Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials

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Background: Choice of antihypertensive drugs is also based on the expected burden of adverse events associated with each class of agents, and we have recently identified treatment discontinuation for adverse events as a measure of treatment tolerability frequently reported in randomized controlled trials (RCTs).

Objectives: To investigate whether all classes of blood pressure (BP) lowering drugs increase discontinuations for adverse events when compared with placebo and whether risk of discontinuation is similar for all classes when compared in head-to-head RCTs.

Methods: RCTs of BP-lowering treatment were subdivided in groups according to class of drug compared with placebo or with other classes. Risk ratios and 95% confidence intervals of major cardiovascular events and of treatment discontinuations for adverse events were calculated (random-effects model).

Results: Thirty-eight placebo-controlled RCTs (147 788 patients) and 37 head-to-head RCTs (242 481 patients) provided comparative information on discontinuations for adverse events. All classes of drugs significantly increased discontinuations for adverse events over those occurring on placebo: risk ratio diuretics 2.23 (1.32–3.76), beta-blockers 2.88 (1.58–5.28), calcium antagonists 2.03 (1.17–3.56), angiotensin-converting enzyme inhibitors 2.78 (1.37–5.47), central agents 1.74 (1.24–2.45), with the single exception of angiotensin receptor blockers, which did not significantly increase adverse events over placebo [risk ratio 1.13 (0.78–1.62)]. Similarly, in head-to-head comparison RCTs with other classes, angiotensin receptor blockers were the only class associated with a significantly lower risk of adverse events [risk ratio 0.71 (0.58–0.87)] when head-to-head compared with other classes. Regression analysis also shows that incidence of discontinuations for adverse events is proportional to the number of antihypertensive and other cardiovascular drugs, which accounts for the high incidence of this outcome often found in groups randomized to placebo.

Conclusion: Reduction of cardiovascular events by all classes of BP-lowering drugs is accompanied by increased treatment discontinuations for adverse events, except when angiotensin receptor blockers are used. Treatment discontinuations are also related to treatment often accompanying antihypertensive agents.

Keywords: adverse events, antihypertensive drugs, blood-pressure-lowering trials, cardiovascular event reduction, hypertension, meta-analysis, randomized controlled trials, treatment discontinuations

Abbreviations: ACE, angiotensin-converting enzyme; AE, adverse events; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; NNT, number needed to treat; RCT, randomized controlled trial; RR, risk ratio

INTRODUCTION

In previous meta-analyses of blood pressure (BP) lowering randomized controlled trials (RCTs), we identified 55 RCTs (involving 195 267 individuals) in which placebo treatment (or no treatment) was compared with a specific compound or compounds belonging to a specific drug class [1]. Meta-analyses of RCTs grouped by six major pharmacological classes showed 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 [1]. A more direct comparison of the relative effectiveness of different classes of antihypertensive drugs in reducing cardiovascular morbidity and mortality was made by another set of meta-analyses of RCTs head-to-

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head comparing antihypertensive drugs belonging to different pharmacological classes. Fifty RCTs for 58 two-drug comparisons were found eligible, and the resulting meta-analyses showed that the effects of all drug classes are not significantly different on most outcomes when their BP effect is equivalent, though some between-class differences were found, particularly as far as stroke and heart failure prevention was concerned [2]. It was concluded that there was no fixed paradigm of drug choice valuable for all hypertension patients.

Drug choice, however, is not only based on the expected benefits of cardiovascular morbidity and mortality reduction, but also on the burden of adverse events, often drug-class-specific, that may occur during antihypertensive treatment. The latter have never been systematically surveyed because of the multiple ways treatment adverse events were reported in RCTs. Recently, we have identified permanent treatment discontinuation attributed to treatment adverse events as a meaningful index of relevant adverse events frequently reported in RCTs, thus being able to quantitatively compare the benefits of outcome reduction and the burden of treatment discontinuations in BP-lowering RCTs, also as a function of the extent of BP lowering, the values of BP achieved and the levels of overall cardiovascular risk [3]. In the meta-analyses reported here, we have investigated the effects of different antihypertensive drug classes on permanent discontinuations of treatment due to adverse events, both in RCTs in which drugs of each class were compared with placebo (or no treatment) and in RCTs in which drugs of different classes were directly (head-to-head) compared, to establish whether the burden of adverse events is different when BP is lowered by different classes of drugs.

METHODS

Trial eligibility

The initial dataset of the present meta-analyses consists of the 70 RCTs of BP-lowering treatment (vs placebo or less-intense treatment) [4,5] and the 50 RCTs with 58 two-drug head-to-head comparisons [2] we have already mentioned. In creating the dataset, we had excluded all RCTs the data of which had been retracted by the authors.

Among the RCTs of placebo-controlled BP lowering, we have previously identified 50 RCTs providing information on permanent treatment discontinuations attributed to adverse events or, alternatively, on serious adverse events related to treatment [3]. This subset of placebo-controlled RCTs was reexamined to subdivide it in groups according to the drug class by which active treatment had been compared with placebo (see detailed criteria in [1]). The other set of RCTs, that of 58 head-to-head comparisons of the effect of BP lowering by drugs belonging to different classes, had already been subdivided in a number of groups according to the drug classes being compared [2]. These groups of RCTs have been further reexamined to identify those providing information on permanent treatment discontinuation attributed to adverse events or, in absence of this information, reporting serious adverse events to treatment. All searches were done by two of the authors (C.T. and A.Z.), and any difference was settled by agreement.

Outcomes

Data on the seven morbidity and mortality outcomes analyzed in our previous meta-analyses [1–3] were extracted, but only for the RCTs providing data on treatment discontinuations (or serious adverse events) attributed to treatment, in order that benefits and adverse effects of treatment could be compared in the same RCTs.

Drugs administered

For placebo-controlled RCTs, data were also extracted relative to the number of cardiovascular drugs administered in the placebo and in the active treatment groups. Cardiovascular drugs included, in addition to antihypertensive agents, any lipid-lowering drug, antiplatelet drugs and antidiabetic agents. A few trials on hypertensive patients with diabetes did not report information on antidiabetic agents; in these cases, an average 1.5 antidiabetic drugs per patient has arbitrarily been assumed.

Statistical analyses

As in previous meta-analyses, data were used as tabulated in the original publications. For discontinuations due to adverse events (or serious adverse events), for which time-dependent data were not available, incidences in each treatment group were calculated for each RCT and the relative risk (RR) (risk ratio) estimates were combined using a random-effects model, in which the log risk ratio for every trial was weighted by the reciprocal of the variance of the log risk ratio. The random-effects model was used because for discontinuations the χ^2Q statistics always detected significant heterogeneity ($P \leq 0.05$). For uniformity, the random-effects model was also used for morbidity and mortality outcomes.

In placebo-controlled RCTs, the effects of BP-lowering treatment were standardized to a difference of 10 mmHg SBP and 5 mmHg DBP by multiplying the risk ratio estimates in each trial by the appropriate factor after having considered the effects of the inverse variance of individual trials [4]. In head-to-head comparison RCTs, whenever the SBP/DBP difference between the treatment groups exceeded 1 mmHg, appropriate adjustments were done using factors derived from our meta-regression analyses [2].

In placebo-controlled RCTs, 5-year absolute risk changes (both reductions and increases), weighted for follow-up period inverse variance and sample size, of standardized BP-lowering treatment were also calculated as well as the number of patients needed to treat for 5 years to prevent one outcome or to cause one treatment discontinuation due to adverse events.

Relationship between number of cardiovascular drugs administered and incidence of treatment discontinuations due to adverse effects was studied by correlation and regression analyses.

All statistical analyses were done by the Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey, USA). Statistical significance was defined as P value less

TABLE 1. Trials providing information on permanent discontinuations attributed to adverse events or on serious adverse events*

D vs placebo ($n = 29\,038$)	BB vs placebo ($n = 17\,976$)	CA vs placebo ($n = 11\,479$)	ACEI vs placebo ($n = 31\,499$)	ARB vs placebo ($n = 56\,240$)	Central vs placebo ($n = 1556$)
Australian [6]	HEP* [12]	ACTION [14]	AIPRI [20]	DIRECT-2 [27]	Barraclough [38]
HYVET* [7]	MRC mild [8]	CAMELOT [15]	BENEDICT* [21]	GISSI-AF [28]	Carter [39]
MRC mild [8]	MRC old [9]	Fogari [16]	CAMELOT [15]	IDNT [17]	HSCGS [40]
MRC old [9]	TEST [13]	IDNT [17]	DIABHYCAR [22]	I-PRESERVE [29]	Sprackling [41]
OSLO [10]		NICOLE [18]	DREAM [23]	IRMA-2 [30]	USPHS [42]
SHEP [11]		REIN-2 [19]	Fogari [16]	NAVIGATOR [31]	VA-2 [43]
			HOPE [24]	ORIENT [32]	
			Lewis [25]	PROFESS [33]	
			PEACE [26]	RENAAL [34]	
				ROADMAP [35]	
				SCOPE [36]	
				TRANSCEND [37]	

The acronyms of the trials are explained in the reference papers. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; Central, centrally acting drugs; D, diuretics. * Indicates the trials that did not provide data on discontinuations for adverse events, but data on serious adverse events.

than 0.05, but no correction was made for multiple comparisons.

RESULTS

Trials and patients

Of the 50 RCTs of BP-lowering treatment previously found to report discontinuations attributed to adverse events or, alternatively, the occurrence of serious adverse events, 38 were identified as suitable for 43 comparisons with placebo (or no treatment) of the effects of treatment with drugs belonging to one of the six major classes of antihypertensive drugs. Of the 38 RCTs, 19 were among those we had defined as intentional BP-lowering trials and 19 among those defined as nonintentional BP-lowering trials, the latter comparing BP-lowering drugs with placebo and achieving a BP difference, although without the intention of investigating the effects of BP differences [4]. Inclusion criteria required that at least 40% of the patients included in a trial were hypertensive [4]. As indicated in Table 1, six trials (29 038 patients) gave information on comparisons between diuretics and placebo, four trials (17 976 patients) on comparisons between beta-blockers and placebo, six trials (11 479 patients) on comparisons between calcium antagonists and placebo, nine trials (31 499 patients) on comparisons between angiotensin-converting enzyme inhibitors (ACEIs) and placebo, 12 trials (56 240 patients) on comparisons between angiotensin receptor blockers and placebo and six trials (1556 patients) on comparisons between central agents and placebo.

Among the 50 RCTs providing information on head-to-head comparisons of drugs belonging to different classes [2], 37 were found to report discontinuations for adverse events or the occurrence of serious adverse events, and could be used for six comparisons between diuretics and beta-blockers (26 294 patients), six comparisons between diuretics and calcium antagonists (48 568 patients), two comparisons between diuretics and ACE inhibitors (24 878 patients), one comparison between diuretics and angiotensin receptor blockers (2204 patients), 15 comparisons between diuretics and all other classes (85 595 patients), four comparisons between beta-blockers and calcium antagonists (44 825 patients), two comparisons between beta-blockers and ACE inhibitors (1635 patients), two comparisons between beta-blockers and angiotensin receptor blockers (11 392 patients), 14 comparisons between beta-blockers and all other classes (82 616 patients), nine comparisons between calcium antagonists and ACE inhibitors (23 836 patients), four comparisons between calcium antagonists and angiotensin receptor blockers (22 244 patients), 24 comparisons between calcium antagonists and all other classes (146 684 patients), three comparisons between ACE inhibitors and angiotensin receptor blockers (17 728 patients), 18 comparisons between ACE inhibitors and all other classes (58 939 patients) and 11 comparisons between angiotensin receptor blockers and all other classes (54 507 patients) (Table 2).

Adverse events in placebo-controlled randomized controlled trials of blood pressure lowering by different classes of drugs

Comparisons of different drug classes with placebo

Figure 1 summarizes benefits and adverse events of BP lowering (standardized to a SBP/DBP lowering of 10/5 mmHg) by different classes of drugs. For sake of brevity, benefits are represented by reduction in major cardiovascular events [the composite of stroke + coronary heart diseases (CHDs) + hospitalized heart failure, unless the composite of stroke and CHD was reported in a larger number of trials]. All classes of BP-lowering drugs significantly reduced cardiovascular events with the only exception of calcium antagonists, which however significantly reduced fatal and nonfatal stroke [risk ratio 0.53 (0.35–0.75)]. All classes of drugs significantly increased adverse events (as measured by treatment discontinuations due to adverse events) over those occurring with placebo by between two and three times, with a single relevant exception, that of angiotensin receptor blockers. BP lowering by this class of drugs was associated with a risk of discontinuations substantially similar to that occurring on placebo [risk ratio 1.13 (0.78–1.62)]. In terms of absolute risk changes, the excess of discontinuations due to adverse events was between two-fold and eight-fold higher than the reductions in major cardiovascular events when

TABLE 2. Trials of head-to-head comparisons of different drug classes providing information on permanent discontinuations attributed to adverse events or on serious adverse events*

D vs BB ($n = 26\,294$)	D vs CA ($n = 48\,568$)	D vs ACEI ($n = 24\,878$)	D vs ARB ($n = 2204$)	D vs All ($n = 85\,595$)
COPE* [44]	ACCOMPLISH [48]	ALLHAT [49]	COPE* [44]	All mentioned
HAPPHY [45]	ALLHAT [49]	NESTOR* [54]		
IPPPSH [46]	COLM [50]			
MRC mild [8]	INSIGHT [51]			
MRC old [9]	MIDAS [52]			
VA-COOP [47]	NICS-EH [53]			
	BB vs CA ($n = 44\,825$)	**BB vs ACEI ($n = 1635$)**	**BB vs ARB ($n = 11\,392$)**	**BB vs All ($n = 82\,616$)**
	AASK [55]	AASK [55]	COPE* [44]	All mentioned
	ASCOT [56]	UKPDS-39 [59]	LIFE [60]	
	ELSA [57]			
	INVEST [58]			
		CA vs ACEI ($n = 23\,836$)	**CA vs ARB ($n = 22\,244$)**	**CA vs All ($n = 146\,684$)**
		AASK [55]	CASE-J [65]	All mentioned +
		ABCD-H [61]	IDNT [17]	CONVINCE [68]
		ALLHAT [49]	NAGOYA* [66]	
		BENEDICT* [21]	VALUE [67]	
		CAMELOT [15]		
		FACET [62]		
		Fogari [16]		
		JMIC-B [63]		
		JMIND* [64]		
			ACEI vs ARB ($n = 17\,728$)	**ACEI vs All ($n = 58\,939$)**
			DETAIL [69]	All mentioned +
			ONTARGET [70]	REIN-stratum 1 [72]
			ROAD [71]	REIN-stratum 2 [73]
				ARB vs All ($n = 54\,507$)
				All mentioned +
				HIJ-CREATE [74]

The acronyms of the trials are explained in the reference papers. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; D, diuretics. * Indicate the trials that did not provide data on discontinuations for adverse events, but data on serious adverse events.

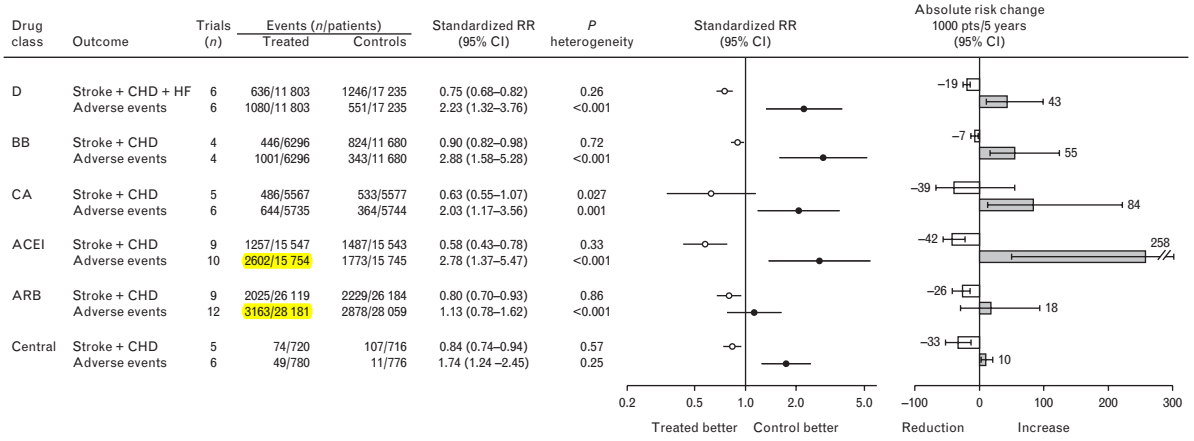

FIGURE 1 Changes in relative and absolute risk of cardiovascular events and of treatment discontinuations for adverse events attributed to treatment (Adverse events) in placebo-controlled randomized controlled trials using drugs of the pharmacological class indicated at the left. Standardized risk ratios and forest plots are risk ratios standardized to a SBP/DBP difference of 10/5 mmHg. Absolute risk changes are expressed for 1000 patients treated for 5 years with a standard SBP/DBP reduction of 10/5 mmHg. Cardiovascular outcomes are the composite of stroke and coronary heart disease or the composite of stroke, coronary heart disease and heart failure as indicated. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; Central, centrally acting drugs; CHD, coronary heart disease; CI, confidence interval; D, diuretics; HF, heart failure; RR, risk ratio.

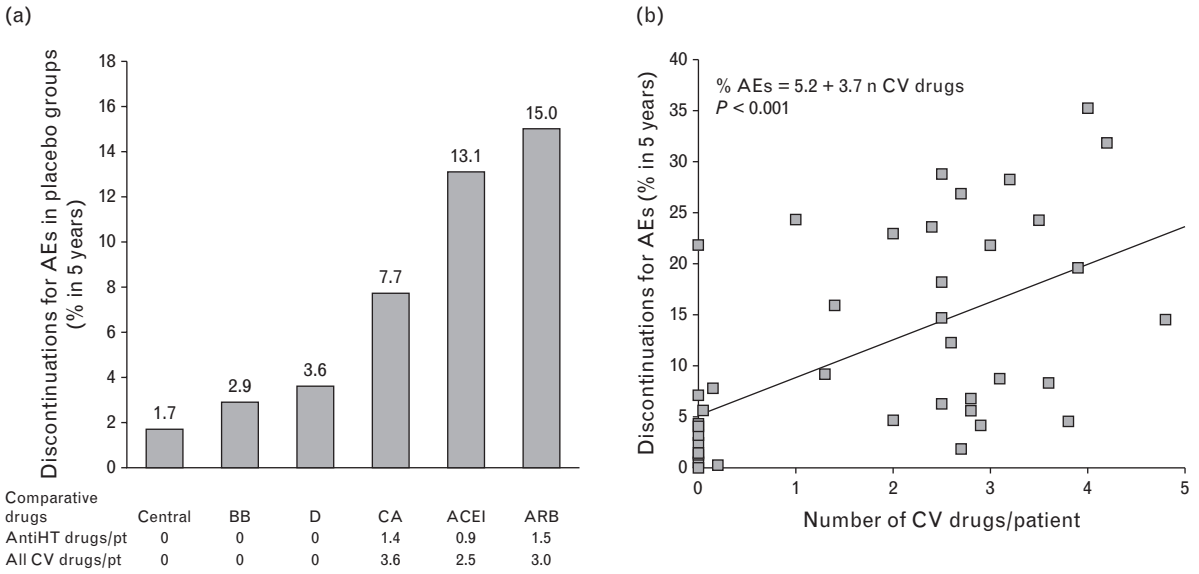

FIGURE 2 Relationships of treatment discontinuations for adverse events with number (mean per patient) of antihypertensive drugs and all cardiovascular drugs given to placebo-treated patients in trials comparing different classes of antihypertensive drugs with placebo. (a) Data from placebo patients grouped according to the active drug used for comparison: ACEI, angiotensin-converting enzyme inhibitors; AE, adverse events; AntiHT, antihypertensive; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; Central, centrally acting drugs; CV, cardiovascular; D, diuretics. (b) Data for placebo patients from individual trials and regression line of discontinuation for adverse events (% in 5 years) on mean number of cardiovascular drugs per patient.

a 10/5 mmHg SBP/DBP lowering was induced by diuretics, calcium antagonists or ACE inhibitors. On the other hand, with angiotensin receptor blockers, excess of adverse events was lower than the absolute reduction of cardiovascular outcomes.

Effect of concomitant medications

As apparent from Fig. 2a, even in the placebo control groups, the risk of discontinuations due to adverse events was quite lower in earlier trials using diuretics, beta-blockers and centrally acting agents as active drugs (between 1.7 and 3.6% in 5 years) than in trials using more recent classes of compounds (calcium antagonists 7.7%, ACE inhibitors 13.1% and angiotensin receptor blockers 15% in 5 years). The bottom lines of Fig. 2a report weighted means of the number of antihypertensive agents and, separately, of all cardiovascular drugs (antihypertensive, lipid lowering, antiplatelet, antidiabetic agents etc.) administered to each patient as a background treatment both in the placebo and actively treated groups. RCTs comparing diuretics, beta-blockers or centrally active drugs with placebo were generally older studies designed to prove the still unknown benefits of BP lowering, and the placebo patients did not receive any antihypertensive or cardiovascular drugs. On the other hand, RCTs comparing calcium antagonists, ACE inhibitors or angiotensin receptor blockers with placebo were done when the benefits of BP lowering had already been established and patients, including those randomized to placebo, received a background of 0.9–1.5 antihypertensive drugs, upon which either the active drug or placebo was added. In these more recent RCTs, increased awareness of the benefits of treating

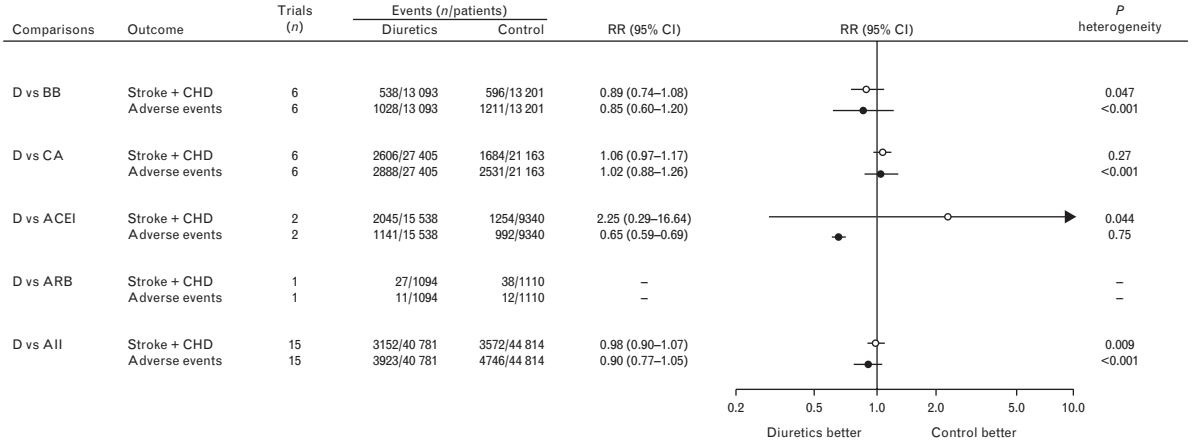

FIGURE 3 Comparisons of the effects of blood-pressure-lowering treatment based on diuretics vs the same blood pressure lowering based on other pharmacological classes on cardiovascular events and on treatment discontinuations for adverse events (Adverse events). The type of cardiovascular event considered was the composite of stroke and coronary heart disease. ACEI, angiotensin-converting enzyme inhibitors; All, all other classes together; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; CHD, coronary heart disease; CI, confidence interval; D, diuretics; RR, risk ratio.

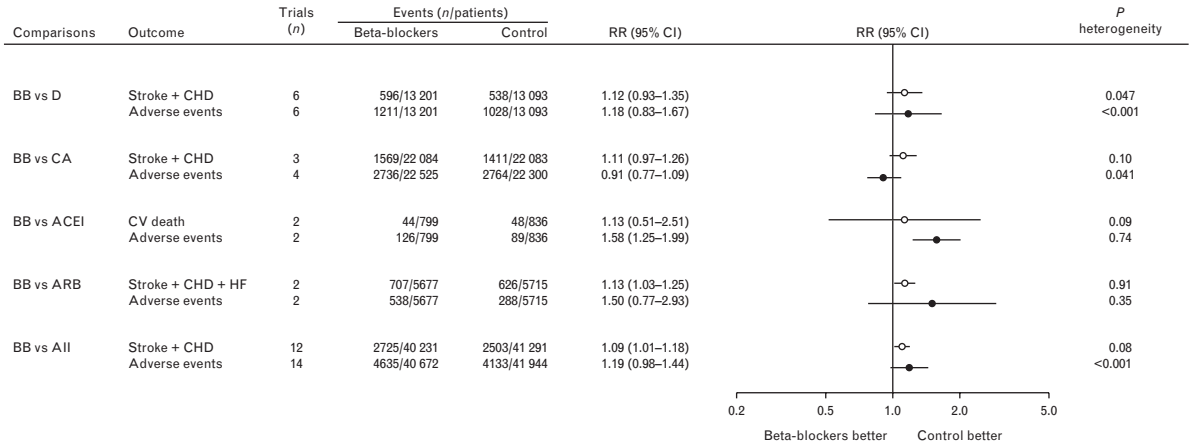

FIGURE 4 Comparisons of the effects of blood-pressure-lowering treatment based on beta-blockers vs the same blood pressure lowering based on other pharmacological classes on cardiovascular events and on treatment discontinuations for adverse events (Adverse events). The type of cardiovascular events considered was the composite of stroke and coronary heart disease or the composite of stroke, coronary heart disease and heart failure; or cardiovascular death, as indicated. ACEI, angiotensin-converting enzyme inhibitors; AII, all other classes together; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; D, diuretics; HF, heart failure; RR, risk ratio.

concomitant risk factors and the frequent involvement of high-risk patients caused a wide use of other cardiovascular drugs administered as background therapy to all patients, including those randomized to placebo, averaging 2.5–3.6 drugs.

The graph of Fig. 2b shows that a significant regression could be calculated from plotting the 5-year incidence of discontinuations for adverse events over the mean number of cardiovascular drugs received by patients randomized to placebo in the 38 RCTs here considered. A significant regression (P value <0.001) was found according to which discontinuations for adverse events increase by about 3.7% in 5 years every cardiovascular drug is added to the therapeutic regimen. The intercept of about 5% (for no active drug administration) probably represents discontinuations related to the awareness of possibly receiving treatment (in most RCTs placebo was masked) or to the constraints of a trial.

Further, correlation and regression analyses were done to investigate the relationship between the 5-year rate of discontinuations for adverse events in the placebo groups of all 38 RCTs (43 comparisons) and the RR of increased discontinuations in the actively treated groups. The RR of discontinuations caused by active antihypertensive treatment was found to progressively decrease with progressive increase of the discontinuations caused by concomitant treatment in the placebo group [ln RR = 0.97–0.038 adverse events (% in 5 years) in placebo group, $P < 0.001$]. This also means that concomitant treatment does not emphasize, but rather can partly obscure the contribution of randomized therapy to the discontinuations.

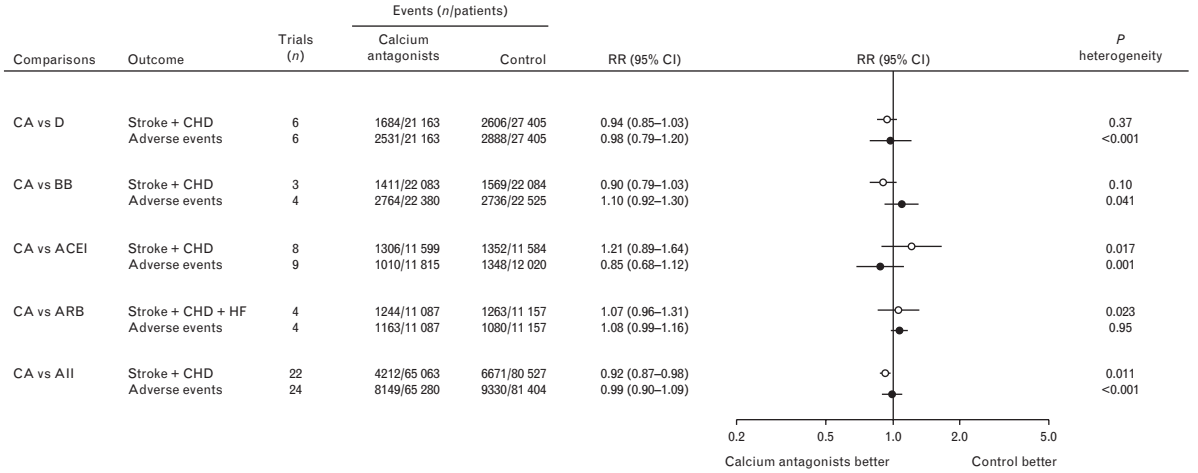

FIGURE 5 Comparisons of the effects of blood-pressure-lowering treatment based on calcium antagonists vs the same blood pressure lowering based on other pharmacological classes on cardiovascular events and on treatment discontinuations for adverse events (Adverse events). The type of cardiovascular events considered the composite of stroke and coronary heart disease or the composite of stroke, coronary heart disease and heart failure, as indicated. ACEI, angiotensin-converting enzyme inhibitors; All, all other classes together; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; CHD, coronary heart disease; CI, confidence interval; D, diuretics; HF, heart failure; RR, risk ratio.

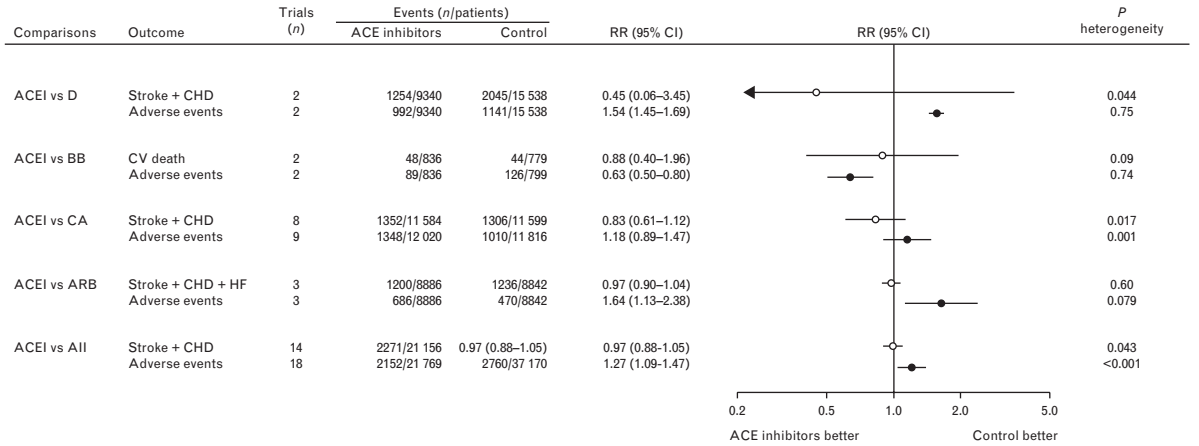

FIGURE 6 Comparisons of the effects of blood-pressure-lowering treatment based on angiotensin-converting enzyme inhibitors vs the same blood pressure lowering based on other pharmacological classes on cardiovascular events and on treatment discontinuations for adverse events (Adverse events). The type of cardiovascular events considered was the composite of stroke and coronary heart disease or the composite of stroke, coronary heart disease and heart failure; or cardiovascular death, as indicated. ACEI, angiotensin-converting enzyme inhibitors; All, all other classes together; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; D, diuretics; HF, heart failure; RR, risk ratio.

Adverse events in randomized controlled trials head-to-head comparing blood pressure lowering belonging to different pharmacological classes

Figures 3–7 summarize effects on cardiovascular events (the composite of stroke and coronary events or of stroke, coronary events and heart failure) and on adverse events (discontinuations attributed to adverse events and serious adverse events) in RCTs comparing BP-lowering drugs belonging to different classes.

Although differences between classes of antihypertensive drugs on the risk of major cardiovascular events are usually small and seldom statistically significant [2], differences on the risk of adverse events are more remarkable. Diuretics, beta-blockers and calcium antagonists do not show any significant difference in the risk of discontinuations when each of the three classes is compared with the other four classes together (Figs. 3–5). ACE inhibitors appear to be associated with a small (27%) higher risk of discontinuations than the other classes (Fig. 6), and angiotensin receptor blockers are the only class of BP-lowering drugs that is associated with a significant 29% lower risk of discontinuations for adverse events (Fig. 7).

There is some suggestion that the slightly higher risk of discontinuations with ACE inhibitors compared with all other classes [risk ratio 1.27 (1.09–1.47), 18 RCTs] may mostly result from a large prevalence of patients (30%) in whom ACE inhibitors were compared with angiotensin receptor blockers [risk ratio 1.64 (1.13–2.38)]. As angiotensin receptor blockers differed from all other classes by a lower risk of discontinuation and prevalence of comparisons with angiotensin receptor blockers was quite different for different drug classes (only 3% of patients for diuretics, 14% for beta-blockers, 15% for calcium antagonists and as many as 30% for ACE inhibitors), an additional analysis was done comparing each major BP-lowering drug class with all

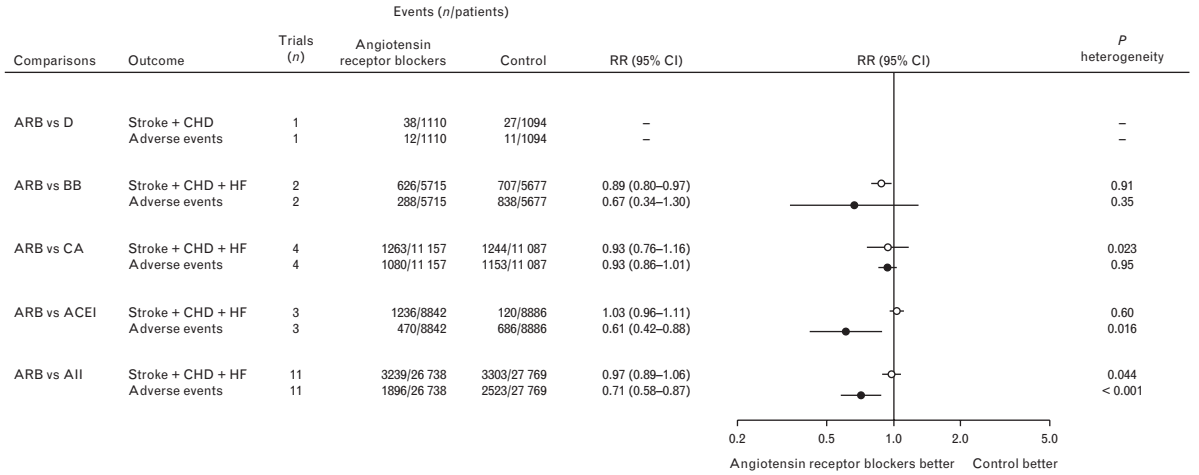

FIGURE 7 Comparisons of the effects of blood-pressure-lowering treatment based on angiotensin receptor blockers vs the same blood pressure lowering based on other pharmacological classes on cardiovascular events and on treatment discontinuations for adverse events (Adverse events). The type of cardiovascular events considered was the composite of stroke and coronary heart disease or the composite of stroke, coronary heart disease and heart failure, as indicated. ACEI, angiotensin-converting enzyme inhibitors; All, all other classes together; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; CHD, coronary heart disease; CI, confidence interval; D, diuretics; HF, heart failure; RR, risk ratio.

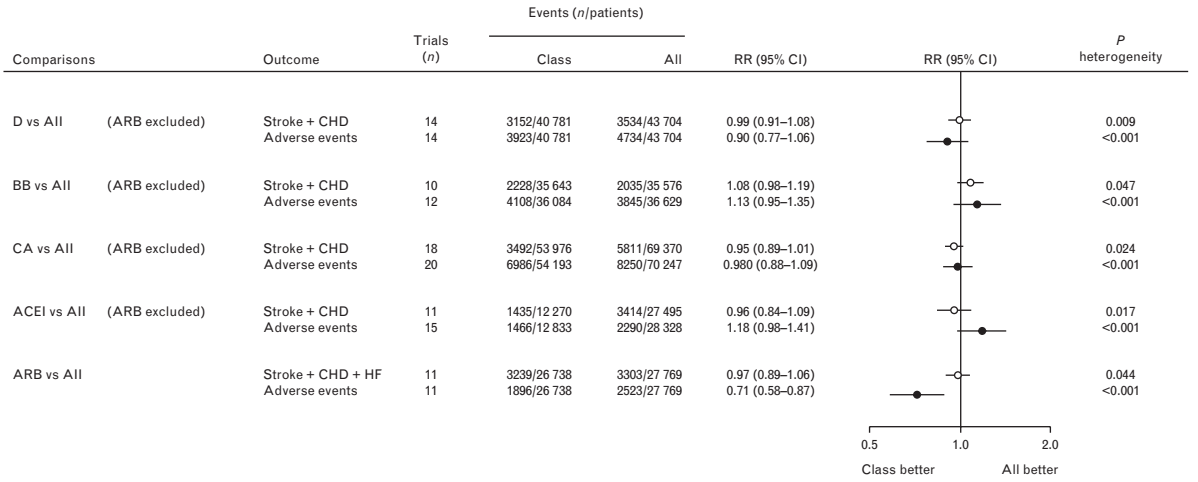

FIGURE 8 Comparisons of the effects of blood-pressure-lowering treatments based on diuretics, beta-blockers, calcium antagonists and angiotensin-converting enzyme inhibitors vs all other classes of drugs excluding angiotensin receptor blockers. The type of cardiovascular events considered was the composite of stroke and coronary heart disease or the composite of stroke, coronary heart disease and heart failure, as indicated. ACEI, angiotensin-converting enzyme inhibitors; All, all other classes together; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; CHD, coronary heart disease; CI, confidence interval; D, diuretics; HF, heart failure; RR, risk ratio.

other drug classes, angiotensin receptor blockers excluded. Figure 8 shows that, once angiotensin receptor blockers are considered separately, each drug class did not differ from all others together as far as discontinuations for adverse events or serious adverse events.

DISCUSSION

For the first time, the present set of meta-analyses has investigated the effects of different classes of BP-lowering drugs (either compared with placebo or directly compared each with others) on both cardiovascular events and a meaningful index of treatment-related adverse events, such as permanent treatment discontinuation attributed to adverse events.

The most relevant conclusion of these analyses is that although the beneficial effect of the various classes of antihypertensive agents on major cardiovascular events is substantially similar once SBP/DBP values are reduced to the same extent [2], the untoward effects represented by adverse events leading to permanent treatment discontinuation are not the same with all classes of drugs. When compared with placebo treatment, all major classes of BP-lowering drugs (diuretics, beta-blockers, calcium antagonists, ACE inhibitors and central agents) significantly and markedly (two-fold to three-fold) increase treatment discontinuations, with the relevant exception of angiotensin receptor blockers that have been found not to increase discontinuations over those occurring with placebo.

Similarly, when directly compared in head-to-head trials, diuretics, beta-blockers, calcium antagonists and ACE inhibitors (in particular, each class vs all the other classes together) have shown no differences or only small differences in the risk of discontinuations for adverse events, confirming what suggested by the meta-analysis of placebo-controlled RCTs, namely that all these classes of drugs are increasing treatment discontinuations for adverse events. Also in head-to-head comparison RCTs, the only exception appears to be represented by angiotensin receptor blockers, which is the only class of BP-lowering agents associated with a significant 29% lower risk of discontinuations when compared with all other drugs together. In a sensitivity analysis, considering angiotensin receptor blockers separately, small differences in discontinuations between the other classes disappear (Fig. 7). This perfectly agrees with the abovementioned results of the meta-analyses of placebo-controlled RCTs, showing that angiotensin receptor blockers are the only class of antihypertensive agents not increasing the risk of discontinuations over those occurring with placebo.

The significantly lower risk of treatment discontinuations with angiotensin receptor blockers than other BP-lowering drugs found in our meta-analyses is consistent with the lower rate of discontinuations reported in observational studies, mostly from general practitioners and healthcare registries [75–78], although observational studies could not provide the additional information we have presented, that treatment with angiotensin receptor antagonists is indeed associated with a discontinuation risk not significantly different from placebo treatment. Significant differences in discontinuation risk between the other antihypertensive drug classes have been described in some [77,78] but not all [75,76] observational studies, but were not apparent in our meta-analyses of randomized comparative studies.

Although the advantage of current antihypertensive therapy is to have available a wide range of pharmacological classes substantially similar in their beneficial effects of lowering BP and reducing cardiovascular events, knowing that available classes display different levels of tolerability and have different levels of risk of leading to permanent treatment discontinuations may influence choice of antihypertensive agents in current medical practice. Indeed, even if caused by adverse events of trivial health impact, permanent discontinuations of treatment have obvious untoward implications on health by depriving the hypertensive patients of the beneficial effects of BP lowering [3].

Our present meta-analyses contribute another important piece of information. In a large number of

placebo-controlled RCTs, particularly those using the more recently introduced classes of BP-lowering drugs (calcium antagonists, ACE inhibitors and angiotensin receptor blockers), the risk of discontinuations was rather high even in the placebo group and associated with the high number of antihypertensive and cardiovascular drugs given as a background therapy accompanying randomized treatment. The highly significant regression equation we have been able to calculate indicates that any single drug added to the therapeutic regimen was accompanied by almost 4% of patients permanently discontinuing treatment in 5 years. Although increasing the number of antihypertensive agents to achieve BP goal and association of other cardiovascular drugs to treat other risk factors or concomitant diseases have been shown to potentiate cardiovascular disease prevention and should therefore continue to be recommended as prescribed by guidelines [79], awareness that in so doing there is an increased risk of treatment discontinuations for adverse events is likely to help physicians in finding the most tolerable drugs among those available and in strictly following up and supporting the patients receiving a large burden of drugs and therefore at greater risk of quitting treatment because of adverse events.

The strength of the analyses reported here is that the analyses are founded on all available RCTs in which a BP-lowering drug belonging to one of the major pharmacological classes was compared with placebo or with a drug of a different class, provided information was given on discontinuations for adverse events or on serious adverse events. This means data from 38 placebo-controlled RCTs with 43 comparisons in 147 788 patients followed up for about 4 years and from 37 RCTs with 43 head-to-head comparisons of two drugs of different classes in 242 481 patients followed up for about 4 years have been used. Also, the drug subgroups that have been separately analyzed have usually been large. The comparison with placebo of diuretics included 29 038 patients, that of beta-blockers 17 976, that of calcium antagonists 11 479, that of ACE inhibitors 31 499 and that of angiotensin receptor blockers 56 240. Only the comparison of centrally acting drugs with placebo was small (1556 patients) because it was based on old trials, which used to be small. Head-to-head comparisons of drugs of a given class vs all other classes could take advantage from big data: 85 595, 82 616, 146 684, 58 939 and 54 507 patients for diuretics, beta-blockers, calcium antagonists, ACE inhibitors and angiotensin receptor blockers, respectively. Also, the regression analysis showing that the risk of treatment discontinuations in placebo patients progressively increases with the increase in the number of cardiovascular drugs concomitantly prescribed is based on data from 66 687 patients.

Our analyses also have limitations. Head-to-head comparisons between BP-lowering drugs belonging to two specific classes were sometimes limited to a few trials (one, two or three trials). Therefore, although reporting these data for descriptive purposes, we have based our conclusions on comparisons of drugs belonging to a given class with drugs belonging to any other class (founded on at least 11 RCTs and 54 507 patients). The limitations of the outcome we have chosen as a measurement of adverse events have been discussed at length in a previous article [3]. Although the adverse event leading to discontinuation may sometimes be trivial and not directly impacting on health (such as ankle edema with calcium antagonists or cough with ACE inhibitors), the consequent permanent treatment discontinuation has a meaningful impact on health, depriving the patient of the protective effects exerted by BP-lowering drugs on mortality and cardiovascular morbidity. However, though discontinuation is an objective, hard outcome, its attribution to treatment adverse events remains subjective, that is dependent on the patient's opinion or the doctor's judgment, which probably accounts for the significant heterogeneity of most of the meta-analyses of adverse effects.

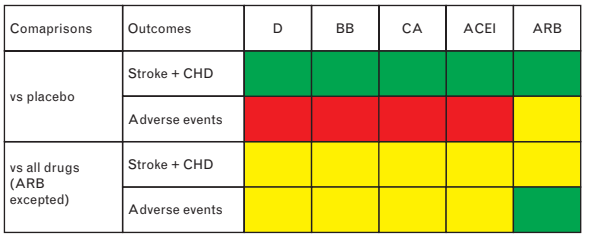

FIGURE 9 Benefits and burdens of various classes of antihypertensive drugs when compared with placebo (two upper rows) or with all other classes (angiotensin receptor blockers excepted). Effects considered are on the composite of stroke and coronary heart disease and on treatment discontinuations for adverse events. The direction of the effects of the class of drug indicated on the top of each column vs control (placebo or vs all other classes together, angiotensin receptor blockers excepted) is indicated by the colors – green, significantly better than control; yellow, not significantly different from control; red, significantly worse than control. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; CA, calcium antagonists; D, diuretics.

CONCLUSION

The first major conclusion of the present meta-analyses is that when compared with placebo, all classes of BP-lowering drugs, though able to significantly reduce the risk of major cardiovascular events, significantly increase risk of adverse events leading to permanent treatment discontinuations, with the distinct exception of angiotensin receptor blockers, the cardiovascular protective effect of which is not associated with increased discontinuations over those occurring on placebo. A second conclusion is that head-to-head comparisons of BP-lowering drugs belonging to different classes show that risk of cardiovascular outcomes and risk of adverse events leading to treatment discontinuations are not significantly different between different classes, again with the exception of angiotensin receptor blockers, which have similar effects as other drug classes on risk of cardiovascular outcomes, associated, however, with a significantly lower risk of discontinuations for adverse events. Characteristics of effectiveness and tolerability of the various BP-lowering drug classes are outlined in Fig. 9.

A further major conclusion of our analysis is that the risk of adverse events leading to treatment discontinuations is proportional to the number of drugs prescribed for cardiovascular prevention, including not only BP-lowering drugs, but also lipid-lowering, antiplatelet and antidiabetic agents.

A better awareness of the impact of drug-induced adverse events should not lead to a lesser use of life-saving

agents, but may help in a careful choice of the drugs best tolerated by the individual patient, in avoiding addition of drug to drug without controlling whether the added drug is effective (as often happens in the treatment of so-called resistant hypertension) and in a more successful follow-up of high-risk patients who require multiple drugs and whose adherence to this complex treatment requires closer assistance and newer approaches than those followed so far.

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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 and Servier; 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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Reviewers' Summary Evaluations

Reviewer 1

In many of the trials meta-analyzed in this paper the drugs were given for other indications than hypertension. As pointed out by the authors, inclusion criteria required that at least 40% of the patients included in a trial were hypertensive. However, the ARB finding seems strong whatever indication despite using the discontinuations as the index of drug-related adverse events. It is a finding that fits well with experience in clinical practice and data from pharmacy registries, and it seems to be a strong argument for physicians to make the choice of ARB over ACEI (in particular), maybe even ARB over non-RAAS blockers for the indication hypertension.

Reviewer 2

This meta-analysis focused on antihypertensive treatment discontinuations due to adverse events in randomized controlled studies is certainly of interest and nicely complements the other meta-analysis published by the same authors.

With the notable exception of angiotensin receptor blockers, all antihypertensive drug classes appear to be associated with increased, similar rates of adverse events compared to placebo.

The impact of the number of other drugs prescribed for cardiovascular prevention, especially in more recent trials testing newer antihypertensive drugs, is also nicely emphasized.