,52,53,55] only slightly increased the risk reductions (stroke 37%, CHD 22%, heart failure 46%, cardiovascular death 20%, and all-cause death 12%; Fig. 3). The same was the case for another sensitivity analysis excluding trials with lower quality assessment (score $\leq$3 out of 6) [22,28,33,44,45,48,52,53,60,61,65,71,73] and Syst-China [35] from the meta-analysis of Fig. 2e (online Supplemental Figure S1, http://links.lww.com/HJH/A412). Whenever a fixed-effect model could also be implemented, risk ratios and their significance did not substantially change. For example, for the all intentional BP-lowering trials of Fig. 1d, fixed-effect model risk ratios were 0.86 (0.84–0.91) for CHD, 0.81 (0.78–0.84) for stroke and CHD, 0.86 (0.80–0.91) for cardiovascular death, and 0.92 (0.87–0.96) for all-cause deaths compared with the respective values of 0.86 (0.81–0.97), 0.80 (0.76–0.84), 0.85 (0.80–0.91), and 0.91 (0.87–0.96) for random-effects models.

Relationships of different outcome reductions to the extent of blood pressure reductions

Relationships of different outcome reductions to the extent of blood pressure reductions were investigated by the meta-regression analyses of 47 trials of intentional BP lowering [9–57], that is, those trials specifically designed to explore the effects of BP reduction. The natural logarithm of the risk ratio of stroke was significantly related to the extent of SBP, DBP, and PP reductions, and that of cardiovascular mortality to SBP and PP reductions. For heart failure, relationships with SBP, DBP, and PP reductions fell short of statistical significance, probably because heart failure was reported by fewer trials. Risk ratios of CHD and all-cause mortality did not show significant relationships with any BP reduction (Fig. 4). Risk ratios of the composite outcomes of stroke and CHD, and stroke, CHD, and heart failure both showed significant relationships with all BP reductions. Adjusting meta-regressions of log risk ratios over SBP, DBP, and PP reductions by, respectively, DBP, SBP, and SBP/DBP differences did not change the regression slopes or their statistical significance. Relationships were steeper for stroke and heart failure than for cardiovascular mortality and for DBP than SBP reductions; relationships with PP reductions were intermediate. However, the span of BP reductions was wider for SBP than for DBP and PP (about 40, 25, and 15 mmHg, respectively). When meta-regressions were calculated by using percentage changes in BP, which were similar for SBP, DBP, and PP (maximum reductions of 22, 22, and 25%), regression coefficients were very similar for all types of BP, and stroke risk ratios with maximum achieved SBP, DBP, and PP reductions were, respectively, 0.44, 0.36, and 0.41, and cardiovascular death risk ratios were 0.66, 0.68, and 0.66, respectively (Fig. 5).

The linear relationships of SBP, DBP, and PP reductions with risk ratio logarithms imply risk ratios decreased to a progressively lower extent at progressively larger BP reductions: for example, stroke risk ratio decreased from 0.88 to 0.72 with a 10 mmHg SBP reduction, from 0.72 to 0.58 with a further 10 mmHg SBP reduction (total reduction 20 mmHg), from 0.58 to 0.48 with a further 10 mmHg SBP reduction (total reduction 30 mmHg), and from 0.48 to 0.39 with an additional 10 mmHg SBP reduction (total 40 mmHg).

Publication bias

For this assessment, reference is made to online Supplemental Figure S2 A–G, http://links.lww.com/HJH/A412 and Table S3, http://links.lww.com/HJH/A412. Although graphic representations could not exclude publication bias for stroke and heart failure, significant bias was denied by the trim-and-fill method.

DISCUSSION

This overview was aimed at investigating two clinically relevant questions: the extent of the benefits of BP lowering in hypertensive patients, and whether all benefits are proportional to BP reduction and which reduction (SBP, DBP or PP) plays a major role.

Outcome	Trials (n)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	Standardized RR (95% CI)	Absolute Risk reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
Stroke	31	–9.0/–4.8	1262/51179	1869/56326	0.68 (0.62–0.75)	0.63 (0.56–0.71)	–15 (–18, –12)	67 (57, 84)
CHD	35	–9.0/–4.8	1443/52168	1723/56868	0.82 (0.77–0.88)	0.78 (0.72–0.85)	–8 (–11, –6)	118 (94, 171)
HF	20	–10.6/–4.8	231/21517	415/20605	0.55 (0.46–0.65)	0.54 (0.45–0.64)	–12 (–14, –10)	81 (70, 101)
Stroke + CHD	32	–9.0/–4.8	2632/50705	3471/55848	0.77 (0.73–0.81)	0.75 (0.71–0.79)	–17 (–20, –15)	57 (50, 68)
Stroke + CHD + HF	22	–11.2/–5.4	1969/31902	2536/30979	0.73 (0.68–0.80)	0.74 (0.69–0.81)	–25 (–31, –19)	40 (32, 52)
CV death	33	–9.1/–4.8	1473/51245	1778/56402	0.82 (0.76–0.89)	0.80 (0.73–0.88)	–7 (–10, –5)	134 (100, 221)
All-cause death	37	–9.0/–4.8	2913/53140	3335/58288	0.89 (0.84–0.94)	0.88 (0.82–0.93)	–8 (–12, –5)	124 (83, 212)

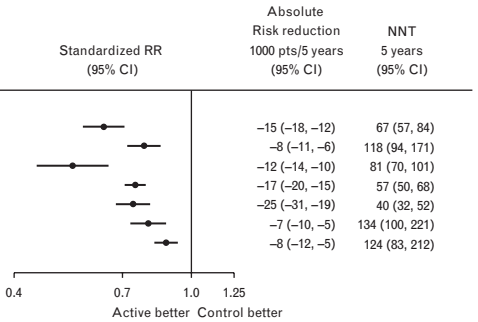

FIGURE 3 Relative and absolute risk reduction of various outcomes in the blood-pressure-lowering trials. Sensitivity analysis including intentional trials exclusively in hypertensive patients.. Standardized RR is to a SBP/DBP reduction of 10/5 mmHg. The column absolute risk reduction reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with a standardized RR. NNT is the numbers (and 95% CI) of patients needed to treat for 5 years to prevent one event. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number needed to treat; pts, patients; RR, Mantel–Haenszel risk ratios.

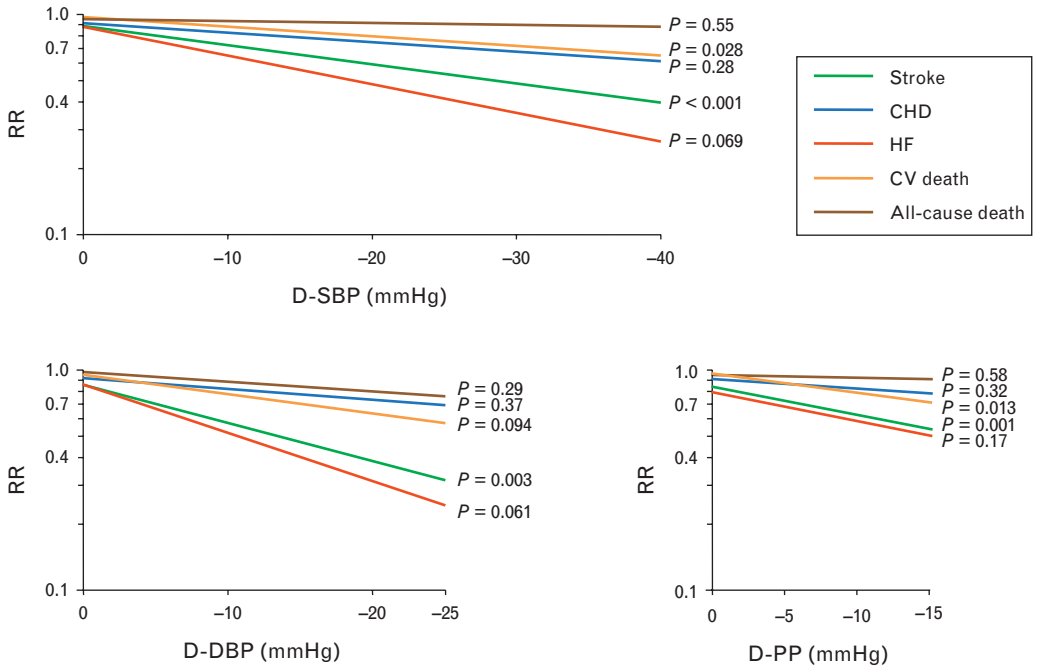

FIGURE 4 Relationships of outcome reductions to the extent of BP reductions. Metaregressions of risk ratios on absolute BP differences (active treatment group minus placebo or less active treatment group) in 47 trials of intentional BP lowering. Regressions relative to stroke are in green; CHD in blue; HF in red; CV death in orange; All-cause death is shown in brown. BP, blood pressure; CHD, coronary heart disease event; CV, cardiovascular; D-DBP, DBP difference; D-PP, pulse pressure difference; D-SBP, SBP difference; HF, heart failure; RR, Mantel–Haenszel risk ratios.

Extent of the benefits of blood-presure-lowering treatment in hypertensive patients

With respect to the two seminal meta-analyses of BP-lowering trials by Collins *et al.* [2,3] (the latter meta-analysis including 17 trials on 47 653 patients), our primary meta-analysis includes 47 trials on 153 825 patients, and our secondary meta-analysis includes 68 trials on 245 885 patients. Despite the much larger number of trials and patients, RR reductions by a standardized 10/5 mmHg

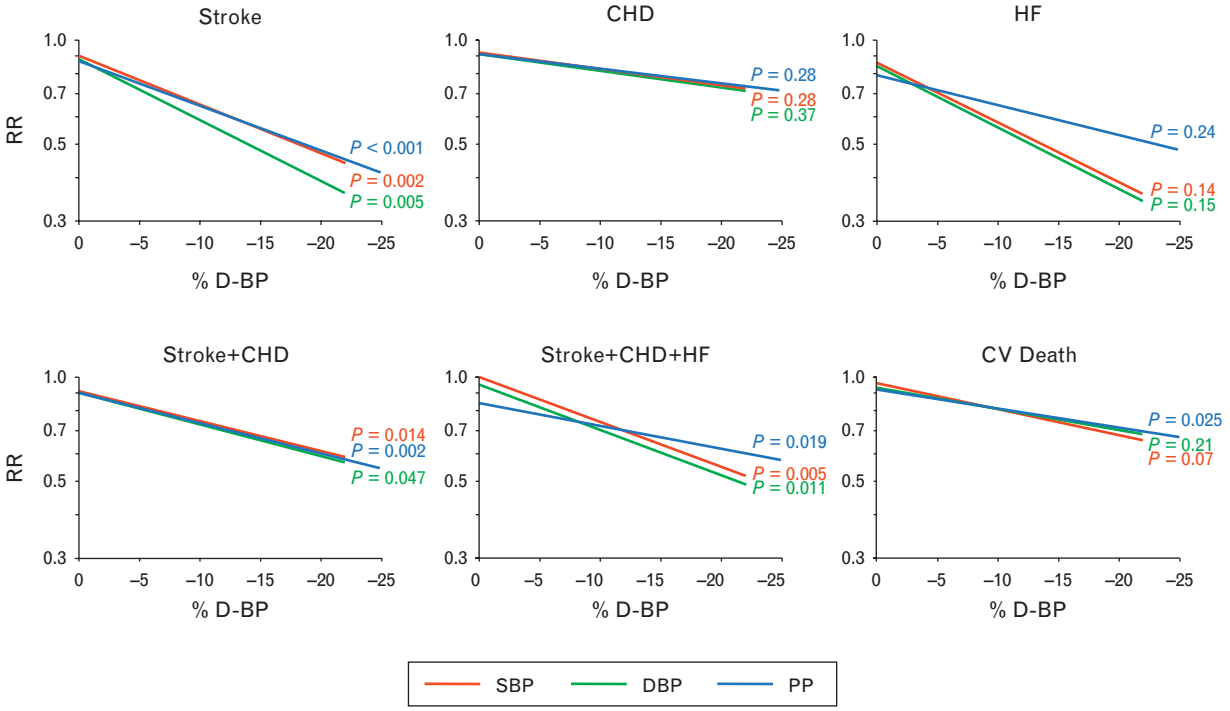

FIGURE 5 Relationships of outcome reductions to percentage BP reductions. The meta-regressions of Fig. 4 are calculated on percentage BP differences (BP differences as percentage of on-treatment BP in the control group). Regressions relative to SBP are in red, those relative to DBP in green, those relative to PP in blue. BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; D-BP, blood pressure difference; HF, heart failure; PP, pulse pressure; RR, Mantel–Haenszel risk ratios.

SBP/DBP difference are remarkably similar in our primary analysis and in the study by Collins and MacMahon [3] (standardized to a 5–6 mmHg DBP difference): 36 versus 38% reduction in stroke, 16 versus 16% reduction in CHD, and 18 versus 21% reduction in cardiovascular death. RR reductions found in our meta-analyses are also rather similar to those reported by Psaty *et al.* [80] in their meta-analysis including 25 trials, but a close comparison is difficult because it is not clear to which BP differences the Psaty *et al.*'s risk ratios refer. With respect to the more recent and comprehensive meta-analysis by Law *et al.* [6] (71 trials), the 68 trials of our overview include 33 trials not considered by Law *et al.* [12,24,30,33,43,44,46,48–55,57–63,65–72,74,76–79], 17 of which published after their overview, and are exclusive of all the trials in patients on conditions other than hypertension or in which less than 40% of hypertensive individuals were enrolled. RR reduction of stroke for a standardized 10/5 mmHg SBP/DBP difference was somewhat lower in our primary and secondary meta-analyses (36 versus 41%) and that of CHD also lower in our meta-analyses (16 and 20% versus 22%), suggesting that inclusion of patients with acute CHD or heart failure may inflate the benefit of BP-lowering treatment, possibly through specific effects of drugs in these conditions.

Our primary meta-analysis (Fig. 1d) confirms that stroke and heart failure were the events most effectively prevented by BP lowering (heart failure to an even larger extent than stroke), but also CHD and cardiovascular and all-cause deaths were significantly prevented though to a smaller extent. For 10/5 mmHg SBP/DBP lowering, 17 strokes were avoided every 1000 hypertensive patients treated for 5 years (this means that 58 patients had to be treated for 5 years to prevent 1 stroke), 28 major cardiovascular events (CHD, heart failure) were avoided (this means that 36 patients had to be treated to prevent one event), whereas seven cardiovascular deaths were avoided (this means that 141 patients had to be treated to prevent one cardiovascular death).

Our secondary meta-analysis, comprehensive of intentional and nonintentional BP-lowering RCTs (Fig. 1e), is entirely consistent with the conclusion of the primary analysis. The greater efficiency of BP lowering in preventing stroke than CHD parallels the well known steeper relationship of BP with stroke than CHD [80] in the observational studies.

Relationships of different outcome reductions to the extent of blood pressure reductions

The relationship between the extent of RR reduction and that of BP reduction has been investigated in the previous meta-regression analyses [4,6,82–84]. However, to our knowledge, ours are not only the most comprehensive ones, but also the first to have searched for a relationship with PP reductions. The finding that PP, often considered a sign of more advanced vascular disease, was not in closer relationship with cardiovascular outcomes may be taken to mean that changes in SBP and DBP values can be used as safe guides to treatment. When BP reductions were expressed as percentages of BP in the control group, regression coefficients were very similar for SBP, DBP, and PP reductions, indicating no preferential relationship of outcome reduction with any BP parameter.

The finding that the relationships of the BP reductions were with the logarithm of the outcome risk ratios adds the important information that progressively greater BP reductions result in progressively lower increments of risk reduction. This parallels the semilogarithmic relation between BP and cardiovascular event rates in the observational studies [81].

Our finding that not all reductons in cardiovascular outcomes have significant relations with BP decreases is not without precedents. The Blood Pressure Lowering Treatment Trialists' Collaboration reported the relationship of SBP reductions with stroke, CHD, and cardiovascular mortality, but not with heart failure [5], but subsequently described a positive relation with heart failure as well [82]. Verdecchia *et al.* [83] also described a positive relation between SBP reduction and both stroke and CHD, but in a subsequent analysis limited to patients with diabetes they confirmed a positive relationship of BP lowering with stroke reduction but not with CHD [84]. The latter meta-regression analyses [84] included trials on nonhypertensive patients with diabetes and studies with quite small between-treatment BP differences, and the overall span of SBP and DBP differences was of only 14 and 8 mmHg, respectively. Our findings are in line with what reported in the above-mentioned meta-regression analysis [84]: our analyses have not been limited to patients with diabetes, have only included trials of intentional BP lowering, and the span of SBP and DBP differences was quite wide (40 and 25 mmHg, respectively).

The reasons why CHD events, though significantly reduced by BP lowering, are not reduced in proportion to the BP reduction remain unclear. The lack of correlation is unlikely because of the confounding caused by wide use of statins or aspirin, because the use of these drugs was quite moderate in most of the intentional trials included in our meta-analysis. The lack of correlation may result from the moderate size of the benefit for CHD (16% reduction) and the limited power of meta-regressions to detect small RR changes, although we could find significant correlations between SBP and PP reductions, and an equally small reduction (17%) in the cardiovascular mortality. An alternative explanation is that the maximum risk reduction of CHD occurs after a small BP reduction, and greater BP reductions cannot further decrease CHD, at variance with what is found with stroke, because the bottom autoregulatory threshold for coronary blood flow in hypertension may be set at a higher level than that of the cerebral blood flow [85].

Strengths and limitations

Our overview and meta-analyses have both strengths and limitations. The major strengths are the number of trials included; the comprehensive inclusion criteria, that is, considering all RCTs that have randomized hypertensive patients to any BP-lowering drug treatment, thus avoiding the biases of strict, but often arbitrary, inclusion criteria; restricting inclusion to the trials predominantly enrolling hypertensive patients, that is, patients for whom antihypertensive therapy is prescribed, and avoiding conditions, such as acute myocardial infarction and heart failure, in which the effects of antihypertensive drugs may be independent

of, and in some cases hindered by BP lowering. The above strengths also apply to our meta-regression analyses.

Our analyses also have limitations. In our primary and secondary meta-analyses, we have not only exclusively included trials enrolling hypertensive patients only, but also a few trials also enrolling nonhypertensive patients, provided the proportion of hypertensive patients was at least 40%. However, in order to follow more stringent criteria, we have done sensitivity analyses including only the 38 trials exclusively on hypertensive individuals, finding similar results. The same was the case when trials with lower quality assessment were excluded.

In the meta-analyses comparing the BP-lowering effects on different types of outcome, we have standardized the risk reductions to a 10/5 mmHg SBP/DBP reduction. Our observation that, at variance with other outcomes, CHD and all-cause mortality do not appear to show a significant continuous relation with SBP and DBP reduction may suggest standardization may have induced some bias. However, in placebo-controlled intentional BP-lowering trials, the BP differences actually occurring were extremely close to those used for standardization (by <1 mmHg), and in the intentional BP-lowering trials comparing more with less intense treatment the SBP/DBP differences were of about 7/4 mmHg, thus minimizing the possible bias of extrapolation.

It should finally be mentioned that meta-regression analyses, though instrumental to investigating the quantitative relationships between risk and intervention, are a less safe tool than traditional meta-analyses aiming at estimating the mean effect of a given intervention. Therefore, the evidence provided here by meta-analyses that CHD can be reduced by BP lowering should be considered stronger than the evidence provided by the meta-regressions that this benefit is not related to the BP-lowering extent.

CONCLUSION

Meta-analyses comprehensive of all BP-lowering trials from 1966 to 2013 but specifically involving hypertensive individuals provide the most precise estimate of antihypertensive treatment benefits, these being not only larger for stroke and heart failure, but also significant for CHD and cardiovascular and all-cause mortality. Absolute risk reductions are also substantial, amounting to the prevention of about 28 major cardiovascular events every 1000 hypertensive patients treated for 5 years. Benefits are proportional to the reduction of SBP, DBP, and PP, but the logarithmic relationship implies risk reduction increases to a progressively smaller extent the larger the BP reduction. The data provided can help the scientific societies and health services in providing recommendations and doctors in taking decisions.

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A.Z. is responsible for the design of the study and preparation of the first draft of the manuscript, A.Z. and C.T. have done the systematic review of the literature and extracted data, C.T. has conducted the meta-analyses, but all three authors (C.T., G.P., and A.Z.) have substantially contributed to interpretation of data, critical revision of the manuscript for important intellectual content, and given final approval of the version to be published. A.Z. and C.T. take responsibility for the integrity of the analyses.

Conflicts of interest

The authors declare no conflicts of interest regarding the overview and meta-analyses, but C.T. declares consultancy fees from Astra Zeneca and lecture honoraria from Sanofi; G.P. declares lecture honoraria from Bayer, Daiichi Sankyo, Guidotti, and Boehringer Ingelheim; and A.Z. declares lecture honoraria from Menarini International, Recordati SpA, and CVRx.

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