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

Sébastien Czernichow[a,b], Alberto Zanchetti[c], Fiona Turnbull[a], Federica Barzi[a], Toshiaru Ninomiya[a], André-Pascal Kengne[a], Hiddo J. Lambers Heerspink[d], Vlado Perkovic[a], Rachel Huxley[a], Hisatomi Arima[a], Anushka Patel[a], John Chalmers[a], Mark Woodward[a], Stephen MacMahon[a] and Bruce Neal[a], on behalf of the Blood Pressure Lowering Treatment Trialists' Collaboration

Background **The benefits of reducing blood pressure are well established, but there remains uncertainty about whether the magnitude of the effect varies with the initial blood pressure level. The objective was to compare the risk reductions achieved by different blood pressure-lowering regimens among individuals with different baseline blood pressures.**

Methods **Thirty-two randomized controlled trials were included and seven comparisons between different types of treatments were made. For each comparison, the primary prespecified analysis included calculation of summary estimates of effect using random-effects meta-analysis for major cardiovascular events in four groups defined by baseline SBP (<140, 140–159, 160–179, and ≥180 mmHg).**

Results **There were 201 566 participants among whom 20 079 primary outcome events were observed. There was no evidence of differences in the proportionate risk reductions achieved with different blood pressure-lowering regimens across groups defined according to higher or lower levels of baseline SBP (all *P* for trend >0.17). This finding was broadly consistent for comparisons of different regimens, for DBP categories, and for commonly used blood pressure cut-points.**

Conclusion **It appears unlikely that the effectiveness of blood pressure-lowering treatments depends substantively upon starting blood pressure level. As the majority of patients in the trials contributing to these overviews had a history of hypertension or were receiving background blood pressure-lowering therapy, the findings suggest that additional blood pressure reduction in hypertensive patients meeting initial blood pressure targets will produce further benefits. More broadly, the data are supportive of the utilization of blood pressure-lowering regimens in high-risk patients with and without hypertension. *J Hypertens* 29:4–16 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Abbreviation: ACE, angiotensin-converting enzyme

[a]The George Institute, Sydney, Australia, [b]Public Health Department, Hôpital Avicenne and University of Paris 13, Bobigny, France, [c]University of Milan and Instituto Auxologico Italiano, Milan, Italy and [d]Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Correspondence to Associate Professor Sébastien Czernichow, MD, PhD, Unité de Recherche en Epidémiologie Nutritionnelle, Faculté SMBH. 74, rue Marcel Cachin, 93017 Bobigny, France
Tel: +33 1 48 38 89 53; fax: +33 1 48 38 89 31;
e-mail: czernichow@uren.smbh.univ-paris13.fr

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Background

It is well recognized that blood pressure increases risk not just among individuals with hypertension but across the full range of blood pressure levels [1,2]. Large-scale observational studies on individuals free of overt cardiovascular disease have demonstrated that the relationship between blood pressure and cardiovascular risk is log-linear and continuous with no evidence of a plateau effect down to SBP levels of 110 mmHg and DBP levels of 70 mmHg [3]. As a result, the last decade has seen a shift away from the allocation of blood pressure-lowering treatment based only on conventional thresholds (i.e., 140 mmHg for systolic and 90 mmHg for diastolic) and a move toward the allocation of treatment based on an assessment of absolute cardiovascular risk [4,5]. This reorientation is based upon the findings of a number of trials that have demonstrated benefits that can be achieved among individuals selected on the basis of risk, rather than blood pressure level [6,7]. A number of recent reports have recommended a much broader use of blood

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pressure-lowering agents [8], although there is still fairly limited evidence about the efficacy of blood pressure reduction in patients with SBPs much below 140 mmHg [9] and whether there is a limit to the protection afforded by further blood pressure lowering [10–13].

The Blood Pressure Lowering Treatment Trialists' Collaboration was established to perform prespecified overviews of trials investigating the effects of blood pressure-lowering drugs on cardiovascular mortality and morbidity, including assessments of the comparative effects of drugs between patient subgroups [14]. The aim of the current analysis was to compare the effects of blood pressure reduction and different blood pressure-lowering drug regimens in patient groups defined according to baseline blood pressure levels.

Methods

Trials included

Trials were eligible for inclusion in these overviews if they met one of the following criteria: randomization of patients between a blood pressure-lowering drug and control (placebo or less intensive blood pressure-lowering regimen) or randomization of patients between regimens based on different classes of blood pressure-lowering drugs. Trials were also required to have a minimum of 1000 patient-years planned follow-up in each randomized group and must not have presented or published their main results prior to finalization of the overview protocol in July 1995. Trials for which individual data or data stratified by initial blood pressure had been obtained by December 2008 were included. Additional information about the identification of the trials and inclusion criteria are described in the protocol [14].

Baseline blood pressure categories

The SBP categories defined *a priori* [14] were less than 140, 140–159, 160–179, and at least 180 mmHg and these constitute the primary analysis. For secondary analyses, as there were no *a priori* DBP categories defined, we used those specified in the Joint National Committee Guidelines for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (<80, 80–89, 90–99, and ≥100 mmHg) [15]. Additional secondary analyses were also done for the SBP categories defined in those guidelines (<120, 120–139, 140–159, and ≥160 mmHg) and for patients with SBP levels less than and at least 140 mmHg and DBP levels less than and at least 90 mmHg.

Comparisons between blood pressure-lowering regimens

Seven prespecified comparisons between different blood pressure-lowering regimens were made [16]. Three of these comparisons included trials aiming at greater blood pressure reduction in one group [angiotensin-converting enzyme (ACE) inhibitor-based regimens compared with placebo; calcium antagonist-based regimens compared with placebo; and more intense compared with less intense blood pressure-lowering regimens]. The remaining four comparisons included trials comparing different active regimens but with similar blood pressure lowering in the two treatment arms [ACE inhibitor-based regimens compared with diuretic/β-blocker-based regimens; calcium antagonist-based regimens compared with diuretic/β-blocker-based regimens; ACE inhibitor-based regimens compared with calcium antagonist-based regimens; and angiotensin receptor blocker-based regimens compared with control regimens].

Outcomes

The primary outcome for these analyses was major cardiovascular events, comprising stroke (nonfatal stroke or death from cerebrovascular disease), coronary heart disease (nonfatal myocardial infarction or death from coronary heart disease, including sudden death) and heart failure (causing death or requiring hospitalization). Secondary outcomes were stroke, coronary heart disease, heart failure, cardiovascular death, and total mortality. All outcomes were defined as per the original overview protocol [14].

Statistical analyses

All the analyses were conducted according to the principle of intention-to-treat. Only the first event of any type was counted. Throughout, *P* values less than 0.05 were considered unlikely to have arisen by chance, although the outcomes of all analyses were interpreted in light of the multiple comparisons that were made. Analyses were done using STATA (V 9.0; Stata Corporation, College Station, Texas, USA) and SAS (V 9.1; SAS Institute Inc., Cary, North Carolina, USA). The blood pressure reduction in each trial arm was calculated as the mean of the differences between each participant's blood pressure during follow-up and their blood pressure at baseline. The mean difference in blood pressure indices between randomized groups was then calculated by subtracting the values for the treatment arms compared. Overall estimates for each blood pressure subgroup were obtained by weighing the estimates from each individual study in proportion to the number of individuals in each baseline SBP or DBP category in that study. The average achieved blood pressure was also calculated by the same weighting technique.

Three different sets of analyses were done to explore the effects of the different blood pressure-lowering regimens among patients with different baseline blood pressure levels.

(1) Meta-analyses to estimate the proportionate risk reductions achieved with different blood pressure-lowering regimens in patient groups categorized by baseline blood pressure – for each trial, and for each

outcome, estimates of the relative risk and its variance were calculated separately for each of the blood pressure categories. Overall estimates of effect and corresponding 95% confidence intervals were calculated separately for each blood pressure category using random-effects models and inverse variance weighting. Where there were four blood pressure subcategories, a test for linear trend of treatment effects across the blood pressure categories was performed by regressing each log relative risk on the ordinal variable for blood pressure in four levels using random-effects meta-regression. Similarly, where there were just two blood pressure subcategories, the consistency of the effects of each treatment regimen across the two groups was examined using χ^2 tests of homogeneity.

For trials comparing ACE inhibitors to placebo, subsidiary analyses were also conducted in order to determine whether there might be differences in the effects of blood pressure lowering among patients who were normotensive and receiving prerandomization blood pressure treatment, compared with those patients who were normotensive without treatment, at baseline. These analyses were only able to use data from five trials (8765 participants) [6,17–20], for which information about blood pressure-lowering treatment at baseline was available.

(2) Meta-analyses to estimate the proportionate risk reductions achieved with different blood pressure-lowering regimens using continuous measures of baseline blood pressure – using individual participant data, Cox regression models, including treatment, blood pressure as a continuous variable, and their interaction term were fitted for each trial. Analysis of Schoenfeld residuals confirmed that the Cox proportional hazards model assumption was verified. Overall estimates for the interaction term and 95% confidence intervals were calculated for each comparison using random-effects models and inverse variance weighting. Results were expressed as the proportionate difference in relative risk achieved with treatment compared to control/other active treatment for a given higher starting blood pressure level. The linearity of the associations of risk reduction with baseline blood pressure was also tested within these models by fitting quadratic and cubic terms for blood pressure: no evidence of nonlinearity was identified (all P values >0.05).

(3) Meta-regressions describing the association of achieved blood pressure reductions with relative risk reductions for patient groups with different baseline blood pressure levels – using individual participant data, the differences in follow-up blood pressure levels between randomized groups for each comparison were plotted against the relative risk reductions achieved for major cardiovascular events separately for the four baseline blood pressure groups. Weighted regression lines were fitted to the data for each of the four baseline blood pressure groups and the slopes were compared by including an interaction term. Assumptions of linear associations between differences in follow-up blood pressure levels and log relative risk were tested with standard graphical methods. As trial participants could contribute only once to a given meta-regression analysis, for factorial trials that included randomization to different intensities of blood pressure lowering and randomization to different drug treatments, we included only the results of the randomization to different intensities of blood pressure lowering. Likewise for trials with randomization to three treatment arms only, two of the possible three treatment comparisons were included with the control arm participants divided equally between the two comparisons.

Results

Trials, patients, and outcomes

The primary analysis, based on the predefined SBP criteria, uses data from all 32 trials and 201 566 participants (Table 1 and also Online Supplement, http://links.lww.com/HJH/A52). Of these, 17 trials (75 150 participants) compared different degrees of blood pressure reduction, whereas the remaining 15 trials (126 416 participants) compared different active blood pressure-lowering regimens. The mean duration of follow-up in the trials ranged from 2.0 to 8.4 years. Mean baseline SBP and DBP levels in the trials ranged from 128 to 194 mmHg and 76 to 105 mmHg, respectively. There were 20 079 first major cardiovascular events recorded, comprising 6877 strokes, 9962 coronary heart disease events, and 3897 heart failure events. There were 15 539 deaths, of which 7871 (51%) were vascular in origin. The secondary analyses excluded data from six trials [7,21–25] and 23 988 participants, for which individual participant data were not available.

Meta-analyses of trials comparing an active regimen with control regimen (placebo-controlled trials and trials targeting different blood pressure goals)

Major cardiovascular events

For the primary analysis comparing the effects of blood pressure reduction (trials of active treatment vs. placebo or more vs. less intense blood pressure reduction) on major cardiovascular events according to prespecified SBP categories, there was no evidence that the proportionate effects varied according to the baseline blood pressure level (all P for trend ≥ 0.17; Fig. 1a). The same was true when analyses were done grouping patients on the basis of SBP levels less than or at least 140 mmHg (all P for heterogeneity ≥ 0.16; Fig. 1b) and for analyses done grouping patients according to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Table 1 Characteristics of included trials

Trials		*N*	Trial design	Entry criteria*	Follow-up (years)	Mean SBP/DBP (mmHg)	SBP distribution (*n*)			
							<140	140–159	160–179	≥180
Trials comparing active treatment and placebo										
ACE inhibitor vs. placebo										
BENEDICT	Trandolapril vs. placebo	604	DB	HBP+DM	3.6	151/87	103	329	139	33
DIAB- HYCAR	Ramipril vs. placebo	4912	DB	DM+nephropathy	3.9	146/82	1242	2617	838	182
EUROPA	Perindopril vs. placebo	12218	DB	CHD	4.2	137/89	6751	4210	1185	72
HOPE	Ramipril vs. placebo	9297	DB	CHD, CVD, or DM + RF	4.5	139/79	4749	3005	1204	339
PART2	Ramipril vs. placebo	617	DB	CHD or CVD	4.7	133/79	395	181	36	5
PROGRESS	Perindopril (+/- indapamide) vs. placebo(s)	6105	DB	Cerebrovascular disease	3.9	147/86	2137	2396	1254	318
SCAT	Enalapril vs. placebo	460	DB	CHD	4.0	128/77	320	98	31	8
PREVEND-IT	Fosinopril vs. placebo	864	DB	microalbuminuria	3.8	129/76	608	211	37	8
ADVANCE	Perindopril + indapamide vs. placebo(s)	11140	DB	DM+RF	4.3	145/81	4704	3947	1748	740
Calcium antagonist vs. placebo										
BENEDICT	Verapamil vs. placebo	605	DB	HBP+DM +nephropathy	2.6	150/88	102	347	132	24
NICOLE	Nisoldipine vs. placebo	826	DB	CHD	3.0	NA	571	188	52	15
PREVENT	Amlodipine vs. placebo	825	DB	CHD	3.0	129/79	596	184	39	6
SYST-EUR	Nitrendipine vs. placebo	4695	DB	HBP, ≥60 years	2.6	174/86		3	3567	1125
Trials comparing more intensive and less intensive regimens										
AASK	MAP ≤92 vs. 102–107 mmHg	1094	Open	HBP+nephropathy, Afr	4.1	NA	381	360	231	122
ABCD (H)	DBP ≤75 vs. ≤90 mmHg	470	Open	HBP+DM	5.3	156/98	89	211	130	40
ABCD (N)	DBP 10 mmHg below baseline vs. 80–89 mmHg	480	Open	DM	5.3	136/84	295	158	26	
HOT**	DBP ≤80 mmHg vs. ≤85 or ≤90 mmHg	18790	Open	HBP	3.8	170/105	122	4553	10001	4114
UKPDS-HDS	DBP <85 mmHg vs. <105 mmHg	1148	Open	HBP+DM	8.4	158/93	155	394	468	111
Trials comparing regimens based on angiotensin receptor blockers and control regimens										
MOSES	Eprosartan vs. nitrendipine	1352	DB	HBP +CVD RF	4.8	151/87	268	576	392	116
RENAAL	Losartan vs. placebo#	1513	DB	DM +nephropathy	3.4	152/82	378	610	373	152
SCOPE	Candesartan vs. placebo#	4937	DB	HBP, 70–89 years	4.5	166/90	45	723	4101	68
Trials comparing regimens based on different drug classes										
ACE inhibitor vs. diuretic or ß-blocker										
AASK	Ramipril vs. metoprolol	877	DB	HBP+nephropathy, Afr	4.1	NA	306	289	185	97
ALLHAT	Lisinopril vs. chlorthalidone	24309	DB	HBP + RF	4.9	146/84	7469	11621	4941	278
ANBP2	Enalapril vs. hydrochlorothiazide	6083	Open^	HBP, 65–84 years	4.1	168/91		1280	3898	905
CAPPP	Captopril vs. ß-blocker or diuretic	10985	Open^	HBP	6.1	162/100	1133	3749	3927	2176
STOP-2	Enalapril or lisinopril vs. atenolol or metoprolol or pindolol or hydrochlorothiazide + amiloride	4418	Open^	HBP, 70–84 years	5.0	194/98	7	63	260	4088
UKPDS-HDS	Captopril vs. atenolol	758	DB	HBP+DM	8.4	158/93	110	261	308	69
Calcium antagonist vs. diuretic or ß-blocker										
AASK	Amlodipine vs. metoprolol	658	DB	HBP+nephropathy, Afr	4.1	NA	226	220	143	69
ALLHAT	Amlodipine vs. chlorthalidone	24303	DB	HBP+ RF	4.9	146/84	7566	11560	4869	308
CONVINCE	COER-Verapamil vs. hydrochlorothiazide or atenolol	16476	DB	HBP+ RF	3.0	150/87	3839	7221	4828	514
ELSA	Lacidipine vs. atenolol	2334	DB	HBP	4.0	160/98	212	885	1024	211
INSIGHT	Nifedipine GITS vs. hydrochlorothiazide + amiloride	6321	DB	HBP + RF	4.0	167/96	0	1045	3249	2027
INVEST	Verapamil vs. atenolol +/- + trandolapril and/or hydrochlorothiazide	22576	DB	HBP + CHD	2.7	151/87	5766	9406	5486	1918
NICS-EH	Nicardipine vs. trichlormethiazide	429	DB	HBP, ≥60 years	5.0	172/94	1	16	294	118
NORDIL	Diltiazem vs. ß-blocker or diuretic	10881	Open^	HBP	5.0	174/106	77	1890	5012	3874
STOP-2	Felodipine or isradipine vs. atenolol or metoprolol or pindolol or hydrochlorothiazide + amiloride	4409	Open^	HBP, 70–84 years	5.0	194/98	6	58	277	4068
VHAS	Verapamil vs. chlorthalidone	1414	DB/Open	HBP	2.0	169/102	0	100	1041	273

Table 1 (*continued*)

Trials	*N*	Trial design	Entry criteria*	Follow-up (years)	Mean SBP/DBP (mmHg)	SBP distribution (*n*)			
						<140	140–159	160–179	≥180
ACE inhibitor vs. calcium antagonist									
AASK	653	DB	HBP+nephropathy, Afr	4.1	NA	230	211	134	78
ABCD (H)	470	DB	HBP+DM	5.3	158/98	89	211	130	40
ABCD (N)	480	DB	DM	5.3	137/85	295	158	26	
ALLHAT	18 102	DB	HBP +CVD RF	4.9	146/84	5561	8689	3636	216
BENEDICT	605				151/87	103	352	127	23
JMIC-B	1650	Open^	HBP +CHD	3.0	145/82	593	596	341	77
STOP-2	4401	Open^	HBP, 70–84 years	5.0	194/98	9	55	273	4064
Ramipril vs. amlodipine									
Enalapril vs. nisoldipine									
Enalapril vs. nisoldipine									
Lisinopril vs. amlodipine									
Trandolapril vs. verapamil									
ACE inhibitor vs. nifedipine									
Enalapril or lisinopril vs. felodipine or isradipine									

Afr, African–American; CHD, coronary heart disease; COER, controlled onset-extended release; CVD, cardiovascular disease; DB, double-blind; DM, diabetes mellitus; GITS, gastrointestinal transport system; HBP high blood pressure; MAP, mean arterial pressure; *N*, number of all randomized participants (with and without diabetes); RF, other CVD risk factor. #These placebo-controlled trials either had similar blood pressure goals in each randomized group or introduced active treatment into the placebo arm for another reason for a large proportion of participants prior to the completion of follow-up. ^PROBE (Prospective, Randomized, Open with Blinded Endpoint evaluation) design trials **HOT trial data analyzed as most intensively treated group vs. others.

(JNCVII) SBP categories (all *P* for trend ≥0.24; Supplementary Table 1, http://links.lww.com/HJH/A52).

When patients were stratified according to DBP categories defined by JNCVII, there was evidence of greater protection against major cardiovascular events with ACE inhibitors compared to placebo among individuals with higher baseline DBP levels (*P* for trend = 0.046) (Fig. 2a). There was no corresponding finding for the other two comparisons (calcium antagonist vs. placebo and more vs. less intense treatment). Nor was there significant heterogeneity between subgroups of participants with DBPs less than or at least 90 mmHg ($P \geq 0.25$; Fig. 2b).

Secondary outcomes

Meta-analyses of trials comparing the effects of active treatment with control on the secondary outcomes of stroke, coronary heart disease, heart failure, vascular death, and total mortality showed no evidence of differences in efficacy between patient groups when defined according to SBP less than 140 and at least 140 mmHg (all $P \geq 0.20$; Supplementary Table 2, http://links.lww.com/HJH/A52) or DBP less than 90 and at least 90 mmHg (all $P \geq 0.18$; Supplementary Table 3, http://links.lww.com/HJH/A52).

Meta-analyses of trials comparing different active regimens

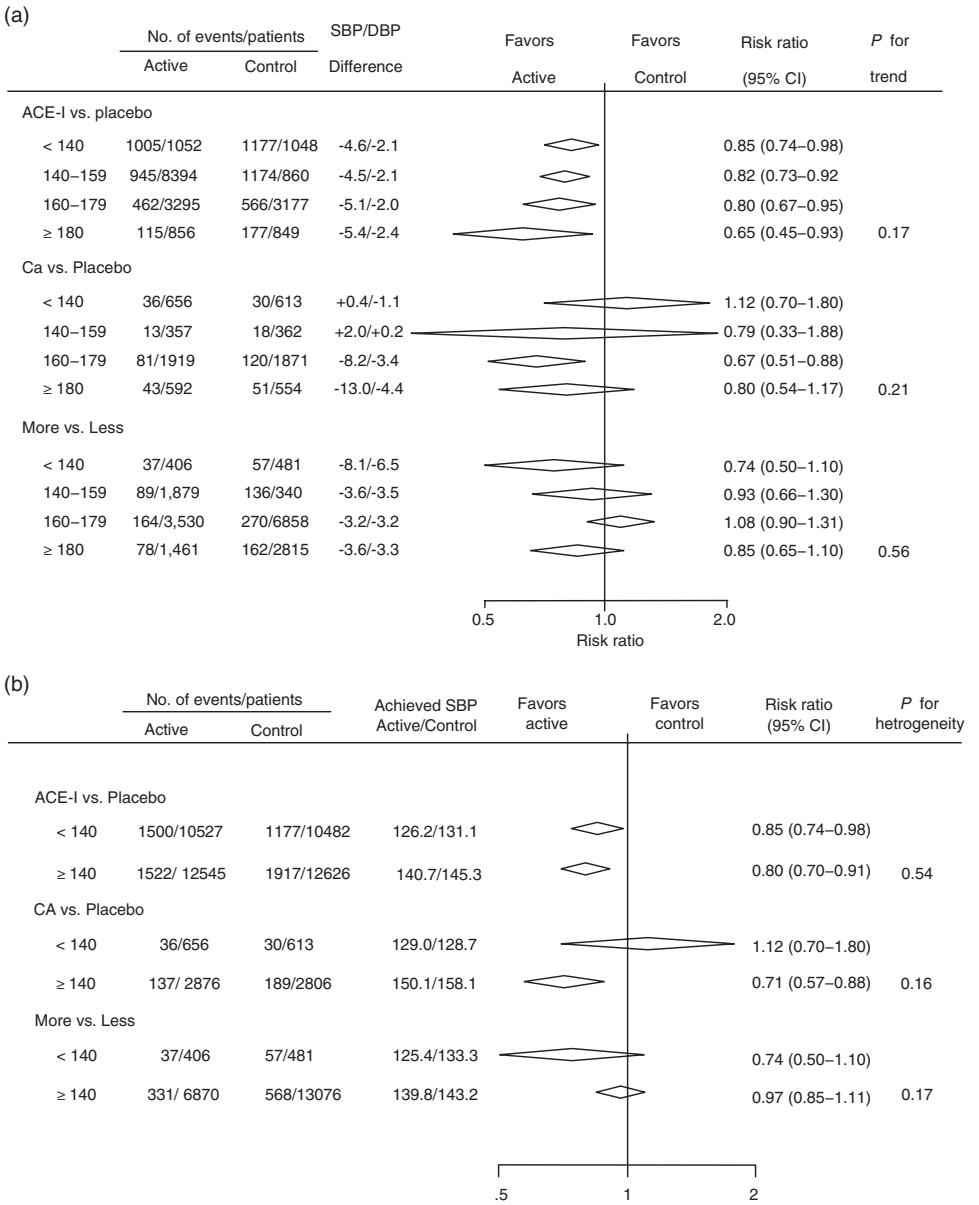
Major cardiovascular events

For the meta-analyses of trials comparing the effects of different active regimens, there was no evidence, for any treatment regimen, that the risk of major cardiovascular events differed according to prespecified SBP levels (*P* for trend ≥0.26; Fig. 3a). For the analyses done grouping patients on the basis of SBP levels less than or at least 140 mmHg, only one comparison (that of ACE inhibitors vs. calcium antagonists with SBP < or ≥140 mmHg) yielded a statistically significant difference ($P = 0.03$) in favor of a greater protective effects of ACE inhibitors at less than 140 mmHg (Fig. 3b). For the analyses done grouping patients on the basis of JNCVII DBP levels (Fig. 4a) and DBP levels less than or at least 90 mmHg (Fig. 4b), there was no evidence of a difference in the effect of any treatment regimen on major cardiovascular events (*P* for trend ≥0.14 and $P \geq 0.15$).

Secondary outcomes

In meta-analyses of trials comparing the effects of different active treatments on the secondary outcomes of stroke, coronary heart disease, heart failure, vascular death, and total mortality, there was no clear evidence of a difference in efficacy between patient groups when defined according to SBP less than 140 and at least 40 mmHg (Supplementary Table 2, http://links.lww.com/HJH/A52). Similarly, when patients were categorized on the basis of DBP less than 90 and at least

Fig. 1



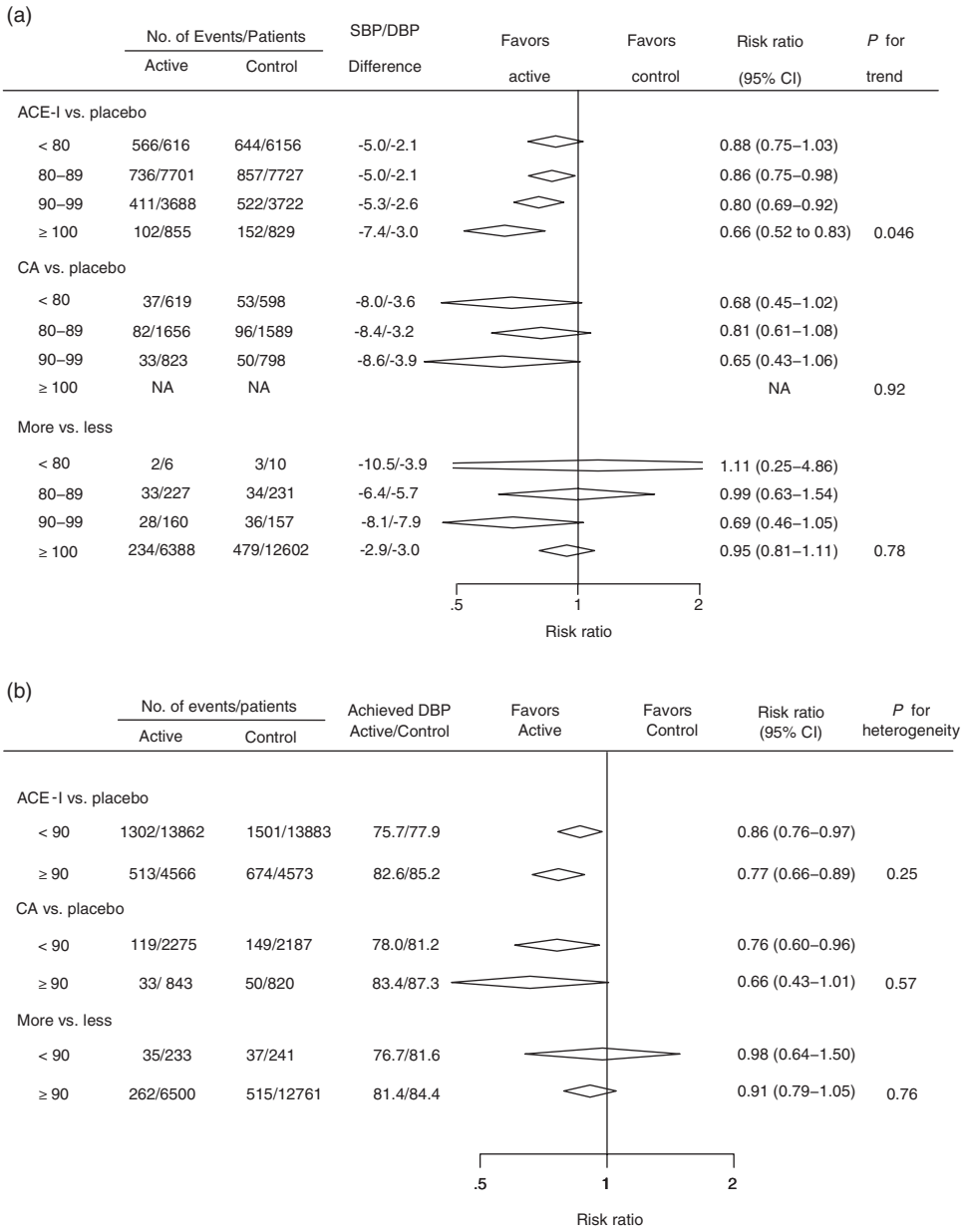
Comparisons of blood pressure-lowering drugs against placebo or less intensive control for the outcome total major cardiovascular events, according to baseline SBP categorized as (a) less than 140, 140–159, 160–179, at least 180 mmHg and (b) less than 140 and at least 140 mmHg. SBP/DBP difference = overall mean blood pressure difference during follow-up between treatment groups (the actively treated group compared with the control group), calculated by weighing the difference observed in each contributing trial by the number of individuals in the trial, within SBP categories. Negative blood pressure values indicate lower mean follow-up blood pressure levels in the first listed than in second listed groups. Achieved blood pressure = mean blood pressure during follow-up calculated by weighing the estimates from each individual trial by number of individuals in each baseline SBP category. ACE-I, angiotensin-converting enzyme inhibitor; CA, calcium antagonist; Less, less intensive blood pressure-lowering regimen; More, more intensive blood pressure-lowering regimen.

90 mmHg (Supplementary Table 3, http://links.lww.com/HJH/A52), there was no consistent pattern of a difference in the efficacy of active treatments.

Analyses of baseline blood pressure as a continuous variable

The meta-regression analyses showed no difference in the magnitude of the relative risk reduction achieved per unit blood pressure lowering for patients with different starting SBP or DBP levels (Fig. 5). Also, meta-analyses with blood pressure as a continuous variable identified no consistent interaction between the baseline blood pressure level and the effectiveness of the various blood pressure-lowering treatments studied (Supplementary Figure 1, http://links.lww.com/HJH/A52).

Fig. 2



Comparisons of blood pressure-lowering regimens against placebo or less intensive control for the outcome total major cardiovascular events, according to baseline DBP categorized as (a) less than 80, 80–89, 90–90, at least 100 mmHg and (b) less than 90 and 90+ mmHg. SBP/DBP difference = overall mean blood pressure difference during follow-up between treatment groups (the actively treated group compared with the control group), calculated by weighing the difference observed in each contributing trial by the number of individuals in the trial. Negative blood pressure values indicate lower mean follow-up blood pressure levels in the first listed than in second listed groups. Achieved blood pressure = mean blood pressure during follow-up calculated by weighing the estimates from each individual trial by number of individuals in each baseline DBP category. ACE-I, angiotensin-converting enzyme inhibitor; CA, calcium antagonist; Less, less intensive blood pressure-lowering regimen; More, more intensive blood pressure-lowering regimen.

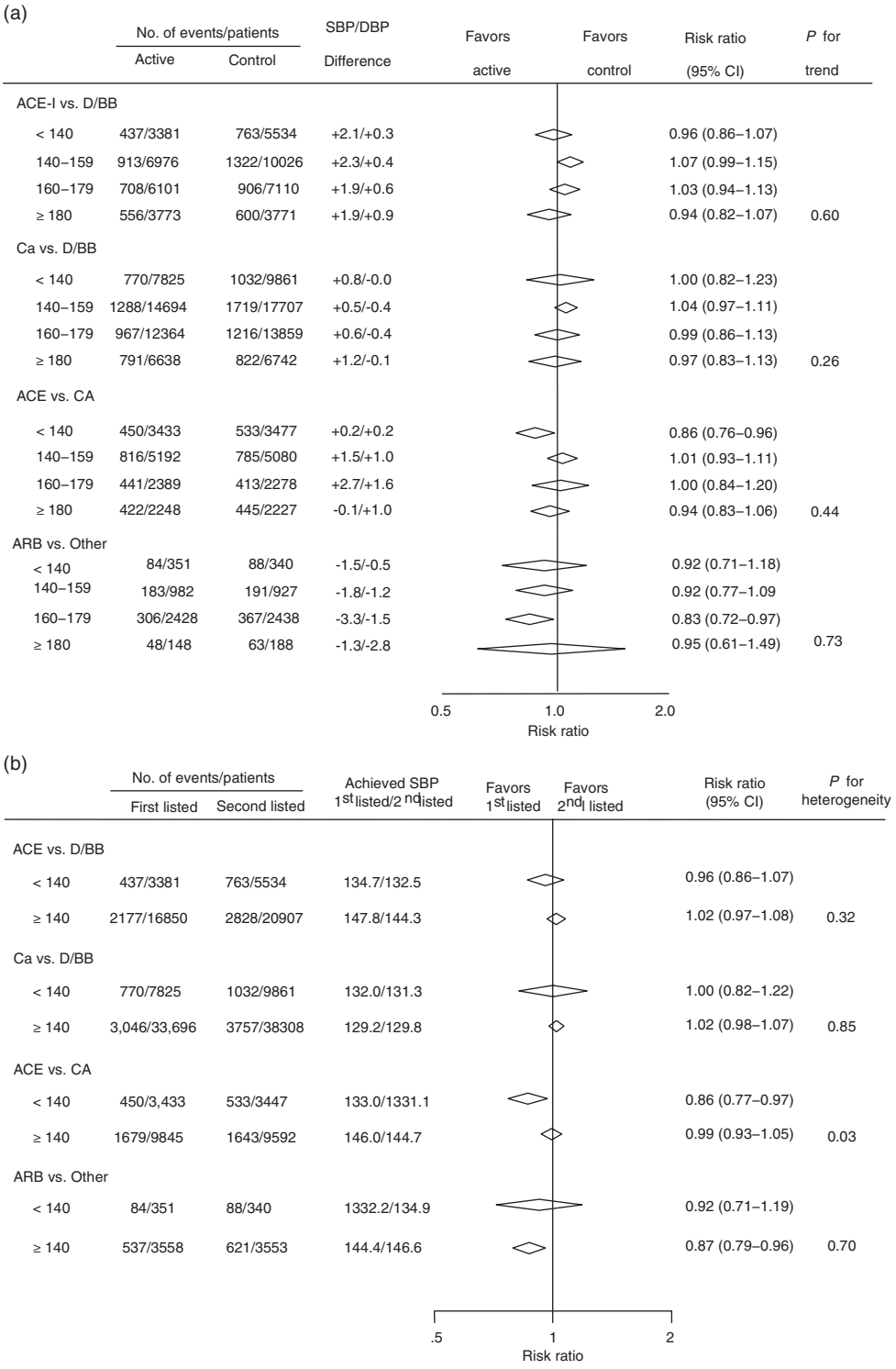
Subsidiary analyses of patients on and off blood pressure-lowering treatment at baseline

In the subgroup of patients not using any blood pressure-lowering agent at baseline, there was no evidence that the effects of blood pressure reduction on risk differed according to baseline SBP when defined according to the prespecified categories (P for trend ≥ 0.46) or dichotomized as less than or at least 140 mmHg ($P > 0.06$).

Discussion

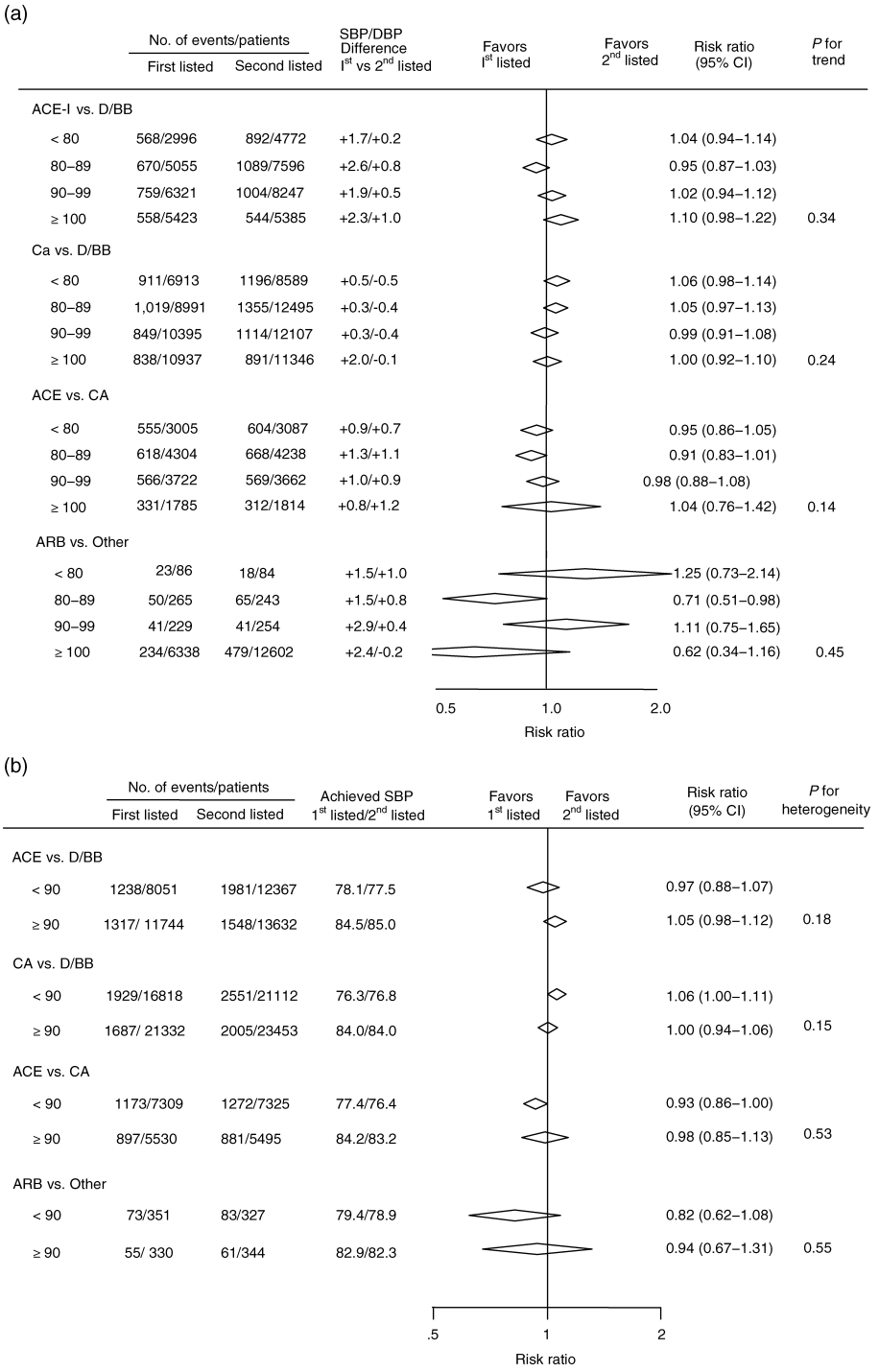
These overviews of randomized trials found little evidence that blood pressure lowering produces proportional

Fig. 3



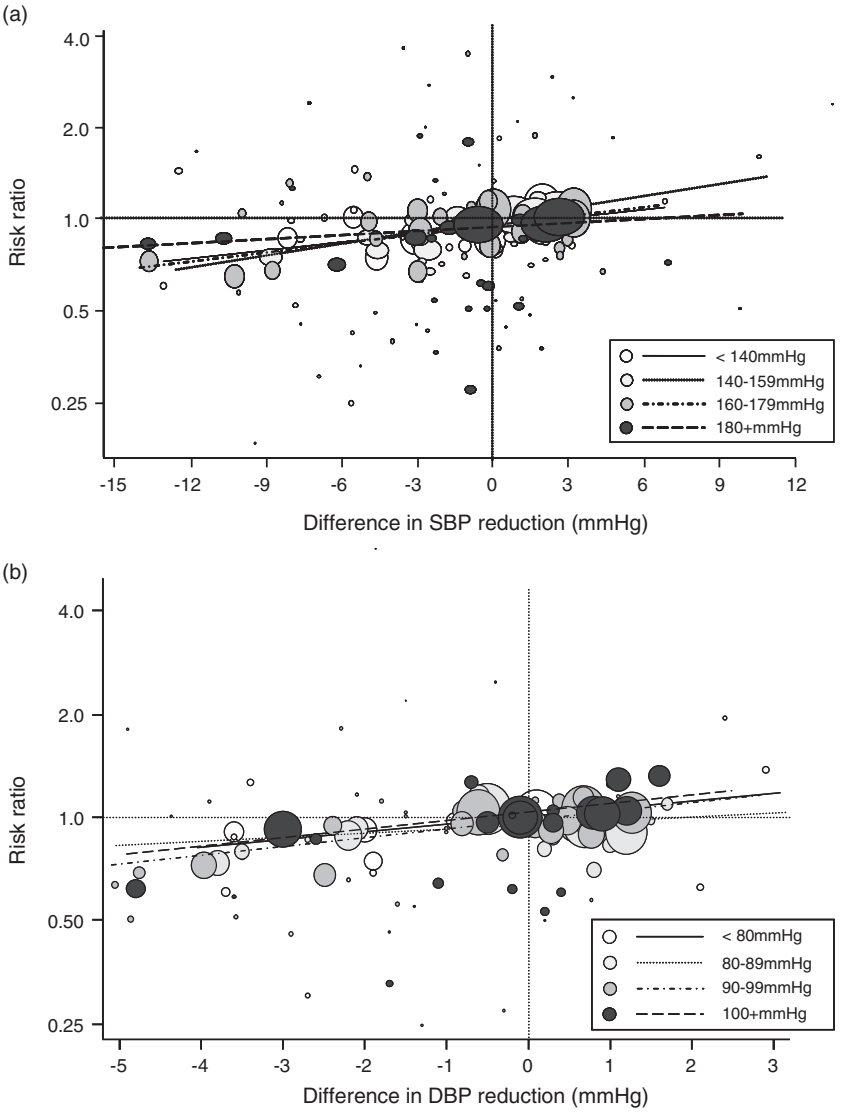
Comparisons of blood pressure-lowering regimens based on different drug classes and of angiotensin receptor blocker-based regimens with other regimens for the outcome total major cardiovascular events, according to baseline SBP categorized as (a) less than 140, 140–159, 160–179, at least 180 mmHg and (b) less than 140 and at least 140 mmHg. SBP/DBP difference = overall mean blood pressure difference during follow-up between treatment groups (the group assigned the first listed treatment compared with the group assigned the second-listed treatment), calculated by weighing the difference observed in each contributing trial by the number of individuals in the trial, within SBP categories. Negative blood pressure values indicate lower mean follow-up blood pressure levels in the first listed than in second listed groups. Achieved blood pressure = mean blood pressure during follow-up calculated by weighing the estimates from each individual trial by number of individuals in each baseline SBP category. ACEI, ACE inhibitor, ARB, angiotensin receptor blocker, Ca, calcium antagonist, D/BB, diuretic or beta-blocker.

Fig. 4



Comparisons of blood pressure-lowering regimens based on different drug classes and for ARB-based regimens with other regimens for the outcome total major cardiovascular events, according to baseline DBP categorised as a) <80, 80–89, 90–90, ≥100 mmHg and b) <90 and ≥90 mm Hg. SBP/DBP difference = overall mean blood pressure difference during follow-up between treatment groups (the first listed treatment compared with the group assigned the second-listed treatment), calculated by weighting the difference observed in each contributing trial by the number of individuals in the trial. Negative blood pressure values indicate lower mean follow-up blood pressure levels in the first listed than in second listed groups. Achieved blood pressure = mean blood pressure during follow-up calculated by weighting the estimates from each individual trial by number of individuals in each baseline DBP category. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CA, calcium antagonist; D/BB, diuretic or β-blocker.

Fig. 5



Comparison of the associations between blood pressure change and risk ratio reduction in total major cardiovascular events according to categories of (a) SBP and (b) DBP. The area of each circle is proportional to the inverse variance of the log odds ratio. Fitted lines represent the summary meta-regressions for total major cardiovascular events.

reductions in the risks of major vascular events that are quantitatively different in patients with a range of initial blood pressure levels and background use of other blood pressure-lowering therapies. These conclusions are most safely based on meta-analyses of trials comparing active treatment with placebo and trials targeting different blood pressure goals. However, the conclusions are further strengthened by meta-analyses of trials comparing different active regimens, in which risk ratios were consistently close to unity.

The findings of these overviews concur with large-scale observational studies [2,3], as with those of trials done primarily on nonhypertensive patient groups with other disease states, which show proportional reductions in risk that are directly comparable to those achieved in hypertensive populations [8].

The clinical implications of the new findings reported here are important as they assert a greater role for blood pressure lowering in high-risk patients with nonhypertensive blood pressure levels. They also suggest that additional blood pressure-lowering treatment in hypertensive patients who have met initial blood pressure goals (mostly because of the concomitant use of other blood pressure-lowering agents) may produce further benefits. As a result, these findings support the progressive shift in the recommendations of guidelines toward the allocation

of blood pressure-lowering treatment on the basis of overall vascular risk rather than blood pressure threshold alone [4,5].

In addition to providing strong evidence for the broader use of blood pressure-lowering agents in clinical practice, the results of these overviews also serve to simplify decisions about drug choice for physicians seeking to avert blood pressure-related diseases. The overviews have provided no clear evidence of greater or lesser benefits for any particular drug class in patients with higher or lower blood pressure levels. The few significant *P* values that were obtained for secondary analyses and secondary outcomes most likely reflect the large number of analyses undertaken and have probably arisen by chance. The likelihood of this explanation is further supported by the borderline statistical significance of the few differences that were observed and the absence of any consistent pattern favoring one drug regimen or another. The conclusions are also in line with the findings of prior analyses addressing the effects of blood pressure-lowering regimens on mortality and major morbidity in other patient subgroups, which have shown comparable effects of the major drug classes in subsets of individuals defined according to age, sex, and presence or absence of diabetes [26–28].

The results of these overviews need to be considered in the context of the trials that could be incorporated. First, only those trials for which individual patient data or data stratified by baseline blood pressure had been obtained by December 2008 were included. As a consequence, these analyses do not include data from a number of recent trials, some of which were unable to show significant benefits of blood pressure-lowering drugs in patients with relatively low baseline blood pressure [11–13,29]. It remains to be seen whether inclusion of these data, when available, might modify the present conclusions [9,10]. Second, we have separately considered SBP and DBP values, whereas definition of hypertension is usually made by considering both types of values. Therefore, it is possible that a part at least of individuals with SBP of 140 mmHg or less had DBP at least 90 mmHg, and even more likely that a majority of individuals with DBP less than 90 mmHg had SBP values at least 140 mmHg (several trials included patients with isolated systolic hypertension). However, misclassification is unlikely, due to the results of the meta-analyses performed. Third, many of the patients in the trials included in this overview were treated with blood pressure-lowering regimens at baseline and the randomized treatments were added to these background regimens. This has implications for the interpretation of the overview findings because the baseline blood pressure levels of the patients are, in most cases, actually 'on-treatment' blood pressure levels. Accordingly, the patient subgroups defined here include a mix of patients, with the minority only having a low baseline blood pressure level without treatment. Therefore, the conclusions of the present overviews mostly apply to the effects of additional blood pressure reductions in patients whose blood pressure had been reduced to different levels by background therapy and indicate the proportional benefits of these additional reductions. It should also be emphasized that no major trial has specifically been aimed at investigating the effect of blood pressure lowering in normotensive individuals, defined by blood pressure levels below the usual cut-off for hypertension and without receiving blood pressure-lowering agents. Furthermore, the population of high-risk individuals included in our meta-analysis were likely to receive other preventive therapies at baseline, such as lipid-lowering and antiplatelet agents. This may have further reduced the cardiovascular benefit of blood pressure lowering in those with the lowest baseline systolic or diastolic values [10].

Fourth, these analyses included thousands of major cardiovascular events and for the primary outcome provided reasonably precise estimates of the effects of the different regimens in most of the patient subgroups studied. The overviews are, nonetheless, subject to several limitations and need to be interpreted with these in mind. The conclusions were limited by the small numbers of patients with blood pressure levels at the extremes of the distribution. In large part, this reflects the entry criteria of the contributing trials and as a consequence, the confidence intervals around the estimates of treatment effect in these subgroups are wide. Fitting baseline blood pressure as a continuous variable provided somewhat better statistical power to explore the effects of interventions across the broader range of blood pressure levels, although uncertainty about possible interactions between blood pressure level and treatment regimens at the extremes does persist. It is also possible that differences in the characteristics of the subgroups of patients other than baseline blood pressure levels could have obscured differences in the effects of treatment. This does not, however, seem especially likely, given the failure of methodologically comparable prior studies to detect interactions between drug treatment effects and other patient characteristics such as age, sex, and diabetes.

Finally, the overviews defined only the short-term to medium-term effects of the regimens studied and cannot exclude the evolution of differences between the effects in each baseline blood pressure group in the longer term. Although it is impossible to absolutely exclude effects of any of these limitations on the study findings, the constancy of the effect estimates and the broad comparability of the results across the different analytic methods utilized do provide reassurance about the likely validity of the primary conclusions drawn.

Accordingly, these overviews suggest that the proportional risk reductions achieved with a given blood pressure-lowering regimen are similar across the SBP and

DBP levels usual for most of the population. When viewed in conjunction with the observational data that provide clear evidence of a progressive graded association of blood pressure with risk across the full range of usual blood pressure levels [2], these results indicate a similar graded association exists also in patients at high cardiovascular risk and provide support for the recommendation to achieve low blood pressure targets in these patients. The results of these overviews mostly refer to patients using background antihypertensive therapy. Randomized trials in untreated patients with baseline normotensive blood pressure are needed [30].

Nonetheless, the evidence that blood pressure-lowering treatments provide proportional reductions in risk that are largely independent of the starting blood pressure strengthens the recommendation of some guidelines [31,32] that selection of patients for treatment should be done on the basis of the absolute level of cardiovascular risk, and provide new impetus for a greater use of blood pressure-lowering therapies in high-risk individuals rather than just among individuals with hypertension. With one half of all blood pressure-related disease occurring in patients without hypertension [33], there is enormous potential for this shift in the use of blood pressure-lowering therapy to positively impact upon the enormous global burden of disease caused by high blood pressure and to maximize the efficiency of healthcare in developed and developing countries alike [33,34].

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Members of the Blood Pressure Lowering Treatment Trialists' Collaboration are as follows: L. Agodoa, C. Anderson, F.W. Asselbergs, C. Baigent, H. Black, B. Brenner, M. Brown, C. Bulpitt, R. Byington, J.C., R Collins, J. Cutler, B. Dahlof, B. Davis, D. de Zeeuw, J. Dens, R. Estacio, R. Fagard, K. Fox, T. Fukui, L. Hansson (deceased), R. Holman, Y. Imai, M. Ishii, Y. Kanno, J. Kostis, K. Kuramoto, E. Lewis, M. Lièvre, L.H. Lindholm, L. Liu, J. Lubsen, S. Lueders, S. MacMahon, E. Malacco, G. Mancia, M. Matsuzaki, B. Neal, S. Nissen, T. Ohkubo, T. Ogihara, C.R. Palmer, C. Pepine, M. Pfeffer, B. Pitt, P. Poole-Wilson, N. Poulter, M. Rahman, W. Remme, G. Remuzzi, A. Rodgers, P. Ruggenenti, T. Saruta, J. Schrader, R. Schrier, P. Sever, P. Sleight, J. Staessen, H. Suzuki, K. Teo, W.H. van Gilst, G. Viberti, J. Wang, P. Whelton, L. Wing, Y. Yui, S. Yusuf, and A. Zanchetti.

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