Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels – overview and meta-analyses of randomized trials

Costas Thomopoulos[a], Gianfranco Parati[b,c], and Alberto Zanchetti[d,e]

Background: Relevant clinical questions not approached by randomized controlled trials (RCTs) of blood pressure (BP)-lowering treatment can be explored by meta-analyses stratified by clinical criteria.

Objectives: Investigating whether all grades of hypertension benefit from BP-lowering treatment and which are the target BP levels to maximize outcome reduction.

Methods: Of the 68 RCTs of intentional and nonintentional BP-lowering, those without baseline antihypertensive drugs were stratified by the average baseline SBP and DBP (hypertension grades 1, 2, and 3). RCTs with or without baseline treatment were considered for investigating the effects of mean achieved SBP/DBP across three SBP cutoffs and two DBP cutoffs. Risk ratios (RR) and 95% confidence interval (CI) (random-effects model), standardized to 10/5 mmHg SBP/DBP reduction, and absolute risk reductions of seven fatal and nonfatal outcomes were calculated. Differences between relative and absolute risk reductions in the different strata of baseline or achieved SBP/DBP were evaluated by trend or heterogeneity analyses.

Results: In 32 RCTs (104 359 individuals), significant reductions in all outcomes were found independently of the hypertension grade, with no trend toward risk ratio changes with increasing baseline BP. A secondary analysis limited to RCTs on grade 1 hypertension at low-to-moderate risk showed significant outcome reductions [risk ratio: stroke 0.33 (0.11–0.98), coronary events 0.68 (0.48–0.95), and death 0.53 (0.35–0.80)]. In 32 RCTs (128 232 individuals), relative and absolute outcome reductions were significant for the SBP differences across 150 and 140 mmHg cutoffs. Below 130 mmHg, only stroke and all-cause death were significantly reduced. Absolute outcome reduction showed a significant trend to decrease, the lower the SBP cutoff considered. In 29 RCTs (107 665 individuals), outcomes were significantly reduced across DBP cutoffs of 90 and 80 mmHg. After excluding RCTs with baseline DBP less than 90 mmHg, only stroke reduction was significant at achieved DBP less than 80 mmHg.

Conclusion: Meta-analyses favor BP-lowering treatment even in grade 1 hypertension at low-to-moderate risk, and lowering SBP/DBP to less than 140/90 mmHg. Achieving less than 130/80 mmHg appears safe, but only adds further reduction in stroke.

Keywords: blood-pressure-lowering treatment, grade 1 hypertension, hypertension, meta-analysis, randomized controlled trials, target blood pressure

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HF, heart failure; JNC, Joint National Committee; NICE, National Institute for Health and Clinical Excellence; NNT, number needed to treat; RCT, randomized controlled trial; RR, relative risk

INTRODUCTION

We have previously completed an overview and meta-analysis of all the randomized controlled trials (RCTs) of blood pressure (BP) lowering in patients with hypertension, comprehensive of 68 trials on almost 250 000 individuals [1]. However, there are questions, important in medical practice, that have been rarely, if ever, approached by individual trials and meta-analyses. Two such questions are whether all grades (or stages) of hypertension are worth being treated by the BP-lowering drugs, and which are the levels to which BP should be

Journal of Hypertension 2014, 32:000–000

[a]Department of Cardiology, Helena Venizelou Hospital, Athens, Greece, [b]Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Istituto Auxologico Italiano IRCCS, [c]Department of Health Sciences, University of Milan Bicocca, [d]Scientific Direction, Istituto Auxologico Italiano IRCCS and [e]Centro Interuniversitario di Fisiologia Clinica e Ipertensione, University of Milan, Milan, Italy

Correspondence to Alberto Zanchetti, Professor, Direzione Scientifica, Istituto Auxologico Italiano, Via L. Ariosto, 13, I-20145, Milan, Italy. Tel: +39 2 619112237; fax: +39 2 619112901; e-mail: alberto.zanchetti@auxologico.it

Received 7 July 2014 **Revised** 6 August 2014 **Accepted** 7 August 2014

J Hypertens 32:000–000

DOI:10.1097/HJH.0000000000000379

brought to maximize outcome reductions. These questions were specifically raised by a review published in 2009 [2] and underlined by a guideline reappraisal document of the European Society of Hypertension Task Force [3]. More recently, the 2013 European Society of Hypertension (ESH)–European Society of Cardiology (ESC) hypertension guidelines [4] and the 2014 high BP guidelines prepared by the members of the Eighth Joint National Committee (JNC 8) [5] recognized that the trial-based evidence to recommend BP levels for initiation and as a target of treatment is weak.

The meta-analyses reported here have been aimed at approaching the two questions mentioned above.

METHODS

Trial eligibility

These meta-analyses are based on the 68 RCTs found eligible in a preceding overview [1]. Criteria of eligibility were intentional BP lowering comparing active drug treatment with placebo, or less active treatment (intentional BP-lowering trials), or comparison of an active drug with placebo over baseline antihypertensive treatment, resulting in a BP difference of at least 2 mmHg in either SBP or DBP (nonintentional BP-lowering trials); enrolling of hypertensive individuals only or a high proportion (at least 40%) of them. Other inclusion criteria can be found in the preceding paper [1].

Effects of blood pressure lowering treatment on various outcomes in individuals at different levels of high blood pressure

For these meta-analyses, only intentional BP-lowering RCTs in which patients were not receiving antihypertensive drugs or only received low-dose treatment at baseline were considered to define the grade of hypertension to which trials were assigned. Trials were grouped according to the average SBP and DBP values at baseline, in the following hypertension grades (stages in USA style), as defined in ESH–ESC hypertension guidelines [4]: SBP 140–159 mmHg or DBP 90–99 mmHg; SBP 160–179 mmHg or DBP 100–109 mmHg; and SBP at least 180 mmHg or DBP at least 110 mmHg [4].

To avoid limitations inherent in post hoc subgroup analyses, integral data from each trial were entered, unless the subgroup was stratified in the trial design. Other subgroups were entered into the secondary analyses only.

Effects of blood-pressure-lowering treatment to SBP and DBP levels below vs. above predeterminate cutoffs

Both intentional and nonintentional BP-lowering RCTs were considered independently of antihypertensive drugs at baseline, as these did not influence the assessment of effects of achieved BP. Trials were classified into three groups defined by SBP cutoffs (140–149 mmHg vs. ≥150 mmHg; 130–139 mmHg vs. ≥140 mmHg; and <130 mmHg vs. ≥130 mmHg) and two groups defined by DBP cutoffs (<90 mmHg vs. ≥90 mmHg and <80 mmHg vs. ≥80 mmHg). Trials in which SBP or DBP of both treatment arms were on the same side of a given cutoff were excluded. Achieved SBP and DBP values represented the average values throughout the follow-up. Secondary analyses were done by limiting the inclusion to RCTs with achieved SBP within 10 mmHg and DBP within 5 mmHg from each cutoff.

Statistical analyses

Statistical analyses were done according to the methods detailed in a preceding publication [1]. Data used were weighted by the patient number and follow-up duration. Risk ratios (RR) and their 95% confidence interval (CI) were calculated using the Mantel–Haenszel method, standardized to a 10/5 mmHg SBP/DBP difference and illustrated with forest plots. A random-effects model was used for all analyses. Five-year absolute risk reductions of standardized BP lowering and the number of patients needed to treat (NNT) for 5 years were also calculated. A trend analysis tested whether relative or absolute risk reductions had tendency to change progressively in trials with baseline BP values within three different hypertension grades or with achieved SBP values across three different cutoffs. For achieved DBP values (two cutoffs only), Q-statistics was used. All statistical analyses were done by the Comprehensive Meta Analysis version 2 (Biostat, Englewood, New Jersey, USA). Statistical significance was defined as P less than 0.05, but no corrections were made for multiple comparisons.

RESULTS

Trials

Fifty-one trials were found eligible either for assessing BP-lowering effects in different hypertension grades or for assessing the effects of achieving different BP levels [e1–e53, http://links.lww.com/HJH/A413] (Table 1).

Effects of blood-pressure-lowering treatment on various outcomes in trials grouped by baseline blood pressure levels

A total of 32 trials were considered, 29 of which with no baseline treatment (e2–e5, e8–e18, e21–e32, e34, e38, e39) and three with low-dose (e6, e20) or low prevalence treatment (e43). A total of six trials (16 036 individuals) were classified as grade 1, 17 (75 816 individuals) as grade 2, and 9 (12 507 individuals) as grade 3 hypertension (Table 1).

Between-treatment SBP/DBP differences tended to be larger in trials on grade 3 hypertensive patients, and all risk ratios were standardized to 10/5 mmHg SBP/DBP. BP lowering was found to significantly reduce the risk of all outcomes at all hypertension grades, with the exception of heart failure in grade 1 hypertension trials (in which only two trials provided heart failure outcomes, however), and of all-cause mortality in grade 3 hypertension trials. The largest relative reductions were for stroke (27–42%) and heart failure (20–55%), with smaller reductions in coronary heart disease (CHD; 14–17%), cardiovascular mortality (13–22%), and all-cause mortality (7–18%). Risk ratios did not show any significant trend to change with increasing baseline BP levels (Fig. 1).

As some trials were done on low-risk patients, others on higher risk patients, no evaluation of absolute risk reduction was made. However, a secondary analysis was done including trials or trial subgroups with mean baseline SBP/DBP values in grade 1 range and a low-to-moderate risk

TABLE 1. BP-lowering trials included in the analyses based on the baseline or achieved SBP and DBP

Trial acronym	Baseline anti hypertensive drugs	Baseline SBP/DBP (mmHg)	Baseline hypertension grade	Achieved SBP (mmHg)		Achieved DBP (mmHg)	
				Active	Control	Active	Control
Intentional, placebo (or no treatment) controlled BP-lowering trials							
ADVANCE [e1]	Yes	145/81	–	134.7	140.3	–	–
AUSTRALIAN-Mild [e2]	No	158/101	2	–	–	88.4	94.0
Barraclough [e3]	No	–	–	–	–	89.8	104.2
Carter [e4]	No	>160/≥110	3	–	–	–	–
EWPHE [e5]	No	182/101	3	149.6	171.7	86.4	94.7
FEVER							
All [e6]	Yes, low	154/91	2	137.5	142.5	–	–
<153 mmHg [e7]	Yes, low	144/89	1	–	–	–	–
HDFP							
All [e8]	No	159/101	–	–	–	85.7	92.0
Stratum 90–94 [e9]	No	145/92	1	–	–	–	–
Stratum 1 [e9]	No	152/96	1	129.5	139.5	–	–
Stratum 2–3 [e8]	No	177/112	3	135.2	148.9	–	–
HEP [e10]	No	196/96	3	–	–	77.0	88.0
HSCSG [e11]	No	167/100	2	141.0	166.0	88.0	100.0
Hunan province [e12]	No	161/99	2	–	–	85.2	90.6
HYVET pilot [e13]	No	182/100	3	–	–	83.6	94.5
HYVET [e14]	No	173/91	2	144.7	158.0	78.2	83.1
MRC-mild [e15]	No	161/98	2	138.1	149.5	87.0	93.0
MRC-old [e16]	No	185/90	3	–	–	77.7	85.5
OSLO [e17]	No	157/97	1	131.0	148.0	89.2	98.0
PATS [e18]	No	154/97	1	–	–	–	–
PROGRESS [e19]	Yes	147/86	–	133.7	142.7	78.8	82.8
SCOPE [e20]	Yes, low	166/90	2	–	–	79.9	81.6
SHEP-pilot [e21]	No	172/75	2	140.7	157.6	–	–
SHEP [e22]	No	170/77	2	142.5	155.2	–	–
Sprackling [e23]	No	201/107	3	–	–	–	–
STOP [e24]	No	195/109	3	–	–	87.2	96.7
SystChina [e25]	No	170/86	2	–	–	–	–
Syst-Eur [e26]	No	174/86	2	–	–	78.7	84.3
TEST [e27]	No	161/89	2	–	–	–	–
TOMHS [e28]	No	140/91	1	124.2	132.0	78.3	81.9
USPHS [e29]	No	147/99	1	131.5	147.4	88.4	98.4
VA1 [e30]	No	186/121	3	142.6	182.0	–	–
VA-2 [e31]	No	164/104	2	134.9	169.3	86.4	105.0
Wolff [e32]	No	177/109	2	–	–	–	–
Intentional, more vs. less-intense BP-lowering trials							
AASK [e33]	Yes	151/96	–	128.0	141.0	78.0	85.0
ABCD-HT [e34]	No	155/98	1	–	–	78.0	86.0
ACCORD [e35]	Yes	139/76	–	119.2	133.4	–	–
BBB [e36]	Yes	155/95	–	141.0	152.0	83.0	91.0
CARDIO-SIS [e37]	Yes	163/89	–	136.0	140.0	79.2	80.8
Fogari [e38]	No	160/99	2	132.4	141.3	–	–
HOT [e39]	No	170/105	2	139.7	142.5	–	–
JATOS [e40]	Yes	172/89	–	136.0	145.6	–	–
MDRD [e41]	Yes	129/79	–	121.7	132.4	74.6	81.5
SPS-3 [e42]	Yes	143/79	–	125.8	137.9	–	–
UKPDS [e43]	Yes, low	159/94	2	144.0	154.0	–	–
VALISH [e44]	Yes	170/81	–	136.6	142.0	–	–
Nonintentional BP-lowering trials							
AIPRI [e45]	Yes	143/88	–	135.3	145.4	–	–
BENEDICT [e46]	Yes	151/88	–	139.7	142.0	–	–
DREAM [e47]	Yes	136/83	–	127.9	132.1	78.6	81.0
MICROHOPE [e48]	Yes	142/80	–	138.4	142.3	–	–
IDNT [e49]	Yes	159/87	–	–	–	77.0	80.0
Lewis [e50]	Yes	139/86	–	–	–	79.5	82.0
NAVIGATOR [e51]	Yes	140/83	–	–	–	78.0	80.0
PEACE [e52]	Yes	134/78	–	129.6	131.6	–	–
PROFESS [e53]	Yes	144/84	–	–	–	79.2	81.3

In all RCTs in which randomization was to more than two groups, comparisons are between the average of all treatment groups and placebo (e15, e16, e28, e46, e49) or between the average of all treated groups and placebo (e38). In HOT (e39), comparison is between groups randomized to DBP target less than 80 vs. DBP targets less than 85 and less than 90 mmHg together. FEVER less than 153 mmHg (baseline values below median) (e7) and HDFP-stratum 90–94 (baseline values DBP 90–94 mmHg and no cardiovascular disease) (e9) are subgroups not predetermined in the FEVER and HDFP protocols, and used only in secondary analyses. Carter has been classified as grade 3 in the absence of average baseline SBP/DBP, because average DBP on-placebo treatment was 115 mmHg. References to RCT publications [e1–e53] can be found in http://links.lww.com/HJH/A413.References to RCT publications [e1–e53] can be found in http://links.lww.com/HJH/A413. BP, blood pressure.

Outcome	HT grade (stage)	Trials (*n*)	Baseline SBP/DBP (mmHg)	Difference SBP/DBP (mmHg)	Events (*n*/patients) Treated	Events (*n*/patients) Controls	RR (95% CI)	Standardized RR (95% CI)	*P*-value for trend
Stroke	1	4	153/95	–8.7/–5.3	218/7343	312/7321	0.71 (0.60–0.83)	0.64 (0.51–0.78)	0.19
	2	17	165/96	–7.6/–4.3	879/35131	1322/40685	0.68 (0.61–0.77)	0.58 (0.50–0.69)	
	3	8	185/100	–18.1/–8.6	255/6392	376/5995	0.64 (0.54–0.76)	0.73 (0.64–0.82)	
CHD	1	5	151/96	–10.4/–6.3	343/5407	382/4964	0.85 (0.74–0.98)	0.86 (0.76–0.98)	0.82
	2	16	165/95	–7.6/–4.2	720/34091	847/39645	0.85 (0.77–0.94)	0.83 (0.74–0.93)	
	3	8	185/100	–18.1/–8.6	339/6392	455/5995	0.75 (0.64–0.86)	0.83 (0.75–0.91)	
HF	1	2	153/98	–16.4/–9.9	0/599	3/575	0.25 (0.03–2.24)	0.46 (0.14–1.57)	0.12
	2	11	164/89	–9.4/–4.2	159/16176	297/15250	0.50 (0.39–0.65)	0.45 (0.34–0.61)	
	3	4	192/102	–21.8/–10.3	60/1720	100/1774	0.64 (0.47–0.87)	0.80 (0.69–0.93)	
Stroke + CHD	1	3	154/97	–10.8/–4.8	360/4502	451/4497	0.80 (0.70–0.91)	0.83 (0.74–0.92)	0.27
	2	16	165/94	–8.2/–4.4	1562/34091	2080/39645	0.77 (0.72–0.83)	0.71 (0.65–0.79)	
	3	8	184/100	–18.1/–8.6	604/6392	831/5995	0.71 (0.64–0.79)	0.76 (0.70–0.83)	
Stroke + CHD + HF	1	2	153/98	–16.4/–9.9	15/599	24/575	0.61 (0.32–1.15)	0.76 (0.53–1.08)	0.09
	2	12	163/92	–10.2/–4.9	1384/24876	1788/23904	0.70 (0.64–0.77)	0.69 (0.62–0.76)	
	3	6	188/96	–17.4/–8.8	508/3963	665/4047	0.78 (0.66–0.91)	0.86 (0.78–0.94)	
CV death	1	4	153/95	–8.7/–5.3	218/7343	274/7321	0.79 (0.67–0.95)	0.78 (0.65–0.95)	0.48
	2	16	165/94	–8.2/–4.4	889/34091	1085/39645	0.83 (0.75–0.91)	0.79 (0.69–0.89)	
	3	8	184/100	–18.3/–8.7	410/6392	478/5995	0.80 (0.65–0.97)	0.87 (0.74–0.98)	
All-cause death	1	5	153/95	–8.6/–5.4	402/7580	487/7556	0.83 (0.73–0.94)	0.82 (0.72–0.94)	0.24
	2	17	165/95	–8.2/–4.4	1750/35131	2048/40685	0.88 (0.82–0.95)	0.85 (0.77–0.94)	
	3	9	185/100	–18.3/–8.7	774/6452	828/6055	0.91 (0.81–1.02)	0.93 (0.86–1.01)	

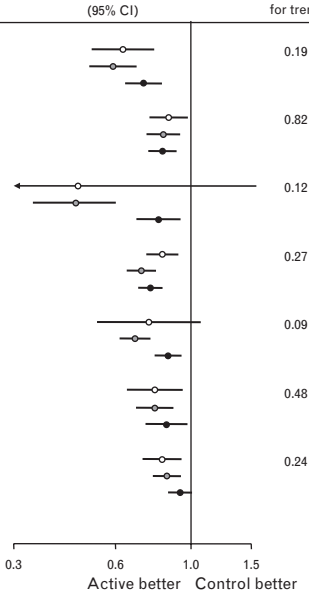

FIGURE 1 Effects of blood pressure lowering in trials stratified by the mean hypertension grade at randomization. . Standardized RR is to a SBP/DBP reduction of 10/5 mmHg; *P*-values for trend refer to the standardized RRs at the different hypertension grades. Mean SBP/DBP at randomization in the three hypertension grade groups were 152.8/95.0, 164.6/94.5, and 184.6/100.3 mmHg. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; HT, hypertension; *n*, number; RR, Mantel–Haenszel risk ratios.

(<5% cardiovascular deaths in 10 years in controls): FEVER stratum with baseline SBP below the median (<153 mmHg) (e7); HDFP stratum with baseline DBP 90–94 mmHg and no cardiovascular disease (e9); OSLO (e17); TOMHS (e28) and USPHS (e29). Risks of stroke, CHD, the composite of stroke and CHD, and all-cause death were significantly reduced by BP lowering in these low-to-moderate risk patients (control group: average cardiovascular mortality 4.5% in 10 years) with a moderate BP elevation (average SBP/DBP 145.5/91 mmHg) at randomization (Fig. 2). Absolute risk reduction was of 34 strokes and CHD every 1000 patients treated for 5 years, and NNT for 5 years was 29.

Effects of blood-pressure-lowering treatment to SBP and DBP levels below vs. above predeterminate cutoffs

In 32 trials, treatment lowered SBP across predeterminate SBP cutoffs, and in 29 trials across predeterminate DBP cutoffs (Table 1). Eight trials (13 841 individuals) (e5, e11, e14, e21, e22, e30, e36, e43), allowed the comparisons of SBP 140–149 mmHg with SBP at least 150 mmHg; sixteen trials (82 421 individuals) (e1, e6, e8, e15, e17, e19, e29, e31, e37–e40, e44–e46, e48), allowed comparisons of SBP 130–139 mmHg with SBP at least 140 mmHg; and eight trials (31 970 individuals) (e9, e28, e33, e35, e41, e42, e47, e52) allowed comparisons of SBP less than 130 mmHg with SBP greater than 130 mmHg. Thirteen trials (41 790 individuals) (e2, e3, e5, e8, e11–e13, e15, e17, e24, e29, e31, e36) allowed comparisons of DBP less than 90 mmHg with DBP at least 90 mmHg; and 16 trials (65 875 individuals) (e10, e14, e16, e19, e20, e26, e28, e33, e34, e37, e41, e47, e49–e51, e53) allowed comparisons of DBP less than 80 mmHg with DBP at least 80 mmHg.

SBP/DBP differences were greater in trials comparing SBP 140–149 mmHg with at least 150 mmHg than in the other two comparisons, and risk reductions were

Outcome	Trials (*n*)	Baseline SBP/DBP (mmHg)	Difference SBP/DBP (mmHg)	Events (*n*/patients) Treated	Events (*n*/patients) Controls	RR (95% CI)	Standardized RR (95% CI)	Standardized RR (95% CI)	Absolute risk reduction 1000 pts/5 years (95%CI)	NNT 5 years (95% CI)
Stroke	4	146/91	–7.1/–4.5	71/4061	110/4012	0.58 (0.34–0.99)	0.33 (0.11–0.98)		–21 (–26, –1)	47 (39, 1301)
CHD	5	145/91	–6.5/–4.2	114/4729	129/4246	0.75 (0.58–0.96)	0.68 (0.48–0.95)		–12 (–18, –2)	86 (55, 531)
Stroke + CHD	4	146/91	–7.1/–4.5	159/4061	227/4012	0.69 (0.57–0.85)	0.51 (0.36–0.75)		–34 (–43, –19)	29 (23, 54)
CV death	4	146/91	–7.1/–4.5	53/4061	74/4012	0.71 (0.50–1.01)	0.57 (0.32–1.02)		–9 (–14, +1)	110 (72, –2223)
All-cause death	4	146/91	–7.1/–4.5	90/4061	133/4012	0.67 (0.51–0.87)	0.53 (0.35–0.80)		–19 (–25, –8)	54 (40, 119)

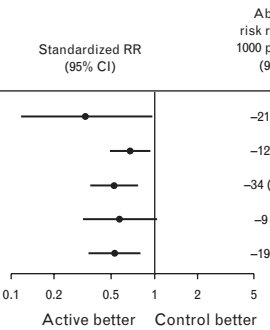

FIGURE 2 Effects of BP lowering in trials with average baseline BP in grade 1 and average low-to-moderate cardiovascular risk. Standardized RR is to a SBP/DBP reduction of 10/5 mmHg; The column 'absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 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. CV death rate in the control group (index of CV risk) was 4.5% over 10 years. BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HT, hypertension; *n*, number; NNT, number needed to treat; pts, patients; RR, Mantel–Haenszel risk ratios.

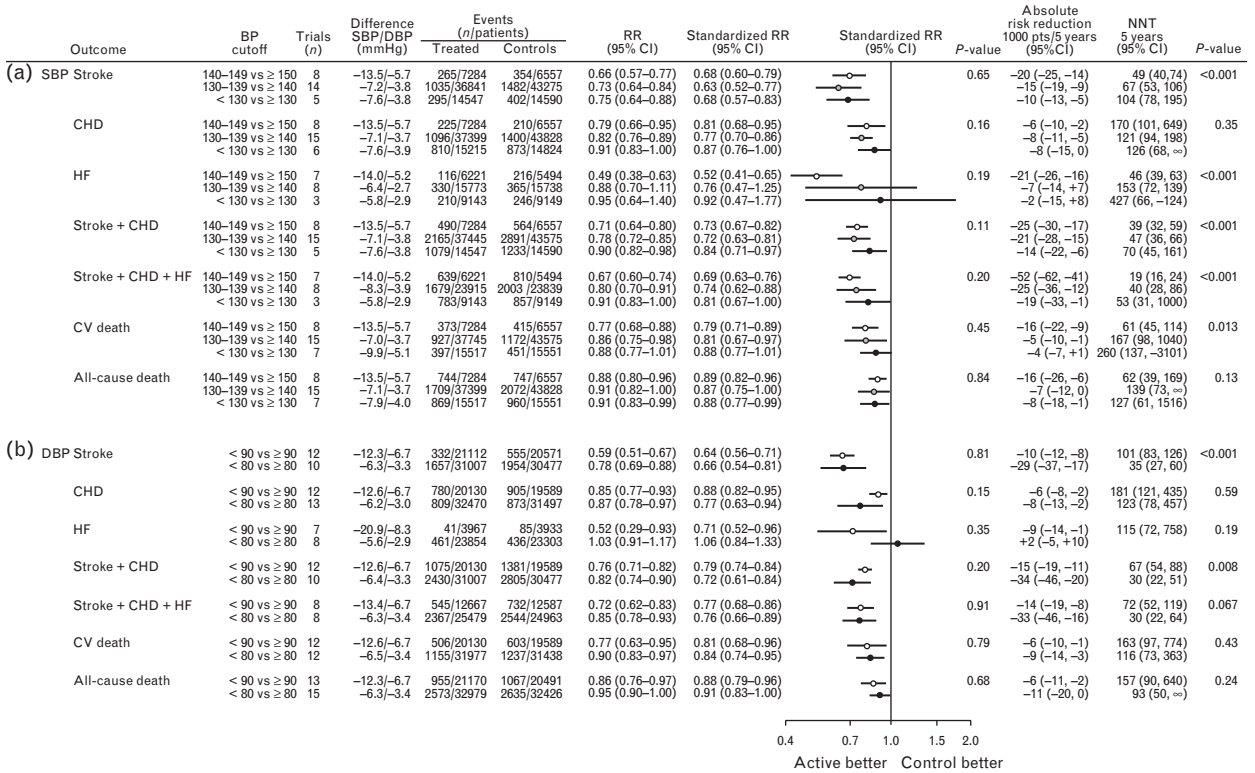

FIGURE 3 Effects of BP lowering in trials with mean on-treatment SBP (a) and DBP (b) below and above different cutoffs. Standardized RR is to a SBP/DBP reduction of 10/5 mmHg. The column 'absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with a standardized RR. NNT is the number (and 95% CI) of patients needed to treat for 5 years to prevent one event. The two columns with *P*-values refer, the first, to standardized RRs and, the second, to absolute risk reductions. For part A (SBP), *P*-values were calculated for trend, whereas for section B (DBP), *P*-values were calculated for the differences between the two cutoffs (*P* for heterogeneity). Mean SBP/DBP achieved on treatment were for SBP cutoffs: cutoff 150, 143.3/76.4 (active) and 157.1/82.2 (control); cutoff 140 137.2/81.1 and 144.3/84.8; cutoff 130, 126.8/78.7 and 136.8/83.7 mmHg. For DBP cutoffs: cutoff 90, 138.1/86.6 and 150.7/93.3; cutoff 80, 138.2/78.6 and 144.6/82.0 mmHg. BP, blood pressure; CHD, coronary heart disease; CI, confidence intervals; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number needed to treat; pts, patients; RR, Mantel–Haenszel risk ratios; vs., versus; y, years.

standardized to a 10/5 mmHg SBP/DBP difference. Relative risk reductions were greater for stroke than for CHD and cardiovascular or all-cause mortality. Reductions were all statistically significant for comparisons across the two higher SBP cutoffs except for heart failure (significant only across the 150 mmHg cutoff). SBP values below 130 mmHg were associated with significant reductions of strokes, but not CHD, heart failure, and cardiovascular mortality (Fig. 3). Trends to a lower relative risk reduction the lower the SBP cutoff were never significant, but trends to lower absolute risk reductions were significant for most outcomes, with absolute reduction of the composite of stroke, CHD, and heart failure decreasing from 52 to 25 and 19 events every 1000 patients treated for 5 years when SBP values less than vs. at least 150 mmHg, less than vs. at least 140 mmHg, and less than vs. at least 130 mmHg were compared (Fig. 3a).

Limiting the analysis to the trials with achieved SBP within 10 mmHg below and above the cutoffs of 150, 140, and 130 mmHg (excluding trials e5, e11, e17, e30, e31, e33, e35) gave similar results, showing that risk reductions, when significant, were really because of BP differences across the selected cutoff (Fig. 4a).

Also in analyses on DBP cutoffs (Fig. 3b), RR reductions standardized to a 10/5 mmHg SBP/DBP difference were greater for stroke than for CHD and cardiovascular or all-cause mortality. Reductions were statistically significant for all comparisons not only across the higher, but also across the lower cutoff, with the exception of heart failure and all-cause death for the lower cutoff. There was no significant difference in the relative risk reductions at different DBP cutoffs, but absolute risk reductions of stroke and composite outcomes including stroke was significantly greater across the lower DBP cutoff because of a higher risk of stroke in these trials. Limiting the analysis to trials with achieved DBP within 5 mmHg across the cutoffs of 90 (e2, e5, e8, e12, e15) and 80 mmHg (e14, e19, e20, e26, e28, e37, e41, e49, e50, e51, e53) gave substantially similar results (Fig. 4b). However, when trials with baseline DBP lower than 90 mmHg (predominantly isolated systolic hypertension) (e19, e26, e37, e41, e47, e49, e50, e51, e53) were excluded from the trials with achieved DBP across the 80 mmHg cutoff, lowering DBP to less than 80 mmHg was associated with significant reductions in stroke [risk ratios 0.77 (0.65–0.90)] and composites outcomes including stroke, but reductions in CHD [risk ratio 0.87 (0.71–1.08)] and cardiovascular [risk ratio 0.89 (0.78–1.00)] and all-cause death [risk ratio 0.91 (0.83–1.01)] were no longer significant (Fig. 5).

DISCUSSION

We investigated two clinically relevant questions: the significance and extent of benefits of BP lowering in hypertensive individuals at different baseline hypertension

	Outcome	BP cut-off	Trials (*n*)	Difference SBP/DBP (mmHg)	Events (*n*/patients) Treated	Events (*n*/patients) Controls	RR (95% CI)	Standardized RR (95% CI)	Standardized RR (95% CI)	*P*-value	Absolute risk reduction 1000 pts/5 years (95%CI)	NNT 5 years (95% CI)	*P*-value
(a) SBP	Stroke	140–149 vs 150–159	5	–12.6/–5.0	204/6562	272/5844	0.64 (0.53–0.76)	0.65 (0.54–0.77)		0.62	–19 (–24, –12)	52 (40, 78)	<0.001
		130–139 vs 140–149	13	–7.0/–3.7	1030/36655	1462/43081	0.75 (0.65–0.85)	0.73 (0.63–0.83)			–11 (–15, –7)	90 (67, 142)	
		120–129 vs 130–139	4	–6.3/–3.3	259/12185	340/12219	0.77 (0.66–0.90)	0.69 (0.55–0.86)			–9 (–14, –4)	106 (74, 231)	
	CHD	140–149 vs 150–159	5	–12.6/–5.0	194/6562	173/5844	0.78 (0.64–0.96)	0.79 (0.65–0.96)		0.12	–6 (–10, –1)	169 (100, 889)	0.37
		130–139 vs 140–149	15	–7.0/–3.7	1089/37213	1395/43634	0.82 (0.76–0.89)	0.77 (0.70–0.86)			–8 (–11, –5)	122 (94, 198)	
		120–129 vs 130–139	5	–6.3/–3.5	684/12853	727/12453	0.92 (0.83–1.01)	0.88 (0.75–1.02)			–7 (–15, +1)	136 (67, –827)	
	Stroke + CHD	140–149 vs 150–159	5	–12.6/–5.0	398/6562	445/5844	0.70 (0.61–0.79)	0.71 (0.62–0.80)		0.24	–24 (–31, –16)	42 (32, 61)	0.26
		130–139 vs 140–149	14	–7.0/–3.7	2153/37559	2866/43381	0.79 (0.72–0.86)	0.73 (0.64–0.84)			–21 (–28, –13)	47 (36, 76)	
		120–129 vs 130–139	4	–6.3/–3.3	917/12185	1055/12219	0.87 (0.80–0.95)	0.81 (0.71–0.92)			–17 (–26, –7)	59 (39, 140)	
	CV death	140–149 vs 150–159	5	–12.6/–5.0	291/6562	299/5844	0.79 (0.68–0.93)	0.80 (0.70–0.93)		0.68	–13 (–19, –5)	77 (52, 215)	0.097
		130–139 vs 140–149	14	–7.0/–3.7	919/37559	1153/43381	0.87 (0.77–0.99)	0.82 (0.69–0.98)			–6 (–9, –1)	176 (103, 1040)	
		120–129 vs 130–139	5	–9.3/–4.5	325/12615	377/12626	0.86 (0.74–1.00)	0.86 (0.74–1.00)			–5 (–9, 0)	216 (117, ∞)	
	All-cause death	140–149 vs 150–159	5	–12.6/–5.0	583/6562	570/5844	0.86 (0.77–0.96)	0.87 (0.78–0.96)		0.29	–16 (–27, –5)	61 (37, 195)	0.22
		130–139 vs 140–149	14	–7.0/–3.7	1699/37213	2051/43634	0.92 (0.83–1.01)	0.89 (0.76–1.01)			–6 (–13, –1)	164 (76, –1785)	
		120–129 vs 130–139	5	–6.4/–3.4	682/12615	773/12626	0.88 (0.80–0.97)	0.81 (0.70–0.95)			–12 (–19, –3)	83 (53, 315)	
(b) DBP	Stroke	85–89 vs 90–94	5	–11.0/–6.0	235/17362	404/17279	0.58 (0.50–0.68)	0.62 (0.55–0.72)		0.93	–9 (–11, –7)	110 (93, 149)	<0.001
		75–79 vs 80–84	8	–5.6/–2.8	1526/28405	1781/27799	0.78 (0.68–0.89)	0.63 (0.49–0.81)			–32 (–42, –17)	31 (24, 57)	
	CHD	85–89 vs 90–94	4	–11.2/–6.0	698/16322	831/16239	0.85 (0.75–0.97)	0.87 (0.78–0.97)		0.30	–7 (–11, –2)	151 (89, 654)	0.99
		75–79 vs 80–84	10	–5.4/–2.4	650/29631	662/28586	0.90 (0.81–1.00)	0.78 (0.61–1.00)			–7 (–11, 0)	149 (87, ∞)	
	Stroke + CHD	85–89 vs 90–94	4	–11.2/–6.0	896/16322	1156/16239	0.77 (0.71–0.84)	0.80 (0.75–0.86)		0.21	–14 (–18, –10)	69 (55, 99)	0.014
		75–79 vs 80–84	8	–5.6/–2.8	2146/28405	2435/27799	0.82 (0.73–0.92)	0.71 (0.58–0.87)			–38 (–52, –18)	26 (19, 55)	
	CV death	85–89 vs 90–94	4	–11.2/–6.0	404/16322	490/16239	0.81 (0.69–0.96)	0.83 (0.72–0.97)		0.92	–5 (–8, –1)	196 (119, 1111)	0.45
		75–79 vs 80–84	9	–5.6/–2.9	945/28835	992/28206	0.91 (0.83–0.99)	0.84 (0.70–0.98)			–8 (–15, –1)	123 (68, 948)	
	All-cause death	85–89 vs 90–94	5	–11.0/–6.0	805/17362	918/17141	0.87 (0.79–0.95)	0.89 (0.81–0.96)		0.86	–6 (–10, –2)	168 (97, 463)	0.25
		75–79 vs 80–84	11	–5.5/–2.9	2162/29600	2183/28961	0.95 (0.90–1.00)	0.90 (0.81–1.00)			–11 (–21, 0)	88 (48, ∞)	

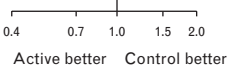

FIGURE 4 Effects of BP lowering in trials with mean on-treatment SBP (a) and DBP (b) below and above different cutoffs. Only trials with SBP within 10 mmHg and DBP with 5 mmHg from cutoffs were included. Data on heart failure not included because only two trials with achieved SBP 120–129 vs. 130–139 or DBP 85–89 vs. 90–94 mmHg reported heart failure as the outcome. 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. The two columns with *P*-values refer, the first, to standardized RRs and, the second, to absolute risk reductions. For part A (SBP), *P*-values were calculated for trend, whereas for section B (DBP), *P*-values were calculated for the differences between the two cutoffs (*P* for heterogeneity). Mean SBP/DBP achieved on treatment were for SBP cutoffs: cutoff 150, 143.0/75.1 (active) and 155.5/80.1 (control); cutoff 140, 137.2/81.0 and 144.1/84.8; and cutoff 130, 127.1/80.1 and 136.3/84.4 mmHg. For DBP cutoffs: cutoff 90, 136.0/86.8 and 147.5/92.8; cutoff 80, 130.9/78.7 and 142.4/81.6 mmHg. BP, blood pressure; 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; y, years.

grades (stages); and the levels to which BP should be brought by drugs to maximize the outcome reductions. The results of these meta-analyses are intended to help decisions in medical practice about the initiation and target of BP-lowering therapy.

Preventive benefits of initiating blood-pressure-lowering treatment in hypertensive patients at different baseline blood pressure levels

Untreated hypertensive patients are usually stratified in hypertension grades (stages) according to the SBP/DBP levels to guide therapeutic decisions [4,6,7]. Trials of antihypertensive therapy were rarely designed by stratifying patients in this way. Some placebo-controlled trials, mostly in the 1970s and 1980s, were focused on the so-called 'mild hypertension (e2, e8, e15, e28, e29), but its definition was different from the current one on grade or stage 1 hypertension [2,3]. A recent Cochrane collaboration meta-analysis [8], limited to individuals in 'mild' hypertension trials matching the BP values defining grade 1 hypertension, had limited power to detect significant risk reductions, although stroke reduction came close to statistical significance. A

Outcome	DBP cut-off	Trials (*n*)	Difference SBP/DBP (mmHg)	Events (*n*/patients) Treated	Events (*n*/patients) Controls	RR (95% CI)	Standardized RR (95% CI)	Standardized RR (95% CI)	*P*-value	Absolute risk reduction 1000 pts/5 years (95%CI)	NNT 5 years (95% CI)	*P*-value
Stroke	< 90 vs ≥ 90	12	–12.3/–6.7	332/21112	555/20751	0.59 (0.51–0.67)	0.64 (0.56–0.71)		0.21	–10 (–12, –8)	101 (83, 126)	0.52
	< 80 vs ≥ 80	4	–10.3/–5.1	271/7012	357/7050	0.77 (0.66–0.90)	0.77 (0.65–0.90)			–13 (–20, –6)	75 (50, 170)	
CHD	< 90 vs ≥ 90	12	–12.6/–6.7	780/20130	905/19589	0.85 (0.77–0.93)	0.88 (0.82–0.95)		0.93	–6 (–8, –2)	181 (121, 435)	0.99
	< 80 vs ≥ 80	6	–10.0/–5.0	264/7917	298/7517	0.87 (0.71–1.08)	0.87 (0.72–1.08)			–6 (–12, +3)	181 (85, –293)	
Stroke + CHD	< 90 vs ≥ 90	12	–12.6/–6.7	1075/20130	1381/19589	0.76 (0.71–0.82)	0.79 (0.74–0.84)		0.66	–15 (–19, –11)	67 (54, 88)	0.77
	< 80 vs ≥ 80	4	–10.3/–5.1	503/7012	629/7050	0.81 (0.73–0.91)	0.82 (0.74–0.91)			–17 (–25, –9)	58 (40, 115)	
CV Death	< 90 vs ≥ 90	12	–12.6/–6.7	506/20130	603/19589	0.77 (0.63–0.95)	0.81 (0.68–0.96)		0.51	–6 (–10, –1)	163 (97, 774)	0.55
	< 80 vs ≥ 80	5	–10.5/–5.2	454/7552	518/7604	0.89 (0.78–1.00)	0.89 (0.78–1.00)			–9 (–17, 0)	113 (57, ∞)	
All-cause Death	< 90 vs ≥ 90	13	–12.3/–6.7	955/21170	1067/20491	0.86 (0.76–0.97)	0.88 (0.79–0.97)		0.71	–6 (–11, –2)	157 (90, 640)	0.27
	< 80 vs ≥ 80	6	–10.1/–5.3	866/7789	953/7837	0.91 (0.83–1.01)	0.91 (0.83–1.01)			–13 (–25, 0)	76 (41, ∞)	

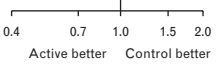

FIGURE 5 Effects of blood pressure lowering in trials with mean on-treatment DBP below and above different cutoffs. Trials with baseline DBP less than 90 mmHg excluded from cutoff less than vs. at least 80 mmHg. Data on heart failure were not included because only two trials with DBP less than 80 vs. at least 80 mmHg reported heart failure as outcome. 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. The two columns with *P*-values refer, the first, to standardized RRs and, the second, to absolute risk reductions (*P*-value for heterogeneity of differences between the two cutoffs). Mean SBP/DBP achieved on treatment were for DBP cutoff 90, 138.1/86.6 (active) and 150.7/93.3 (control); cutoff 80, 147.1/78.5 and 157.6/83.7 mmHg. BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; *n*, number; NNT, number needed to treat; pts, patients; RR, Mantel–Haenszel risk ratios; vs., versus; y, years.

meta-analysis by Czernichow *et al.* [9] of a larger number of trials including individuals at different baseline BP levels showed significant risk reductions at all BP levels, but 'initial'' BP values were from individuals the majority of whom received antihypertensive treatment at the trial beginning, and who were different from the individuals for whom decisions on the initiation of drug treatment are taken. In a meta-analysis in Law *et al.*'s overview [10] and in that by Thompson *et al.* [11], not only most patients stratified by initial BP were under treatment, but also most of those at the lowest BP values were patients with myocardial infarction or heart failure. In both Czernichow *et al.* [9] and Law *et al.*'s meta-analyses [10], risk reductions were separately calculated for SBP and DBP, whereas clinical definition of hypertension grade should be made considering both SBP and DBP. Therefore, major guidelines vary about the recommendations for drug treatment in grade 1 hypertension: drugs are recommended for all patients with SBP/DBP at least 140/90 mmHg in the JNC-7 report [6], only for grade 1 hypertension at high cardiovascular risk in the 2011 National Institute for Health and Clinical Excellence (NICE) guideline [12], only for grade 1 hypertensive individuals after several months of unsuccessful lifestyle measures in the 2013 ESH–ESC guidelines [4] and the 2014 American Society of Hypertension–International Society of Hypertension guidelines [7], and only as an 'expert opinion' in the 2014 report by the members appointed to JNC-8 [5]. Furthermore, there is no information whether relative risk reduction by BP lowering is of similar extent at different levels of untreated BP.

We have considered all BP-lowering trials in which baseline BP was measured in the absence of background antihypertensive treatment, and stratified these trials as grade 1, 2, or 3 hypertension according to the average baseline SBP and DBP values. In this way, we could meta-analyze 6 trials with 16 000 individuals predominantly with grade 1 hypertension, 17 trials with more than 75 000 individuals mostly with grade 2 hypertension, and 9 trials with about 12 500 individuals mostly with grade 3 hypertension. Significant reduction in most type of outcomes, including fatal events, was found at all hypertension grades, with no significant trend for risk ratio changes at different grades. Even when grade 1 trials were limited to those predominantly enrolling individuals at low-to-moderate cardiovascular risk, significant benefits from BP-lowering drugs were found, with a low NNT for 5 years to prevent one major cardiovascular event (NNT = 29).

Effects of blood-pressure-lowering treatment to SBP and DBP levels below vs. above predeterminate cutoffs

The major finding of this set of meta-analyses is that significant risk reductions occurred when SBP was lowered to below any cutoff considered, that is, 150, 140, and 130 mmHg. This suggests that achieving SBP values just below 130 mmHg (average 127 mmHg) is safe. However, whereas bringing SBP below 150 and 140 mmHg significantly reduced all types of cardiovascular events, including mortality, a BP difference across the lowest cutoff of 130 mmHg significantly reduced stroke (32%) and, modestly (12%), all-cause death only. Loss of significance for most outcome reductions in trials with achieved SBP values less than 130 mmHg vs. greater than 130 mmHg is unlikely caused by loss of statistical power, as the group included over 30 000 individuals presenting more than 1500 CHD and 1800 deaths. The finding that bringing SBP just less than 130 mmHg further reduces stroke incidence is in agreement with our previous report [1] that meta-regressions of cardiovascular risk reductions over SBP reductions are steeper for stroke than cardiovascular death, and are nonsignificant for CHD. Relationship of BP reductions to the logarithm of cardiovascular RRs implies benefits of BP reduction increment to a progressively lower extent the larger the BP reduction and the lower the achieved BP. In the present analyses, although there was no significant trend for relative risk reductions to decrease at lower SBP cutoffs, there was a consistent trend to a progressive reduction of absolute risk reduction of most outcomes at lower SBP cutoffs, probably indicating hypertensive patients with SBP values around lower cutoffs are at progressively lower cardiovascular risk, this further contributing to restrict BP-lowering benefits to the outcome most sensitive to the BP intervention.

At variance with what was observed for SBP cutoffs, significant and similar reductions of major outcomes were observed when DBP differences were investigated at cutoffs of 90 and 80 mmHg. This suggests that bringing DBP just below 80 mmHg (an average value of 78.6 mmHg) is safe and may be beneficial: the difference with what we find with SBP cutoffs may be because of the steeper meta-regression of cardiovascular risk reduction for DBP rather than SBP reduction we have previously calculated [1]. However, when trials with baseline DBP already lower than 90 mmHg (predominantly isolated systolic hypertension) were excluded from the meta-analyses, lowering of DBP to less than 80 mmHg was no longer significantly effective on CHD and mortality, and its efficacy was limited mostly to stroke reduction, as was lowering SBP below the lowest cutoff of 130 mmHg.

Strengths and limitations

A major strength of our meta-analyses is having organized them around the questions of interest for the practice of medicine and debated in the recent hypertension guidelines [3–5,7,12]: what are the effects of BP lowering in patients at different grades of BP elevation and, therefore, whether there is evidence in favor of initiating BP-lowering treatment in all patients with SBP/DBP at least 140/90 mmHg; what are the benefits of reducing SBP and DBP at progressively lower levels, and, therefore, what is the evidence about the optimal BP targets to be achieved by BP lowering.

An additional strength is that the meta-analyses are based on the overview of all trials investigating BP-lowering effects on the cardiovascular outcomes of hypertensive patients published over a span of almost 50 years (from 1966 to December 2013). They differ from the Blood Pressure Lowering Treatment Trialists's Collaboration meta-analyses [13–15], which analyze only trials posterior to 1995, and from Law *et al.*'s meta-analyses [10], which also include trials in which antihypertensive drugs were administered in acute myocardial infarction, left ventricular dysfunction and heart failure, and do not include trials

posterior to December 2007. As a result of our extensive overview, each set of meta-analyses addressing either of the major practical questions we have investigated is based on a very large number of trials, individuals, and events: 32 trials, 104 359 individuals, and 5929 deaths for investigating the effects of BP lowering at different grades of hypertension; 32 trials, 127 929 individuals and 7101 deaths, and 29 trials, 107 665 individuals, and 7230 deaths for investigating the effects of achieving different SBP and DBP levels, respectively.

Our analyses have another strength, that of using data from each trial in their integrity, avoiding – except in secondary analyses – the temptation of doing meta-analyses of the subgroups. Individual data meta-analyses not only have attractions as individual patients can be selected with precise criteria, but also have limitations. First, they cannot be done by using on-treatment criteria, such as achieved BP, because randomization is lost, but even when data at randomization are used, such as baseline BP, they are based on a larger number of post hoc decisions than the meta-analyses of integral data, and are restricted to those few trials the individual data of which are available to the investigators. In addition to having preserved randomization, another strength of our analyses is that of having excluded patients under baseline antihypertensive treatment from the groups defined according to the hypertension grade. Background treatment obscures the real levels of baseline BP, and the results of meta-analyses including baseline treated individuals [9,10] cannot be used to decide about treatment initiation.

Our meta-analyses also have limitations. The first one is implicit in our using trial data in their integrity, and grouping trials according to the average SBP/DBP values. If this approach has the advantages mentioned above, it also has the limitations of probably including a number of patients with BP out of the range predetermined for stratifying baseline or achieved BPs. However, this number is unlikely to be large, as within each BP group, the average value was near the middle values of each range: for example, for grade 1 hypertension (SBP 140–159 mmHg, DBP 90–99 mmHg), average SBP/DBP values were about 153/96 mmHg (and for grade 1 low-to-moderate risk 145/91 mmHg), and for on-treatment SBP 130–139 vs. at least 140 mmHg average values were 137.1 vs. 144.2 mmHg. Furthermore, our finding that relative risk reduction has no trend to change between different hypertension grades or targets makes it unlikely that relative risk reduction was significantly different in patients within and outside the BP ranges used for stratification.

An additional limitation is that the necessarily separated analysis of cutoffs of achieved SBP and DBP cannot account for the fact that BP-lowering treatment simultaneously affects SBP and DBP, and indeed the data of Fig. 3 show that across SBP cutoffs the expected differences in SBP were accompanied by DBP differences, and the same occurred across DBP cutoffs, with SBP differences being consistently about twice as large as DBP differences. This is the reason why RRs were standardized to a simultaneous SBP/DBP reduction of 10/5 mmHg. Actually, the three groups of trials across different SBP cutoffs all had DBP across the same cutoff (across 80 mmHg), and the two groups across different DBP cutoffs had SBP across the same cutoff of 140 mmHg.

A final limitation is that the two sets of meta-analyses, though stimulated by the need to answer questions relevant to medical practice, have put together trials that were not intended to investigate these questions, as unfortunately no trial approached these questions in the form these questions are asked nowadays.

CONCLUSION

Our meta-analyses provide data favoring drug treatment even in grade 1 hypertensive individuals at low-to-moderate cardiovascular risk, and indicate lowering SBP to less than 140 mmHg can significantly reduce all types of fatal and nonfatal cardiovascular events, whereas achieving SBP less than 130 mmHg is safe, but can add some further significant reduction in stroke incidence only. On the other hand, reducing DBP to less than 80 mmHg can further and significantly decrease all types of cardiovascular events without the evidence of attenuated benefits, although exclusion of trials with baseline DBP less than 90 mmHg (i.e., trials on predominantly isolated systolic hypertension) reduces the benefits of DBP less than 80 mmHg only to stroke reduction. The results of these meta-analyses provide support to the present opinion-based recommendations [4,5,7] of treating with antihypertensive drugs all patients with SBP/DBP at least 140/90 mmHg, and using a SBP target of less than 140 mmHg, with SBP values just less than 130 mmHg and DBP values just less than 80 mmHg being safe and potentially beneficial particularly regarding stroke. However, meta-analyses are hypothesis-raising instruments, not a body of proof [16], and the conclusions of the present meta-analyses are not the substitute of randomized trials intended to answer the questions they have approached. They can be considered a stimulus to have trials properly designed and conducted, and a support to doctors having to take decisions before trial evidence is obtained.

ACKNOWLEDGEMENTS

The overview and meta-analyses were designed and conducted with the funds made available to Istituto Auxologico Italiano by the current research grants of the Ministry of Health of Italy, and in the context of contract EC 278249 (EU-MASCARA). C.T. was a visiting investigator at the Istituto Auxologico Italiano, Milan, Italy, under a fellowship granted by the Hellenic Society of Cardiology. The valuable help of Mrs Donatella Mihalich for literature searching and manuscript preparation, and that of Mrs Paulina Wijnmaalen for the preparation of illustrations are gratefully acknowledged.

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 the three authors (C.T., G.P., and A.Z.) have substantially contributed to the 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 of 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.

REFERENCES

1. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. *J Hypertens* 2014; 32:000–000.
2. Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical re-appraisal. *J Hypertens* 2009; 27:923–934.
3. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield M, *et al*. Re-appraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; 27:2121–2158.
4. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al*., The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013 ESH/ESC guidelines for the management of arterial hypertension. *J Hypertens* 2013; 31:1281–1357.
5. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al*. 2014 Evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
6. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, *et al*. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206–1252.
7. Weber MA, Schiffrin EL, White B, Mann S, Lindholm L, Kenerson JG, *et al*. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens* 2014; 32:3–15.
8. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. *Cochrane Database Syst Rev* 2012; 8:CD006742.
9. Czernichow S, Zanchetti A, Turnbull F, Barzi F, Ninomiya T, Kengne A-P, *et al*. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. *J Hypertens* 2011; 29:4–16.
10. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *Br Med J* 2009; 338:b1665. doi: 10.1136/bmj.b1665.
11. Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. *JAMA* 2011; 305:913–922.
12. National Institute for Health and Clinical Excellence. Hypertension (CG127): clinical management of primary hypertension in adults. http://www.nice.org.uk/guidance/CG127.
13. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000; 356:1955–1964.
14. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362:1527–1535.
15. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; 165:1410–1419.
16. Zanchetti A. Hypertension meta-analyses: first rank evidence or second hand information? *Nat Rev Cardiol* 2011; 8:249–251.