Review

Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs – overview and meta-analyses

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Background and objectives: We have recently published an overview and meta-analysis of the effects of the five major classes of blood pressure-lowering drugs on cardiovascular outcomes when compared with placebo. However, possible differences in effectiveness of the various classes can correctly be estimated only by head-to-head comparisons of different classes of agents. This has been the objective of a new survey and meta-analysis.

Methods: A database search between 1966 and August 2014 identified 50 eligible randomized controlled trials for 58 two-drug comparisons (247 006 patients for 1 029 768 patient-years). Risk ratios and their 95% confidence intervals of seven outcomes were estimated by a random-effects model.

Results: The effects of all drug classes are not significantly different on most outcomes when their blood pressure effect is equivalent. However, there are also significant differences involving almost all classes of drugs. When compared to all other classes together, diuretics are superior in preventing heart failure; beta-blockers less effective in preventing stroke; calcium antagonists superior in preventing stroke and all-cause death, but inferior in preventing heart failure; angiotensin-converting enzyme inhibitors more effective in preventing coronary heart disease and less in preventing stroke; angiotensin receptor blockers inferior in preventing coronary heart disease; and renin–angiotensin system blockers more effective in preventing heart failure. When stratifying randomized controlled trials according to total cardiovascular risk, no drug class was found to change in effectiveness with the level of risk.

Conclusions: The results of all available evidence from head-to-head drug class comparisons do not allow the formulation of a fixed paradigm of drug choice valuable for all hypertensive patients, but the differences found may suggest specific choices in specific conditions, or preferable combinations of drugs.

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

Abbreviations: ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; BPLTTC, Blood Pressure Lowering Treatment Trialists' Collaboration; CHD, coronary heart disease; CI, confidence interval; RAS, renin–angiotensin system; RASB, renin–angiotensin system blocker; RCT, randomized controlled trial

INTRODUCTION

We had previously published meta-analyses of 68 randomized controlled trials (RCTs) in which blood pressure (BP)-lowering by drugs was compared with placebo or no treatment, or less intense BP-lowering treatment in cohorts of hypertensive patients, or including at least 40% hypertensive individuals, with exclusion of all trials in which BP-lowering drugs were investigated in the treatment of acute myocardial infarction, heart failure, acute stroke, or in patients on dialysis [1–3]. Of the 68 RCTs comparing BP-lowering treatment with no or less intense treatment, 55 (195 267 individuals) were found suitable for drug class-specific meta-analyses. As recently published [4], these meta-analyses have shown that BP-lowering by all classes of antihypertensive drugs is accompanied by significant reductions of stroke and major cardiovascular events, supporting the concept that reduction of these events is due to BP-lowering *per se* rather than to specific drug properties. However, evidence of risk reduction of other events and particularly mortality was found with some drug classes only. Differences in the

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evidence available for every drug class versus no treatment cannot be taken to mean that BP-lowering by different classes of agents has partly different effectiveness on the risk of cardiovascular outcomes. Indeed, these possible differences can only be estimated by head-to-head comparisons of two or more classes of agents [4,5].

A number of meta-analyses comparing the effects of different antihypertensive drug classes are available, but some of these are dated back to several years ago and do not include a number of recent RCTs [6–10], or analyze together RCTs in which drugs with BP-lowering properties have been given to treat different conditions, such as acute myocardial infarction and heart failure, in which the BP-lowering properties of the drugs may represent a limiting factor rather than the beneficial mechanism [10,11]. Furthermore, many of the available meta-analyses have focused on the comparison of few drug classes only [12–16], have sometimes analyzed together RCTs comparing active treatments with RCTs using placebo as comparison [17], and have often surrendered to the temptation of comparing the effects of drug classes tested separately in differently designed RCTs [6,16], rather than relying on direct head-to-head comparisons.

We present here the results of an overview and meta-analysis of all RCTs we have been able to identify in which at least two BP-lowering drugs belonging to different pharmacological classes have been compared head to head, exclusively in cohorts of hypertensive patients or in which at least 40% of hypertensive patients were included.

METHODS

Trial eligibility

The initial database search for these meta-analyses was similar to that done for our previous meta-analyses [1–4], but was extended till 31 August 2014. As in our previous meta-analyses, trials had to meet the following criteria: enrolling individuals with hypertension (SBP $\geq$140 or DBP $\geq$90 mmHg or current antihypertensive treatment) or a proportion of at least 40% hypertensive individuals among those randomized, with exclusion of trials investigating acute myocardial infarction, heart failure, acute stroke, and patients on dialysis; protocol including measurement of at least one type of cardiovascular events as primary or secondary endpoints; BP values available during follow-up; follow-up of at least 6 months; a minimum of five events during follow-up; and randomized allocation to treatments.

Whereas in our previous meta-analyses [1–4], final selection was limited to those RCTs comparing active treatment to placebo, all RCTs exclusively comparing an active drug with placebo were excluded from the meta-analyses reported here, which included only RCTs in which at least two drugs belonging to two different classes of antihypertensive agents [diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARB)] were specifically compared.

The database search was done by two of the authors (C.T. and A.Z.) by consulting PubMed between 1966 and end of August 2014 (any language), the Cochrane Collaboration Library database, and the reference list of all major previous meta-analyses of antihypertensive treatment trials. Whenever possible, in case of doubt or missing information, the trial authors were consulted. Recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5] were adhered to.

Outcomes

As in our previous meta-analyses [1–4], data were extracted independently by two authors (C.T. and A.Z.), with differences resolved by discussion. Seven predetermined outcomes were considered: 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. Definition of the outcomes has been detailed in [1].

Quality assessment

Details on quality assessment of the two RCTs considered can be found in a previous publication [1]. In brief, our quality assessment was not substantially different from that proposed by the Cochrane Collaboration tool to assess the risk of bias; however, our modified procedure further aimed at evaluating the prevalence of hypertensive patients in each RCT, integrated specific additional criteria of bias beyond randomization and blindness, and finally took into account the magnitude of the product 'patient-years'.

Statistical analyses

Randomized controlled trials were divided into groups according to the two drug classes being compared, with trials comparing more than two classes being entered in more than one group. RCTs were attributed to a given comparison on the basis of randomized assignment to either of the two BP-lowering drugs belonging to different classes, independently of background treatment (no previous treatment, switch from previous treatment, or background treatment maintained). In case of randomization to two-drug combination treatment, a trial was included if the combinations being compared had an agent in common. In RCTs in which one group could receive different treatments at the investigator's choice (commonly either a diuretic or a beta-blocker) that group was only included, when suitable, in the treatment group 'all other drugs'. Subanalyses were done for subclasses of antihypertensive drugs (dihydropyridines and nondihydropyridines for calcium antagonists). Finally, meta-analyses were also done of RCTs comparing each given drug class with any other class.

Statistical analyses were done with the methods described in the studies reporting our previous meta-analyses of placebo (or no treatment)-controlled trials [1–4]. In brief, risk ratios and their 95% confidence intervals (CIs) for each trial calculated by the Mantel–Haenszel method were weighted by patient number and follow-up duration, and combined using a random-effects model. The random-effects model was chosen to avoid the assumption that participants in the individual trials were sampled from populations in which the intervention had the same quantitative effect [10]. However, we also quantified the

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proportion of inconsistency across the studies not explained by chance by using the I^2 and the χ^2Q statistics, and whenever P was greater than 0.1, we also used the fixed-effects model as sensitivity analysis. Heterogeneity was considered low when I^2 was between 0 and 25%, intermediate between 25 and 75%, and high above 75%.

Randomized controlled trials comparing active drug treatments were all designed with the intention of achieving the same average SBP and DBP during follow-up with both treatments. Small, and sometimes larger, SBP/DBP differences occurred; however, in most trials and for each drug class comparison, the means of every individual trial SBP/DBP differences were weighted by patients' number and follow-up duration, and were averaged. When the mean of the SBP and DBP differences was less than 1 mmHg, no adjustment was made, but whenever this was at least 1 mmHg, adjustment to 0 mmHg differences was made by using the α-coefficients of the meta-regression of risk ratio logarithms over BP differences which we previously calculated from 47 RCTs of intentional BP-lowering versus placebo [1].

The influence of individual RCTs 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.

In an additional set of analyses, the influence of the level of total cardiovascular risk on the effects of each class of BP-lowering agents versus all other classes was investigated by stratifying RCTs in low-moderate, high, and very high risk on the basis of the 10-year rates of cardiovascular death observed during the trial (low-moderate <5%, high risk 5 to <10%, very high ≥10%), and carrying out trend analysis to investigate whether risk ratios tended to change with the level of risk.

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

Comprehensive Meta-Analysis version 2 (Biostat, Englewood, 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

Figure 1 illustrates the investigated steps to identify RCTs to be included. Searching strategies are indicated in online Supplemental Table S1 (http://links.lww.com/HJH/A487) and RCTs excluded are listed in online Supplemental Table S2 (http://links.lww.com/HJH/A487). This procedure identified 50 eligible RCTs for 58 two-drug comparisons [17–66]. Online Supplemental Table S3 (http://links.lww.com/HJH/A487) indicates the characteristics of the 50 RCTs for a total of 247 006 patients followed up for an average of 4.17 years (1 029 768 patient-years). Forty-three of the 50 RCTs (86%) were of higher quality (scoring from 4 to 6), with only seven (14%) of lower quality.

Meta-analyses were done for comparisons of each of the five major classes of BP-lowering drugs with the other classes, separately and joined together. The drug classes considered were: diuretics, beta-blockers, calcium antagonists, ACE-inhibitors, and ARBs. An additional type of comparison was done by combining ACE-inhibitors and ARBs into a single group of renin–angiotensin system (RAS) blockers. The class of calcium antagonists was also analyzed separately for dihydropyridine and nondihydropyridine compounds. An additional meta-analysis was done of all RCTs comparing an ACE-inhibitor or an ARB or a beta-blocker versus either a diuretic or a calcium antagonist.

Diuretics versus other drug classes

Table 1 lists the RCTs and RCT subgroups available for comparisons of diuretics with each of the other drug classes. In the comparison of diuretics and beta-blockers (Fig. 2a), no significant differences could be found in the risk of any outcome. Heterogeneity was low to moderate for all outcomes. Use of a fixed-effects model in cases in

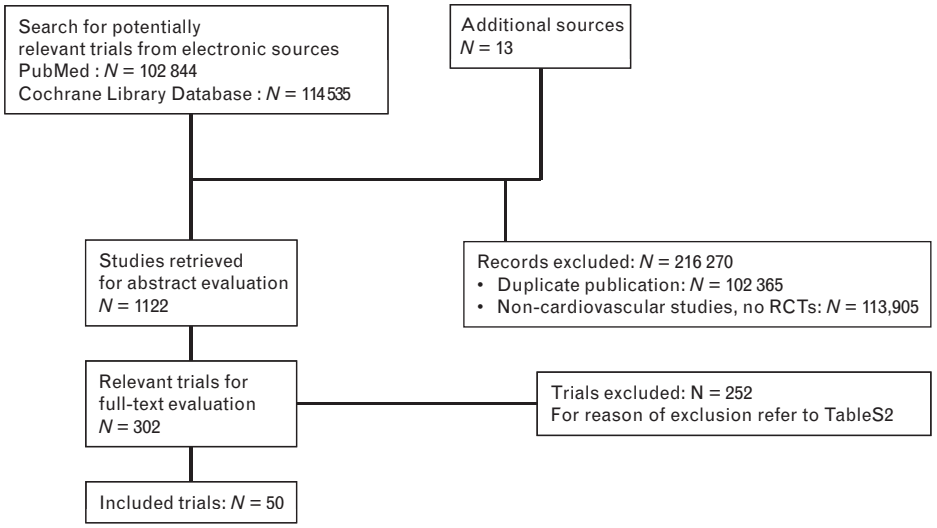

FIGURE 1 Identification process for eligible randomized controlled trials.

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TABLE 1. Comparisons of diuretics with other drug classes

Trial	Drugs compared		Patient number	Follow-up (years)	Baseline treatment		Baseline		On treatment			
									Diuretic		Control	
	Diuretic	Control			Random	Continued	SBP	DBP	SBP	DBP	SBP	DBP
(a) Diuretics vs. beta-blockers												
VA-COOP [64]	HCTZ	Propranolol	302	1	No	No	145.8	101.6	129.2	88.5	133.1	90.2
MRC-mild [49]	BFTZ	Propranolol	8700	5	No	No	161.4	98.5	135.2	85.3	138.9	86.5
IPPPSH [43]	Any TZ	Oxprenolol	6357	4	Yes	Yes[a]	173.0	107.8	147.4	90.1	143.6	88.9
Berglund [24]	BFTZ	Propranolol	106	10	No	No						
HAPPHY [37]	BFTZ or HCTZ	Atenolol or Metoprolol	6569	3.8	No	No	166	107	140.5	90	140	89
MRC-old [50]	HCTZ + Amil	Atenolol	2183	5.8	No	No	184.8	90.9	152	79	155.3	79
USSR [63]	Diuretics	Propranolol	304	4.1	No	No	168.5	105.9	152.7	98.7	152.4	98.8
COPE [30]	Any TZ	Any BB	2183	3.6	No	No	153.9	88.7	134	76.6	133.9	77
All			*26704*	*4.4*			*166.5*	*101.5*	*140.8*	*86.6*	*141.3*	*86.5*
(b) Diuretics vs. calcium antagonists												
MIDAS [47]	HCTZ	Isradipine	883	3	No	No	149.8	96.5	138.9	83.2	134.6	83.7
VHAS [66]	Chlorthalidone	Verapamil SR	456	4	No	No	167.6	102.3	139.9	86.5	142.7	86.7
NICS-EH [53]	TCMTZ	Nicardipine	414	5	No	No	172.3	93.8	149.6	82.7	150.1	82.3
INSIGHT [41]	HCTZ + Amil	Nifedipine GITS	6321	3.5	No	No	173	99	138	82	138	82
ALLHAT [20]	Chlorthalidone	Amlodipine	24303	4.9	Yes	No	146	84	135.3	77.7	136.4	77
SHELL [60]	Chlorthalidone	Lacidipine	1882	2.7	No	No	178.2	86.8	143.2	79.6	142	78.9
ACCOMPLISH [19][b]	HCTZ	Amlodipine	11506	3	Yes	No	145.4	80	132.5	74.4	131.6	73.3
COLM [28][b]	TZ or Indapamide	Amlodipine or Azelnidipine	5141	3.3	Yes	No	158	87	132.9	73.5	132.9	73.2
All			*50906*	*4.0*			*152.1*	*85.8*	*135.3*	*77.4*	*135.5*	*76.7*
(c) Diuretics vs. ACE-inhibitors												
ALLHAT [20]	Chlorthalidone	Lisinopril	24309	4.9	Yes	No	146	84	135.3	77.7	137.7	78
ANBP2 [21]	HCTZ	Enalapril	6083	4.1	No	No	168	91	144.8	81.3	145.1	81.3
HYVET pilot [39]	BFTZ	Lisinopril	857	1.1	No	No	181.8	99.8	151.5	83.6	151.9	83.6
NESTOR [52]	Indapamide SR	Enalapril	569	1	No	No	160.6	93.7	137.3	81	139.3	81.4
PHYLLIS [56]	HCTZ	Fosinopril	508	2.6	No	No	159.7	98.3	142.2	85.6	141.8	84.7
All			*32326*	*4.5*			*151.6*	*86.1*	*137.7*	*78.7*	*139.6*	*78.9*
(d) Diuretics vs. angiotensin receptor blockers												
COPE [30]	Any thiazide	Any ARB	2204	3.6	No	No	154	88.7	134	76.6	134.7	77.2
(e) Diuretics vs. RAS blockers[c]												
(c) + (d) [20,21,30,39,52,56]			*34530*	*4.5*			*151.7*	86.3	*137.4*	*78.6*	*139.3*	*78.8*
(f) Diuretics vs. all other drug classes[d]												
All [19–21,24,28,30,37,39, 41,43,47,49,50,52,53,56, 60,63,64,66]			*95971*	*4.1*			*156.9*	*90.6*	*137.6*	*80.3*	*138.4*	*80.1*

ACE, angiotensin-converting enzyme; Amil, amiloride; ARB, angiotensin receptor blocker; BB, beta-blocker; BFTZ, bendroflumethiazide; DBP, diastolic blood pressure; GITS, gastrointestinal transit system; HCTZ, hydrochlorothiazide; Random, at the time of randomization; RAS, renin–angiotensin system; SBP, systolic blood pressure; SR, slow release; TCMTZ, trichlormethiazide; TZ, thiazide.

[a]Only in part of the patients.

[b]In ACCOMPLISH randomization to the two-drug combinations benazepril + HCTZ and benazepril + amlodipine; in COLM to the two-drug combinations olmesartan + HCTZ and olmesartan + amlodipine.

[c]Inclusive of all RCTs comparing diuretics vs. ACE-inhibitors, and of the single trial comparing a diuretic with an angiotensin receptor blocker.

[d]Inclusive of all RCTs comparing diuretics with any other antihypertensive agent.

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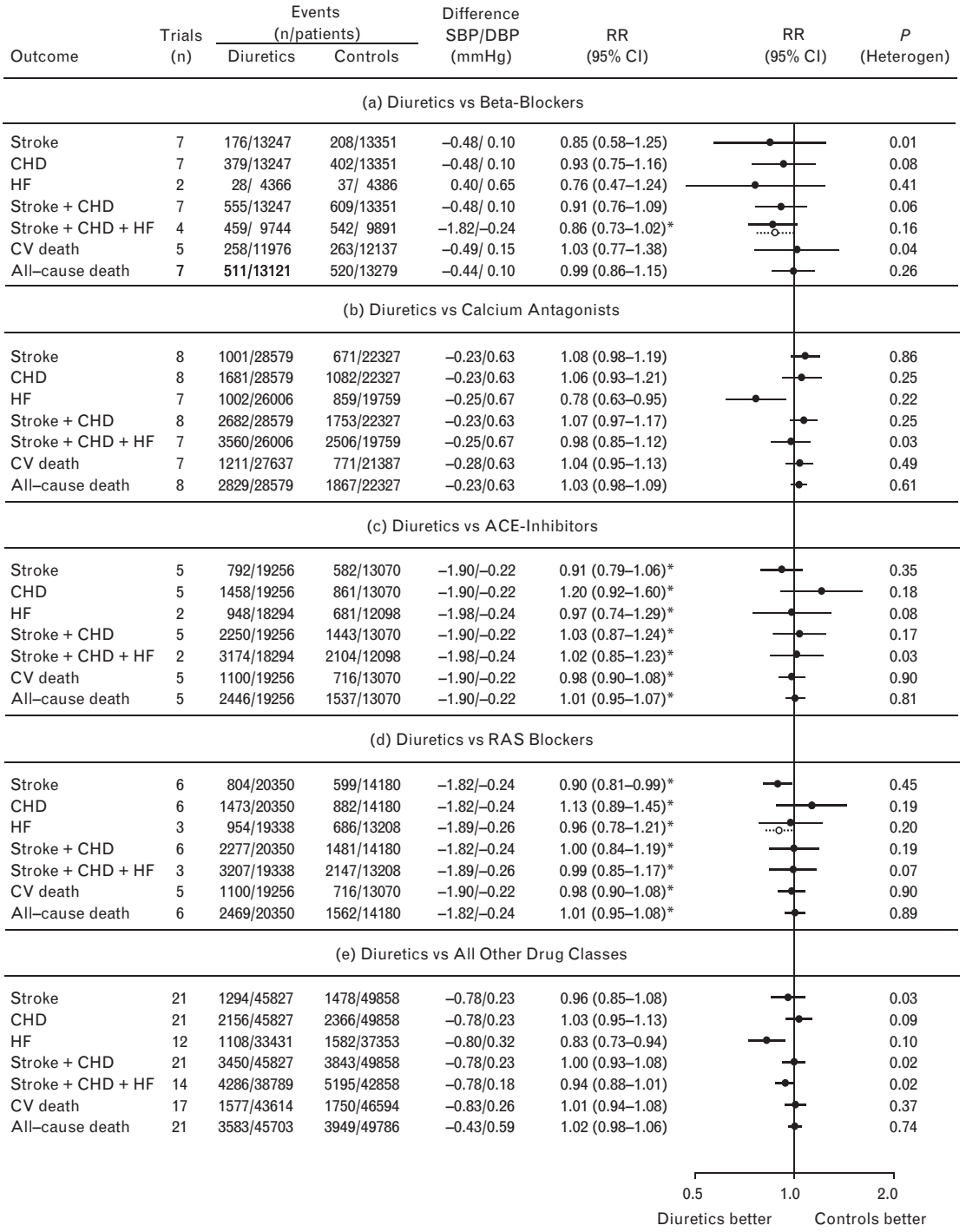

Outcome	Trials (n)	Events (n/patients) Diuretics	Events (n/patients) Controls	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)	P (Heterogen)
(a) Diuretics vs Beta-Blockers							
Stroke	7	176/13247	208/13351	–0.48/ 0.10	0.85 (0.58–1.25)		0.01
CHD	7	379/13247	402/13351	–0.48/ 0.10	0.93 (0.75–1.16)		0.08
HF	2	28/ 4366	37/ 4386	0.40/ 0.65	0.76 (0.47–1.24)		0.41
Stroke + CHD	7	555/13247	609/13351	–0.48/ 0.10	0.91 (0.76–1.09)		0.06
Stroke + CHD + HF	4	459/ 9744	542/ 9891	–1.82/–0.24	0.86 (0.73–1.02)*		0.16
CV death	5	258/11976	263/12137	–0.49/ 0.15	1.03 (0.77–1.38)		0.04
All–cause death	7	**511/13121**	520/13279	–0.44/ 0.10	0.99 (0.86–1.15)		0.26
(b) Diuretics vs Calcium Antagonists							
Stroke	8	1001/28579	671/22327	–0.23/0.63	1.08 (0.98–1.19)		0.86
CHD	8	1681/28579	1082/22327	–0.23/0.63	1.06 (0.93–1.21)		0.25
HF	7	1002/26006	859/19759	–0.25/0.67	0.78 (0.63–0.95)		0.22
Stroke + CHD	8	2682/28579	1753/22327	–0.23/0.63	1.07 (0.97–1.17)		0.25
Stroke + CHD + HF	7	3560/26006	2506/19759	–0.25/0.67	0.98 (0.85–1.12)		0.03
CV death	7	1211/27637	771/21387	–0.28/0.63	1.04 (0.95–1.13)		0.49
All–cause death	8	2829/28579	1867/22327	–0.23/0.63	1.03 (0.98–1.09)		0.61
(c) Diuretics vs ACE-Inhibitors							
Stroke	5	792/19256	582/13070	–1.90/–0.22	0.91 (0.79–1.06)*		0.35
CHD	5	1458/19256	861/13070	–1.90/–0.22	1.20 (0.92–1.60)*		0.18
HF	2	948/18294	681/12098	–1.98/–0.24	0.97 (0.74–1.29)*		0.08
Stroke + CHD	5	2250/19256	1443/13070	–1.90/–0.22	1.03 (0.87–1.24)*		0.17
Stroke + CHD + HF	2	3174/18294	2104/12098	–1.98/–0.24	1.02 (0.85–1.23)*		0.03
CV death	5	1100/19256	716/13070	–1.90/–0.22	0.98 (0.90–1.08)*		0.90
All–cause death	5	2446/19256	1537/13070	–1.90/–0.22	1.01 (0.95–1.07)*		0.81
(d) Diuretics vs RAS Blockers							
Stroke	6	804/20350	599/14180	–1.82/–0.24	0.90 (0.81–0.99)*		0.45
CHD	6	1473/20350	882/14180	–1.82/–0.24	1.13 (0.89–1.45)*		0.19
HF	3	954/19338	686/13208	–1.89/–0.26	0.96 (0.78–1.21)*		0.20
Stroke + CHD	6	2277/20350	1481/14180	–1.82/–0.24	1.00 (0.84–1.19)*		0.19
Stroke + CHD + HF	3	3207/19338	2147/13208	–1.89/–0.26	0.99 (0.85–1.17)*		0.07
CV death	5	1100/19256	716/13070	–1.90/–0.22	0.98 (0.90–1.08)*		0.90
All–cause death	6	2469/20350	1562/14180	–1.82/–0.24	1.01 (0.95–1.08)*		0.89
(e) Diuretics vs All Other Drug Classes							
Stroke	21	1294/45827	1478/49858	–0.78/0.23	0.96 (0.85–1.08)		0.03
CHD	21	2156/45827	2366/49858	–0.78/0.23	1.03 (0.95–1.13)		0.09
HF	12	1108/33431	1582/37353	–0.80/0.32	0.83 (0.73–0.94)		0.10
Stroke + CHD	21	3450/45827	3843/49858	–0.78/0.23	1.00 (0.93–1.08)		0.02
Stroke + CHD + HF	14	4286/38789	5195/42858	–0.78/0.18	0.94 (0.88–1.01)		0.02
CV death	17	1577/43614	1750/46594	–0.83/0.26	1.01 (0.94–1.08)		0.37
All–cause death	21	3583/45703	3949/49786	–0.43/0.59	1.02 (0.98–1.06)		0.74

FIGURE 2 Comparisons of BP-lowering treatment based on diuretics with treatments based on other drug classes: (a) beta-blockers; (b) calcium antagonists; (c) ACE-inhibitors; (d) RAS blockers; (e) all other drug classes. From left to right, the columns indicate the type of outcome, the number of trials (or comparisons) analyzed, the number of events and of patients in each treatment group, the differences between the on-treatment SBP/DBP values in the two treatment groups (the minus sign indicates a lower BP value in the first group), the risk ratios and 95% confidence intervals calculated by the random-effects model (the asterisk signals values that had to be adjusted for the SBP/DBP difference), the forest plots of risk ratios and 95% confidence intervals calculated by random-effects model (open circles and dotted lines indicate risk ratios and 95% confidence intervals calculated with the fixed-effects model, reported only when their statistical significance differed from that of the random-effects model), *P* value for heterogeneity. ACE, angiotensin-converting enzyme; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; RAS, renin–angiotensin system; RR, risk ratio; *vs*., versus.

which *P* for heterogeneity was greater than 0.1 only minimally changed the risk ratio values, but in the case of the composite outcome of stroke, CHD, and heart failure, the fixed-effects model changed a nonsignificant risk ratio [0.86 (0.73–1.02)] into a significant one [0.88 (0.78–0.99)]. No trial was found to have an excessive influence.

In the comparison of diuretics with calcium antagonist-based treatments (Fig. 2b), risk ratios indicate no significant

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differences in the risk of any outcome, except for heart failure, for which a significant 22% lower risk was found in the diuretic-treated group. There was low to moderate heterogeneity between the trials considered, and use of a fixed-effects model confirmed the results of the random-effects model. ALLHAT was found to exert an excessive influence, but was limited to the estimation of cardiovascular death. Exclusion of the only trial that used a nondihydropyridine compound [23] left the results of the meta-analyses unmodified. Addition of three RCTs in which a calcium antagonist-based treatment was compared with one in which the investigator had the choice of using either a diuretic or a beta-blocker [29,54,61] also left the results of the meta-analyses substantially unmodified.

In the comparison between diuretic and ACE-inhibitor-based treatments (Fig. 2c), no significant differences could be found in the risk of any outcome between the two treatment groups. Between-treatment BP differences required adjustment that did not modify the risk ratio significance. When the heterogeneity test allowed the use of the fixed-effects model, this did not cause any substantial change. ALLHAT was found to exert an excessive influence, but was limited to all-cause death. However, when the single trial comparing diuretics with ARBs [30] was added to compare diuretics with RAS blockers (Fig. 2d), a 10% lower risk of stroke with diuretics attained significance [risk ratio 0.90 (0.81–0.99) both by the random and fixed-effects models], and a significant 10% lower heart failure risk with diuretics was found with the fixed-effects model [risk ratio 0.90 (0.82–0.99)]. A lower incidence of heart failure with diuretics was also found when these drugs were compared with drugs of any other class [risk ratio 0.83 (0.83–0.94), random-effects model], whereas no significant difference was found for the other outcomes (Fig. 2e). Heterogeneity was low to moderate for all outcomes.

Beta-blockers versus other drug classes

Comparison of beta-blockers with diuretics has been reported in the previous section and Fig. 2a. Table 2 and Fig. 3 summarize comparisons with other classes of BP-lowering drugs. Whereas no significant difference in the risk of any outcome was found in the comparison of beta-blockers and diuretics with the random-effects model (Fig. 2a), comparing beta-blockers with calcium antagonists (Fig. 3a) showed that risk of stroke was significantly higher (25%) with beta-blockers. All the other outcomes were nonsignificantly different with the two treatments. Heterogeneity was low for stroke, and calculation of the stroke risk ratio by the fixed-effects model confirmed a risk point estimate of 1.25 (1.11–1.40). Use of the fixed-effects model to estimate the relative risk of the composite of stroke and CHD showed a significantly higher risk for beta-blockers [risk ratio 1.11 (1.04–1.19)], whereas the random-effects model gave a nonsignificant risk ratio [1.11 (0.97–1.26)]. No trial appeared to exert an excessive influence.

Separate meta-analyses comparing beta-blocker-based treatment with either ACE-inhibitors (Fig. 3b) or ARBs (Fig. 3c) are of uncertain interpretation, each including only two trials. Comparison of beta-blockers with ACE-inhibitors did not reveal any significant difference in either of the two available outcomes, whereas comparison with ARBs revealed a significantly higher (35%) risk of stroke in beta-blocker-treated patients. Comparison of beta-blockers with the combined group of RAS blockers (Fig. 3d) confirmed a significant difference limited to stroke [risk ratio 1.32 (1.13–1.54) both with random and fixed-effects models].

Combining all RCTs in which beta-blockers were compared to treatments based on any other drug class (Fig. 3e) confirmed a significantly higher (23%) risk of stroke with beta-blockers than with the other agents considered together. Heterogeneity was low to moderate for all outcomes, and when a fixed-effects model could be employed, risk ratios were very similar to those calculated by the random-effects model, confirming the only substantial difference between the effects of beta-blockers and the other BP-lowering drug classes is limited to the risk of stroke.

Calcium antagonists versus other drug classes

Comparison of calcium antagonists with diuretics and beta-blockers has been reported in the previous sections and Fig. 2b and 3a, showing that the effects of calcium antagonists were nonsignificantly different from those of diuretics and beta-blockers for all outcomes, except for stroke, in which case calcium antagonists appeared significantly superior to beta-blockers (Fig. 3a), and heart failure in which they appeared to be significantly inferior to diuretics (Fig. 2b). Table 3 and Fig. 4 summarize other comparisons. Calcium antagonist and ACE-inhibitor-based treatments were associated with nonsignificantly different risks of all studied outcomes, with the exception of stroke and heart failure (Fig. 4a). A lower risk of stroke with calcium antagonists did not attain statistical significance when the random-effects model was used, but became significant with the fixed-effects model [risk ratio 0.90 (0.82–0.99)]. On the contrary, risk of heart failure, after correction for the small BP difference, was 21% more frequent with the calcium antagonists. Application of a fixed-effects model confirmed the 21% excess of heart failure with calcium antagonists compared with the ACE-inhibitors. For CHD and composite outcomes, heterogeneity between the trials was moderate, and low for stroke, heart failure, and death. Exclusion from the meta-analysis of the only trial having used a nondihydropyridine calcium antagonist [23] left the results unmodified. A significantly higher heart failure incidence (27%) could also be found when comparing calcium antagonists with ARBs (Fig. 4b). However, a lower risk of CHD with a calcium antagonist than an ARB therapy reached statistical significance when a fixed-effects model could be used [risk ratio for CHD 0.87 (0.76–0.99)]. Comparison of calcium antagonists with RAS blockers confirmed a significantly higher risk of heart failure with calcium antagonists, but also a lower risk of stroke, which attained statistical significance both with the random-effects and the fixed-effects models [risk ratio 0.90 (0.82–0.98)]. For CHD and composite outcomes, heterogeneity was moderate, but low for stroke, heart failure, and death. In all these analyses, no trial exerted an excessive influence.

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TABLE 2. Comparisons of beta-blockers with other drug classes[b]

Trial	Drugs compared		Patient number	Follow-up (years)	Baseline treatment		Baseline		On treatment			
									Beta-Blocker		Control	
	Beta-blocker	Control			Random	Continued	SBP	DBP	SBP	DBP	SBP	DBP
(a) Beta-blockers vs. calcium antagonists												
ELSA [34]	Atenolol	Lacidipine	2334	3.8	No	No	163.5	101.4	141.5	85.7	142.1	85.9
AASK [17]	Metoprolol	Amlodipine	658	3	Yes	Yes	150	95.3	135	81	133	81
INVEST [42]	Atenolol	Verapamil SR	22576	2.7	Yes	No	149.5	86.3	130.5	76.1	130.8	76.3
ASCOT [22]	Atenolol	Amlodipine	19257	5.5	Yes	No	164	94.7	138.9	79.1	136.3	77.8
All			*44825*	*4.0*			*156.5*	90.8	*134.7*	*78.0*	*133.8*	*77.5*
(b) Beta-blockers vs. ACE-inhibitors												
UKPDS [62]	Atenolol	Captopril	758	8.4	Yes[a]	Yes[a]	159	93.5	143	81	144	83
AASK [17]	Metoprolol	Ramipril	877	4	Yes	Yes	150.5	95.5	135	81	135	82
All			*1635*	*6.0*			*154.4*	*94.6*	*138.7*	*81.0*	*139.2*	*82.5*
(c) Beta-blockers vs. angiotensin receptor blockers												
LIFE [46]	Atenolol	Losartan	9193	4.8	No	No	174.4	97.8	145.4	80.9	144.1	81.3
COPE [30]	Any BB	Any ARB	2199	3.6	No	No	153.8	88.7	133.9	77	134.7	77.2
All			*11392*	*4.6*			*170.4*	*96.0*	*143.2*	*80.2*	*142.3*	*80.5*
(d) Beta-blockers vs. RAS blockers[c]												
(b) + (c) [17,30,46,62]			*13027*	*4.8*			*168.4*	*95.9*	*142.6*	*80.3*	*141.9*	*80.8*
(e) Beta-blockers vs. all other drug classes[d]												
All [17,22,24,30,34,37, 42,43,46,49,50,62–64]			*83026*	*4.2*			*161.6*	*95.1*	*138.1*	*81.1*	*137.3*	*80.9*

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta-blocker; DBP, diastolic blood pressure; Random, at the time of randomization; RAS, renin–angiotensin system; SR, slow release.
[a]Only in part of the patients.
[b]Comparisons of beta-blockers with diuretics are reported in Table 1a.
[c]This comparison includes the two trials comparing beta-blockers with ACE-inhibitors and the two in which the control drug is an angiotensin receptor blocker.
[d]The comparison of beta-blockers with all other drug classes includes all trials listed above and the comparison with diuretics in Table 1.

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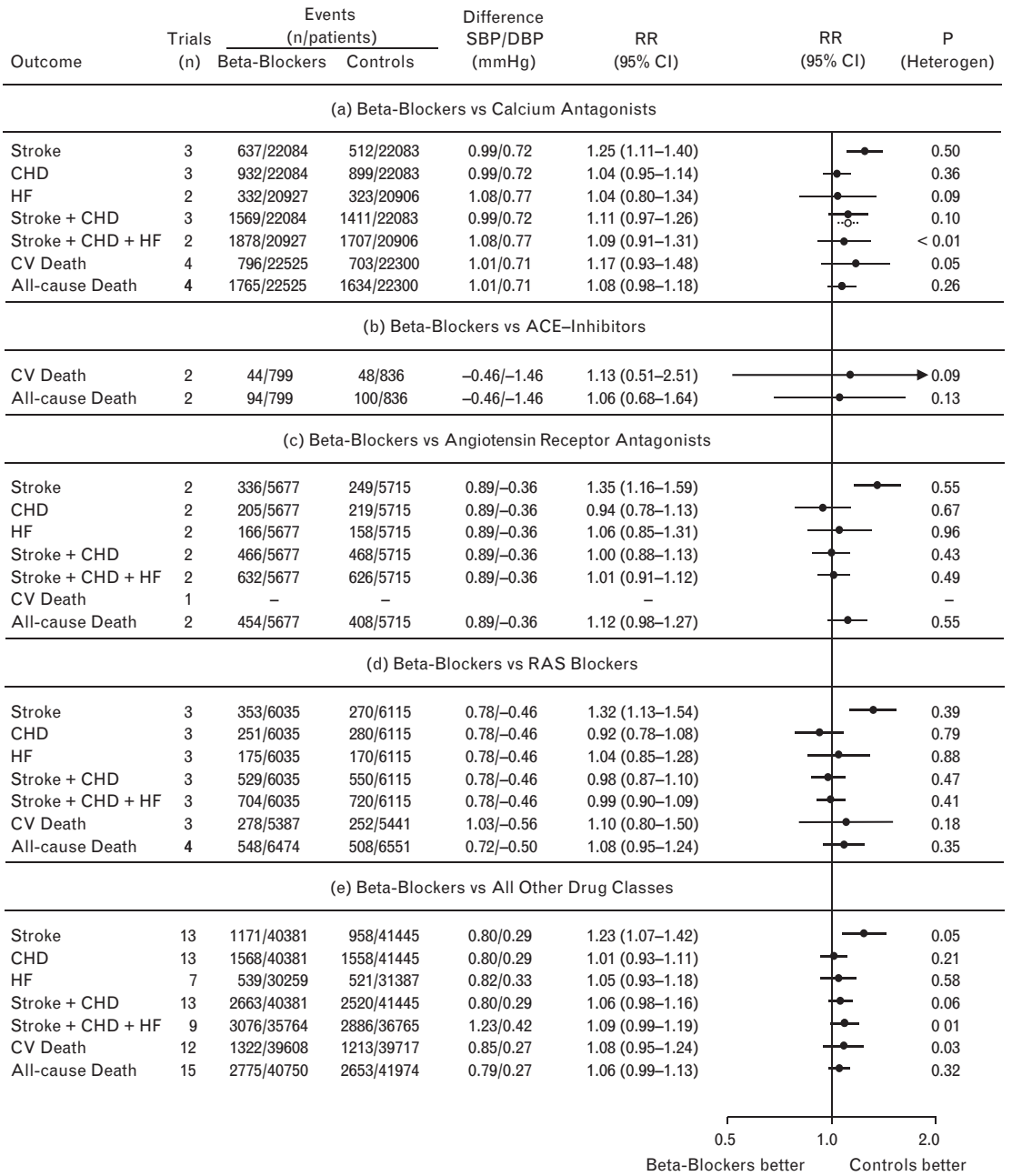

FIGURE 3 Comparisons of BP-lowering treatment based on beta-blockers with treatments based on other drug classes: (a) calcium antagonists; (b) ACE-inhibitors; (c) angiotensin receptor blockers; (d) RAS blockers; (e) all other drug classes. ACE, angiotensin-converting enzyme; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; RAS, renin–angiotensin system; RR, risk ratio. Other explanations as in Fig. 2.

The large combined meta-analysis comparing calcium antagonist-based treatment with treatment based on any other drugs (Fig. 4d) showed a significantly lower (−12%) incidence of stroke and a significantly higher (19%) incidence of heart failure with the calcium antagonist treatment. Risk of all-cause death was also slightly (−3%) but significantly lower with calcium antagonists. No significant difference was found for other outcomes (low heterogeneity). The decreases in stroke and all-cause death risk were confirmed by using a fixed-effects model. No trial exerted an excessive influence.

Further separate analyses were done of RCTs comparing dihydropyridine and nondihydropyridine calcium antagonists with any other classes of BP-lowering drugs (Table 3e and f). The separate meta-analyses largely confirmed the results of the meta-analysis including the two calcium antagonist subclasses together. However, whereas a higher risk of heart failure was significant with either subclass, and was quantitatively similar (Fig. 4e), a lower risk of stroke, cardiovascular, and all-cause death attained significance with dihydropyridines only (Fig. 4e).

Angiotensin-converting enzyme-inhibitors versus other drug classes

Figures 2c, 3b, and 4a show that the effects of ACE-inhibitors were not significantly different from those of diuretics

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TABLE 3. Comparisons of calcium antagonists with other drug classes[b]

Trial	Drugs compared		Patient number	Follow-up (years)	Baseline treatment		Baseline		On treatment			
									Calcium antagonist		Control	
	Calcium antagonist	Control			Random	Continued	SBP	DBP	SBP	DBP	SBP	DBP
(a) Calcium antagonists vs. ACE-inhibitors												
ABCD-H [18]	Nisoldipine	Enalapril	470	5	No	No	155.5	98	135	81	139	82
FACET [35]	Amlodipine	Fosinopril	380	3.5	No	No	170.5	94.5	153	86	157	88
STOP-2 [61]	Felodipine or Isradipine	Enalapril or Lisinopril	4400	5			194	98	159.5	80.5	159.5	81.8
J-MIND [45]	Nifedipine Ret.	Enalapril	436	2	No	No	161.5	90	145.3	82.6	147.7	85.2
Fogari [36]	Amlodipine	Fosinopril	205	4	No	No	160	99.2	140.4	86.5	142.3	87.3
AASK [17]	Amlodipine	Ramipril	653	3	Yes	Yes	150.7	96	133	81	135	82
ALLHAT [20]	Amlodipine	Lisinopril	18102	4.9	Yes	No	146	84	136.4	77	137.7	82
CAMELOT [25]	Amlodipine	Enalapril	1336	2	Yes	Yes	129.3	77.4	124.7	75.2	124	74.8
JMIC-B [44]	Nifedipine Ret.	Any ACEI	1650	3	Yes	No	146	82	136	77	138	79
BENEDICT [23]	Verapamil	Trandolapril	604	3.6	Yes	Yes[a]	150.4	87.5	141	82	139	81
All			*28236*	*4.5*			*153.7*	*86.7*	*139.8*	*78.0*	*140.9*	*79.0*
(b) Calcium antagonists vs. angiotensin receptor blockers												
IDNT [40]	Amlodipine	Irbesartan	1146	2.6	Yes	Yes	159.5	87	141	77	140	77
VALUE [65]	Amlodipine	Valsartan	15245	4.2	Yes	No	154.6	87.4	138	78	139	79
MOSES [48]	Nitrendipine	Eprosartan	1405	2.5	Yes	No	151.3	87.1	135	79.9	136.7	80.8
CASE-J [27]	Amlodipine	Candesartan	4703	3.2	Yes	Yes[a]	162.8	91.7	134.4	76.7	136.1	77.3
NAGOYA [51]	Amlodipine	Valsartan	1150	3.2	Yes	Yes[a]	144.5	81.5	132	74	131	73
All			*23649*	*3.8*			*155.8*	87.9	*137.0*	*77.6*	*137.9*	*78.4*
(c) Calcium antagonists vs. RAS blockers[c]												
(a) + (b) [17,18,20,23,25, 27,35,36,40,44,45, 48,51,61,65]			*51885*	*4.2*			*154.7*	*87.3*	*138.5*	*77.8*	*139.6*	*78.7*
(d) Calcium antagonists vs. all other drug classes[d]												
Additional trials												
STOP-2 [61]	Felodipine or Isradipine	Atenolol or Metoprolol or Pindolol or HCTZ + Amil	4408	5			194	98	159.5	80.5	159.2	81.4
NORDIL [54]	Diltiazem	Any BB or TZ	10881	4.5	No	No	173.4	105.7	154.9	88.6	151.7	88.7
CONVINCE [29]	Verapamil-COER	Atenolol or HCTZ	16476	3	Yes	No	150.1	86.8	136.5	79	136.6	79.7
All [17–20,22,23,25, 27–29,34–36,40–42, 44,45,47,48,51,53, 54,60,61,65,66]			*167921*	*4.0*			*156.1*	*89.2*	*137.6*	*78.3*	*137.8*	*78.9*
(e) Dihydropyridines vs. all other drug classes												
All [17–20,22,25,27,28, 34–36,40,41,44,45,47, 48,51,53,60,61,65]			*116928*	*4.3*			*156.6*	*88.6*	*137.4*	*77.6*	*138.1*	*78.4*
(f) Nondihydropyridines vs. all other drug classes												
All [23,29,42,54,66]			*50993*	*3.2*			*155.0*	*90.8*	*138.0*	*80.0*	*137.2*	*80.1*

ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; Amil, amiloride; ARB, angiotensin receptor blocker; BB, beta-blocker; HCTZ, hydrochlorothiazide; Random, at the time of randomization; RAS, renin–angiotensin system; Ret., retard; TZ, thiazide.

[a]Only in part of the patients.

[b]Comparisons of calcium antagonists with diuretics are reported in Table 1b and with beta-blockers in Table 2a.

[c]Inclusive of all RCTs comparing calcium antagonists with either ACE-inhibitors or angiotensin receptor blockers.

[d]Inclusive of all RCTs comparing calcium antagonists with any other antihypertensive agent as in Tables 1–3 (also of additional trials in which the control drug could be either a diuretic or a beta-blocker.

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Outcome		Trials (n)	Events (n/patients) Calcium Antagonists	Events (n/patients) Controls	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)	P (Heterogen)
(a) Calcium Antagonists vs ACE-Inhibitors								
Stroke		8	631/ 13491	715/ 13488	–1.14/–1.08	0.92 (0.80–1.06)*		0.34
CHD		8	1050/ 13491	978/ 13488	–1.14/–1.08	1.29 (0.99–1.67)*		0.03
HF		6	914/ 13197	779/ 13197	–1.09/–1.07	1.21 (1.10–1.32)*		0.95
Stroke + CHD		9	1692/ 13794	1706/ 13789	–1.07/–1.03	1.13 (0.94–1.37)*		0.01
Stroke + CHD + HF		6	2563/ 13197	2452/ 13197	–1.09/–1.07	1.14 (0.98–1.35)*		0.01
CV Death		8	833/ 13592	862/ 13828	–1.03/–0.99	0.98 (0.90–1.08)*		0.95
All-cause Death		8	1673/ 13480	1762/ 13716	–1.14/–1.06	0.96 (0.90–1.03)*		0.98
(b) Calcium Antagonists vs Angiotensin Receptor Blockers								
Stroke		5	401/ 11782	459/ 11867	–0.99/–0.77	0.88 (0.73-1.07)		0.25
CHD		5	409/ 11782	476/ 11867	–0.99/–0.77	0.88 (0.69-1.12)		0.17
HF		5	570/ 11782	467/ 11867	–0.99/–0.77	1.37 (1.01-1.85)		0.02
Stroke + CHD		5	810/ 11782	935/ 11867	–0.99/–0.77	0.88 (0.72-1.07)		0.05
Stroke + CHD + HF		5	1380/ 11782	1368/ 11867	–0.99/–0.77	1.12 (0.92-1.35)		< 0.01
CV Death		2	341/ 8163	356/ 8228	–0.86/–0.93	0.90 (0.67-1.22)		0.14
All-cause Death		5	1055/ 11782	1080/ 11867	–0.99/–0.77	0.98 (0.91-1.06)		0.68
(c) Calcium Antagonists vs RAS Blockers								
Stroke		13	1032/ 25273	1174/ 25355	–1.07/–0.93	0.91 (0.82–0.99)*		0.35
CHD		13	1459/ 25273	1454/ 25355	–1.07/–0.93	1.08 (0.91–1.29)*		< 0.01
HF		11	1484/ 24979	1246/ 25064	–1.04/–0.93	1.27 (1.14–1.42)*		0.22
Stroke + CHD		14	2502/ 25576	2641/ 25646	–1.03/–0.91	1.00 (0.89–1.15)*		< 0.01
Stroke + CHD + HF		11	3943/ 24979	3820/ 25064	–1.04/–0.93	1.13 (1.02–1.25)*		< 0.01
CV Death		10	1174/ 21755	1218/ 22056	–0.97/–0.97	0.98 (0.91–1.06)*		0.89
All–cause Death		13	2728/ 25262	2842/ 25583	–1.07/–0.92	0.98 (0.93–1.03)*		0.98
(d) Calcium Antagonists vs All Other Drug Classes								
Stroke		27	2130/ 74224	3363/ 91999	–0.29/–0.72	0.88 (0.84–0.93)		0.45
CHD		27	2958/ 74224	4544/ 91999	–0.29/–0.72	1.00 (0.93–1.08)		< 0.01
HF		23	2149/ 70185	2910/ 87978	–0.30/–0.74	1.19 (1.09–1.30)		0.02
Stroke + CHD		28	5099/ 74527	7920/ 92300	–0.28/–0.71	0.95 (0.90–1.01)		< 0.01
Stroke + CHD + HF		23	7072/ 70185	10616/ 87978	–0.30/–0.74	1.04 (0.98–1.10)		< 0.01
CV Death		24	2334/ 69766	3704/ 88199	–0.23/–0.72	0.96 (0.92–1.01)		0.48
All-cause Death		28	5531/ 74430	8352/ 92668	–0.30/–0.71	0.97 (0.94–0.99)		0.93
(e) Calcium Antagonists vs All Other Drug Classes, separately for Dihydropyridines and Non–dihydropyridines								
Stroke	DHP	23	1661/ 49144	2844/ 66690	–0.73/–0.94	0.88 (0.83–0.93)		0.56
	N–DHP	4	469/ 25080	519/ 25309	0.82/–0.16	0.92 (0.76–1.11)		0.13
CHD	DHP	23	2187/ 49144	3773/ 66690	–0.73/–0.94	1.00 (0.92–1.10)		< 0.01
	N–DHP	4	771/ 25080	771/ 25309	0.82/–0.16	0.99 (0.82–1.19)		0.07
HF	DHP	19	1769/ 45105	2582/ 62669	–0.78/–0.99	1.20 (1.08–1.33)		< 0.010
	N–DHP	4	380/ 25080	328/ 25309	0.82/–0.16	1.17 (1.01–1.35)		0.83
Stroke + CHD	DHP	23	3845/ 49144	6617/ 66690	–0.73/–0.94	0.95 (0.89–1.02)		< 0.01
	N–DHP	5	1254/ 25383	1303/ 25610	0.83/–0.15	0.97 (0.90–1.05)		0.58
Stroke + CHD + HF	DHP	19	5452/ 45105	8998/ 62669	–0.78/–0.99	1.05 (0.98–1.13)		< 0.01
	N–DHP	4	1620/ 25080	1618/ 25309	0.82/–0.16	1.01 (0.94–1.08)		0.47
CV Death	DHP	19	1617/ 44383	3010/ 62589	–0.69/–0.96	0.94 (0.89–0.99)		0.44
	N–DHP	5	717/ 25383	694/ 25610	0.82/–0.16	1.04 (0.94–1.15)		0.79
All-cause Death	DHP	24	4088/ 49133	6908/ 67359	–0.74/–0.93	0.96 (0.93–0.99)		0.93
	N–DHP	4	1443/ 25080	1444/ 25309	0.82/–0.16	1.01 (0.94–1.08)		0.66

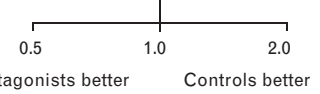

FIGURE 4 Comparisons of BP-lowering treatment based on calcium antagonists with treatments based on other drug classes: (a) ACE-inhibitors; (b) angiotensin receptor blockers; (c) RAS blockers; (d) all other drug classes. In (e) the comparison of calcium antagonists with all other drug classes is made separately for dihydropyridine (DHP, filled squares) and nondihydropyridine (N-DHP, open squares) calcium antagonists. ACE, angiotensin-converting enzyme; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; RAS, renin–angiotensin system; RR, risk ratio. Other explanations as in Fig. 2.

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on all outcomes; did not differ from those of beta-blockers as far as mortality was concerned; and differed from those of calcium antagonists in being significantly more effective in the prevention of heart failure and marginally less effective on stroke risk. Table 4a indicates comparison of ACE-inhibitor with ARB-based treatment, and Fig. 5a shows that the two treatments had the same effect on all outcomes. However, 17 118 of the 17 728 patients were from the ONTARGET trial [55], so the meta-analysis substantially reflected the results of the ONTARGET trial.

A meta-analysis of RCTs comparing ACE-inhibitor-based treatment with treatment based on any other BP-lowering drug (Table 4b) shows the two types of treatment were not associated with differences in the risk of any outcome, except for stroke and CHD. Indeed, ACE-inhibitor treatment, even after adjustment for a small SBP/DBP difference in favor of other drugs, was associated with a slightly but significantly higher risk of stroke [risk ratio 1.08 (1.01–1.14)] and with a slightly but significantly lower CHD risk [risk ratio 0.91 (0.83–0.99)] (Fig. 5b).

Angiotensin receptor blockers versus other drug classes

The previous sections, tables, and figures have shown that only one relatively small RCT was available for comparing an ARB with diuretic therapy (Table 1d); this class was more effective than beta-blockers on the risk of stroke, but not on the risk of all other outcomes (Fig. 2c); this class was more effective than calcium antagonists on the risk of heart failure, but marginally less effective than these compounds on the risk of CHD (Fig. 4b); and equally effective as ACE-inhibitors on all types of outcome (Fig. 5a). An additional comparison is shown in Table 4c of ARBs with 'conventional' therapy. Despite the smallness of the sample, a significant 27% lower risk of stroke was found with ARBs (both by random-effects and fixed-effects models). All other outcomes were not significantly influenced by either therapy versus the other (Fig. 5c). No single RCT was found to exert an excessive influence.

Comparison of ARB therapy with all other drug classes (Table 4d) did not show significantly different risk ratios for all outcomes, except for CHD events, for which a 10% higher risk was found with ARB therapy, which attained statistical significance when the fixed-effects model was used [risk ratio 1.10 (1.01–1.19)] (Fig. 5d).

Other comparisons

When RCTs comparing either ACE-inhibitors or ARBs with drugs of other classes were analyzed together (RAS blockers; Table 4e), there was a moderate degree of heterogeneity for most outcomes, but risk ratios were very close to unity for all outcomes, with the single exception of heart failure that was 12% lower in the RAS blocker group (Fig. 5e). No trial exerted an excessive influence.

If also beta-blockers were included among RAS blockers (30 RCTs with 33 comparisons in 147 579 patients) and ACE-inhibitors, ARBs and beta-blockers were compared with diuretics and calcium antagonists, heterogeneity was moderate for most of the outcomes. Risk ratios of all outcomes were very close to unity, with rather narrow CIs, with the only exception of stroke, the risk of which was significantly higher (15%) in the group of the antihypertensive agents including ACE-inhibitors, ARBs, and beta-blockers.

Influence of total cardiovascular risk on the effects of blood pressure-lowering drug classes

Numbers of trial comparisons and of patients for each testing are indicated in Fig. 6. With a few exceptions, the number of trial comparisons was substantial and the number of patients large, the few exceptions being: in the comparison of beta-blockers with all other classes, there were only two trials giving data on heart failure in the high-risk and the very-high-risk strata; in the comparison of ACE-inhibitors with all other classes, only two trials gave heart failure data in the high-risk stratum; and in the comparison of ARBs with other classes, only two trials provided information on cardiovascular death in the low-to-moderate risk stratum, with only six events reported.

Figure 6 shows that for no class of BP-lowering drugs was there a significant trend toward increasing or decreasing relative effectiveness with increasing cardiovascular risk.

Publication bias

For this assessment, reference is made to online Supplemental Figs. S1–5a–g (http://links.lww.com/HJH/A487) and Tables S4–S8 (http://links.lww.com/HJH/A487). Although graphic representations could not exclude publication bias in a number of cases, in most of these cases, significant bias was denied by the trim-and-fill method. Publication bias could not be denied only in the comparison of ACE-inhibitors versus all other drug classes for CHD events.

DISCUSSION

Strengths of the analyses

This is the most comprehensive, updated, and specific set of meta-analyses of RCTs with head-to-head comparisons of BP-lowering drugs so far published. It is the most comprehensive and updated one because it includes all head-to-head comparisons of antihypertensive drug classes since 1966 (but the first published comparisons are dated 1985 [43,45]) up to August 2014, and the most specific set because it includes only RCTs in which BP-lowering drugs were used in hypertensive patients or in cohorts with at least 40% of hypertensive patients. Indeed, of the 50 trials included for 58 comparisons in 247 006 individuals, only five trials [25,55,57–59] were not entirely in hypertensive patients [although in these 5 trials, prevalence of hypertension ranged between 60 and 88% (Table S1)]. Thus, only 6023 of the 247 006 individuals included in our meta-analyses were not hypertensive.

Ours is the most comprehensive set of meta-analyses of direct drug class comparisons also because it includes all available direct comparisons of drugs belonging to the five classes of BP-lowering drugs, and usefully complements our recently published set of meta-analyses of 55 trials in 195 267 patients, in which individual classes of drugs were compared with placebo [4]. The meta-analysis by Psaty *et al.*

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TABLE 4. Comparisons of renin–angiotensin system blockers with other drug classes[a]

Trial	Drugs compared		Patient number	Follow-up (years)	Baseline treatment		Baseline		On treatment			
									RAS blocker		Control	
	RAS blocker	Control			Random	Continued	SBP	DBP	SBP	DBP	SBP	DBP
(a) ACE-inhibitors vs. angiotensin receptor blockers												
DETAIL [31]	Enalapril	Telmisartan	250	5	Yes	Yes	152.1	85.6	148.9	82	145.7	79
ROAD [59]	Benazepril	Losartan	360	3.7	Yes	Yes	150.2	86.2	127	75	127	75.5
ON-TARGET [55]	Ramipril	Telmisartan	17118	4.7	Yes	Yes	141.8	82.1	135.8	77.5	134.8	76.9
All			*17728*	*4.7*			*142.1*	*82.2*	*135.8*	*77.5*	*134.8*	*76.9*
(b) ACE-inhibitors vs. all other drug classes[b]												
Additional trials												
REIN-stratum 2 [58]	Ramipril	Conventional	166	1.3	Yes	Yes	148.8	91.8	144	88.2	144.6	88.9
REIN-stratum 1 [57]	Ramipril	Conventional	186	2.7	Yes	Yes	143.4	89.2	-	84	-	85
CAPPP [26]	Captopril	Atenolol or Metoprolol or HCTZ or BFTZ	10985	6.1	Yes	No	160.7	98.9	152	90	149	89
STOP-2 [61]	Enalapril or Lisinopril	Atenolol or Metoprolol or Pindolol or HCTZ + Amiloride	4418	5			194	98	159.5	81.8	159.2	81.4
All [17,18,20,21,23,25,26,31, 35,36,39,40,45,52, 55–59,61,62]			*83985*	*4.8*			*153.2*	*87.8*	*141.6*	*80.4*	*140.1*	*79.7*
(c) Angiotensin receptor antagonists vs. conventional treatment												
E-COST [32]	Candesartan	Non-ARB	2048	3.1	No	No	163.9	93.4	140.5	80.9	138.2	79.7
E-COST-R [33]	Candesartan	Non-ARB	141	3.1	No	No	144.6	79	134.5	73.1	133.5	73.8
HIJ-CREATE [38]	Candesartan	Non-ARB	2049	4.2	Yes	No	135.3	75.7	130.7	72.9	132.2	74.7
All			*4238*	*3.6*			*149.4*	*84.4*	*135.6*	*76.8*	*135.1*	*77.1*
(d) Angiotensin receptor antagonists vs. all other drug classes[c]												
All [27,30–33,38,40,46,48, 51,55,59,65]			*59211*	*4.2*			*154.0*	*87.6*	*137.6*	*78.2*	*137.6*	*78.0*
(e) RAS blockers vs. all other drug classes[d]												
All [17,18,20,21,23,25–27, 30,32,33,35,36,38–40, 44–46,48,51,52,56–58, 61,62,65]			*106630*	*4.5*			*157.4*	*89.5*	*141.5*	*80.2*	*140.4*	*79.6*

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BFTZ, bendrofluazide; HCTZ, hydrochlorothiazide; RAS, renin–angiotensin system.
[a]Comparisons of angiotensin receptor antagonists and angiotensin receptor blockers with diuretics, beta-blockers, and calcium antagonists can be found in Tables 1c and d, 2b and c, and 3a and b, respectively.
[b]Inclusive of all RCTs comparing ACE-inhibitors with any other antihypertensive agent as in Tables 1–4 (also inclusive of additional trials in which the control treatment could be done with various drugs other than ACE-inhibitors).
[c]Inclusive of all RCTs comparing angiotensin receptor antagonists with any other antihypertensive agent as in Tables 1, 2, 3, 4a and 4c.
[d]Inclusive of all RCTs comparing either an ACE-inhibitor or an angiotensin receptor blocker with any other agent as in Tables 1–4, but exclusive of direct comparison of ACE-inhibitors with angiotensin receptor blockers.

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Outcome	Trials (n)	Events (n/patients)		Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)	P (Heterogen)
		ACE-Inhibitors	Controls	(a) ACE-Inhibitors vs Angiotensin Receptor Blockers			
Storke	3	413/8886	377/8842	1.01/0.61	1.09 (0.95–1.25)		0.95
CHD	3	423/8886	453/8842	1.01/0.61	0.93 (0.82–1.06)		0.72
HF	3	364/8886	406/8842	1.01/0.61	0.89 (0.78–1.02)		0.90
Stroke + CHD	3	836/8886	830/8842	1.01/0.61	1.00 (0.91–1.10)		0.70
Stroke + CHD + HF	3	1200/8886	1236/8842	1.01/0.61	0.97 (0.90–1.04)		0.60
CV Death	2	605/8706	601/8662	1.03/0.63	1.00 (0.90–1.12)		0.59
All-cause Death	2	1020/8706	995/8662	1.03/0.63	1.02 (0.94–1.11)		0.82
				(b) ACE Inhibitors vs All Other Drug Classes			
Stroke	20	1468/32381	2203/49740	1.55/0.65	1.08 (1.02–1.14)*		0.39
CHD	20	1696/32360	3325/49741	1.55/0.65	0.91 (0.83–0.99)*		0.09
HF	15	1299/31118	2522/48484	1.56/0.66	0.89 (0.80–1.01)*		< 0.01
Stroke + CHD	20	3171/32583	5538/49956	1.55/0.65	0.98 (0.91–1.04)*		0.02
Stroke + CHD + HF	14	4417/31019	7991/48397	1.57/0.67	0.95 (0.89–1.02)*		< 0.01
CV Death	21	1693/32619	2894/50190	1.50/0.63	1.01 (0.95–1.06)*		0.96
All-cause Death	21	3267/32507	5768/50078	1.54/0.65	1.01 (0.98–1.04)*		0.99
					0.5 1.0 2.0 ACE-Inhibitors better Controls better		
		ARBs	Controls	(c) Angiotensin Receptor Blockers vs Conventional Therapy			
Stroke	3	107/2146	146/2092	0.42/–0.31	0.73 (0.54–0.99)		0.22
CHD	3	43/2146	51/2092	0.42/–0.31	0.85 (0.37–1.97)		0.05
HF	3	86/2146	102/2092	0.42/–0.31	0.83 (0.63–1.09)		0.76
Stroke + CHD	3	150/2146	197/2092	0.42/–0.31	0.77 (0.51–1.18)		0.02
Stroke + CHD + HF	3	236/2146	299/2092	0.42/–0.31	0.78 (0.59–1.03)		0.05
CV Death	3	33/2146	33/2092	0.42/–0.31	1.13 (0.70–1.85)		0.85
All-cause Death	3	77/2146	67/2092	0.42/–0.31	1.15 (0.84–1.58)		0.95
				(d) Angiotensin Receptor Blockers vs All Other Drug Classes			
Stroke	14	1192/28570	1308/29531	–0.02/0.19	0.92 (0.79–1.07)		0.01
CHD	14	1191/28570	1103/29531	–0.02/0.19	1.09 (0.98–1.22)		0.25
HF	14	1117/28570	1208/29531	–0.02/0.19	0.87 (0.75–1.01)		0.03
Stroke + CHD	14	2383/28570	2336/29531	–0.02/0.19	1.01 (0.90–1.14)		0.01
Stroke + CHD + HF	14	3466/28570	3544/29531	–0.02/0.19	0.93 (0.84–1.02)		0.01
CV Death	8	1194/23641	1209/23549	–0.30/0.14	0.99 (0.91–1.07)		0.61
All-cause Death	13	2560/28390	2619/29531	–0.02/0.19	0.98 (0.94–1.04)		0.88
					0.5 1.0 2.0 ARBs better Controls better		
		RAS Blockers	Controls	(e) RAS Blockers vs All Other Drug Classes			
Stroke	28	1870/43223	2721/61543	1.23/0.62	1.01 (0.91–1.12)		< 0.01
CHD	28	2011/43202	3552/61544	1.23/0.62	0.96 (0.88–1.06)		< 0.01
HF	23	1646/41960	2960/60287	1.22/0.62	0.88 (0.79–0.98)		< 0.01
Stroke + CHD	28	3888/43425	6208/61759	1.21/0.61	0.99 (0.92–1.07)		< 0.01
Stroke + CHD + HF	22	5447/41861	9099/60200	1.23/0.63	0.94 (0.88–1.01)		< 0.01
CV Death	25	1681/38892	2897/56371	1.20/0.61	1.01 (0.96–1.06)		0.90
All-cause Death	30	3812/43529	6372/62061	1.21/0.61	1.01 (0.98–1.04)		0.99
					0.5 1.0 2.0 RAS blockers better Controls better		

FIGURE 5 Comparisons of BP-lowering treatment based on (a) ACE-inhibitors versus angiotensin receptor blockers; (b) ACE-inhibitors versus all other drug classes; (c) angiotensin receptor blockers versus conventional therapy; (d) angiotensin receptor blockers versus all other drug classes; (e) RAS blockers versus all other drug classes. Explanations and abbreviations as in Fig. 2. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; RAS, renin–angiotensin system; RR, risk ratio. Other explanations as in Fig. 2.

[6], though specific for trials in hypertension, could not survey trials published after 2002, and focused on comparisons of diuretics versus other classes. The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) meta-analyses [8,9] were purposefully limited to trials after 1995 [67], the individual data of which were made available to the collaboration. Furthermore, in the BPLTTC meta-analyses, data of trials using diuretics and beta-blockers as comparative agents were pooled together, thus preventing the comparison of several individual classes of drugs. The

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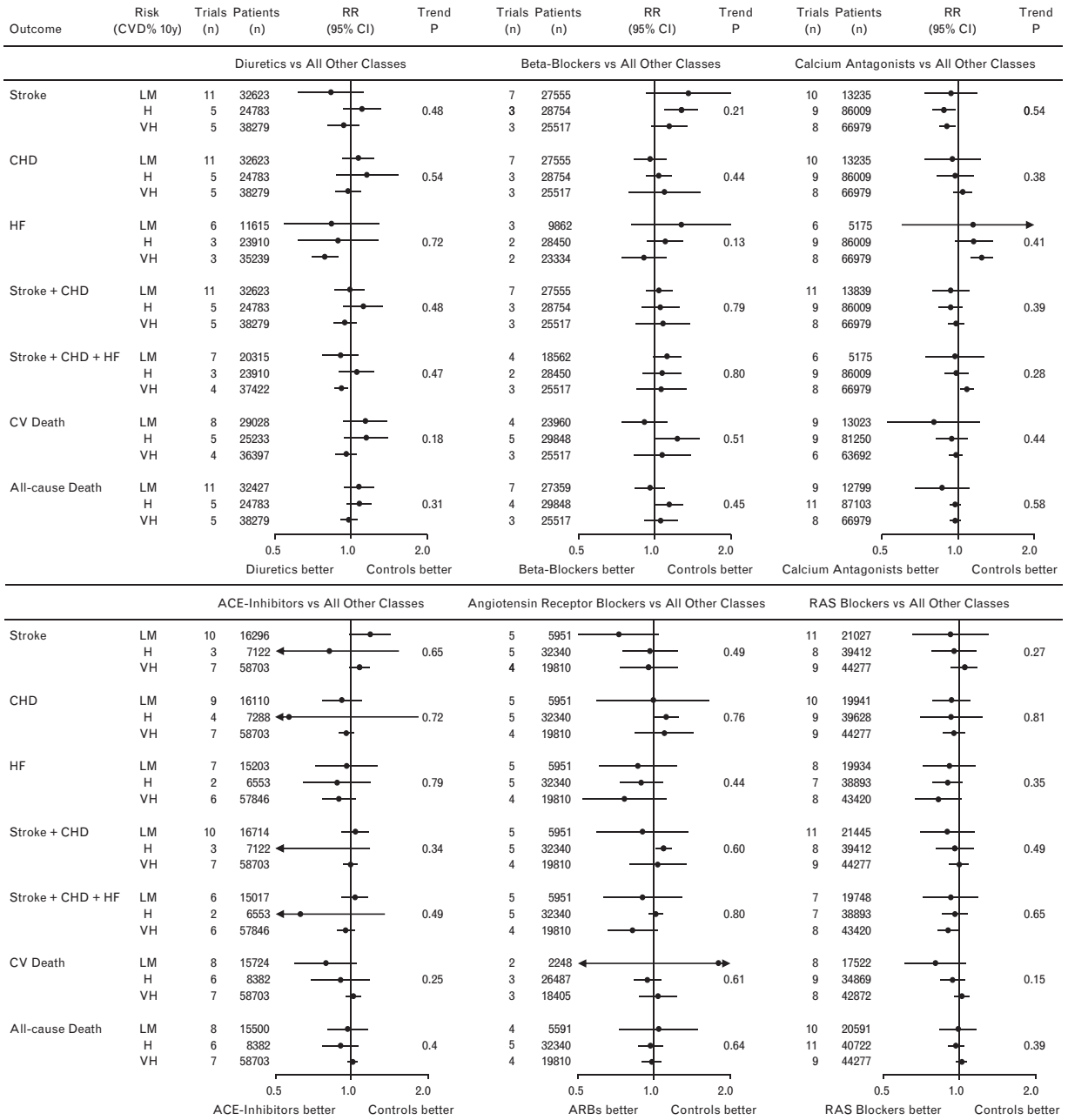

FIGURE 6 Influence of total cardiovascular risk on the effects of different BP-lowering drug classes. In each of the six sections of this figure (each summarizing the comparisons of a drug class versus all the others) trials have been stratified according to the level of total cardiovascular risk [assessed as cardiovascular death (CVD) rate extrapolated to 10 years: low-moderate (LM) risk <5% in 10 years; high (H) risk 5 to <10% in 10 years; very high (VH) ≥10% in 10 years]. The last column in each section reports *P* values for trend. The following RCTs were included: diuretics vs. all, LM risk [24,28,30,37,43,47,49,53,56,64,66], H risk [19,21,41,52,63], VH risk [20,39,50,60]; beta-blockers vs. all, LM [24,30,34,37,43,49,64], H [17,22,46,63], VH [42,50,62]; calcium antagonists vs. all, LM [23,25,28,34–36,44,45,47,53,66], H [17–19,22,27,29,41,51,54,65], VH [20,40,42,48,60,61]; ACE-inhibitors vs. all, LM [23,25,26,31,35,36,44,45,56,57,59], H [17,18,21,52,58], VH [20,39,55,61,62]; angiotensin receptor blockers vs. all, LM [30–32,59], H [27,38,46,51,65], VH [33,40,48,55]; RAS blockers vs. all, LM [23,25,26,30,32,35,36,44,45,56,57], H [17,18,21,27,38,46,51,52,58,65], VH [20,33,39,40,48,61,62]. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HF, heart failure; *n*, number; RAS, renin–angiotensin system; RR, risk ratio.

Cochrane Collaboration meta-analysis by Wiysonge *et al.* [13] and that by Lindholm *et al.* [12] were focused on comparing beta-blockers with other drug classes. Likewise, other meta-analyses [9,11,14,16] were limited to the effects of a class of drugs versus other classes, some mixed placebo-controlled with active-controlled trials [16] or included trials in which antihypertensive drugs had been used in cardiovascular conditions different from hypertension [11,16]. The most extensive meta-analysis of head-to-head drug comparisons published so far – that by Law *et al.* [10] – is limited to trials published before the end of 2007, is inclusive of trials in myocardial infarction and heart failure patients, and only provides pooled data of the comparisons of each of the five major classes of BP-lowering drugs with any other class.

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FIGURE 7 Summary results of the direct comparisons of the major classes of BP-lowering drugs on seven major outcomes. The yellow cases signal nonsignificant differences in risk between the drug class indicated in the heading of each vignette and those indicated on top of each column. The green cases signal significantly lower risk of a given outcome with the drug indicated in the heading compared to the drug class on the top of each column. The red cases indicate significantly higher risk of a given outcome with the drug class in the heading when compared to the drug class on the top of a column. Cases with two different colors signal different significance of drug class comparisons when the random-effects model (upper, left triangle) and the fixed-effects model (lower, right triangle) are used. The last column in each vignette reports the results of placebo-controlled comparisons of each drug class as calculated in a parallel set of meta-analyses [4]. ACEI, angiotensin-converting enzyme inhibitors; ALL, all other drug classes; ARB, angiotensin receptor blockers; BB, beta-blockers; BP, blood pressure; CA, calcium antagonists; CHD, coronary heart disease; CV, cardiovascular; D, diuretics, HF, heart failure; NA, not assessed; PL, placebo; RASB, renin–angiotensin system blockers; St, stroke; vs., versus.

Overview of the results

Figure 7 provides an overview of the results of the many direct comparisons of the major classes of BP-lowering drugs on seven major outcomes. The yellow cases signal nonsignificant differences in risk between the drug class indicated in the heading of each vignette and those indicated on top of each column. The green cases signal significantly lower risk of a given outcome, with the drug class indicated in the heading compared to the drug class on the top of each column, and the red cases indicate significantly higher risk of a given outcome, with the drug class in the heading when compared to the drug class on the top of a column. Two-colour cases indicate significant differences (lower or higher risk) only found with the fixed-effects model.

It is apparent from Fig. 7 that the yellow-color cases widely predominate and that all classes of agents appear to be equivalent on most outcomes when their BP effect is equivalent. However, a nonsignificant difference in the risk of a given outcome between two drug classes cannot be automatically translated into an equivalent 'efficacy' of the two classes in 'reducing' the risk of that outcome, unless both classes have been shown to be significantly more effective than placebo in reducing that risk. For this reason, the last column of each vignette in Fig. 7 reports the results of our recent meta-analyses on the effects of each drug class

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versus placebo [4]. As reported in that set of meta-analyses, whereas there is evidence of the reduction in stroke and composite cardiovascular event risk for all drug classes versus placebo, for some drug classes (beta-blockers, ACE-inhibitors, ARBs, and RAS blockers), evidence of reduced mortality versus placebo is lacking.

Despite the predominant similarities of the results of different drug classes on most of the outcomes, there are also differences that involve almost all classes of drugs (Fig. 7). Diuretics are superior to calcium antagonists, RAS blockers, and all other classes together in the prevention of heart failure, and to RAS blockers in the prevention of stroke. Beta-blockers are inferior to all other individual classes, except diuretics, but superior to placebo [4] in the prevention of stroke. Their action is not significantly different from that of the other drug classes on the risk of all other outcomes, however. Calcium antagonists are superior to beta-blockers, ACE-inhibitors, RAS blockers, and all other drug classes together in the prevention of stroke, and significantly superior to ARBs on the risk of CHD, but inferior to all other individual drug classes (except beta-blockers) and to all other classes together on the risk of heart failure. In comparison with all other drug classes together, calcium antagonists are also slightly, but significantly, more effective in prevention of all-cause death. Evidence for this effect on risk of death is limited to the subclass of dihydropyridines. In comparison with calcium antagonists, ACE-inhibitors are significantly more effective in the prevention of heart failure, but less effective in the prevention of stroke. When compared to all other drug classes together, ACE-inhibitors are significantly more effective in the prevention of CHD, and significantly less effective in the prevention of stroke. ARBs are significantly more effective than beta-blockers in the prevention of stroke and more effective than calcium antagonists in the prevention of heart failure, but inferior to calcium antagonists and all other drug classes together on the risk of CHD. Finally, considering ACE-inhibitor and ARBs together as RAS blockers, these appear to be significantly more effective than beta-blockers, but less effective than diuretics and calcium antagonists in reducing the risk of stroke, and significantly superior to calcium antagonists and all other drug classes together, but less effective than diuretics in reducing the risk of heart failure.

Figure 8 summarizes the results of the drug class comparisons by individual outcomes. As far as the risk of stroke is concerned, diuretics appear to be superior, not only to placebo, but also to RAS blockers; beta-blockers, though superior to placebo, appear to be inferior to calcium antagonists, ARBs, RAS blockers, and all other classes together; calcium antagonists are superior, not only to placebo, but also to beta-blockers, ACE-inhibitors, RAS blockers, and all other classes together; ACE-inhibitors are superior to placebo, but inferior to calcium antagonists and all other classes together; ARBs are superior to placebo and beta-blockers; RAS blockers are superior to placebo and beta-blockers, but inferior to diuretics and calcium antagonists.

As far as the risk of CHD events is concerned, calcium antagonists are better than ARBs, though both have not been shown to be significantly better than placebo; ACE-inhibitors are superior to all other drug classes together, but not significantly better than each individual class; ARBs appear to be inferior not only to calcium antagonists but also to all other classes together.

As far as the risk of heart failure is concerned, diuretics are not only better than placebo, but also better than calcium antagonists, RAS blockers, and all other drug classes together; beta-blockers are superior to placebo, but not significantly different from any other class, considered separately and together; calcium antagonists are not significantly different from placebo and inferior to all other individual classes except beta-blockers; ACE-inhibitors and ARBs are superior to placebo and to calcium antagonists; RAS blockers are superior to placebo, calcium antagonists, and all other drugs together, but inferior to diuretics.

Concerning the composite outcome of stroke and CHD, there is only a significant superiority of calcium antagonists over beta-blockers, whereas for the composite events also including heart failure, there is a marginally significant superiority of diuretics over beta-blockers and a significant superiority of RAS blockers (but not individually of either ACE-inhibitors or ARBs) over calcium antagonists.

As to cardiovascular and all-cause mortalities, there is no significant risk difference with any head-to-head comparison of different drug classes, except for a slight, but significant superiority of calcium antagonists in the pooled comparison with all other drug classes in reducing risk of all-cause death. As previously reported [4], evidence of superiority over placebo in reducing mortality risk is restricted to diuretics and calcium antagonists.

In summary, if the comparison of each drug class with all others together can be thought to provide an overall assessment of their advantages and disadvantages, it can be said that diuretics have advantages over the rest of the drug classes on heart failure risk, beta-blockers have disadvantages on stroke risk, calcium antagonists have advantages on stroke and all-cause mortality and disadvantages on heart failure risk, ACE-inhibitors have advantages on CHD risk and disadvantages on stroke risk, and ARBs have some disadvantage on CHD risk.

In this context, also the results summarized in Fig. 6 deserve some comment. When trials were stratified according to overall cardiovascular risk, no single class of drug compared to all other classes together appeared to change its relative effectiveness at different levels of risk and thus to be specifically preferable to lower or higher levels of risk. This further extends to individual drug classes the evidence provided by previous meta-analyses [3,68] that the relative risk reduction by BP-lowering treatment does not change with the overall cardiovascular risk of the patients.

Comparisons with previous meta-analyses

Comparing the results of our meta-analyses with those of the previous ones is difficult because of the reasons detailed above. The easiest comparison is with the Cochrane Collaboration's meta-analyses of the effects of beta-blockers versus other individual classes of drugs [13], which have used selection criteria similar to ours with very similar results. The same can be said of Lindholm *et al.*'s [12] meta-analysis of beta-blockers compared with all other drug classes. Comparison of any individual class with drugs of all other classes gave substantially similar results in our

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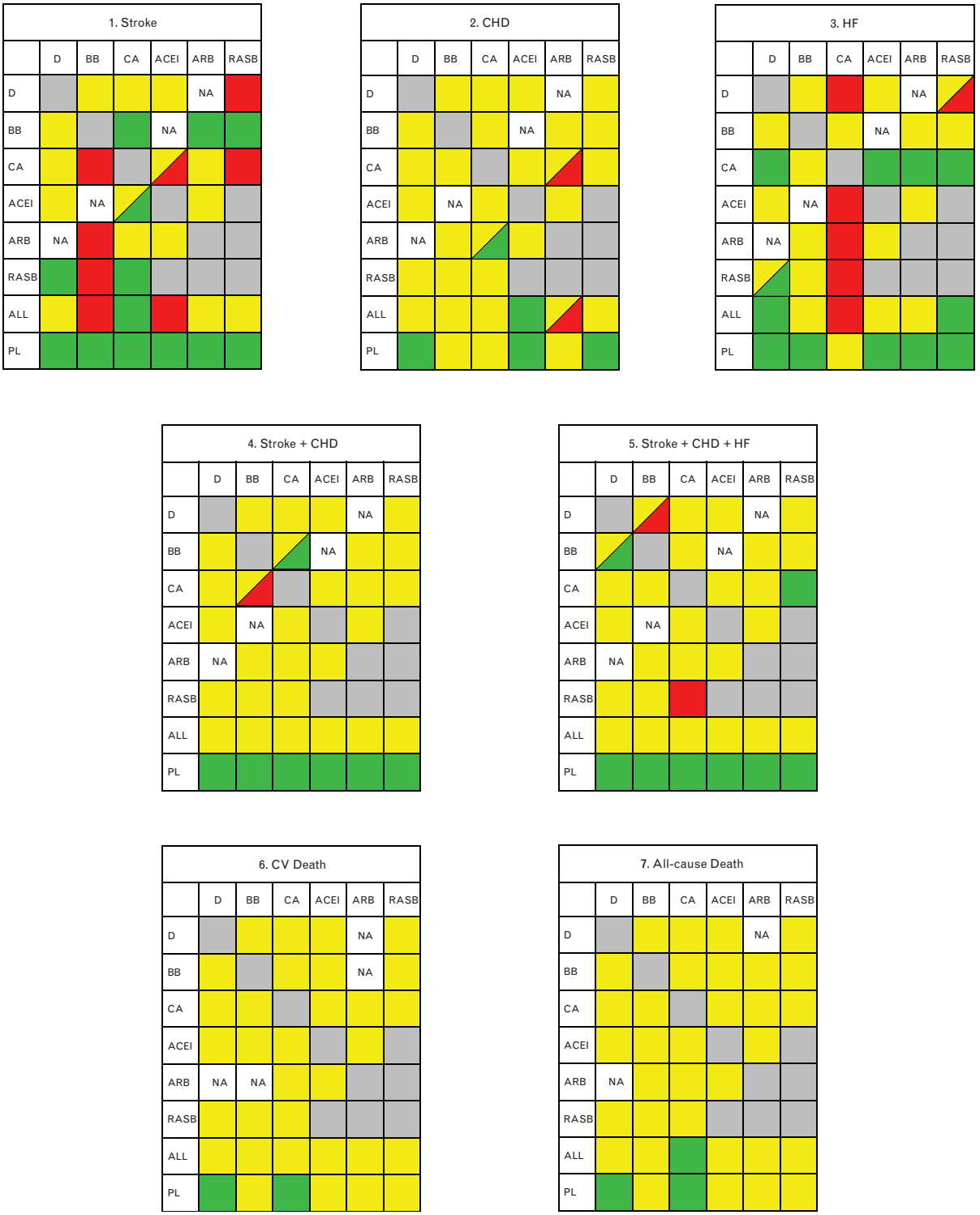

FIGURE 8 Summary results of the direct comparisons of the major classes of BP-lowering drugs grouped in vignettes each referring to one of the seven outcomes considered. Colors refer to the comparisons of each class on the top of the column with each class at the left of each row. Yellow, nonsignificant difference; green, lower risk with class on top of the column versus class at the left of the row; red, higher risk with class on top of the column versus class at the left of the row. Two-color cases indicate comparisons with different significance of random-effects and fixed-effects models (as in Fig. 7). ACEI, angiotensin-converting enzyme inhibitors; ALL, all other drug classes; ARB, angiotensin receptor blockers; BB, beta-blockers; BP, blood pressure; CA, calcium antagonists; CHD, coronary heart disease; CV, cardiovascular; D, diuretics, HF, heart failure; NA, not assessed; PL, placebo; RASB, renin–angiotensin system blockers; St, stroke; vs., versus.

meta-analysis and the previous meta-analysis by Law *et al.* [10], with the exception that a small inferiority of ACE-inhibitors on stroke risk and a small superiority of this drug class on CHD risk attained statistical significance in our meta-analysis, but not in Law *et al.*'s meta-analysis. Our results on the comparison of calcium antagonists with all other classes together were similar not only to those of Law *et al.* [10] but also to those of Costanzo *et al.* [14]. The same

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can be said for our comparison of ARBs with all other classes and the results of Bangalore *et al.*'s [11] meta-analysis and that of ours. Costanzo *et al.* [14] and the BPLTTC [7,8] also provide data on the comparison of calcium antagonists and ACE-inhibitors, with similar results to ours as far as the calcium antagonist inferiority on heart failure risk is concerned, whereas the superiority we found of calcium antagonists over ACE-inhibitors on stroke risk only attained statistical significance in Costanzo *et al.*'s [14] meta-analysis.

Limitations of the analyses

Although the present set of meta-analyses counts upon a very large number of RCTs (50 for 58 comparisons) and a huge number of patients (247 006), it also has limitations. First, the number of RCTs reporting heart failure as an outcome is smaller than that of RCTs reporting the other outcomes. Furthermore, onset of heart failure is a softer endpoint, which may be simply masked, rather than prevented, by those classes of BP-lowering drugs that are known to be effective on heart failure symptoms. Second, for some comparisons, only two RCTs were available for analysis (Figs. 2a and c; 3a–c; 4b; 5a). Third, for some comparisons, a large trial exerted an excessive influence on the meta-analysis, this occurring particularly for the direct comparison between ACE-inhibitors and ARBs largely dominated by the ONTARGET results. Fourth, although heterogeneity was in most cases low to moderate (I^2 <75%), in many cases, it was not negligible and thus prevented the calculation of risk ratios by the fixed-effects model. Fifth, although head-to-head comparison of active BP-lowering compounds assumes an equal BP-lowering in the two arms of each comparison, there were small but presumably non-negligible SBP/DBP differences in several comparisons (particularly those between diuretics and ACE-inhibitors or RAS blockers, favoring diuretics; between calcium antagonists and ACE-inhibitors or RAS blockers, favoring calcium antagonists; between ACE-inhibitors and all other classes, favoring the other classes). Whenever the mean of the SBP/DBP difference was greater than 1 mmHg, adjustments were made on the basis of our recent meta-regression analysis based on the logarithmic relationship of risk ratios with the extent of BP differences in 47 RCTs of intentional BP-lowering [1]. These adjustments, though seldom done in previous meta-analyses, are imperative since a BP difference is one of the most powerful causes of risk differences, but in some cases widened the CIs, thus reducing the chance of attaining statistical significance. Sixth, some of the risk differences that achieved statistical significance were rather small and their clinical importance is open to discussion. Seventh, RCTs were commonly classified as comparison of the initial agents used in the two groups being compared, but most of the trials, especially the most recent ones, allowed or even prescribed addition of one or more drugs in order to achieve a BP goal. So, comparisons are often not between two different drug classes, but rather between two regimens initiated by drugs belonging to two different classes. Eighth, as usually occurs with large sets of meta-analyses, ours is based on multiple testing, and it cannot be ruled out that some of the 'significant' differences in risk may well be due to chance. Finally, we have carefully compared the effectiveness of the various drug classes, but we do not present any data of comparative tolerability. Although tolerability is an equally important aspect of drug treatment as BP-lowering efficacy, the tolerability data are differently reported in each RCT publication and do not lend themselves easily to meta-analysis. Furthermore, in RCTs, tolerability to randomized drugs is necessarily lower than in real practice, since in a RCT, a patient intolerant to the randomized drug has the only choice between continuing to suffer the adverse event or withdrawing from the trial.

Clinical conclusions

Comparing BP-lowering treatments initiated by different drug classes has widely been carried out during the past 30 years in view of establishing, so to say, an order of preference of the several agents in the practice of antihypertensive therapy, the so-called step-care approach, initiated by the first report of the Joint National Committee [69] and the 1978 report of the WHO [70]. The large number of RCTs completed and the number of patients included has allowed a comprehensive analysis of the results of these RCTs, and a critical assessment of these results can provide support to practical recommendations.

As illustrated in this study, the widely predominant result of the multiple drug comparisons available is that there are no significant differences between drug classes for most outcomes, and this despite the fact that most comparisons were founded on a large number of patients and events, and therefore had considerable statistical power. There are some consistent differences, however, that cannot be neglected, with some drug classes combining inferiority for an outcome risk with superiority for the risk of another outcome. As a consequence, the picture emerging from a comprehensive and critical survey of all available evidence is not one that may strongly support a step-care or any other overall treatment paradigm. Undoubtedly, there are classes of compounds, such as calcium antagonists, that appear more effective in preventing stroke; other classes, such as ACE-inhibitors, that appear more effective against the risk of CHD; and other classes which appear definitely more effective in the prevention of heart failure onset, such as RAS blockers and, particularly, diuretics. This may provide a guide to drug choice when a specific outcome is the prevailing target of treatment, but in usual practice antihypertensive treatment is directed to prevent a cardiovascular outcome the type and location of which cannot be predicted [71].

Our recent meta-analyses summarizing the results of placebo-controlled BP-lowering treatment trials definitely show that BP-lowering is of substantial benefit in preventing all types of outcomes [1] and that all drug classes can reduce the risk of stroke and of the composite of major cardiovascular events [4]. Our present set of meta-analyses shows that there are limited systematic differences between the available classes of BP-lowering drugs, particularly when the composite of cardiovascular outcomes to be prevented is considered. Previous meta-analyses by the BPLTTC have clearly shown that the preventive effectiveness of the various drug classes does not differ by age [72], sex [73], and BMI criteria [74], and therefore these easily defined criteria are not useful for the choice of the drug. Some of the meta-analyses reported in this study add the important new information that

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the effect of any drug class on the risk of any outcome does not significantly change with the level of total cardiovascular risk, and, therefore, also the total cardiovascular risk cannot be a guide to drug choice.

In conclusion, the main goal of antihypertensive treatment is BP-lowering, and effective BP-lowering (i.e. achievement and maintenance of the optimal BP target) is an objective to be attained by a careful search in the individual patient, being the result of the individually different BP responsiveness to the various agents (which conditions BP target achievement) and the individual tolerability of the prescribed drugs (which conditions BP target maintenance). This goal seems best attainable by avoiding the constraints of ill-founded or uncertain criteria, which sometimes are more attractive for guidelines authors or experts' debates than useful to practicing physicians and individuals with hypertension. The flexible approach to drug choice presented in the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) hypertension guidelines [75] is strongly supported by results of this set of meta-analyses and those we have recently published [1–4]. The subtle differences in the effects of the various drug classes on different outcomes may suggest some choice when in the continuum of cardiovascular disease [76,77], one type of event may become more likely to occur, or, in the frequent occasions in which combination therapy is used, they may suggest the combination of agents with complementary effectiveness on different cardiovascular events. Finally, within the continuum of cardiovascular disease in which onset and progression of organ damage is an important step, possible differences in the effects of various BP-lowering drugs on organ damage (obviously out of the scope of the present meta-analyses) may influence the drug choice, as suggested by ESH–ESC guidelines [75].

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Conflicts of interest

The authors declare no conflict 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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