Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk – overview and meta-analyses of randomized trials

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

Background: Randomized controlled trials (RCTs) of blood pressure (BP) lowering lend themselves to be meta-analyzed to help providing evidence-based recommendations for hypertension treatment.

Objectives: To investigate whether relative or absolute risk reductions increase at increasing levels of baseline cardiovascular risk and whether BP-lowering treatment should be addressed to patients in risk categories promising larger absolute treatment benefits.

Methods: Sixty-eight RCTs of intentional and nonintentional BP lowering were classified in four strata of increasing average 10-year incidence of cardiovascular death in the placebo or less active treatment group: low-to-moderate risk (<5%; 23 RCTs, 81 675 individuals), high risk (5% to <10%; 11 RCTs, 46 162 individuals), very high risk (10% to <20%; 19 RCTs, 91 152 individuals), and very very high risk (≥20%; 16 RCTs, 26 881 individuals). Risk ratios and 95% confidence intervals (CIs; random-effects model) standardized to 10/5 mmHg SBP/DBP reduction, absolute risk reduction, and residual risk of seven major fatal/nonfatal outcomes were calculated. Relative and absolute risk reductions in the cardiovascular risk strata were compared by the trend analysis, residual risk by calculating odds ratio (OR) relative to low-to-moderate risk.

Results: Relative reductions of all outcomes did not differ in the risk strata, but absolute reductions significantly increased with increasing cardiovascular risk (P for trend always <0.002): a 10/5 mmHg SBP/DBP reduction reduced the incidence of major cardiovascular events by 7 (95% CI 3–10), 30 (9–50), 56 (35–76), and 87 (62–112) events every 1000 patients treated 5 years, with increasing cardiovascular risk. However, also residual risk significantly ($P < 0.001$) increased with increasing cardiovascular risk [up to or 9.43 (8.60–10.35) for cardiovascular death]. The increase in residual risk with increasing level of cardiovascular risk persisted when RCTs with average initial age at least 65 years were excluded, and mean ages at the different cardiovascular risk levels were comparable.

Conclusion: BP-lowering treatment induces greater absolute risk reductions the higher the cardiovascular risk level, but a higher risk level is also associated with higher absolute residual risk, independent of age. Whereas reserving antihypertensive treatment to high-risk hypertensive patients maximizes the cost–benefit ratio, only treatment of low-to-moderate risk hypertensive patients may prevent the increasing number of treatment failures when treatment is initiated at higher risk.

Keywords: blood-pressure-lowering treatment, cardiovascular risk, hypertension, meta-analysis, randomized controlled trials, residual risk

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; HF, heart failure; NNT, number needed to treat; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio

INTRODUCTION

In a previous overview [1] we have identified 47 randomized controlled trials (RCTs) on hypertensive patients or in groups of patients with a higher prevalence of hypertension (at least 40%), in which the effects of blood pressure (BP) lowering by drugs were compared with placebo or less active treatments ('intentional' BP-lowering trials). The overview also included 21 additional RCTs, in which an antihypertensive agent was compared to a placebo, both treatments being added on a background of other antihypertensive drugs, in such a way that a BP difference of at least 2 mmHg in either SBP or DBP between the two trial arms occurred ('nonintentional' BP-lowering trials). These 68 RCTs, including about 250 000 patients,

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[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

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provided the database for a first set of meta-analyses quantifying the risk reductions for various types of outcomes produced by BP lowering [1].

A second set of meta-analyses was done in order to approach two questions of great interest in medical practice, namely whether all grades (or stages) of hypertension are worth being treated by BP-lowering drugs, and which are the BP levels to be targeted in order to optimize the effects of antihypertensive treatment. The results of these meta-analyses have been reported in a preceding study [2]. In brief, statistically significant and quantitatively similar reductions of all major outcomes have been found in the trials predominantly involving individuals at all different grades of hypertension. Statistically significant reductions of cardiovascular outcomes could also be found when comparing on-treatment SBP values just below and above progressively lower cutoffs (150, 140, and 130 mmHg); but below the 130 mmHg cutoff, only stroke was significantly reduced. The results of these meta-analyses may help physicians taking decisions about the initiation and targets of antihypertensive treatment.

There is an additional question of practical medical importance that meta-analyses may help to answer, namely whether relative or absolute reductions of the risk of various outcomes are similar or different at different levels of baseline cardiovascular risk and whether BP-lowering treatment should be preferentially addressed to patients in risk categories promising larger absolute treatment benefits. A number of hypertension and cardiovascular prevention guidelines recommend to stratify patients' total cardiovascular risk, at least for prognosis [3,4], and some past and current guidelines [5–8] base their recommendations about the initiation and targets of treatment on the existing level of cardiovascular risk.

The meta-analyses reported in the present article have investigated the influence of four different levels of cardiovascular risk on the extent of the beneficial effects of BP-lowering drug treatment as well as on the extent of the residual risk, that is, the outcome incidence persisting in the actively or more actively treated group despite treatment [9].

METHODS

Trial eligibility and cardiovascular risk estimation

The meta-analyses presented in this article are based on the set of 68 RCTs found eligible as BP-lowering trials in a preceding overview [1], including comparisons of active treatment with placebo, or of more active with less active treatment, initiated in patients either without baseline antihypertensive treatment or with treatment continued from baseline. For the assessment of the influence of cardiovascular risk on risk reduction induced by BP lowering, all 68 trials could be entered into the meta-analyses [e1–e69, http://links.lww.com/HJH/A407]. Subgroups were considered only when stratified in the trial design.

Trials were grouped according to the level of cardiovascular risk calculated as the incidence rate of cardiovascular death in the placebo (or no treatment) control arm or in the arm receiving less intense treatment. According to the suggestions of European Prevention [8] and Hypertension guidelines [3], cardiovascular death rates less than 5% in 10 years were classified in the low-to-moderate cardiovascular risk group, 10-year rates of 5% to less than 10% as high risk, 10-year rates of 10% to less than 20% as very high risk, and 10-year rates of at least 20% were classified in a further group of very very high-risk trials. Original publications of all eligible trials reported the rate of cardiovascular death, except 10 trials (e3, e12, e20, e23, e25–e27, e39, e41, e68), which, however, reported all-cause death rate from which cardiovascular death rate was calculated using a recently published equation derived from the RCTs of antihypertensive therapy [10]. Risk of other outcomes was also calculated as the incidence of each of the considered outcomes or composite of outcomes [stroke, coronary events (coronary heart disease [CHD]), hospitalized heart failures, their composites, and all-cause death] as reported by the original publications for the control groups. Trials with baseline untreated and treated patients were both entered into the primary analyses, but secondary analyses were done including only trials with baseline untreated patients in order to have a more precise assessment of cardiovascular risk in the control group.

Statistical analyses

Statistical analyses were done according to the methods detailed in two preceding papers [1,2]. Risk ratios and their 95% confidence intervals were calculated by the Mantel–Haenszel method using weighted outcome data reported in the original publications. A random-effects model was used. Risk ratios were reported as unadjusted values (i.e., for the SBP/DBP reductions actually obtained in each group of trials) and as values standardized for a SBP/DBP difference of 10/5 mmHg. Five-year absolute risk reductions were calculated for a standardized SBP/DBP reduction of 10/5 mmHg. Absolute residual risk was calculated as the 5-year incidence of any given outcome in the actively treated groups adjusted to a standard SBP/DBP reduction of 10/5 mmHg. For residual risk, odds ratios (ORs) were calculated comparing the various risk categories to the low-to-moderate one. Differences between risk ratios, absolute risk reductions, and residual risks in the four different risk categories were assessed by calculating the *P*-values for trend. For all statistical analyses, a *P*-value less than 0.05 was taken as a limit for significance.

RESULTS

These analyses included 23 trials on 81 675 individuals at an average low-to-moderate cardiovascular risk, 11 on 46 162 individuals at an average high risk, 19 and 16 on 91 152 and 26 881 individuals at an average very high and at an average very very high risk, respectively (Table 1).

Relative and absolute risk reduction by blood-pressure-lowering treatment in hypertensive patients at increasing level of cardiovascular risk

The summary results of these analyses are shown in Fig. 1. As indicated in Table 1 and Fig. 1, the 10-year rates of cardiovascular death in the control groups (placebo or less

TABLE 1. Blood-pressure-lowering trials stratified by increasing level of cardiovascular risk

Trial acronym	Baseline antihypertensive drugs	Baseline SBP/DBP (mmHg)	Achieved SBP (mmHg)		Cardiovascular death (% in 10 years)
			Treated	Controls	Controls
Low-to-moderate risk					
ROADMAP [e1]	Yes	136/81	125.7/74.3	128.7/76.2	0.4
BBB [e2]	Yes	155/95	141.0/83.0	152.0/91.0	0.6
TOMHS [e3]	No	140/91	124.2/78.3	132.0/81.9	1.2
AIPRI [e4]	Yes	143/88	135.3/82.7	145.4/88.9	1.2
VA-NHLBI [e5]	No	NA/93	NA/82.9	NA/88.0	1.3
DREAM [e6]	Yes	136/83	127.9/78.6	132.1/81.0	1.3
SANDS [e7]	Yes	130/75	117.0/67.0	129.0/73.0	1.3
CAMELOT [e8]	Yes	129/78	124.4/75.0	129.3/78.2	1.5
USPHS [e9]	No	147/99	131.5/88.4	147.4/98.4	1.6
JATOS [e10]	Yes	172/89	136.0/73.7	145.6/77.0	1.6
VALISH [e11]	Yes	170/82	136.6/74.8	142.0/76.5	2.3
CARDIO-SIS [e12]	Yes	163/90	136.0/79.2	140.0/80.8	2.3
Australian-Mild [e13]	No	158/101	NA/88.4	NA/94.0	2.6
BENEDICT-A [e14]	Yes	151/88	139.7/81.0	142.0/83.0	2.8
OSLO [e15]	No	156/97	131.0/88.0	148.0/98.0	2.9
MRC-Mild [e16]	No	161/98	138.1/87.0	149.5/93.0	3.3
ORIENT [e17]	Yes	141/74	132.5/73.0	137.0/74.0	3.3
HOT [e18]	No	170/105	139.7/81.1	142.5/84.2	3.7
NAVIGATOR [e19]	Yes	140/83	133.0/78.0	136.0/80.0	3.8
DIRECT-2 [e20]	Yes	132/78	NA/NA	NA/NA	4.0
DEMAND [e21]	Yes	148/87	138.0/80.8	139.5/89.8	4.1
FOGARI [e22]	No	160/99	132.4/82.3	141.3/86.9	4.9
GISSI-AF [e23]	Yes	139/82	134.0/NA	137.0/NA	4.9
All		156/93	135.4/80.7	141.8/84.6	2.8
High risk					
ACCORD [e24]	Yes	139/76	119.2/64.7	131.4/71.1	5.2
NICOLE [e25]	No	172/94	NA/NA	NA/NA	5.6
IRMA-2 [e26]	No	153/90	142.0/83.0	144.0/84.0	6.2
Hunan province [e27]	No	161/99	140.7/85.2	148.9/90.6	6.4
FEVER [e28]	Low	154/91	137.0/82.4	142.2/85.0	6.4
AASK [e29]	Yes	151/96	128.0/78.0	141.0/85.0	7.2
SPS-3 [e30]	Yes	143/79	125.8/NA	137.9/NA	7.3
REIN-2 [e31]	Yes	137/84	130.0/80.0	134.0/82.0	7.6
PEACE [e32]	Yes	134/78	129.6/74.4	131.6/75.6	7.7
ACTION [e33]	Yes	137/80	130.3/76.2	135.7/79.2	7.9
HDFP-stratum 1 [e34, e35]	No	152/96	129.5/84.5	139.5/90.0	8.4
All		145/86	130.8/77.9	137.8/81.6	7.2
Very high risk					
HDFP-stratum 2–3 [e34]	No	177/112	NA/89.0	NA/96.0	10.0
MDRD [e36]	Yes	129/79	121.7/74.6	132.4/81.5	10.1
PROFESS [e37]	Yes	144/84	135.4/79.2	139.6/81.3	10.4
SHEP [e38]	No	170/77	142.5/68.3	155.2/72.2	10.5
ABCD-HT [e39]	No	155/98	132.0/78.0	138.0/86.0	10.7
ADVANCE [e40]	Yes	145/81	134.7/74.8	140.3/77.0	10.7
Lewis [e41]	Yes	139/86	131.0/79.5	133.0/82.0	11.6
Syst-Eur [e42]	No	174/86	151.7/78.7	160.5/84.3	13.5
MRC-old [e43]	No	185/90	153.0/77.7	167.0/85.5	14.1
DIABHYCAR [e44]	Yes	145/82	143.5/81.3	145.0/81.6	15.1
Syst-China [e45]	No	170/86	150.6/81.1	148.5/84.1	15.2
TRANSCEND [e46]	Yes	141/82	134.1/NA	138.7/NA	16.0
HOPE [e47]	Yes	139/79	134.6/76.0	138.1/77.7	16.2
SHEP-pilot [e48]	No	172/75	140.7/67.7	157.6/71.6	16.3
PROGRESS [e49]	Yes	147/86	133.7/78.8	142.7/87.8	16.6
Wolff [e50]	No	177/109	157.1/95.5	190.0/115.0	16.7
SCOPE [e51]	Low	166/90	145.2/79.9	148.5/81.6	16.7
UKPDS [e52]	Low	159/94	144.0/82.0	154.0/87.0	17.7
PATS [e53]	No	154/97	143.4/86.5	148.7/88.9	19.8
All		153/85	139.1/78.3	148.1/81.3	13.6
Very very high risk					
HEP [e54]	No	196/96	162.1/77.0	180.1/88.0	23.9
STOP [e55]	No	195/102	166.0/87.2	188.3/96.7	23.9
I-PRESERVE [e56]	Yes	137/79	133.2/76.9	135.8/78.9	25.0
VA-2 [e57]	No	164/104	134.9/86.4	169.3/105.0	25.8

TABLE 1 (*Continued*)

Trial acronym	Baseline antihypertensive drugs	Baseline SBP/DBP (mmHg)	Achieved SBP (mmHg)		Cardiovascular death (% in 10 years)
			Treated	Controls	Controls
HSCGS [e58]	No	167/100	141.0/88.0	166.0/100.0	28.9
RENAAL [e59]	Yes	153/82	143.5/76.7	146.2/77.7	30.5
HYVET [e60]	No	173/91	144.7/78.2	158.0/83.1	30.7
IDNT [e61]	Yes	159/87	140.5/77.0	144.0/80.0	31.9
Barraclough [e62]	No	NA/110	NA/89.8	NA/104.2	34.5
ACTIVE-I [e63]	Yes	198/82	131.5/78.1	134.3/79.6	35.0
VA-1 [e64]	No	186/121	142.6/91.9	182.0/118.7	38.1
HYVET-pilot [e65]	No	182/100	151.8/83.6	174.0/94.5	40.5
TEST [e66]	No	161/89	157.0/85.0	161.0/89.0	43.7
EWPHE [e67]	No	182/101	149.5/86.4	171.7/94.7	47.0
Sprackling [e68]	No	201/107	150.8/79.6	196.5/103.3	84.0
Carter [e69]	No	NA/NA	NA/106.0	NA/115.0	86.7
All		156/88	140.8/79.6	149.4/83.7	32.6

In all RCTs in which randomization was to more than two groups, comparisons are between the average of all actively treated groups and placebo [e3, e8, e14, e16, e21, e43, e61] or between combination therapy and average of monotherapies [e22]. In HOT [e18], comparison is between groups randomized to DBP target less than 80 vs. DBP targets less than 85 and less than 90 mmHg together. Note the HDFP trial [e34, e35] was split into two predeterminant groups: stratum 1 and stratum 2–3. All e-references (e1–e69) can be found in http://links.lww.com/HJH/A407. NA, not assessable.

intensely treated) groups were within the ranges selected for stratifying risk and roughly doubled at each higher risk level. Figure 1 also shows that 5-year rates of stroke, heart failure, and cardiovascular and all-cause death approximately doubled from each level of risk to the successive one, with the exception of CHD that strongly increased in high-risk patients compared with low-to-moderate risk patients, and did not further increase in very high and very very high risk patients. On treatment SBP/DBP differences were rather similar in the four groups of trials stratified by

Outcome	CV risk	Trials (*n*)	Outcome risk (% in 5 y)	Difference SBP/DBP (mmHg)	Events (*n*/patients) Treated	Events (*n*/patients) Controls	Standardized RR (95% CI)	*P*-value for trend	Absolute risk reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)	*P*-value for trend
Stroke	Low-moderate	17	1.6	–6.3/–3.8	382/34666	599/40495	0.67 (0.53–0.83)	0.91	–5 (–7, –3)	185 (134, 363)	< 0.001
	High	8	4.4	–7.0/–3.6	591/22038	839/22105	0.58 (0.47–0.68)		–18 (–23, –14)	54 (44, 70)	
	Very high	16	9.1	–6.2/–3.0	2429/45153	2917/44285	0.63 (0.52–0.75)		–31 (–39, –22)	32 (25, 46)	
	Very very high	14	10.3	–8.5/–4.4	813/13833	943/12812	0.64 (0.51–0.80)		–34 (–45, –20)	29 (22, 51)	
CHD	Low-moderate	19	1.7	–6.3/–3.9	607/35678	698/41066	0.90 (0.80–1.04)	0.50	–1 (–3, +1)	780 (289,–1440)	0.09
	High	8	6.4	–6.9/–3.5	1183/21387	1263/21266	0.88 (0.76–1.04)		–7 (–14, +1)	135 (68, –815)	
	Very high	16	6.1	–6.2/–2.8	1724/42549	2049/41692	0.67 (0.57–0.76)		–19 (–24, –13)	53 (41, 72)	
	Very very high	15	4.6	–8.5/–4.4	475/13891	467/12870	0.85 (0.65–1.11)		–6 (–16, +5)	166 (64, –194)	
HF	Low-moderate	10	0.9	–5.5/–3.2	143/14214	149/13547	0.82 (0.44–1.57)	0.83	–1 (–5, +5)	806 (186, –203)	< 0.001
	High	4	3.0	–5.6/–2.8	333/15186	427/15213	0.63 (0.49–0.82)		–11 (–15, –5)	92 (67, 187)	
	Very high	11	5.3	–5.8/–2.5	1093/33019	1307/32199	0.60 (0.43–0.86)		–20 (–29, –10)	50 (37, 107)	
	Very very high	11	14.0	–7.9/–4.0	1097/12554	1238/11989	0.57 (0.41–0.82)		–54 (–74, –34)	18 (14, 25)	
Stroke + CHD	Low-moderate	19	3.3	–6.2/–3.8	1001/35609	1297/40706	0.81 (0.73–0.91)	0.15	–6 (–9, –3)	167 (112, 334)	< 0.001
	High	7	10.7	–6.9/–3.6	1732/20998	1988/21065	0.81 (0.71–0.94)		–18 (–30, –6)	56 (33, 157)	
	Very high	15	14.6	–6.3/–3.0	3988/42312	4735/41459	0.67 (0.58–0.77)		–46 (–58, –32)	22 (17, 31)	
	Very very high	15	14.9	–8.5/–4.3	1288/13891	1410/12870	0.71 (0.60–0.84)		–41 (–55, –25)	24 (18, 41)	
Stroke + CHD + HF	Low-moderate	10	4.1	–8.1/–4.3	847/22356	957/21648	0.84 (0.76–0.93)	0.76	–7 (–10, –3)	152 (101, 362)	< 0.001
	High	4	13.2	–5.6/–2.8	1539/15186	1773/15213	0.75 (0.61–0.93)		–30 (–50, –9)	33 (20, 108)	
	Very high	12	19.2	–6.3/–2.8	4376/35202	5033/34412	0.69 (0.57–0.81)		–56 (–76, –35)	18 (13, 28)	
	Very very high	12	30.5	–7.9/–4.0	2345/12614	2601/12049	0.69 (0.59–0.82)		–87 (–112, –62)	11 (9, 16)	
CV death	Low-moderate	19	1.3	–6.2/–3.8	463/35609	508/40706	1.19 (0.86–1.65)	0.69	+3 (–2, +8)		< 0.001
	High	8	3.5	–7.1/–3.6	604/21298	684/21375	0.83 (0.69–0.98)		–6 (–10, –1)	166 (98, 852)	
	Very high	17	6.7	–6.3/–3.1	2022/45583	2276/44690	0.76 (0.68–0.86)		–15 (–20, –9)	64 (49, 109)	
	Very very high	15	16.1	–8.5/–4.4	1488/13891	1498/12870	0.80 (0.64–0.98)		–28 (–54, –3)	32 (19, 312)	
All-cause death	Low-moderate	21	3.0	–6.2/–3.8	1031/36936	1221/42633	1.00 (0.88–1.14)	0.79	0 (–4, +4)		< 0.001
	High	11	6.7	–7.1/–3.7	1318/23135	1439/23027	0.87 (0.76–1.00)		–9 (–17, 0)	114 (59, ∞)	
	Very high	19	12.7	–6.3/–3.1	4075/46027	4246/45125	0.88 (0.79–0.96)		–14 (–26, –5)	67 (39, 198)	
	Very very high	16	24.4	–8.6/–4.4	2361/13951	2340/12930	0.88 (0.77–1.02)		–25 (–54, +4)	40 (18, –204)	

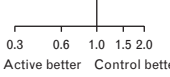

FIGURE 1 Effects of BP lowering in trials stratified by different levels of cardiovascular risk (all trials). The column Outcome risk (% in 5 y) indicates the average incidence of each given outcome in the control group at each stratum of risk. Standardized Mantel–Haenszel risk ratio is to a SBP/DBP 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 Mantel–Haenszel risk ratio. 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 for trend refer, the first, to the standardized Mantel–Haenszel risk ratios and, the second, to absolute risk reductions. Mean SBP/DBP achieved in the actively treated groups were low-to-moderate risk 135.4/80.7 mmHg, high risk 130.8/77.9 mmHg, very high risk 139.1/78.3 mmHg, and very very high risk 140.8/79.6 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; vs., versus; y, years.

low-moderate, high, very high, and very very high risk; but for a more precise comparison, risk reductions were standardized to a 10 mmHg SBP/5 mmHg DBP difference. The relative reduction of the risk of stroke by BP lowering was significant in trials including patients at all levels of risk, whereas the relative risk reduction of CHD only reached statistical significance in the group at very high cardiovascular risk. The risk of heart failure was also significantly reduced at all levels of risk, except the low-to-moderate one in which incidence of heart failure was very low. However, the composite outcomes of stroke and CHD, and of stroke, CHD, and heart failure were significantly reduced at all levels of cardiovascular risk. Risk of cardiovascular death was significantly reduced at all levels of risk except the low-to-moderate one, and all-cause death only at very high risk. For each outcome, there was no significant trend to changes in relative risk reduction, but when absolute risk reduction was calculated, there were significant trends to a progressive increase in absolute risk reduction for all outcomes except CHD with increasing level of cardiovascular risk. Considering the most comprehensive composite outcome (stroke, CHD, and heart failure), 10/5 mmHg SBP/DBP reductions were associated with reductions of 7, 30, 56, and 87 events every 1000 patients treated for 5 years, and the number needed to treat (NNT) for 5 years to prevent 1 event was 152, 33, 18, and 11 at low-to-moderate, high, very high, and very very high levels of risk.

The finding of a uniform relative risk reduction and a progressively increasing absolute risk reduction in trials that included patients at increasing levels of cardiovascular risk was confirmed in a secondary analysis that only considered trials with no or minimal antihypertensive treatment at baseline (e3, e5, e9, e13, e15, e16, e18, e22, e25–e28, e34, e35, e38, e39, e42, e43, e45, e48, e50–e55, e57, e58, e60, e62, e64–e69) (8, 5, 11, and 12 trials at increasing levels of cardiovascular risk, see Table 1), thus allowing a more precise assessment of the cardiovascular risk without the influence of antihypertensive drugs in the control arm of the trials (Fig. 2). Even in these more selected groups of trials, there was no significant trend for relative risk reduction to change with increasing cardiovascular risk category, but absolute event reduction induced by a standardized SBP/DBP reduction of 10/5 mmHg significantly increased with increasing level of risk.

Residual risk after blood-pressure-lowering treatment in hypertensive patients at increasing level of risk

Table 2 shows that, notwithstanding the increasing reduction of absolute risk by BP lowering the higher was the baseline cardiovascular risk, the rates of events occurring in the actively treated groups of patients (residual risk) remained progressively higher the higher was the risk level in the control group (*P* for trend always significant except for borderline significance for CHD). This was true both in analyses including all trials (Table 2a) and in those restricted to trials in which patients were untreated or minimally treated at baseline (Table 2b). Table 2 shows that residual cardiovascular death amounted to 16, 29, 52, and 133 events for each 1000 patients during 5 years in low-to-moderate,

Outcome	CV risk	Trials (*n*)	Outcome risk (% in 5 y)	Difference SBP/DBP (mmHg)	Events (*n*/patients) Treated	Events (*n*/patients) Controls	Standardized RR (95% CI)	*P*-value for trend	Absolute risk reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)	*P*-value for trend
Stroke	Low-moderate	6	1.3	–11.8/–6.1	75/11376	144/11387	0.59 (0.47–0.75)	0.77	–5 (–7, –3)	187 (145, 308)	0.002
	High	3	5.1	–7.1/–3.9	240/9152	346/9203	0.55 (0.41–0.72)		–21 (–27, –14)	48 (37, 70)	
	Very high	10	8.0	–8.8/–4.7	641/16345	867/15379	0.66 (0.58–0.74)		–25 (–30, –20)	40 (33, 51)	
	Very very high	10	15.4	–17.5/–8.3	275/5351	377/4922	0.75 (0.65–0.87)		–31 (–44, –19)	32 (22, 53)	
CHD	Low-moderate	8	3.2	–11.6/–6.0	305/12552	307/12125	0.96 (0.86–1.07)	0.76	–1 (–3, +2)	1117 (317, –642)	0.26
	High	4	5.0	–6.9/–3.8	378/9541	459/9404	0.83 (0.73–0.94)		–8 (–13, –3)	118 (74, 334)	
	Very high	10	5.4	–9.6/–5.0	537/13741	633/12788	0.78 (0.69–0.87)		–12 (–17, –7)	85 (60, 142)	
	Very very high	11	5.5	–17.5/–8.3	151/5409	164/4980	0.93 (0.81–1.08)		–4 (–10, +3)	266 (102, –355)	
HF	Low-moderate	4	0.3	–15.1/–6.2	4/2572	7/2528	0.74 (0.31–1.79)	0.90	–1 (–2, +1)	1085 (438, –1060)	< 0.001
	High	1	0.9	–4.7/–2.3	18/4841	27/4870	0.42 (0.12–1.53)		–2 (–8, +4)	458 (127, –242)	
	Very high	6	4.1	–10.7/–4.7	116/7262	193/6349	0.53 (0.40–0.68)		–17 (–21, –12)	58 (47, 82)	
	Very very high	7	7.8	–18.0/–8.2	82/4072	174/4099	0.65 (0.50–0.84)		–23 (–33, –12)	43 (30, 86)	
Stroke + CHD	Low-moderate	7	3.7	–11.7/–6.1	354/11884	439/11891	0.84 (0.75–0.94)	0.69	–6 (–9, –2)	169 (108, 450)	0.012
	High	3	10.4	–7.1/–3.9	613/9152	800/9203	0.72 (0.62–0.83)		–28 (–38, –17)	36 (26, 58)	
	Very high	9	11.1	–9.7/–4.9	1013/13504	1259/12555	0.72 (0.67–0.80)		–31 (–40, –22)	33 (25, 46)	
	Very very high	11	20.8	–17.5/–8.3	426/5409	541/4980	0.84 (0.77–0.90)		–31 (–43, –21)	32 (23, 47)	
Stroke + CHD + HF	Low-moderate	5	3.7	–11.8/–6.1	354/11272	438/11820	0.83 (0.74–0.93)	0.66	–7 (–10, –3)	151 (99, 366)	< 0.001
	High	1	11.7	–4.7/–2.3	266/4841	377/4870	0.48 (0.35–0.67)		–52 (–67, –36)	19 (15, 28)	
	Very high	7	13.5	–11.5/–5.5	849/9445	1021/8562	0.74 (0.64–0.85)		–34 (–47, –20)	29 (21, 50)	
	Very very high	7	28.7	–18.0/–8.2	411/4072	612/4099	0.78 (0.70–0.87)		–57 (–74, –40)	18 (14, 25)	
CV Death	Low-moderate	7	1.1	–11.8/–6.1	155/11884	170/11891	0.93 (0.77–1.12)	0.81	–1 (–3, +2)	1020 (302, –595)	< 0.001
	High	2	3.5	–7.1/–4.0	195/8744	266/8792	0.69 (0.55–0.86)		–10 (–15, –5)	95 (67, 207)	
	Very high	10	6.3	–8.8/–4.7	742/16345	804/15379	0.84 (0.75–0.92)		–10 (–16, –5)	98 (64, 194)	
	Very very high	11	17.0	–17.5/–8.3	332/5409	425/4980	0.80 (0.72–0.91)		–28 (–41, –15)	36 (24, 68)	
All-cause death	Low-moderate	7	2.6	–11.7/–6.1	292/11884	313/11891	0.95 (0.83–1.08)	0.80	–1 (–4, +2)	769 (226, –481)	0.01
	High	4	4.3	–6.9/–3.8	366/9541	461/9404	0.76 (0.65–0.88)		–13 (–19, –7)	76 (53, 151)	
	Very high	11	10.1	–8.8/–4.7	1403/16582	1445/15612	0.89 (0.83–0.97)		–12 (–19, –4)	81 (53, 283)	
	Very very high	11	23.1	–17.6/–8.3	585/5409	672/4980	0.88 (0.79–0.97)		–29 (–49, –8)	34 (20, 130)	

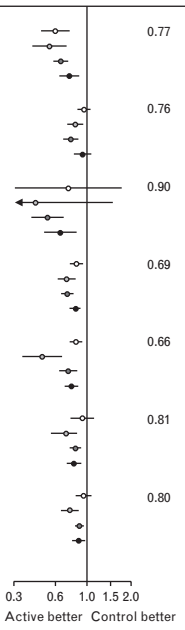

FIGURE 2 Effects of BP lowering in trials stratified by different levels of cardiovascular risk (only trials with untreated or minimally treated patients at baseline). The column Outcome risk (% in 5 y) indicates an average incidence of each given outcome in the control group at each stratum of risk. Standardized Mantel–Haenszel risk ratio 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 Mantel–Haenszel risk ratio. 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 for trend refer, the first, to the standardized Mantel–Haenszel risk ratios and, the second, to absolute risk reductions. Mean SBP/DBP achieved in the actively treated groups were low-to-moderate risk 137.0/86.6 mmHg, high risk 134.4/83.3 mmHg, very high risk 146.7/97.7 mmHg, and very very high risk 151.2/82.6 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; vs., versus; y, years.

TABLE 2. Residual risk in the actively treated groups of trials at different levels of cardiovascular risk

Outcome	Cardiovascular risk	Residual risk 1000 patients/5 years (95% CI)	Odds ratio (95% CI)	*P*-value for trend
a) *All trials*				
Stroke	Low to moderate	11 (9–13)	REF	
	High	28 (23–32)	2.59 (2.29–2.93)	
	Very high	60 (52–69)	5.74 (5.19–6.35)	<0.001
	Very very high	69 (58–83)	6.66 (5.94–7.48)	
CHD	Low to moderate	16 (14–18)	REF	
	High	57 (50–65)	3.71 (3.38–4.10)	
	Very high	42 (37–48)	2.70 (2.46–2.95)	0.09
	Very very high	40 (30–51)	2.56 (2.28–2.88)	
Heart failure	Low to moderate	8 (4–14)	REF	
	High	19 (15–25)	2.40 (1.92–3.00)	
	Very high	33 (24–43)	4.23 (3.47–5.16)	<0.001
	Very very high	86 (66–106)	11.67 (9.56–14.24)	
Stroke and CHD	Low to moderate	27 (24–30)	REF	
	High	89 (77–101)	3.52 (3.26–3.80)	
	Very high	100 (88–114)	4.00 (3.74–4.29)	<0.001
	Very very high	108 (94–124)	4.36 (4.02–4.74)	
Stroke, CHD, and heart failure	Low to moderate	34 (31–38)	REF	
	High	102 (82–123)	3.22 (2.95–3.53)	
	Very high	136 (116–157)	4.47 (4.13–4.84)	<0.001
	Very very high	218 (193–243)	7.92 (7.27–8.63)	
Cardiovascular death	Low to moderate	16 (11–21)	REF	
	High	29 (25–34)	1.84 (1.64–2.05)	
	Very high	52 (47–58)	3.37 (3.09–3.68)	<0.001
	Very very high	133 (107–158)	9.43 (8.60–10.35)	
All-cause death	Low to moderate	30 (26–34)	REF	
	High	58 (50–67)	1.99 (1.84–2.15)	
	Very high	113 (101–122)	4.12 (3.87–4.39)	<0.001
	Very very high	219 (190–248)	9.07 (8.46–9.72)	
b) *Only trials with untreated or minimally treated patients at baseline*				
Stroke	Low to moderate	8 (6–10)	REF	
	High	30 (24–37)	3.83 (3.02–4.87)	
	Very high	55 (50–60)	7.21 (5.81–8.97)	<0.001
	Very very high	123 (110–135)	17.40 (13.91–21.73)	
CHD	Low to moderate	21 (19–24)	REF	
	High	42 (37–47)	2.04 (1.74–2.39)	
	Very high	42 (37–47)	2.04 (1.76–2.38)	<0.05
	Very very high	51 (45–58)	2.50 (2.10–2.99)	
Heart failure	Low to moderate	3 (2–5)	REF	
	High	7 (1–13)	2.34 (1.07–5.15)	
	Very high	24 (20–29)	8.17 (3.94–16.97)	<0.001
	Very very high	55 (45–66)	19.34 (9.37–39.94)	
Stroke and CHD	Low to moderate	31 (28–35)	REF	
	High	76 (66–87)	2.57 (2.26–2.93)	
	Very high	80 (71–89)	2.72 (2.41–3.07)	<0.001
	Very very high	177 (165–187)	6.72 (5.92–7.63)	
Stroke, CHD, and heart failure	Low to moderate	30 (27–34)	REF	
	High	65 (50–81)	2.25 (1.92–2.63)	
	Very high	101 (88–115)	3.63 (3.20–4.12)	<0.001
	Very very high	230 (213–252)	9.66 (8.50–10.98)	
Cardiovascular death	Low to moderate	13 (11–16)	REF	
	High	25 (20–30)	1.95 (1.58–2.40)	
	Very high	53 (47–58)	4.24 (3.57–5.05)	<0.001
	Very very high	142 (129–155)	12.25 (10.26–14.64)	
All-cause death	Low to moderate	25 (22–28)	REF	
	High	43 (37–49)	1.75 (1.50–2.04)	
	Very high	101 (94–109)	4.38 (3.86–4.97)	<0.001
	Very very high	231 (211–252)	11.72 (10.26–13.37)	

Residual risk is expressed as the number of incident outcomes in the actively or more actively treated groups adjusted to a 5-year period, as expressed per 1000 treated patients. Odds ratios are referred to the low-to-moderate cardiovascular risk stratum. *P*-values for trend indicate the significance of increasing odds ratios with increasing level of risk. All trials includes all the trials listed in Table 1. Only trials with untreated or minimally treated patients at baseline includes only trials with baseline antihypertensive drugs no or low in Table 1. CHD, coronary heart disease; CI, confidence interval.

high, very high, and very very high risk groups, with ORs of 1.84, 3.37, and 9.43 with respect to the low-to-moderate risk group, and Fig. 3 illustrates that for all the outcomes, the increase in absolute risk reduction with increasing risk category was paralleled and outnumbered by an increase in the residual risk.

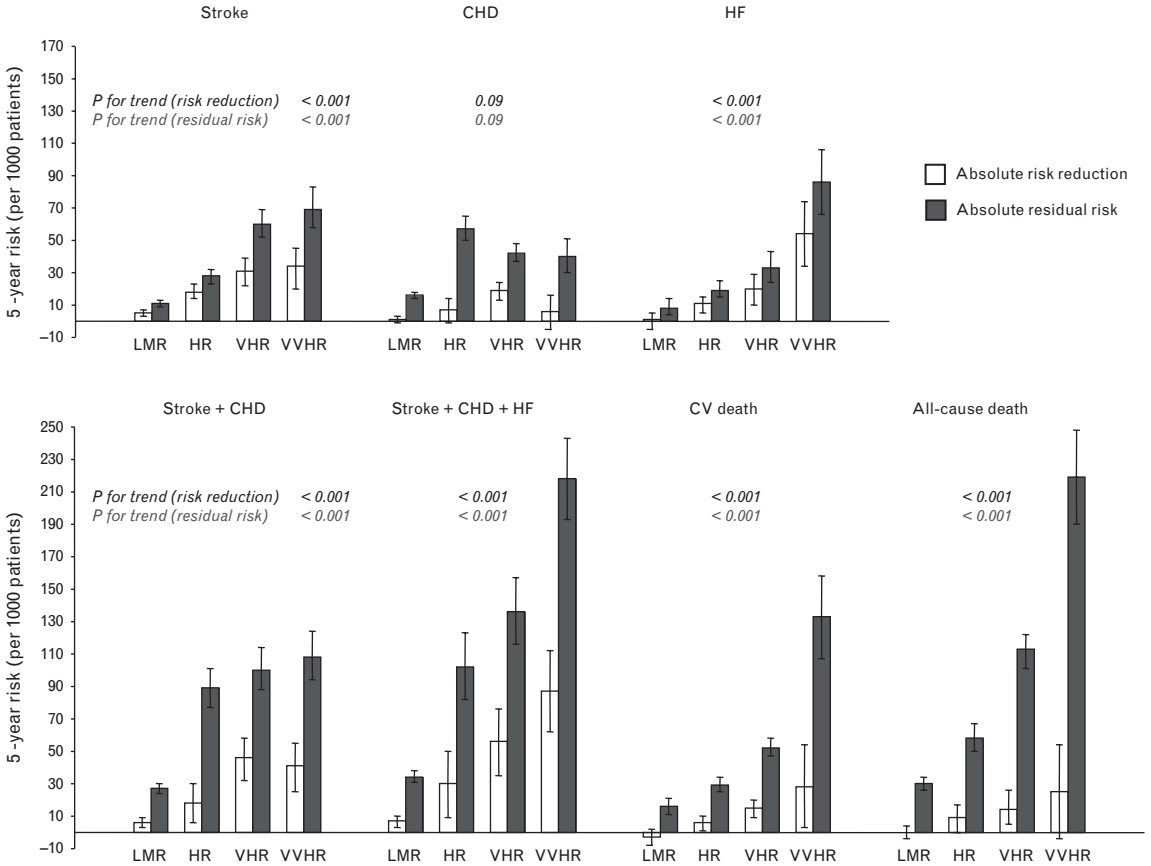

FIGURE 3 Absolute risk reduction by blood-pressure-lowering treatment (standardized to 10/5 mmHg SBP/DBP) and residual risk in the trials stratified by increased level of cardiovascular risk in the control group. Absolute risk reductions (empty rectangles) and residual risk (shaded rectangles) are expressed as the number of events prevented or residual every 1000 patients treated for 5 years. Vertical bars are 95% confidence intervals. It is apparent that both benefits (risk reduction) and failures (residual risk) progressively increase with the increasing level of risk, but residual risk, particularly of mortality, increases more markedly. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; LMR, low-to-moderate risk; HR, high risk; VHR, very high risk; VVHR, very very high risk; y, years.

In the two higher strata of cardiovascular risk, baseline BP values were higher than in high-risk strata, but not in low-to-moderate risk strata (Table 1). Furthermore, BP lowering brought SBP below the recommended target of 140 mmHg [3,4,7,11] in the first three risk strata (135.4, 130.8, and 139.1 mmHg), and just above it (140.8 mmHg) in the highest risk stratum. However, standardization of the SBP reduction to 10 mmHg (instead of the actual 8.5 mmHg) means that also in the highest risk group, the effect of BP lowering was calculated to a value below the recommended target of 140 mmHg. In all four risk groups, achieved DBP was well below the recommended target of 90 mmHg [3,4,7,11] (80.7, 77.9, 78.3 and 79.6 mmHg). This indicates that the high residual risk in patients at higher levels of cardiovascular risk cannot be ascribed to BP lowering failing to achieve the recommended targets.

In the two higher strata of cardiovascular risk, mean age at baseline was higher than in the low-to-moderate and high-risk groups (59.1, 59.9, 65.9, and 71.3 years from low-to-moderate to very very high risk). In order to exclude that the increasing level of residual cardiovascular risk with increasing levels of overall risk was because of older age, a secondary analysis was done after excluding RCTs with mean age at baseline at least 65 years. This secondary analysis included 19 RCTs [e1–e9, e13–e22, http://links.lww.com/HJH/A407] and 41 444 individuals of mean age 57.1 years in the low-to-moderate risk stratum; 11 RCTS [e24–e34, http://links.lww.com/HJH/A407] and 46 162 individuals of mean age 59.9 years in the high-risk stratum; 9 RCTs [e34, e36, e39, e41, e44, e49, e50, e52, e53, http://links.lww.com/HJH/A407] and 22 748 individuals of mean age 59.9 in the very high risk stratum; and 6 RCTs [e57–e59, e61, e62, e64, http://links.lww.com/HJH/A407] and 32 078 individuals of mean age 58.3 years in the very very high risk stratum. Figure 4 illustrates that the pattern of increasing reductions in the absolute risk associated with an even greater progressive increase of residual risk at increasing level of overall cardiovascular risk was also found when mean ages were similar in the four risk strata, thus showing that increasing residual risk was not because of increasing age.

DISCUSSION

It is often assumed that BP-lowering treatment produces a larger absolute reduction of cardiovascular outcomes in hypertensive patients at higher cardiovascular risk, but this assumption has rarely been tested in a systematic overview and meta-analysis. Law *et al.* [12] have shown that relative risk reduction of coronary events and stroke was similar in patients with previous coronary or cerebrovascular disease events, and in patients without a history of cardiovascular

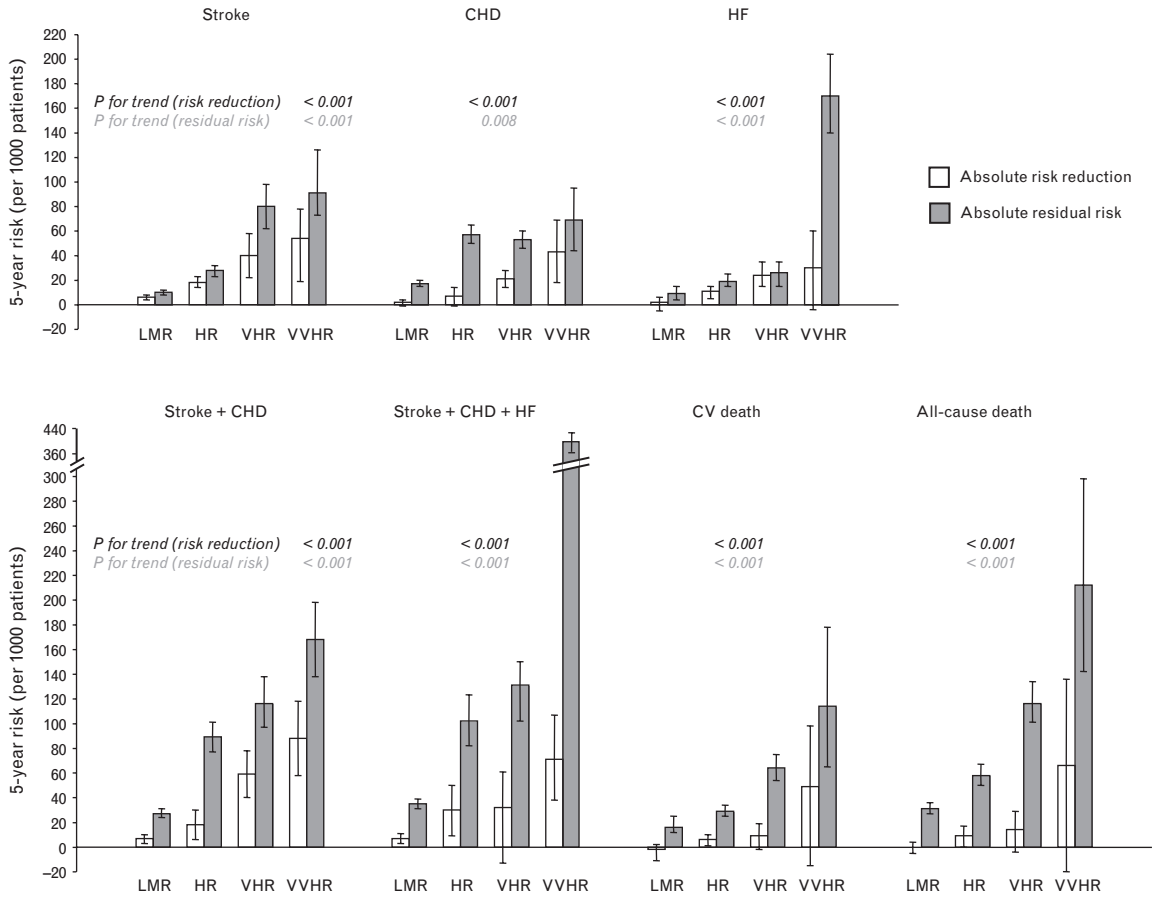

FIGURE 4 Absolute risk reduction by blood-pressure-lowering treatment (standardized to 10/5 mmHg SBP/DBP) and residual risk in trials stratified by increased level of cardiovascular risk in the control group, after exclusion of trials with mean age at baseline at least 65 years. Absolute risk reductions (empty rectangles) and residual risk (shaded rectangles) are expressed as the number of events prevented or residual every 1000 patients treated for 5 years. Vertical bars are 95% confidence intervals. It is apparent that both benefits (risk reduction) and failures (residual risk) progressively increase with increasing level of risk, despite similar mean age in the four risk levels (57.1, 59.9, 59.9, and 58.3 years). CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; LMR, low-to-moderate risk; HR, high risk; VHR, very high risk; VVHR, very very high risk; y, years.

disease, but the latter group in Law *et al.*'s meta-analyses assembled the trials investigating patients at quite different levels of cardiovascular risk. In parallel with our meta-analysis, the BP-Lowering Treatment Trialists' Collaboration has also explored the influence of different levels of baseline cardiovascular risk (calculated by a risk equation) on the relative and absolute risk reduction in 11 RCTs of antihypertensive treatment, in which individual data were available to the collaboration (51 917 patients; 4167 major cardiovascular events), reporting similar relative risk reductions but increasing absolute risk reductions with increasing baseline cardiovascular risk [13].

By calculating the average cardiovascular risk in each trial on the basis of incidence of cardiovascular death in the group of the placebo-treated or less-actively treated patients, and stratifying the trials in four categories of increasing cardiovascular risk, we have been able to include in our meta-analysis all BP-lowering trials carried out between 1966 and 2013 (68 trials; 245 885 individuals; 17 439 strokes and coronary events), and to show that a standardized SBP/DBP lowering of 10/5 mmHg has indeed no significantly different relative effect (for each outcome) in patients at different levels of cardiovascular risk, and therefore it has increasingly larger absolute effects the higher is the initial risk. This translates, for example, into the need to treat for 5 years only 11 patients at very very high risk for avoiding one cardiovascular event compared to 152 patients at low-to-moderate risk. This finding is obviously important not only for designing antihypertensive treatment trials, but also for cost-effectiveness analyses and public health decisions.

However, any enthusiasm for basing antihypertensive treatment decisions only on risk stratification should be tempered by another important finding of our analyses, namely that, despite the greater absolute reduction in risk at the highest level of initial risk, the risk level that is found after BP lowering (residual risk) remains much higher (almost 10 times higher for cardiovascular death) when treatment is initiated at the highest rather than at the lowest stratum of cardiovascular risk. This means that, if the success of BP lowering is measured only by the absolute reduction in outcomes it achieves, BP lowering is obviously most successful when initiated in the highest risk category, for example, 87 instead of seven major cardiovascular events can be prevented by treating 1000 patients for 5 years. However, if the success is measured by the absolute level to which risk can be brought by treatment (residual risk), it is undoubted that the greatest success of BP

lowering is achieved in the low-to-moderate risk patients, that is, before some irreversible or scarcely reversible organ damage occurs (only 34 instead of 218 major cardiovascular events occurring in 1000 patients treated for 5 years). This confirms in a more systematic and quantitatively more precise way what had been described by one of us in a previous survey of antihypertensive trials without meta-analysis [9].

Strengths and limitations

The meta-analyses presented here have their own strengths and limitations. Some of the major strengths are those underlined when discussing two previous sets of meta-analyses [1,2] using the same database. The comprehensive attempt to include all trials of BP lowering in hypertensive patients has allowed us to meta-analyze as many as 23, 11, 19, and 16 trials on hypertensive patients at four different average levels of cardiovascular risk. Cardiovascular risk has been classified on the base of the incidence of the hardest type of cardiovascular outcome, cardiovascular death, in the control (placebo or less actively treated) groups. Stratification has been done by using the arbitrary cutoffs suggested in European prevention [8] and hypertension guidelines [3], adding a very very high risk stratum in order to better assess the effects of a continuous increase of risk.

The greatest strength of our analyses is, in our opinion, that of having investigated not only the effects of increasing cardiovascular risk on risk reduction by BP lowering (i.e., the benefits), but, in parallel, also the effects of increasing cardiovascular risk on the residual level of risk (i.e., the failures). This has never been done before, except in a preliminary review of one of us [9], showing that BP lowering in trials on high-risk patients could seldom reduce cardiovascular risk below the threshold defining high risk. Therefore, our meta-analyses are the only ones providing quantitative data from the largest available trial database on the benefits and, at the same time, the failures of BP lowering in hypertensive patients at different levels of risk. We have also shown that the progressive increase of residual risk the higher is baseline risk is not due to older age, as the progressive increase in residual risk could be seen also after exclusion of RCTs in the elderly, when mean ages were comparable in all risk strata.

Our meta-analyses also have limitations. The first one is that trials have necessarily been stratified according to the average level of risk (cardiovascular death rate) in the control group. Obviously, not all patients were at the same level of risk, and it is known that within a given group, events more commonly occur in higher risk individuals. It is unlikely, however, that this may have altered substantially the conclusions of our meta-analysis: first, because average cardiovascular risk in a trial is mostly dependent on inclusion and exclusion criteria for enrolment and therefore risk does not vary too widely within the patients of an individual trial; second, because the continuous relationship between increasing risk and benefits and failures of BP-lowering treatment makes it unlikely that differences between using average rather than individual risk values are relevant.

The fact that trials including patients at very high and very very high risk achieved SBP (but not DBP) slightly higher than in trials in patients at low-to-moderate and high risk may be considered another limitation, but the differences were small and SBP/DBP achieved in trials in highest risk patients were anyway below or very close to the targets recommended by all guidelines [3,4,7,11]. However, that SBP can be consistently reduced in hypertensive patients at the highest level of risk to the same low levels as in lower risk patients remains to be demonstrated, and contrasts with the well known evidence that worldwide control of BP below the recommended values of 140/90 mmHg is less successful than desirable [14] and among high-risk patients treatment resistant hypertension is frequent [15].

Finally, all meta-analyses are known to have limitations [16], and are not substitutes of well designed trials. However, comparison of benefits and failures of BP lowering in hypertensive patients at different levels of cardiovascular risk is a problem of importance for medical practice that can better be solved by a large comprehensive meta-analysis than by a single trial.

CONCLUSION

Our meta-analyses show that BP-lowering treatment produces greater absolute risk reductions the higher is the level of cardiovascular risk, but a higher level of risk is also associated with a higher absolute residual risk, measuring the failure of BP-lowering treatment. Both absolute benefits and failures should be considered by experts writing guidelines, health providers, and doctors taking individual decisions. As cardiovascular disease can be seen as a continuum of increasing risk [17–19], that is a continuum of increasing benefits but also of increasing failures of treatment, the results of the present meta-analyses support expert opinion of recent hypertension guidelines [3,4,11] favoring SBP/DBP below 140/90 mmHg in all individuals with SBP at least 140/90 mmHg: in a preceding meta-analysis [2] we have shown that even in grade 1, low-to-moderate risk hypertensive individuals benefits are significant, and the present meta-analysis adds the evidence that treating these individuals with BP-lowering drugs prevents an increasing number of treatment failures if, with time, the risk of the untreated hypertensive patient unavoidably increases.

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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 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.

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