Review

Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs – Overview and meta-analyses

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Background and objectives: In 68 randomized controlled trials (RCTs), blood pressure (BP) lowering was obtained by using drugs of different classes. We have investigated whether BP lowering by any of the major drug classes is effective in reducing the cardiovascular outcomes.

Methods: A total of 55 RCTs (195 267 individuals) were suitable for drug-class meta-analyses. Risk ratios and their 95% confidence intervals of seven fatal and nonfatal outcomes were estimated by a random-effects model.

Results: Twelve RCTs (48 898 patients) compared a diuretic with no treatment. SBP/DBP differences of about −12/−5 mmHg were accompanied by significant reductions of all outcomes, including mortality. The same results were obtained by limiting analyses to eight RCTs using low-dose diuretics. Separate analyses for thiazides, chlorthalidone and indapamide (all low dose) showed each subclass was associated with significant reduction of some major outcome. Five RCTs (18 724 patients; SBP/DBP difference −10.5/−7 mmHg) showed beta-blockers significantly reduced stroke, heart failure and major cardiovascular events. In RCTs comparing calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) with placebo smaller SBP/DBP differences were achieved, mostly because in the majority of these later RCTs the antihypertensive drug and placebo were added on a background treatment with other antihypertensive agents. Nonetheless, significant reductions of stroke, major cardiovascular events, cardiovascular and all-cause death were obtained with calcium antagonists (10 RCTs, 30 359 patients); stroke, coronary heart disease, heart failure and major cardiovascular events by ACE inhibitors (12 RCTs, 35 707 patients); and stroke, heart failure and major cardiovascular events by ARBs (13 RCTs, 65 256 patients).

Conclusion: BP lowering by all classes of antihypertensive drugs is accompanied by significant reductions of stroke and major cardiovascular events. This supports the concept that reduction of these events is because of BP lowering *per se* rather than specific drug properties. However, evidence of risk reduction of other events and particularly mortality was obtained so far with some drug classes only. As a result of marked differences in the trial design, total cardiovascular risk, SBP/DBP differences and statistical power, comparisons of meta-analyses of different drug-specific placebo-controlled RCTs appear unwarranted.

Keywords: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, blood-pressure-lowering treatment, calcium antagonists, diuretics, drug class, hypertension, meta-analysis, randomized controlled trials

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; BPLTTC, Blood Pressure Lowering Treatment Trialists' Collaboration; CHD, coronary heart disease; CI, confidence interval; *n*, number; NNT, number needed to treat; RCT, randomized controlled trial; RR, risk ratio

INTRODUCTION

We have previously conducted an overview of the randomized controlled trials (RCTs) of blood pressure (BP) lowering by drugs and identified 68 RCTs responding to the following prespecified criteria: BP-lowering drugs compared with placebo or no treatment, or more intense compared with less intense treatment with the intention to investigate the effects of BP differences on cardiovascular outcomes (intentional BP-lowering trials) or BP-lowering drugs compared with placebo, often on a background of baseline antihypertensive therapy, even if the trial design was not that of investigating the effects of BP differences provided that a between-group difference of at

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least 2 mmHg in either SBP or DBP occurred (nonintentional BP-lowering trials); enrolling at least 40% hypertensive individuals (SBP >140 or DBP >90 mmHg or current antihypertensive drugs); exclusion of trials investigating acute myocardial infarction, heart failure, acute stroke and patients on dialysis; protocol including measurement of at least one type of cardiovascular events amongst primary or secondary endpoints; BP measured at baseline and follow-up; follow-up of at least 6 months; a minimum of five events during follow-up; randomized allocation to treatments; and publication within 31 December 2013 [1]. Meta-analysis of these BP-lowering RCTs showed all major cardiovascular outcomes were significantly reduced by BP-lowering treatment, most of them in a proportional way to the extent of the between-group BP difference [1].

In the above trials, BP lowering was obtained by using drugs of different pharmacological classes. There is an obvious interest in investigating whether BP lowering by any of the major classes of antihypertensive drugs is effective in reducing all or part of cardiovascular outcomes. A number of meta-analyses have approached this problem in the past [2–13], but none of them has been comprehensive of all BP-lowering RCTs conducted from 1966 to end of 2013, and simultaneously exclusive of RCTs comparing different active regimens (the latter type of trials aim at avoiding, instead of inducing, a between-group BP difference) as well as of RCTs investigating antihypertensive drugs in conditions different from hypertension (such as myocardial infarction and heart failure).

METHODS

Trial eligibility

Of the 68 BP-lowering trials [1], those considered for the present meta-analyses of drug-related effects had to satisfy one of these additional criteria: randomization to a drug of a given class in monotherapy (versus placebo or no or usual therapy) or one group randomized to two drugs of different classes in combination compared with another group randomized to one of those drugs (RCT included into the class of the drug present in the combination and absent in the monotherapy group). Trials were included in the primary analyses even if randomization occurred on a background of baseline therapy and if drugs of other classes could be subsequently added according to protocol.

Secondary meta-analyses could additionally include RCTs in which randomization to the active group allowed the initial drug to be chosen amongst two different classes (e.g. diuretics or beta-blockers) and RCTs in which the active group was initially randomized to a drug combination (versus placebo). These RCTs were included in the secondary meta-analyses of two separate drug classes.

Those BP-lowering RCTs in which the active or more active group could receive different drugs to the investigator's discretion could not be included in the current meta-analysis.

Outcomes

Data on seven predetermined outcomes were extracted: stroke (fatal and nonfatal); coronary heart disease (CHD) events (coronary death and nonfatal myocardial infarction); hospitalized heart failure; major cardiovascular events, composite of stroke and CHD; major cardiovascular events, composite of stroke, CHD and heart failure; cardiovascular death and all-cause death. The definition of outcomes reported in the original study was retained, but whenever possible transient ischaemic attacks, angina, revascularization procedures and nonhospitalized nonfatal heart failure were excluded.

Statistical analyses

RCTs were divided in drug-class-specific groups according to the criteria detailed in the trial eligibility section. Statistical analyses were done with the methods described in the studies reporting previous meta-analyses [1,14,15]. Risk ratios and their 95% confidence intervals (CIs) for each trial were calculated by the Mantel–Haenszel methods weighted by patient number and follow-up duration, and combined using a random-effects model. This model was chosen for all the meta-analyses because it avoids the assumption that participants in the individual trials are sampled from populations in which the intervention has the same quantitative effect [8]. However, the proportion of inconsistency across the studies not explained by chance was quantified with the I^2 and the χ^2 Q statistics ($P > 0.1$). Furthermore, the influence of individual trials on pooled effect sizes was tested by excluding one trial at a time: if the point estimate of the combined effect size with a given trial excluded lay outside the CI of the overall estimate risk with all available trials, the trial in question was considered to have an excessive influence.

Calculations of the 5-year incidence of each outcome in the placebo or control group were made, and the 5-year absolute risk reductions by BP-lowering treatment calculated, as well as the numbers of patients needed to treat for 5 years in order to prevent an outcome (NNT). Standardization of risk ratios to a 10/5 mmHg SBP/DBP difference was also made as described previously [1].

Comprehensive Meta Analysis version 2 (Biostat, Eaglewood, New Jersey, USA) was used for all the analyses. In each meta-analysis, a P value less than 0.05 was considered to indicate statistical significance; however, this statistical threshold should be interpreted with caution because of the multiple comparisons performed.

RESULTS

Trial and patients

Amongst the 68 BP-lowering RCTs identified in our initial survey of BP-lowering trials, 55 (195 267 individuals and 773 137 individual years) were found suitable for drug-class specific meta-analyses because they satisfied all the prespecified criteria (see trial eligibility) [16–73]. The remaining 13 RCTs (mostly of more versus less intense BP lowering) could not be included in any drug-class-specific group because more intense treatment could be done by different drugs at the choice of the investigator.

Meta-analyses were done for six different drug classes: diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and centrally acting drugs. An additional

meta-analysis was done by considering ACE inhibitors and ARBs together (renin–angiotensin system blockers).

Diuretics

Table 1 lists the 12 RCTs (48 898 patients) suitable for the primary analysis of placebo-controlled studies with active treatment initiated with a diuretic and the nine additional studies included in a secondary analysis (66 788 patients). In the primary analysis, a SBP/DBP difference of about −13/−5.5 mmHg between diuretic therapy and placebo was accompanied by a significant reduction in all outcomes considered (Fig. 1). The relative risks (RRs) of not only stroke and heart failure were most markedly reduced [−37% (95% CI −28%, −45%) for stroke, −49% (−34%, −61%) for heart failure], but also CHD [−18% (−6%, −27%)], cardiovascular death [−18% (−10%, −25%)] and all-cause death [−11% (−5%, −17%)] were significantly reduced. Inclusion of additional trials in which diuretics were used in association with other drugs (secondary analysis) did not substantially change the RR reduction. Heterogeneity was low in the primary analysis, but markedly increased in the secondary analysis.

Figure 1 also indicates the absolute incidences of cardiovascular outcomes in the control group: cardiovascular death incidence averaged 4.4% in 5 years. Diuretics prevented 15 strokes, 24 major cardiovascular events and eight deaths every 1000 patients treated for 5 years (with NNT of 67, 41 and 118, respectively).

Risk ratios standardized to 10/5 mmHg SBP/DBP differences, which are slightly lower than those actually found, were for stroke 0.65 (0.57–0.74); CHD 0.86 (0.77–0.96); heart failure 0.55 (0.44–0.69); composite of stroke and CHD

TABLE 1. BP lowering by diuretics

Trial	Proportion of hypertensive patients in the study (%)	Baseline treatment	Drugs compared		Patient number	Follow-up (years)	Baseline BP (mmHg)		Achieved SBP (mmHg)		Achieved DBP (mmHg)	
			Active	Control			SBP	DBP	Active	Control	Active	Control
Trials for primary analysis												
VA-NHLBI [16]	100	No	Chlorthalidone	Placebo	1012	1.5	160	95	NR	NR	82.9	88
AUSTRALIAN [17]	100	No	Chlorthalidone	Placebo	3427	4	157	100.5	NR	NR	88.4	94
HDFP [18,19]	100	No	Chlorthalidone	Usual care	10940	5	159	101.5	131.5	142.5	86	92
MRC-mild [20][a]	100	No	Bendrofluazide	Placebo	12951	5	161	98	136.5	149.3	87.5	93
Oslo [21]	100	No	Hydrochlorothiazide	Untreated	785	5.5	156	97	131	148	88	98
EWPHE [22]	100	No	Hydrochlorothiazide and triamterene	Placebo	840	4.7	182	101	149.5	171.7	86.4	94.7
SHEP-pilot [23]	100	No	Chlorthalidone	Placebo	551	2.8	172	75	140.7	157.6	67.7	71.6
SHEP [24]	100	No	Chlorthalidone	Placebo	4736	4.5	170	76.5	142.5	155.2	68.3	75
MRC-old [25][a]	100	No	Hydrochlorothiazide and amiloride	Placebo	3294	5.8	185	90.5	152	167	78.5	85.5
PATS [26]	84	No	Indapamide	Placebo	5665	1.8	154	93	143.4	148.7	86.5	88.9
HYVET-pilot [27][a]	100	No	Bendroflumethiazide	Untreated	852	1.1	181	100	151.6	174	83.6	94.5
HYVET [28]	100	No	Indapamide	Placebo	3845	2.1	173	91	144.7	158	78.2	83.1
Total primary					48898	4.2	163.7	95.0	139.1	150.9	83.5	88.9
Additional trials for secondary analysis												
VA-1 [29]	100	No	Hydrochlorothiazide, reserpine,hydralazine	Placebo	143	1.5	186	121	142.6	182	91.9	118.7
VA-2 [30]	100	No	Hydrochlorothiazide, reserpine, hydralazine	Placebo	380	3.8	164	104	134.9	189.3	86.4	105
Carter [31]	100	No	Thiazide and methyldopa or debrisoquine	Untreated	99	4	>160	≥110	NR	NR	106	115
Barraclough [32]	100	No	Bendrofluazide or methyldopa or debrisoquine	Placebo	116	2	NR	110	NR	NR	89.8	104.2
HSCSG [33]	100	No	Methyclothiazide, deserpidine	Placebo	452	3	164	100	141	166	88	100
USPHS [34]	100	No	Chlorthalidone, rauwolfia	Placebo	389	7	147	99	131.5	147.4	88.4	98.4
STOP [35]	100	No	Hydrochlorothiazide/ amiloride or atenolol or metoprolol or pindolol	Placebo	1627	2.1	195	102	166	188.3	87.2	96.7
PROGRESS [36] [b]	>48	Yes	Indapamide and perindopril	Placebo	3544	3.9	149	87	133.1	145.2	79.1	84.1
ADVANCE [37]	>75	Yes	Indapamide and perindopril	Placebo	11140	4.3	145	81	134.7	140.3	74.8	77
Total secondary					66788	4.1	160.5	92.6	138.6	150.0	82.1	87.2

BP, blood pressure.
[a]In MRC-mild, MRC-old and HYVET-pilot trials, the arm randomized to a diuretic has been included together with the entire arm randomized to placebo.
[b]In PROGRESS, the subgroup randomized to the combination diuretic and ACE inhibitor has been included with the exclusion of the subgroup randomized to ACE-inhibitor only, and compared to the matched group randomized to placebo.

Outcome	Trials (n)	Outcome risk (% in 5 years)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	RR (95% CI)	*P* (Heterogen)	Absolute 1000 pts/5 years risk reduction (95% CI)	NNT 5 years (95% CI)
Primary analysis										
Stroke	11	4.3	–11.9/–5.5	524/21414	924/26472	0.63 (0.55–0.72)		0.20	–15 (–18,–12)	67 (55, 87)
CHD	12	4.2	–11.9/–5.5	756/21922	1116/26976	0.84 (0.74–0.95)		0.26	–7 (–11, –2)	148 (91, 474)
HF	6	3.8	–13.7/–5.2	98/7284	188/6900	0.51 (0.39–0.66)		0.38	–17 (–20, –12)	60 (50, 84)
Stroke + CHD	12	7.9	–11.9/–5.5	1280/21922	2040/26976	0.76 (0.69–0.83)		0.89	–21 (–24, –16)	47 (41, 61)
Stroke + CHD + HF	8	8.6	–13.9/–5.7	729/12662	1343/17767	0.71 (0.65–0.78)		0.38	–24 (–29, –19)	41 (34, 54)
CV Death	12	4.4	–11.9/–5.5	727/21922	1034/26976	0.82 (0.75–0.90)		0.67	–8 (–11, –4)	129 (94, 231)
All-cause Death	12	7.8	–11.9/–5.5	1400/21922	1845/26976	0.89 (0.83–0.95)		0.62	–8 (–13, –4)	118 (77, 258)
Secondary analysis										
Stroke	19	5.3	–11.4/–5.2	971/30300	1539/35360	0.63 (0.54–0.72)		0.003	–19 (–23, –14)	53 (44, 70)
CHD	21	4.6	–11.4/–5.2	1135/30866	1564/35922	0.83 (0.77–0.89)		0.48	–8 (–11, –5)	128 (95, 197)
HF	12	4.4	–11.5/–4.7	337/14350	479/13965	0.55 (0.37–0.80)		0.001	–18 (–25, –9)	54 (40, 117)
Stroke + CHD	21	9.8	–11.4/–5.2	2106/30866	3103/35922	0.74 (0.67–0.82)		0.04	–26 (–32, –20)	39 (32, 49)
Stroke + CHD + HF	14	10.6	–12.1/–5.1	1564/19728	2315/24832	0.71 (0.62–0.81)		<0.001	–30 (–39, –20)	33 (26, 50)
CV Death	20	4.6	–11.3/–5.2	990/29096	1397/34148	0.79 (0.72–0.87)		0.34	–10 (–13, –6)	104 (78, 167)
All-cause Death	20	8.2	–11.3/–5.2	1896/29096	2457/34148	0.87 (0.81–0.92)		0.35	–11 (–15, –7)	95 (65, 154)

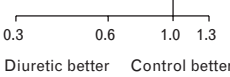

FIGURE 1 Relative and absolute risk reduction of various outcomes in the trials of blood pressure lowering by diuretics. Primary and secondary analyses include trials listed in Table 1. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

0.76 (0.73–0.83); composite of stroke, CHD and heart failure 0.76 (0.71–0.82); cardiovascular death 0.84 (0.77–0.91) and all-cause death 0.90 (0.84–0.96).

As doses of diuretics in antihypertensive therapy have changed through the years, with lower doses being used currently, separate analyses were done of low and high dose diuretics, trials being classified as low dose if the maximum on-treatment dose of diuretic allowed by protocol (mostly as second step) was equal or less than 50 mg hydrochlorothiazide or chlorthalidone and equal or less than 5 mg bendrofluazide or indapamide. Eight trials were classified as low dose [21–28] and four as high dose [16–20]. All outcomes considered were significantly reduced by low-dose diuretics, with risk ratios quite similar to those calculated in the overall diuretic meta-analysis (Fig. 2a). Only stroke and the two composite outcomes were significantly reduced by high-dose diuretics, whereas reductions in CHD and cardiovascular or all-cause mortality did not reach statistical significance (Fig. 2b). It should be noted, however, that total cardiovascular risk was much lower in high-dose than in low-dose diuretic trials (cardiovascular death 4.8%, rather than 17.6% in 10 years) and hence the statistical power of the high-dose diuretic meta-analysis was lower.

Separate analyses were also done according to the type of diuretic used as active drug, limiting the analyses to trials using low doses (Fig. 3). Significant reductions of stroke,

Outcome	Trials (n)	Outcome risk (% in 5 years)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	RR (95% CI)	*P* (Heterogen)	Absolute Risk Reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
A. Low doses										
Stroke	8	9.9	–12.2/–5.1	391/9911	634/10657	0.68 (0.60–0.77)		0.56	–28 (–34, –21)	35 (29, 48)
CHD	8	3.4	–12.2/–5.1	181/9911	308/10657	0.76 (0.63–0.92)		0.42	–8 (–12, –3)	127 (83, 374)
HF	5	4.7	–14.3/–5.0	95/5563	185/5194	0.51 (0.38–0.67)		0.33	–21 (–26, –15)	48 (39, 69)
Stroke + CHD	8	13.0	–12.2/–5.1	572/9911	942/10657	0.70 (0.63–0.77)		0.89	–36 (–44, –28)	39 (32, 49)
Stroke + CHD + HF	6	16.0	–14.4/–5.5	540/6644	993/7407	0.67 (0.61–0.75)		0.52	–51 (–60, –39)	20 (17, 26)
CV Death	8	8.8	–12.2/–5.1	453/9911	637/10657	0.81 (0.72–0.91)		0.88	–16 (–23, –8)	63 (44, 129)
All-cause Death	8	15.2	–12.2/–5.1	896/9911	1137/10657	0.89 (0.82–0.97)		0.80	–16 (–26, –5)	61 (38, 220)
B. High doses										
Stroke	3	1.9	–11.5/–5.7	133/11503	290/15815	0.51 (0.33–0.79)		0.064	–9 (–12, –4)	110 (81, 256)
CHD	4	5.0	–10.4/–5.7	575/12011	808/16319	0.89 (0.73–1.09)		0.13	–5 (–13, +4)	184 (75, –224)
HF	1									
Stroke + CHD	4	6.7	–10.4/–5.7	708/12011	1098/16319	0.76 (0.70–0.84)		0.75	–16 (–20, –11)	62 (50, 93)
Stroke + CHD + HF	2	4.0	–12.8/–5.5	189/6018	410/10360	0.81 (0.68–0.96)		0.84	–8 (–13, –2)	131 (78, 619)
CV Death	4	2.4	–10.4/–5.7	274/12011	397/16319	0.84 (0.64–1.11)		0.16	–4 (–9, +3)	257 (114, –374)
All-cause Death	4	4.3	–10.4/–5.7	504/12011	708/16319	0.88 (0.74–1.06)		0.21	–5 (–11, +3)	192 (89, –385)

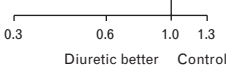

FIGURE 2 Relative and absolute risk reduction of various outcomes in the trials of blood pressure lowering by diuretics at low and high doses. Analyses of trials listed in Table 1. (a) Low-dose diuretic [21–28] and (b) high-dose diuretic [16–20]. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

Outcome	Trials (n)	Outcome risk (% in 5 years)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	RR (95% CI)	P (Heterogen)	Absolute Risk Reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
A. Thiazides										
Stroke	4	5.2	–17.3/–8.1	74/2329	193/3442	0.59 (0.41–0.85)		0.26	–22 (–32, –8)	46 (32, 128)
CHD	4	5.3	–17.3/–8.1	89/2329	199/3442	0.80 (0.56–1.15)		0.23	–11 (–24, +8)	94 (42, –128)
HF	2	2.9	–19.3/–9.0	19/822	24/803	0.81 (0.45–1.46)		0.55	–6 (–16, +13)	179 (62, –74)
Stroke + CHD	4	10.2	–17.3/–8.1	163/2329	392/3442	0.67 (0.56–0.80)		0.90	–34 (–46, –21)	29 (22, 49)
Stroke + CHD + HF	3	11.8	–16.4/–7.7	183/1903	405/3016	0.74 (0.62–0.87)		0.65	–31 (–46, –15)	32 (22, 65)
CV Death	4	8.0	–17.3/–8.1	163/2329	298/3442	0.79 (0.65–0.95)		0.44	–17 (–28, –4)	59 (35, 249)
All-cause Death	4	13.1	–17.3/–8.1	309/2329	495/3442	0.92 (0.81–1.05)		0.48	–10 (–25, +7)	95 (40, –153)
B. Chlorthalidone										
Stroke	2	6.9	–13.4/–3.9	107/2808	155/2479	0.63 (0.50–0.80)		0.47	–25 (–34, –14)	40 (30, 73)
CHD	2	3.4	–13.4/–3.9	58/2808	76/2479	0.69 (0.49–0.97)		0.65	–10 (–17, –1)	97 (60, 980)
HF	2	4.7	–13.4/–3.9	54/2808	104/2479	0.48 (0.35–0.67)		0.60	–23 (–29, –15)	43 (35, 66)
Stroke + CHD	2	10.4	–13.4/–3.9	165/2808	231/2479	0.65 (0.54–0.79)		0.77	–35 (–46, –21)	28 (22, 47)
Stroke + CHD + HF	2	15.0	–13.4/–3.9	219/2808	335/2479	0.60 (0.51–0.71)		0.96	–59 (–71, –43)	17 (14, 23)
CV Death	2	5.2	–13.4/–3.9	104/2808	117/2479	0.80 (0.61–1.04)		0.75	–10 (–20, +2)	96 (50, –476)
All-cause Death	2	11.2	–13.4/–3.9	245/2808	249/2479	0.89 (0.75–1.06)		0.57	–12 (–27, +7)	82 (36, –149)
C. Indapamide										
Stroke	2	15.9	–8.5/–4.0	210/4774	286/4736	0.73 (0.61–0.87)		0.98	–34 (–44, –19)	29 (23, 54)
CHD	2	1.8	–8.5/–4.0	34/4774	33/4736	1.02 (0.63–1.65)		0.38	0 (–5, +9)	
HF	1									
Stroke + CHD	2	17.7	–8.5/–4.0	244/4774	319/4736	0.76 (0.65–0.89)		0.80	–35 (–46, –18)	29 (22, 56)
Stroke + CHD + HF	1									
CV Death	2	12.3	–8.5/–4.0	186/4774	222/4736	0.83 (0.69–1.01)		0.77	–18 (–29, +1)	55 (34, –804)
All-cause Death	2	21.8	–8.5/–4.0	342/4774	393/4736	0.86 (0.75–0.99)		0.46	–27 (–44, –2)	37 (23, 462)

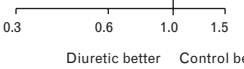

FIGURE 3 Relative and absolute risk reduction of various outcomes in the trials of blood pressure lowering by different classes of diuretics at low dose. Analyses of trials listed in Table 1. (a) Thiazides [21,22,25,27], (b) chlorthalidone [23,24] and (c) indapamide [26,28]. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

composites of stroke and CHD and stroke, CHD and heart failure, and cardiovascular death were found with low-dose thiazides [21,22,25,27]; significant reductions of stroke, CHD, heart failure and their composites (but not of cardiovascular or all-cause mortality) with low-dose chlorthalidone [23,24]; and significant reductions of stroke, composite of stroke and CHD, and all-cause death by low-dose indapamide [26,28].

Beta-blockers

Table 2 lists the five RCTs (18724 patients) suitable for the primary analysis of placebo-controlled studies in which treatment was initiated with a beta-blocker, and one additional trial included in a secondary meta-analysis [Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) trial [35]], in which two-thirds of the patients received treatment with a beta-blocker, but one-third was

TABLE 2. BP lowering by beta-blockers

Trial	Proportion of hypertensive patients in the study (%)	Baseline treatment	Drugs compared: Active	Drugs compared: Control	Patient number	Follow-up (years)	Baseline BP (mmHg): SBP	Baseline BP (mmHg): DBP	Achieved SBP (mmHg): Active	Achieved SBP (mmHg): Control	Achieved DBP (mmHg): Active	Achieved DBP (mmHg): Control
Trials for primary analysis												
MRC-mild [20][a]	100	No	Propranolol	Placebo	13057	5	161	98	139.7	149.5	86.5	93
HEP [38]	100	No	Atenolol	Untreated	884	4.4	196	98	162.1	180.1	77	88
MRC-old [25][a]	100	No	Atenolol	Placebo	3315	5.8	185	91	154.5	167	77	86.5
TEST [39]	100	No	Atenolol	Placebo	720	2.3	163	90	157	161	85	89
UKPDS [40][b]	100	Yes, low	Atenolol	Less active	748	8.4	160	94	143	154	81	87
Total primary					18724	5.1	167.1	96.4	144.2	154.7	84.1	91.0
Additional trials for secondary analysis												
STOP [35][c]	100	No	Atenolol or metoprolol or pindolol or hydrochloro-thiazide	Placebo	1627	2.1	195	102	166	188.3	87.2	96.7
Total secondary					20351	4.9	169.3	96.8	145.9	157.35	84.3	91.5

BP, blood pressure.
[a]In MRC-mild and MRC-old trials, the arm randomized to a beta-blocker has been included together with the entire arm randomized to placebo.
[b]In UKPDS, the subgroup randomized to atenolol in the more intense treatment arm has been included together with the entire group randomized to less intense treatment.
[c]In STOP, 68% of patients in the active arm received a beta-blocker.

Outcome	Trials (n)	Outcome risk (% in 5 years)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	RR (95% CI)	*P* (Heterogen)	Absolute Risk Reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
Primary analysis										
Stroke	5	3.2	–10.5/–7.0	216/6654	394/12070	0.77 (0.61–0.97)		0.12	–7 (–13, –1)	136 (80, 1041)
CHD	5	4.3	–10.5/–7.0	293/6654	538/12070	0.88 (0.77–1.01)		0.47	–5 (–10, 0)	194 (101, ∞)
HF	2	6.5	–14.8/–8.7	31/777	60/855	0.57 (0.35–0.91)		0.28	–28 (–44, –6)	35 (23, 170)
Stroke + CHD	5	7.6	–10.5/–7.0	509/6654	932/12070	0.84 (0.74–0.95)		0.20	–12 (–20, –4)	82 (51, 264)
Stroke + CHD + HF	4	7.4	–10.7/–7.1	446/6282	901/11722	0.79 (0.64–0.97)		0.010	–16 (–27, –2)	64 (37, 451)
CV Death	5	3.7	–10.5/–7.0	260/6654	465/12070	0.85 (0.69–1.05)		0.11	–6 (–12, +2)	79 (86, –540)
All-cause Death	5	6.1	–10.5/–7.0	457/6654	780/12070	0.94 (0.84–1.06)		0.34	–4 (–10, +4)	273 (102, –274)
Secondary analysis										
Stroke	6	3.5	–11.4/–7.2	245/7466	447/12885	0.73 (0.58–0.91)		0.079	–10 (–15, –3)	105 (68, 314)
CHD	6	4.3	–11.4/–7.2	318/7466	566/12885	0.88 (0.77–1.01)		0.61	–5 (–10, 0)	193 (101, ∞)
HF	3	8.0	–18.5/–9.1	50/1589	99/1670	0.54 (0.39–0.76)		0.49	–34 (–43, –18)	30 (23, 54)
Stroke + CHD	6	7.9	–11.4/–7.2	563/7466	1013/12885	0.81 (0.72–0.92)		0.17	–15 (–22, –6)	67 (45, 159)
Stroke + CHD + HF	5	8.1	–11.7/–7.3	519/7094	1021/12537	0.75 (0.62–0.91)		0.005	–20 (–31, –7)	49 (32, 136)
CV Death	6	3.9	–11.4/–7.2	277/7466	506/12885	0.77 (0.60–0.99)		0.014	–9 (–16, 0)	111 (64, ∞)
All-cause Death	6	6.5	–11.4/–7.2	493/7466	843/12885	0.87 (0.74–1.02)		0.070	–9 (–17, +1)	118 (59, –764)

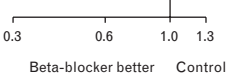

FIGURE 4 Relative and absolute risk reduction of various outcomes in the trials of blood pressure lowering by beta-blockers. Primary and secondary analyses include trials listed in Table 2. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

treated by a diuretic only. In the primary analysis, a SBP/DBP difference of −10.5/−7.0 mmHg between beta-blocker therapy and placebo (or no treatment; Fig. 4) was accompanied by a significant reduction in stroke [−23% (−3% to −39%)] and in major cardiovascular events [−16% (−5 to −26%) composite of stroke and CHD; −21% (−3 to −36%) composite of stroke, CHD and heart failure]. Only two trials provided separate incidences of heart failure, but also the risk of heart failure was found significantly and markedly reduced [−43% (−9 to −69%)]. Risk ratios were also lower than 1.0 for CHD, cardiovascular and all-cause mortality, but the reductions did not achieve statistical significance. Inclusion of the STOP trial [35] in the secondary meta-analysis made RR reduction of cardiovascular death to achieve statistical significance [−23% (−1 to −40%)]. Heterogeneity reached statistical significance ($P < 0.1$) only for the composite of stroke, CHD and heart failure in the primary analysis, but was slightly increased in the secondary analysis (Fig. 4).

Absolute incidences of cardiovascular outcomes in the control group are indicated in Fig. 4: cardiovascular death incidence averaged 3.7% in 5 years. Absolute risk reduction induced by beta-blocker treatment (primary analysis) amounted to seven strokes and 16 major cardiovascular events every 1000 patients treated for 5 years (NNT 136 and 64, respectively).

Risk ratio standardization to 10/5 mmHg SBP/DBP differences (values close to those actually occurring) reduced only slightly the original values: stroke 0.80 (0.66–0.97); heart failure 0.73 (0.55–0.95); composite of stroke, CHD and heart failure 0.82 (0.69–0.98); and cardiovascular death 0.87 (0.73–1.04).

Calcium antagonists

Table 3 lists the 10 RCTs (30 359 individuals) included in the primary analysis of placebo-controlled studies in which active treatment was based on a calcium-antagonist (always a dihydropyridine) and two additional trials included in the secondary analysis. In the primary analysis, a −6/−3.4 mmHg SBP/DBP difference between calcium antagonist therapy and placebo was accompanied by a significant RR reduction of all outcomes except CHD and heart failure: stroke was reduced by −34% (−25 to −42%), major cardiovascular events (composite of stroke and CHD) by −24% (−8 to −38%), cardiovascular death by −18% (−3 to −30%) and all-cause death by −13% (−2 to −23%). A 17% reduction in CHD and a 19% reduction in heart failure did not achieve statistical significance because of the large CIs. Inclusion of two small trials in the secondary analysis could not change the risk ratios and their significance (Fig. 5).

Incidence of cardiovascular death in the placebo group averaged 4.2% in 5 years. Absolute risk reduction induced by calcium antagonist therapy (primary analysis) amounted to 18 strokes, 24 major cardiovascular events (composite of stroke and CHD) and 9 all-cause deaths every 1000 patients treated for 5 years (NNT 55, 41 and 107, respectively).

Standardization of risk ratios to a 10/5 mmHg SBP/DBP difference was also calculated, but with a considerable approximation because of the fact that the real BP reduction was only about one-half of that used for standardization: standardized risk ratio for stroke was 0.48 (0.38–0.60), for composite of stroke and CHD 0.63 (0.45–0.87), for cardiovascular mortality 0.72 (0.55–0.95) and for all-cause mortality 0.80 (0.66–0.97).

At variance with trials using diuretics or beta-blockers, a number of calcium antagonist trials also included a proportion of normotensive individuals and had baseline antihypertensive drugs continued during follow-up, with the calcium antagonist not being used as the initial drug. A sensitivity analysis including the four trials only enrolling hypertensive patients with no or minimal background therapy [42–44,51] showed significant and marked risk reductions of all outcomes, including those (CHD and heart failure), the reduction of which did not reach statistical

TABLE 3. BP lowering by calcium antagonists

Trial	Proportion of hypertensive patients in the study (%)	Baseline treatment	Drugs compared		Patient number	Follow-up (years)	Baseline BP (mmHg)		Achieved SBP (mmHg)		Achieved DBP (mmHg)	
			Active	Control			SBP	DBP	Active	Control	Active	Control
Trials for primary analysis												
Hunan [42]	100	No	Nitrendipine	Untreated	2080	4.7	161	99	140.7	148.9	85.2	90.6
Syst-Eur [43]	100	No	Nitrendipine	Placebo	4695	2	174	86	151.7	160.5	78.7	84.3
Syst-China [44]	100	No	Nitrendipine	Placebo	2394	3	171	86	150.6	158.6	81.1	84.1
IDNT [45][a]	100	Yes	Amlodipine	Placebo	1136	2.6	158	87	141	144	77	80
Fogari [46][b]	100	No	Amlodipine and fosinopril	Fosinopril	206	4	NR	NR	132.4	142.3	82.3	87.3
NICOLE [47]	40	No	Nisoldipine	Placebo	819	3	NR	NR	NR	NR	NR	NR
CAMELOT [48][a]	60	Yes	Amlodipine	Placebo	1318	2	129	78	124.7	129.3	75.2	78.2
ACTION [49]	52	Yes	Nifedipine GITS	Placebo	7665	4.9	NR	NR	130.3	135.7	76.2	79.2
REIN-2 [50]	60	Yes	Felodipine and ramipril	Ramipril	335	1.6	131	84	130	134	80	82
FEVER [51]	100	Yes, low	Felodipine	Placebo	9711	3.3	154	91	137.5	142.2	82.4	85
Total primary					30359		159	89	138.6	144.6	79.7	83.2
Additional trials for secondary analysis												
BENEDICT-A [52][c]	57	Yes	Verapamil and trandolapril	Placebo	600	3.6	151	88	139	142	80	83
DEMAND [53][d]	44.2	Yes	Delapril and manidipine	Placebo	253	3.8	148	87	137.2	139.5	80.5	82.9
Total secondary					31212		159	89	138.6	144.5	79.7	83.2

BP, blood pressure.
[a]In IDNT and CAMELOT, comparison between the arm randomized to amlodipine with the arm randomized to placebo.
[b]In Fogari, comparison of the arm randomized to the combination amlodipine and fosinopril with the arm randomized to fosinopril only.
[c]In BENEDICT-A, comparison of the arm randomized to the combination verapamil and trandolapril with placebo. The comparisons verapamil with placebo, and verapamil and trandolapril versus trandolapril only were not included because the SBP/DBP differences were too small.
[d]In DEMAND, comparison of the arm randomized to the combination delapril and manidipine with the arm randomized to placebo. The comparison delapril and manidipine with delapril only was not included because the SBP/DBP difference was too small.

significance in the primary analysis (Fig. 6). This sensitivity analysis markedly reduced the high heterogeneity between the trials found in the primary analysis (compare Figs. 5 and 6).

Angiotensin-converting enzyme inhibitors

Table 4 lists the 12 RCTs and 13 randomized comparisons (35 707 patients) in which active treatment was based on an ACE inhibitor and which were included in the primary analysis. For the secondary analysis, two additional trials and an additional comparison in two of the trials included in the primary analysis were considered. All the additional groups compared a treatment initiated with an association of an ACE inhibitor and another drug with placebo treatment.

In the primary analysis, a SBP/DBP difference of about −4/−2 mmHg between ACE-inhibitor therapy and placebo

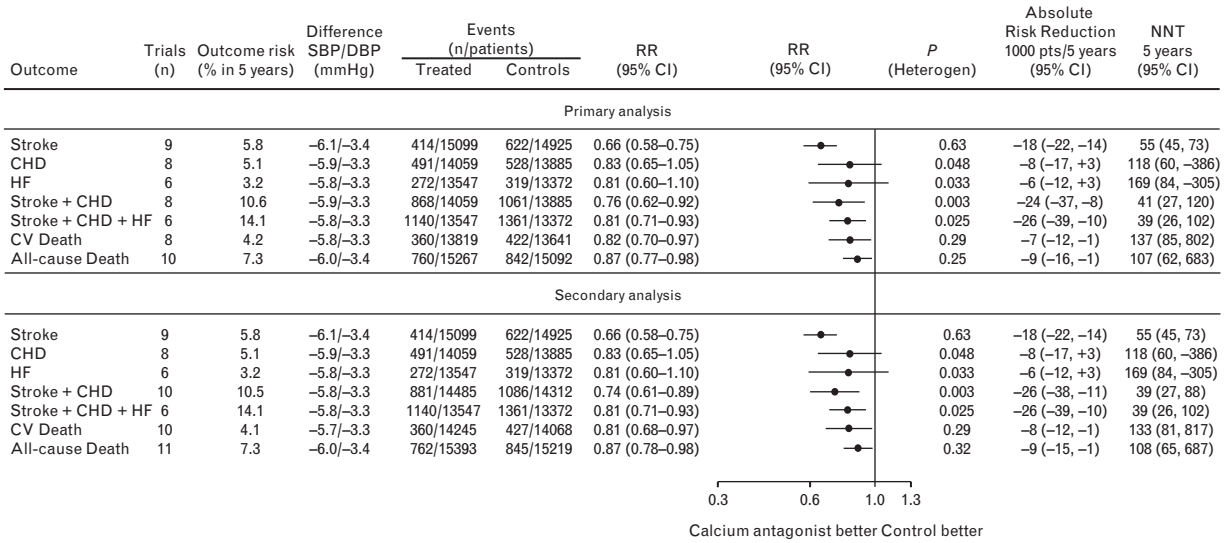

FIGURE 5 Relative and absolute risk reduction of various outcomes in the trials of blood pressure lowering by calcium antagonists. Primary and secondary analyses include trials listed in Table 3. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

Outcome	Trials (n)	Outcome risk (% in 5 years)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	RR (95% CI)	*P* (Heterogen)	Absolute Risk Reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
Sensitivity analysis										
Stroke	4	7.8	–6.5/–3.7	306/9532	466/9348	0.63 (0.53–0.76)		0.25	–26 (–31, –17)	39 (32, 58)
CHD	3	2.9	–6.3/–3.5	113/8492	151/8308	0.74 (0.58–0.94)		0.63	–7 (–11, –2)	143 (94, 579)
HF	3	1.9	–6.3/–3.5	59/8492	84/8308	0.68 (0.49–0.95)		0.77	–5 (–7, –1)	194 (135, 1091)
Stroke + CHD	3	10.3	–6.3/–3.5	382/8492	528/8308	0.71 (0.62–0.81)		0.36	–27 (–34, –18)	37 (29, 55)
Stroke + CHD + HF	3	12.3	–6.3/–3.5	463/8492	612/8308	0.74 (0.66–0.83)		0.64	–29 (–37, –20)	34 (27, 51)
CV Death	3	4.6	–6.3/–3.5	162/8492	221/8308	0.71 (0.58–0.87)		0.87	–12 (–16, –6)	84 (62, 176)
All-cause Death	4	7.7	–6.5/–3.7	344/9532	432/9348	0.77 (0.67–0.89)		0.68	–16 (–23, –8)	61 (44, 123)

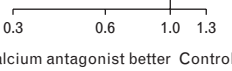

FIGURE 6 Relative and absolute risk reduction of various outcomes in the trials of blood pressure lowering by calcium antagonists (only hypertensive patients with no or minimal baseline therapy). Sensitivity analysis including some of the trials [42–44,51] of Table 3. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

was associated with significant reductions in the RR of all outcomes, except cardiovascular and all-cause mortalities. Stroke was reduced by −20% (−7 to −31%), heart failure by −21% (−7 to −34%), CHD by −13% (−3 to −21%) and major cardiovascular events (composite of stroke, CHD and heart failure) by −17% (−8 to 25%). A 11% reduction in cardiovascular mortality and an 8% reduction in all-cause mortality did not achieve statistical significance (Fig. 7). Addition of 15 237 patients in the secondary analysis, mostly patients on a combination of an ACE inhibitor with a

TABLE 4. BP lowering by angiotensin-converting enzyme inhibitors

Trial	Proportion of hypertensive patients in the study (%)	Baseline treatment	Drugs compared: Active	Drugs compared: Control	Patient number	Follow-up (years)	Baseline BP (mmHg): SBP	Baseline BP (mmHg): DBP	Achieved SBP (mmHg): Active	Achieved SBP (mmHg): Control	Achieved DBP (mmHg): Active	Achieved DBP (mmHg): Control
Trials for primary analysis												
Lewis [54]	75.5	Yes	Captopril	Placebo	409	3	138	86	131	133	79.5	82
AIPRI [55]	82	Yes	Benazepril	Placebo	583	3	143	88	135.3	145.4	82.7	88.9
UKPDS [40,41][a]	100	Yes, low	Captopril	Placebo	790	8.4	160	94	144	154	83	87
HOPE [42]	46.9	Yes	Ramipril	Placebo	9297	5	139	79	134.6	138.1	76	77.7
PROGRESS [36][b]	>48	Yes	Perindopril	Placebo	2561	3.9	144	84	134.5	139.4	78.3	81.1
Fogari [46][c]	100	No	Fosinopril and amlodipine	Amlodipine	207	4	NR	NR	132.4	140.4	82.3	86.5
HYVET-pilot [27][d]	100	No	Lisinopril	Untreated	857	1.1	182	100	151.9	174	83.6	94.5
CAMELOT [48][e]	60	Yes	Enalapril	Placebo	1328	2	129	77	124	129.3	74.7	78.2
BENEDICT-A [52][f]	57	Yes	Trandolapril	Placebo	601	3.6	151	87	139	142	81	86
	57	Yes	Trandolapril and Verapamil	Verapamil	603	3.6	150	87	139	141	80	82
DIABHYCAR [57]	56	Yes	Ramipril	Placebo	4912	3.9	145	82	143.5	145	81.3	82
PEACE [58]	45.5	Yes	Trandolapril	Placebo	8290	4.8	134	78	129.6	131.6	74.4	75.6
DREAM [59]	43.5	Yes	Ramipril	Placebo	5269	3	136	83	127.9	132.1	78.6	81
Total primary					35707	4.2	140.1	81.5	134.0	137.8	77.5	79.6
Additional trials for secondary analysis												
PROGRESS [36][b]	>48	Yes	Perindopril and indapamide	Placebo	3544	3.9	149	87	133.1	145.2	79.1	84.1
BENEDICT-A [52][f]	57	Yes	Trandolapril and verapamil	Placebo	600	3.6	151	87	139	142	80	83
ADVANCE [37]	>75	Yes	Perindopril and Indapamide	Placebo	11140	4.3	145	81	134.7	140.3	74.8	75.6
DEMAND [53][g]	44.2	Yes	Delapril and manidipine	Placebo	253	3.8	148	87	137.2	139.5	80.5	82.8
Total secondary					50944	4.2	141.9	81.9	134.1	138.9	77.1	79.3

BP, blood pressure.
[a]In UKPDS, the subgroup randomized to captopril in the more intense treatment arm has been included together with the entire group randomized to less intense treatment.
[b]In PROGRESS, the comparison between the subgroup randomized to perindopril monotherapy with the matched group randomized to placebo has been included in the primary analysis, whereas the comparison between the subgroup randomized to the combination perindopril and diuretic with the matched group randomized to placebo has been added in the secondary analysis.
[c]In Fogari, comparison of the arm randomized to the combination fosinopril and amlodipine with the arm randomized to amlodipine only.
[d]In the HYVET pilot trial, the arm randomized to lisinopril has been compared to the entire arm randomized to placebo.
[e]In CAMELOT, the arm randomized to enalapril has been compared to the arm randomized to placebo.
[f]In BENEDICT-A, the comparisons trandolapril versus placebo, and trandolapril and verapamil versus verapamil have both been included in the primary analysis, whereas the comparison trandolapril and verapamil with placebo has been added to the secondary analysis (with placebo patients being counted only once).
[g]In DEMAND, the comparison between the combination delapril and manidipine with placebo has been included. The comparison delapril with placebo has not been included because the SBP/DBP difference was too small.

Outcome	Trials (n)	Outcome risk (% in 5 years)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	RR (95% CI)	P (Heterogen)	Absolute Risk Reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
Primary analysis										
Stroke	10	4.3	–4.2/–2.1	550/17058	679/17036	0.80 (0.69–0.93)		0.22	–9 (–13, –3)	116 (76, 331)
CHD	10	6.9	–4.2/–2.1	987/17058	1133/17036	0.87 (0.79–0.97)		0.53	–9 (–14, –2)	111 (69, 481)
HF	6	5.7	–3.5/–1.6	645/14942	822/14944	0.79 (0.66–0.93)		0.17	–12 (–19, –4)	84 (52, 250)
Stroke + CHD	12	10.8	–4.1/–2.1	1561/17659	1834/17639	0.85 (0.79–0.92)		0.38	–16 (–23, –9)	62 (44, 116)
Stroke + CHD + HF	6	16.9	–3.5/–1.6	1951/14952	2377/14944	0.83 (0.75–0.92)		0.059	–29 (–42, –14)	35 (24, 74)
CV Death	11	5.0	–4.1/–2.0	633/16378	770/16359	0.89 (0.75–1.07)		0.097	–5 (–12, +4)	182 (81, –285)
All-cause Death	10	9.3	–4.1/–2.0	1274/15984	1389/15958	0.92 (0.83–1.03)		0.19	–7 (–16, +3)	135 (64, –360)
Secondary analysis										
Stroke	11	5.4	–5.1/–2.3	915/24397	1152/24381	0.79 (0.69–0.90)		0.11	–11 (–16, –5)	90 (62, 188)
CHD	11	6.8	–5.1/–2.3	1322/24397	1533/24381	0.86 (0.79–0.94)		0.29	–10 (–14, –4)	105 (70, 245)
HF	7	5.6	–4.1/–1.8	865/20511	1053/20515	0.83 (0.71–0.96)		0.082	–9 (–16, –2)	106 (63, 449)
Stroke + CHD	15	12.0	–5.0/–2.3	2274/25424	2717/25111	0.83 (0.77–0.91)		0.079	–20 (–27, –11)	49 (37, 93)
Stroke + CHD + HF	7	16.5	–4.1/–1.8	2651/20511	3120/20515	0.86 (0.78–0.94)		0.008	–23 (–36, –10)	43 (28, 101)
CV Death	15	5.3	–5.0/–2.3	1055/25424	1227/25111	0.87 (0.78–0.98)		0.16	–7 (–12, –1)	145 (86, 937)
All-cause Death	13	9.8	–5.0/–2.3	1990/24730	2182/24710	0.91 (0.85–0.98)		0.33	–9 (–15, –2)	114 (69, 510)

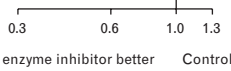

FIGURE 7 Relative and absolute risk reduction of various outcomes in the trials of blood pressure lowering by angiotensin-converting enzyme inhibitors. Primary and secondary analyses include trials listed in Table 4. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

diuretic, only slightly improved the risk reduction of most outcomes, but a 13% reduction in cardiovascular death and a 9% reduction in all-cause death achieved statistical significance (Fig. 7). Significant heterogeneity was found for two outcomes in the primary analysis and for three in the secondary analysis.

Figure 7 also indicates the incidences of each outcome in the control groups, with cardiovascular death risk averaging 5.0% in 5 years. Absolute risk reduction induced by ACE-inhibitor therapy (primary analysis) amounted to 9 strokes, 12 heart failure, nine CHD and 28 major cardiovascular events (composite of strokes, CHD and heart failure) every 1000 patients treated for 5 years (NNT 116, 84, 111 and 35, respectively).

The SBP/DBP difference between ACE inhibitors and control therapy was much smaller in ACE-inhibitor based than in diuretic or beta-blocker initiated trials, probably because most of the trials were of nonintentional BP lowering [1]. Risk ratio standardization to a 10/5 mmHg SBP/DBP difference was made, but should be seen as an uncertain approximation: stroke 0.52 (0.34–0.81); CHD 0.65 (0.48–0.91); heart failure 0.47 (0.26–0.79); and composite of stroke, CHD and heart failure 0.54 (0.39–0.76).

Angiotensin receptor blockers

Table 5 lists the 13 RCTs (65 256 individuals) included in the analysis of placebo-controlled trials, in which active treatment was based on an ARB (only primary analysis available).

TABLE 5. BP lowering by angiotensin receptor blockers

Trial	Proportion of hypertensive patients in the study (%)	Baseline treatment	Drugs compared: Active	Drugs compared: Control	Patient number	Follow-up (years)	Baseline BP (mmHg): SBP	Baseline BP (mmHg): DBP	Achieved SBP (mmHg): Active	Achieved SBP (mmHg): Control	Achieved DBP (mmHg): Active	Achieved DBP (mmHg): Control
Trials for primary analysis												
RENAAL [60]	93	Yes	Losartan	Placebo	1513	3.4	152	82	143.5	146.2	76.7	77.7
IDNT [45][a]	100	Yes	Irbesartan	Placebo	1148	2.6	159	87	140	144	77	80
IRMA-2 [61]	100	No	Irbesartan	Placebo	590	2	153	90	142	144	83	83
SCOPE [62]	100	Yes, low	Candesartan	Placebo	1937	3.7	166	90	145.2	148.5	79.9	81.6
PROFESS [63]	74	Yes	Telmisartan	Placebo	20332	2.5	144	84	135.4	139.6	79.2	81.3
TRANSCEND [64]	76.4	Yes	Telmisartan	Placebo	5926	4.7	141	82	134.1	138.7	NR	NR
DIRECT-2 [65]	62	Yes	Candesartan	Placebo	1905	4.7	133	77	NR	NR	NR	NR
I-PRESERVE [66]	88	Yes	Irbesartan	Placebo	4128	4.1	137	79	133.2	135.8	76.9	78.9
GISSI-AF [67]	85.4	Yes	Valsartan	Placebo	1442	1	139	82	134	137	NR	NR
NAVIGATOR [68]	77.5	Yes	Valsartan	Placebo	9306	6.5	140	83	133	136	78	82
ACTIVE-I [69]	88	Yes	Irbesartan	Placebo	9016	4.1	138	82	131.5	134.3	78.1	79.6
ROADMAP [70]	82	Yes	Olmesartan	Placebo	4447	3.2	136	80	126.7	128.7	74.3	76.2
ORIENT [71]	93	Yes	Olmesartan	Placebo	566	3.2	139	76	132.5	137	73	74
Total primary					65256	3.8	143.1	83.1	134.6	138.1	78.2	80.1

BP, blood pressure.
[a]In IDNT, comparison between the arm randomized to irbesartan and the arm randomized to placebo.

The SBP/DBP difference between active and placebo treatments was rather small (about −3.7/−2.0 mmHg) and associated with a significant relative reduction in stroke [−9% (−3 to −14%)], heart failure [−10% (−3 to −17%)] and major cardiovascular events [composite of stroke, CHD, heart failure −9% (−5 to −14%)], but not in CHD [−6% (+4% to −14%)], cardiovascular death [+3% (+13 to − 6%)] and all-cause death [+1% (+6 to −3%)]. Only for cardiovascular death, heterogeneity achieved statistical significance (Fig. 8).

In the control groups of ARB-based trials, incidence of all outcomes, except CHD, was markedly higher than in trials based on all other classes of antihypertensive drugs, incidence of cardiovascular death averaging 7.9% in 5 years. Absolute risk reduction amounted to nine strokes, seven heart failure and 20 major cardiovascular events (composite of stroke, CHD and heart failure) every 1000 patients treated for 5 years (NNT 114, 144 and 50, respectively; Fig. 8).

Standardizations of risk ratios to 10/5 mmHg SBP/DBP differences were also calculated, but should be taken with caution because of the large approximations: stroke 0.80 (0.70–0.93); heart failure 0.75 (0.60–0.92); and composite of stroke, CHD and heart failure 0.79 (0.69–0.88).

Renin–angiotensin system blockers

Trials in the primary analyses of ACE inhibitors and ARBs were combined together (25 trials, 100 963 individuals). SBP/DBP differences between active and control treatment of about −3.8/−2.0 mmHg were associated with significant reductions in stroke [−13% (−7 to −18%)], heart failure [−14% (−6 to 21%)], CHD [−10% (−3 to −15%)] and composite of stroke, CHD, and heart failure [−13% (−8 to −18%)], but not in cardiovascular mortality [−2% (+8 to −10%)] and all-cause mortality [−2% (+2 to −6%)]. Absolute risk reductions amounted to nine strokes, 10 heart failure, six CHD and 27 major cardiovascular events every 1000 patients treated for 5 years (NNT 109, 99, 180 and 37, respectively).

Centrally acting drugs

Only a secondary analysis of RCTs using centrally acting drugs was possible, as six of the eight trials (but only 1786 patients) listed in Table 6 administered a centrally acting drug in combination with other drugs [29,30,33,34] or as a choice amongst various agents [31,32]. Only two trials initiated active treatment with a centrally acting drug only [72,73]. Most of the trials included in this analysis were early BP-lowering studies, patients had very high baseline and a very high incidence of cardiovascular outcomes in the control group (average cardiovascular death 11.4% in 5 years). SBP/DBP differences between active and placebo treatments were very large (−23/−14 mmHg) and associated with significant and marked reductions in all outcomes, except CHD and all-cause death. Stroke was reduced by −47% (−14 to −68%), heart failure by −91% (−67 to −98%), major cardiovascular events (composite of stroke, CHD and heart failure) by −46% (−14 to 66%) and cardiovascular death by 40% (−12 to −59%). A 13% reduction in CHD and a 17% reduction in all-cause death were not statistically significant (Fig. 9). Heterogeneity was significant for the composite of stroke, CHD and heart failure, and for all-cause death.

As a result of the high risk of the patients and the marked BP reduction, absolute risk reductions were large: 73 strokes, 35 heart failure, 108 major cardiovascular events and 41 cardiovascular deaths every 1000 patients treated 5 years (NNT 14, 26, 9 and 24, respectively).

Influence of individual trials on pooled effect sizes

In none of the primary analyses excluding one trial at a time brought the point estimate of the combined effect on any outcome outside the overall estimate with all available trials, indicating no trial had an excessive influence in any analysis.

DISCUSSION

Strengths and limitations of the evidence concerning the benefits of each class of antihypertensive agents

A large number of trials comparing active BP-lowering treatment based on a diuretic with placebo or no treatment could be included in the primary analysis (12 trials on little less than 50 000 patients). Most of these trials (9 of 12) were completed in an early period of antihypertensive treatment

Outcome	Trials (n)	Outcome risk (% in 5 years)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	RR (95% CI)	*P* (Heterogen)	Absolute Risk Reduction 1000 pts/5 years (95% CI)	NNT 5 years (95% CI)
Primary analysis										
Stroke	11	10.1	−3.7/−2.0	1734/31359	1902/31402	0.91 (0.86–0.97)		0.68	−9 (−13, −3)	114 (74, 334)
CHD	11	3.7	−3.5/−1.6	822/31026	868/30883	0.94 (0.86–1.04)		0.48	−2 (−5, +1)	455 (198, −672)
HF	8	7.0	-3.8/−2.1	1286/25928	1429/26007	0.90 (0.83–0.97)		0.36	−7 (−12, −2)	144 (86, 475)
Stroke + CHD	10	14.1	−3.7/−2.0	2547/30637	2775/30682	0.92 (0.87–0.97)		0.88	−11 (−18, −4)	91 (57, 238)
Stroke + CHD + HF	8	22.5	−3.8/−2.1	3659/25928	4100/26007	0.91 (0.86–0.95)		0.22	−20 (−31, −11)	50 (33, 90)
CV Death	10	7.9	−3.7/−2.0	1867/30637	1833/30682	1.03 (0.94–1.13)		0.078	+2 (−5, +10)	
All-cause Death	13	14.4	−3.7/−2.0	3413/32699	3377/32557	1.01 (0.97–1.06)		0.92	+1 (−4, +9)	

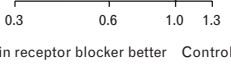

FIGURE 8 Relative and absolute risk reduction of various outcomes in trials of blood pressure lowering by angiotensin receptor blockers. Primary analyses include trials listed in Table 5. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

TABLE 6. BP lowering by centrally acting drugs

Trial	Proportion of hypertensive patients in the study (%)	Baseline treatment	Drugs compared		Patient number	Follow-up (years)	Baseline BP (mmHg)		Achieved SBP (mmHg)		Achieved DBP (mmHg)	
			Active	Control			SBP	DBP	Active	Control	Active	Control
Trials for primary analysis												
Wolff [72]	100	No	Reserpine	Placebo	87	1.4	177	109	157.1	190	95.5	115.3
VA-1 [29]	100	No	Hydrochlorothiazide, reserpine and hydralazine	Placebo	143	1.5	186	121	142.6	182	91.9	118.7
VA-2 [30]	100	No	Hydrochlorothiazide and reserpine and hydralazine	Placebo	380	3.8	164	104	134.9	169.3	86.4	105
Carter [31]	100	No	Thiazide and methyldopa or debrisoquine	Untreated	99	4	>160	≥110	NR	NR	106	115
Barraclough [32]	100	No	Methyldopa or debrisoquine or bendrofluazide	Placebo	116	2	NR	110	NR	NR	89.8	104.2
HSCSG [33]	100	No	Methyclothiazide and deserpidine	Placebo	452	3	164	101	141	166	88	100
USPHS [34]	100	No	Chlorthalidone and rauwolfia	Placebo	389	7	147	99	131.5	147.4	88.4	98.4
Sprackling [73]	100	No	Methyldopa	Untreated	120	5.5	201	108	180	196.5	99	103.3
Total primary					1786	4.0	165.2	104.3	141.2	167.3	90.2	104.3

BP, blood pressure.

(between 1978 and 1992), almost exclusively included hypertensive patients with no background antihypertensive therapy present at randomization and continued over follow-up. Average baseline SBP and DBP were elevated (164/95 mmHg), and on-treatment SBP/DBP differences between active and placebo treatment were relatively large (about 12/5.5 mmHg). Average cardiovascular risk in the control group was in the high category according to the current classifications [15,74,75], with an incidence of cardiovascular death of 8.8% in 10 years, and heterogeneity of the trials was low. All these characteristics gave high statistical power to the meta-analysis and favoured the demonstration that BP-lowering therapy based on diuretics can significantly reduce all types of cardiovascular outcome, including cardiovascular death and all-cause death. Absolute risk reduction was also remarkable, with a NNT for 5 years to prevent one major cardiovascular event of only 41 (34–54).

The high statistical power of the group of BP-lowering RCTs investigating diuretics also allowed separate meta-analyses, showing a number of outcomes could be significantly reduced by low-dose diuretics (i.e. with doses currently recommended) and drugs belonging to each of three major subclasses of diuretics (thiazides, chlorthalidone and indapamide).

Also, trials comparing centrally acting drugs with placebo were mostly done in early times of antihypertensive treatment (1966–1981) in previously untreated hypertensive patients with high baseline SBP/DBP values (mean 165/104 mmHg), at very high cardiovascular risk (cardiovascular death in the control group averaged 22.8% in 10 years), and very large SBP/DBP differences between active and control treatment (over 24/14 mmHg). However, these early trials were quite small and only a total of 1786 patients could be included in this meta-analysis. In spite of

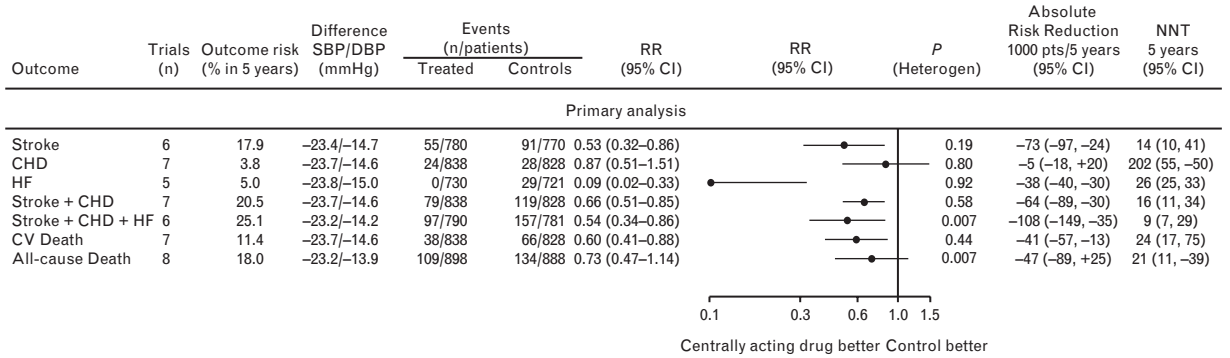

FIGURE 9 Relative and absolute risk reduction of various outcomes in trials of blood pressure lowering by centrally acting drugs. Secondary analyses include trials listed in Table 6. The column 'Outcome risk' reports the percentage incidence of each outcome in the control group calculated on a 5-year span. The column 'Absolute risk reduction' reports the number (and 95% CI) of events prevented every 1000 patients treated for 5 years with the observed RR. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; NNT, number (and 95% CI) of patients needed to treat for 5 years to prevent one event; pts, patients; *P* (Heterogen), *P* for the heterogeneity test χ^2Q; RR, Mantel–Haenszel risk ratios.

the smallness of the population studied, a large and significant reduction of all major cardiovascular events, except CHD but including cardiovascular death (though not all-cause death), could be demonstrated. As a result of the high risk of the population included, absolute risk reductions were large, and NNT for 5 years to prevent one major cardiovascular event was only 9. However, the results of the meta-analysis of centrally acting drugs must be taken with caution, as in most of the trials centrally acting drugs were one of the possible choices of the investigator or were administered in association with other agents since randomization.

Also, trials on beta-blockers versus placebo were conducted in early periods of antihypertensive therapy (between 1980 and 1998), but only 5 trials on less than 19 000 patients could be included in the primary analysis. Although all individuals were hypertensive without baseline treatment continued over follow-up, SBP/DBP differences between randomized treatments were rather large (about 10/7 mmHg) and for most outcomes trial heterogeneity was low, the statistical power of the beta-blocker meta-analysis was lower than that in the diuretic meta-analysis. Despite this limitation, stroke, heart failure and major cardiovascular events (but not CHD) were significantly reduced by beta-blocker-based therapy, and when the STOP study [35], with two-thirds of the actively treated patients receiving a beta-blocker, was added in a sensitivity analysis, also cardiovascular death was significantly reduced. Absolute cardiovascular risk in the control group was in the high stratum (7.4% in 10 years) and absolute risk reduction by beta-blockers was substantial, with a NNT for 5 years to prevent one major cardiovascular event of 64.

Several characteristics of the trials that have used more recent antihypertensive drug classes are different from those of the trials that tested diuretics, centrally acting drugs and beta-blockers. In part because of the ethical reasons resulting from the assumption that the benefits of BP lowering had already been demonstrated by trials with earlier compounds, trials of more recent antihypertensive drugs often enrolled hypertensive patients already on various types of antihypertensive agents, which were continued after randomization on both arms of the trials, in such a way that the drug to be tested and the respective placebo, rather than being the agents by which treatment was initiated, were the last ones to be added upon a background of other antihypertensive drugs. Furthermore, some of the recent trials (which we have defined of 'nonintentional' BP lowering [1]) were aimed at showing BP-independent benefits of new agents, and therefore enrolled also nonhypertensive individuals, although we tried to minimize this limitation by including in our meta-analysis only trials enrolling at least 40% of hypertensive patients and excluding trials on acute myocardial infarction and chronic heart failure. A major consequence of these differences in trial design was a much smaller BP difference between active and placebo arms.

These limitations affect to a lower degree the trials testing BP lowering by calcium antagonists (only data on dihydropyridines available). Of 10 trials (30 359 individuals) included in the primary analysis, six (20 222 individuals) exclusively enrolled hypertensive patients, three of which used no background antihypertensive therapy (hence, active therapy was initiated by a calcium antagonist) and the fourth randomized to a calcium antagonist or placebo on the background of very low dose diuretic therapy. Nonetheless, SBP/DBP differences between active and placebo therapies (~6/3 mmHg) were about half of those in the trials of diuretics or beta-blockers. Despite this limitation, BP lowering by calcium antagonists was found to significantly reduce stroke, the composite of stroke and CHD and the composite of stroke, CHD and heart failure, as well as both cardiovascular and all-cause mortality. A 17% reduction in CHD and a 19% reduction in heart failure, however, did not achieve statistical significance. A sensitivity analysis including only the four trials enrolling exclusively hypertensive patients and in most of which treatment was initiated by a calcium antagonist (i.e. with a design similar to trials testing diuretics, centrally acting drugs and beta-blockers) showed that heterogeneity was reduced, and all outcomes (including CHD and heart failure) could be significantly reduced by BP lowering with calcium antagonists.

Level of total cardiovascular risk was comparable in calcium antagonist and diuretic or beta-blocker based trials (cardiovascular death in the control groups averaging 8.4, 8.8 and 7.4% in 10 years, respectively), and absolute risk reduction induced by calcium antagonists, despite the limited BP reduction versus placebo, was remarkable with a NNT for 5 years to prevent a major cardiovascular event of 39 and of 107 to prevent a death.

The above-mentioned limitations of trials testing more recent drug classes are particularly evident with trials investigating ACE inhibitors. Nine of the twelve trials available for the primary analysis also included nonhypertensive patients and in only two small studies treatment was really initiated by an ACE inhibitor. In most cases the ACE inhibitor and the placebo were added to a background of preexisting antihypertensive therapy common to both arms of the trials. Consequently, the mean SBP/DBP differences between ACE inhibitor and placebo treatments were very small (−4/−2 mmHg), about one-third of those found with diuretics and beta-blockers. Nonetheless, these small BP differences were accompanied by significant reductions in all types of cardiovascular events considered, but a 11% and an 8% reduction in cardiovascular mortality and, respectively, in all-cause mortality did not achieve statistical significance. Whether this was because of the smallness of the SBP/DBP differences obtained because the ACE inhibitor was, in most trials, the last antihypertensive agent added to others cannot be decided. Both types of mortality were found to be significantly reduced (−13 and −9%, respectively) in the secondary meta-analysis, because of the addition of the large Action in Diabetes and Vascular Disease (ADVANCE) trial [37] in which an ACE inhibitor was tested in fixed combination with a diuretic, and of the Perindopril Protection against Recurrent Stroke Study (PROGRESS) trial group [36] randomized to a combination of ACE inhibitor and diuretic. Therefore, the achieved significance might be because of the concomitant use of a diuretic. Total cardiovascular risk in the ACE-inhibitor trials was higher than in trials based on diuretics, beta-blockers or calcium antagonists (cardiovascular death in control groups being 10 rather than 8.8, 7.4 and 8.4% in

10 years), and absolute risk reductions of most cardiovascular events were remarkable (with the exclusion of fatal events), with a NNT for 5 years of 35 to prevent a major cardiovascular event.

Trials that could be included in the meta-analysis of ARB studies suffer the same limitations as those testing ACE inhibitors: 10 of 13 trials also enrolled nonhypertensive patients, background antihypertensive therapy was continued over randomized follow-up in 12 of the 13 trials and a very small SBP/DBP difference versus placebo was obtained (−3.7/−2 mmHg). Consequently, despite the very large number of individuals included in the meta-analysis (65 256 individuals), the small BP lowering produced by addition of ARBs to previous therapy was associated only with significant reductions in strokes, heart failure and the composite of stroke and CHD, and of stroke, CHD and heart failure, but not of CHD and of cardiovascular and all-cause mortalities.

The total cardiovascular risk of patients in the ARB meta-analysis was very high (cardiovascular death in the control group averaged 15.8% in 10 years), and the absolute risk reduction of stroke, heart failure and major cardiovascular event substantial, with a NNT for 5 years of 114, 144 and 50, respectively.

It has to be mentioned that, even when ACE inhibitor and ARB based trials were pooled together (renin–angiotensin system blockers) with over 100 000 patients included, both reductions in cardiovascular and all-cause death did not achieve statistical significance.

A final difference between the trials testing the different classes of antihypertensive agents must be remarked. Mostly because of the trial design of adding the tested drug on a background of other antihypertensive drugs, largely used with ACE inhibitors and ARBs, less frequently used with calcium antagonists and practically unknown with earlier antihypertensive agents, the baseline and the achieved levels of SBP/DBP in the various meta-analyses here reported were highest with centrally acting drugs, followed by beta-blockers, diuretics, calcium antagonists, and were lowest with ACE inhibitors and ARBs. Although a previous meta-analysis has reported that baseline BP values appear not to influence RR reduction [76], a more recent and larger meta-analysis we have recently published [14] has found that at least the absolute benefit of BP lowering tends to decrease when the same BP difference is obtained at lower BP levels, and at the lowest SBP values (across a cutoff of 130 mmHg) only stroke is significantly reduced by BP-lowering therapy. This may be a further reason for the failure so far to demonstrate the effectiveness of ACE inhibitors and ARBs to significantly reduce mortality.

Comparison with previous meta-analyses

Ours is the largest and, at the same time, the most specific and rigorous meta-analysis of BP-lowering trials grouped according to the antihypertensive drug class that was compared to placebo, absence of treatment or usual treatment. It is the largest meta-analysis because it has considered all intentional and nonintentional BP-lowering trials, from the first one in 1966 to the end of 2013 [1], in which a BP difference between the trial arms could be attributed to a specific class of antihypertensive agents. It is the most specific meta-analysis because included trials enrolled either exclusively hypertensive patients or at least 40% of patients with hypertension, and because all trials conducted after an acute myocardial infarction, left ventricular dysfunction, heart failure and acute stroke were excluded. It is the most rigorous meta-analysis because the temptation to compare the various meta-analyses testing different classes in order to estimate their different effectiveness on various outcomes has been resisted; indeed, as remarked above, the characteristics of the patients included in trials using different drug classes were quite different, the design of the trials different (the drug confronted with placebo being the one by which treatment was initiated in trials on diuretics and beta-blockers, and in most of those on calcium antagonists, whereas it was the final one added on a background of other antihypertensive agents in most trials on blockers of the renin–angiotensin system), the BP difference achieved between the active and control arms varying between −23 and −3.5 mmHg SBP, −12.6 and −1.6 mmHg DBP according to the drug class considered. Finally, the only correct design to evaluate the differences in the effectiveness of different therapeutic regimens is head-to-head randomized comparison of different regimens.

As a result of the characteristics mentioned above, our meta-analyses differ from the four major groups of meta-analyses published so far. The major difference from the meta-analysis by Psaty *et al.* [2] is not so much in the number of trials we could include (18 of the trials we have included were published after closure of Psaty *et al.*'s survey at the end of 2002), but in the fact that Psaty *et al.* constructed a so-called network meta-analysis by putting together the trials testing different regimens, provided that they had one treatment in common. Although we understand network meta-analyses are based upon sophisticated statistical assumptions, this large body of assumptions and the consequent adjustments make – in our opinion – indirect comparisons much less valuable clinically than the direct comparisons we have chosen to make. The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), having chosen to make prospective meta-analyses, have excluded all trials published before the establishment of their protocol in 1997 [77], and therefore do not report any meta-analysis of placebo-controlled trials using diuretics or beta-blockers [3,4]. The last BPLTTC meta-analysis reporting comparisons of calcium antagonists and ACE inhibitors with placebo is a recent one on the influence of chronic kidney disease: it includes only three trials comparing a calcium antagonist with placebo (one not included in our meta-analysis because in predominantly nonhypertensive patients), and 10 trials comparing an ACE inhibitor with placebo (5 of which not included in our primary meta-analysis because of predominantly nonhypertensive patients with CHD or atherosclerosis or because testing an ACE inhibitor in fixed combination with a diuretic [78]). Law *et al.*'s meta-analysis [8], apart from not including trials published after 2007, is quite indiscriminate as far as it considers a large number of trials using antihypertensive agents in conditions different from hypertension: in the calcium antagonist versus placebo meta-analysis, seven hypertension trials are diluted by data from 15 other trials mostly on acute myocardial infarction, heart failure and

other conditions different from hypertension; in the ACE inhibitor versus placebo trials, data from seven trials also included in our meta-analysis are confounded by data from other 15 trials on acute myocardial infarction, heart failure, etc.; the ARB versus placebo meta-analysis is limited to four trials in patients with CHD and heart failure rather than hypertension. The design of the 2009 Cochrane Collaboration meta-analyses [10] is rather similar to ours as far as diuretics are concerned, though excluding an important large trial such as the Hypertension Detection Follow-up Program (HDFP) [18,19] and including trials that we have considered for a secondary meta-analysis only, because a diuretic was given together or as an alternative to centrally acting drugs. Regarding more recent antihypertensive drug classes, the 2009 Cochrane collaboration [10] could only consider one trial comparing a calcium antagonist with placebo, three comparing ACE inhibitors with placebo and none comparing ARBs with placebo.

A few authors have focused on the meta-analyses of placebo-controlled trials using a given class of drugs. In their seminal meta-analysis on beta-blockers, Lindholm *et al.* [5] have included the five major trials we have also considered, inclusive of STOP [20,25,35,38,39], but exclusive of UK Prospective Diabetes Study (UKPDS) [40,41], but have also considered Dutch Transient Ischemic Attack (Dutch TIA) [79] (which we have excluded because of uncertainty about the proportion of hypertensives) and IPPPSH [80] (which we have considered a trial comparing active regimens). The 2012 Cochrane Collaboration meta-analyses by Wiysong *et al.* [13] has considered only four beta-blocker initiated trials, three of which [20,25,38] were amongst the six we have included, and the International Prospective Primary Prevention Study in Hypertension (IPPPSH) trial [80]. Costanzo *et al.* [9] in 2009 meta-analyses of trials on calcium antagonists analyzed together the placebo-controlled and active-controlled trials; when separate analyses were done, only four placebo-controlled trials were included [43,48,49,51] (rather than 10 considered in our meta-analysis). Van Vark *et al.* [12] focused on trials using ACE inhibitors or ARBs, but they also mixed placebo-controlled and active-controlled trials, an unsuitable design for estimating the BP-lowering benefits obtained by the use of a specific class of drugs. Furthermore, inclusion in the ACE-inhibitor meta-analysis of the Hypertension in the Very Elderly Trial (HYVET) [28], initiated by a diuretic with the subsequent optional addition of an ACE inhibitor, and of the ADVANCE [37] trial, in which patients in the active group received a fixed combination of an ACE inhibitor and a diuretic, is disputable. Finally, Bangalore *et al.* [11] in their meta-analyses of the effects of ARB treatment, though correctly analyzing separately placebo-controlled and active-controlled trials, have analyzed together data from 10 (of 13) placebo-controlled trials on predominantly hypertensive patients, with data from seven trials on non-hypertensive conditions, mostly heart failure.

For the reasons discussed above, our quantitative estimations of the drug class effects on different outcomes can only be compared with those few meta-analyses that have followed the selection criteria similar to or not excessively dissimilar from ours. As far as diuretics are concerned, the evidence we have found of the beneficial effects of BP lowering by this class of drugs on all types of fatal and nonfatal outcomes, and the quantitative estimation of these benefits are very similar to what was reported by the 2009 Cochrane Collaboration [10], both meta-analyses showing all types of outcomes are significantly reduced by diuretics with extremely similar risk ratios. Although we have used a definition of low diuretic dose based on the maximum dose allowed by the protocol rather than the initial dose, also our meta-analyses show low-dose diuretics, as currently recommended, are associated with significant reduction of all outcomes including cardiovascular and all-cause death. As the Cochrane collaboration [10], we have found only strokes and the composite of major cardiovascular events, but not mortality, are found significantly reduced by high-dose diuretics, but suggest this might be because of the quite lower cardiovascular risk in the trials using high-dose diuretics. In addition, we have separately analyzed diuretic-based trials according to the subclass of diuretic being used (thiazide, chlorthalidone or indapamide) and found a number of clinically important outcomes can be reduced by any of these diuretic subclasses, even at low dose, thus supporting the recent European recommendations that any subclass of diuretic can be prescribed to hypertensive patients [75]. As to beta-blockers, our estimations agree with the meta-analyses of Lindholm *et al.* [5] and the two Cochrane Collaborations [10,13] so far as stroke and major cardiovascular events, but not CHD and all-cause mortality, can significantly be reduced, compared with placebo, by BP lowering with a beta-blocker. Our estimation of the beta-blocker effect on cardiovascular mortality (not calculated by the three previous meta-analyses [5,10,13]) reveals that, when the STOP trial [35] is included, cardiovascular mortality is significantly reduced by beta-blockers. No reasonable comparison can be done with the previous meta-analyses regarding BP lowering by calcium antagonists, ACE inhibitors or ARBs because of the too limited number of trials the previous meta-analyses have considered or the different criteria they have followed.

CONCLUSION

Our meta-analyses show that BP lowering induced by all specific classes of antihypertensive drugs is accompanied by a significant reduction of the relative and absolute risk of stroke and major cardiovascular events, and support the concept that reduction of these events is because of BP lowering *per se* rather than to specific properties of the various classes of agents [75]. However, evidence of risk reduction of other cardiovascular events and, particularly, of mortality differs from class to class. Only for BP lowering by diuretics, there is evidence of significant reduction of all fatal and nonfatal outcomes. For beta-blockers, reductions in CHD and all-cause mortality do not achieve statistical significance, although cardiovascular mortality appears to be significantly reduced when the STOP trial is included. For calcium antagonists, no statistically significant reduction in CHD and heart failure has been found, but stroke and both cardiovascular and all-cause mortality are significantly reduced. However, when more homogeneous trials are considered (only hypertensive patients and no or minimal baseline antihypertensive treatment), also CHD

and heart failure are found to be significantly reduced by calcium antagonists. Finally, no evidence of significant reduction in mortality (both cardiovascular and all-cause) has been achieved by BP lowering using ACE inhibitors and ARBs. Likewise, evidence of significant reductions in the risk of CHD and all-cause mortality (but not cardiovascular mortality) is lacking for the centrally acting drugs.

The above-mentioned differences in the evidence available for every drug class cannot be taken to mean that BP lowering by different classes of agents has partly different effectiveness on the risk of cardiovascular outcomes. Indeed, there are good reasons that may be suggested to explain the differences we have described. Trials using centrally acting drugs were all very small and the power of the meta-analysis low. The same is the case of beta-blocker-based trials, only 6 trials on 28 000 patients being available (to be compared to 12 trials on almost 50 000 patients for diuretics), and the upper confidence limits only slightly above unity suggest a larger number of patients may have led to reach statistical significance also for reductions in CHD and total mortality. BP differences between active and placebo treatments were quite small in trials using calcium antagonists and, particularly, ACE inhibitors and ARBs. It is not unreasonable (though unproven) to suppose that a larger BP reduction with respect to placebo may have significantly reduced the mortality outcomes also.

Possible differences in the effectiveness of different classes of antihypertensive agents at least on some outcomes can only be estimated by head-to-head comparison of two different classes of agents. However, the meta-analyses of class-specific placebo-controlled trials we have presented here must be considered a necessary background for the interpretation of the results of trials comparing head-to-head different active therapeutic regimens and of their meta-analyses (Thomopoulos, Parati, Zanchetti, in preparation). Often, similar incidences of a given outcome in active regimens comparative trials are interpreted as similar 'benefits' of the two active regimens. The data we have reported here are a warning that similar outcome incidences can be defined as 'benefits' only when at least one of the agents tested has been shown to significantly reduce the risk of that outcome in placebo-controlled trials. This we have shown here not to be true, at least at the moment, for all classes of drugs and for all outcomes.

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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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