Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 – Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials

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Background: Type 2 diabetes mellitus is associated with an increased risk of hypertension, and cardiovascular and renal disease, and it has been recommended that management of hypertension should be more aggressive in presence than in absence of diabetes mellitus, but the matter is controversial at present.

Objectives: Meta-analysing all available randomized controlled trials (RCTs) to compare the effects on cardiovascular and renal outcomes of blood pressure BP lowering to different systolic BP (SBP) and diastolic BP (DBP) levels or by different drug classes in patients with and without diabetes mellitus.

Methods: The database consisted of 72 BP-lowering RCTs (260 210 patients) and 50 head-to-head drug comparison RCTs (247 006). Among these two sets, RCTs or RCT subgroups separately reporting data from patients with and without diabetes mellitus were identified, and stratified by in-treatment achieved SBP and DBP, by drug class compared with placebo, and drug class compared with all other classes. Risk ratios and 95% confidence intervals, and absolute risk reductions of six fatal and non-fatal cardiovascular outcomes, all-cause death, and end-stage renal disease (ESRD) were calculated (random-effects model) separately for diabetes mellitus and no diabetes mellitus, and compared by interaction analysis.

Results: We identified 41 RCTs providing data on 61 772 patients with diabetes mellitus and 40 RCTs providing data on 191 353 patients without diabetes mellitus. For achieved SBP at least 140 mmHg, relative and absolute reductions of most cardiovascular outcomes were significantly greater in diabetes mellitus than no diabetes mellitus, whereas for achieved SBP below 130 mmHg, the difference disappeared or reversed (greater outcome reduction in no diabetes mellitus). Significant ESRD reduction was found only in diabetes mellitus, but it was greatest when achieved SBP was at least 140 mmHg, and no further effect was found at SBP below 140 mmHg. All antihypertensive drug classes reduced cardiovascular risk vs. placebo in diabetes mellitus and no diabetes mellitus, but angiotensin-converting enzyme inhibitors were the only class more effective in diabetes mellitus than in no diabetes mellitus. When compared to other classes, renin–angiotensin system blockers were equally effective in cardiovascular prevention in no diabetes mellitus, but moderately, though significantly, more effective in diabetes mellitus.

Conclusion: BP-lowering treatment significantly and importantly reduces cardiovascular risk both in diabetes mellitus and no diabetes mellitus, but evidence for reduced ESRD risk is available only in diabetes. Contrary to past recommendations, in diabetes mellitus there is little or no further benefit in lowering SBP below 130 mmHg, whereas continuing benefit is seen in no diabetes mellitus also at SBP below 130 mmHg. Although all BP-lowering drugs can beneficially be prescribed in hypertensive patients with diabetes mellitus, the current recommendation to initiate or include a renin–angiotensin system blocker is supported by the evidence here presented.

Keywords: antihypertensive drugs, blood-pressure-lowering trials, cardiovascular death, coronary heart disease, diabetes mellitus, end-stage renal disease, meta-analysis, randomized controlled trials, stroke

Abbreviations: ACE, angiotensin-converting enzyme; ARR, absolute risk reduction; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; ESRD, end-stage renal disease; RAS, renin–angiotensin system; RCT, randomized controlled trial; SBP, systolic blood pressure

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INTRODUCTION

Type 2 diabetes mellitus is known to be associated with an increased risk of hypertension [1], and cardiovascular and renal disease [2,3]. On the basis of the enthusiasm raised by the first demonstration provided in 1998 by the publication of the Hypertension Optimal Treatment (HOT) trial [4], and, shortly thereafter, of the UK Prospective Diabetes Study (UKPDS) [5], both showing that more intense blood pressure (BP)-lowering treatment significantly reduced cardiovascular morbidity and mortality in hypertensive patients with type 2 diabetes mellitus, most diabetes and hypertension guidelines published in the first decade of the current century recommended that antihypertensive treatment should be initiated at a lower systolic BP (SBP) threshold ($\geq$130 mmHg) in individuals with rather than without diabetes (SBP $\geq$140 mmHg), and lower SBP targets should be attained by treatment (SBP $<$ 130 mmHg in diabetes vs. SBP $<$ 140 mmHg in non-diabetic individuals) [6–9]. After attention was called on the lack of trial evidence for these recommendations [10], most of the recent guidelines reconsidered their conclusions, and now usually recommend that initiation and target of treatment should be similar both in patients with and without type 2 diabetes [11–15]. Furthermore, recent guidelines recognize that all classes of BP-lowering drugs can be beneficially used in treating hypertensive patients with diabetes, but express the opinion that starting antihypertensive treatment with a blocker of the renin–angiotensin system (RAS) may be reasonable in diabetic patients because of possible specific protective effects of this type of agents on albuminuria and renal function [11–13].

Meta-analyses of randomized controlled trials (RCTs), although not without limitations mostly because of arbitrary and, sometimes, inconsistent inclusion and exclusion criteria [16], nonetheless can provide useful quantitative information when adequate specific RCTs are not available or provide conflicting evidence. In the past, a number of meta-analyses have attempted to quantify the effects of BP-lowering treatment and of different BP-lowering drugs on cardiovascular and, sometimes, renal outcomes in patients with diabetes [17–20], the two most recent ones being that by Emdin *et al.* [21] and that by Brunström and Carlberg [22]. In 2005, the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) also provided comprehensive meta-analyses comparing the effects of BP lowering management in individuals with and without diabetes [17], showing no substantial differences, whereas a recent meta-analysis by Ettehad *et al.* [23] suggests BP-lowering treatment may be slightly less effective on cardiovascular outcomes in diabetic than in non-diabetic individuals.

We have recently completed two comprehensive surveys of BP-lowering RCTs (active treatment vs. placebo, or more vs. less intense treatment) [24,25] and RCTs directly (head-to-head) comparing different classes of antihypertensive agents [26]. Both surveys were done following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. Taking advantage of the data provided by these surveys, we have now tried to answer a number of clinically relevant questions, such as whether the effects of BP lowering on cardiovascular and renal outcomes differ between patients with and without type 2 diabetes mellitus, initiation and targets of BP-lowering treatment should be at similar or different SBP and diastolic BP (DBP) levels in patients with and without diabetes, and different classes of BP-lowering drugs are differently effective on risk of cardiovascular and renal outcomes in hypertensive patients with and without type 2 diabetes.

METHODS

Trial eligibility

The data here analysed are derived from the two above mentioned surveys of BP-lowering RCTs vs. placebo or of more vs. less active BP lowering, as presented in [24] and updated to 31 December 2015 [28], and the further addition of the upper tertile of Heart Outcomes Prevention Evaluation (HOPE)-3 patients [29] (72 RCTs, 260 210 patients, 1 115 334 patient-years); and head-to-head comparisons of different classes of BP-lowering drugs [26] (50 RCTS, 247 006 patients, 1 029 768 patient-years; updating of the survey to 30 June 2016 did not identify any additional RCTs). Both surveys were focused only on RCTs recruiting hypertensive patients or cohorts with at least 40% hypertensive patients, with specific exclusion of RCTs in patients with acute myocardial infarction and chronic heart failure, in whom drugs with BP-lowering potential are administered not to lower BP, but in view of other therapeutic properties [24]. Because of the debate as to whether patients with diabetes should also receive BP-lowering treatment when their BP is in the high-normal range, RCTs recruiting patients with non-optimal BP (high-normal BP or pre-hypertension) with the specific intention of investigating the effects of BP lowering and with exclusion of RCTs in patients with acute or recent myocardial infarction and heart failure were also analysed (4 RCTs, 10 080 patients, 53 295 patient-years) [29–32].

For the current meta-analyses, the two sets of RCTs (BP-lowering RCTs including high-normal BP trials and head-to-head drug comparison RCTs) were examined to identify those RCTs in which recruitment specifically included only patients with type 2 diabetes mellitus; recruitment specifically excluded patients with diabetes mellitus; and recruitment included both patients with and without diabetes mellitus provided outcome data were available separately for the two types of patients.

For further analyses, the first set of RCTs (BP-lowering RCTs) were subdivided, separately, for patients with and without diabetes:

1. according to the levels of baseline SBP/DBP into high-normal BP (or pre-hypertension) RCTs (SBP 130–139 mmHg or DBP 80–89 mmHg); grade 1 RCTs (SBP 140–159 mmHg or DBP 90–99 mmHg); grade 2 RCTs (SBP 160–179 mmHg or DBP 100–109 mmHg), and grade 3 hypertension RCTs (SBP $\geq$180 mmHg or DBP $\geq$110 mmHg), provided antihypertensive treatment at randomization was absent or minimal;

2. according to the average SBP (or DBP) achieved in the active or more intense treatment arm of the RCTs, as follows: SBP 140 to less than 150 mmHg, 130 to less than 140 mmHg, less than 130 mmHg; DBP 80 to less than 90 mmHg, less than 80 mmHg mmHg; and
3. according to the class of BP-lowering drug, the patients were randomly allocated vs. placebo (or no treatment). Further details can be found in the studies with previous meta-analyses [25,28,33].

The second set of RCTs (head-to-head comparisons of drugs belonging to different classes) was also subdivided, separately for patients with and without diabetes, according to the classes of BP-lowering drugs being compared (for further details, see [26]).

RCTs specifically devoted to patients with type 1 diabetes were not considered, as were not considered RCTs or trial subgroups in which combinations of two RAS blockers were used because of evidence that these combinations have unfavourable effects. Selection of the RCTs to be included in each of the new meta-analyses was done on the basis of the criteria detailed above by two of the authors (C.T. and A,Z.), with differences resolved by discussion.

Outcomes

The following predetermined outcomes were considered, as in previous surveys [24,26,28]: fatal and non-fatal stroke: fatal and non-fatal coronary heart disease (CHD) events; fatal and non-fatal hospitalized heart failure; composite of stroke and CHD; composite of stroke, CHD and HF; cardiovascular death; all-cause death. In consideration of the importance of renal failure among complications of diabetes, outcome analysis was extended to end-stage renal disease (ESRD), defined as renal disease resulting in dialysis, transplantation or death. To this purpose, all RCTs included in our previous meta-analyses were re-examined by two of the authors (C.T., A.Z.) to extract data on the renal failure outcome.

Statistical analyses

As in our previous meta-analyses [24,26,28], SBP/DBP differences between randomized treatments were the means of every individual trial values weighted by patients' number and follow-up duration. For every group of comparisons, the null hypothesis of no difference between randomized treatments (active vs. placebo or less active, drug class vs. other drug classes) was tested. Relative risk estimates [risk ratio with 95% confidence intervals (CIs)] 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. For BP-lowering RCTs, whenever standardization of the risk estimates was required, this was done to a SBP/DBP difference of 10/5 mmHg as described in [24]. As the head-to-head comparison of different active treatments implies no BP difference between treatments, whenever mean SBP/DBP differences were above 1 mmHg, suitable statistical adjustments were done [26]. The amount of inconsistency across the studies in each single meta-analysis not explained by chance was quantified by using the I^2 and the chi-square Q statistics: heterogeneity was considered low when I^2 was between 0 and 25%, intermediate between 25 and 75%, and high above 75%. 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 risk estimate with all available trials, the trial in question was considered to have an excessive influence. Random-effect meta-regression models with inverse variance weighting were also constructed (methodological details in [24]) separately for patients with and without diabetes. Comparisons between the treatment effects on the various outcomes in patients with or without diabetes, or in patient groups achieving different BP levels were done by the chi-square test of homogeneity or trend analysis. A P value less than 0.05 for this test was taken to indicate significant heterogeneity between data in patients with and without diabetes (or at different achieved BP), whereas a P value between 0.05 and 0.1 was taken to indicate borderline significance. For all other tests, a P value of less than 0.05 was taken to indicate statistical significance. Because of the descriptive value of these meta-analyses, no correction for multiple testing was done.

All statistical analyses were done using Comprehensive Meta Analysis version 3 (Biostat, Englewood, New Jersey, USA). For all other aspects, the same statistical methodology used for our previous meta-analyses [24,26,28] was employed.

RESULTS

Effects of blood pressure lowering on cardiovascular outcomes in hypertensive patients with and without diabetes

Table 1 lists the BP-lowering RCTs identified according to the above-mentioned criteria as reporting outcome data for patients with and, separately, without diabetes [4,5,29–32,34–102]. There were 17 RCTs that included only patients with diabetes, 16 RCTs that included only patients without diabetes, and 24 RCTs that separately reported data for patients with and without diabetes. On the whole, 57 BP-lowering RCTs were considered, including 61 772 patients with diabetes and 191 353 without diabetes.

As illustrated in Fig. 1, when separately considered for patients with and without diabetes, heterogeneity was in most cases low, and intermediate in the other cases. Most cardiovascular outcomes considered were significantly reduced by a standardized SBP/DBP reduction of 10/5 mmHg in both groups of patients. In patients with diabetes as compared with those without diabetes, relative risk reduction was significantly larger for CHD events and for all-cause death, whereas it was significantly smaller for heart failure. Absolute risk reductions of CHD events, the composite of stroke and CHD, the composite of stroke, CHD and heart failure, cardiovascular death and all-cause death were significantly higher in patients with diabetes than in those without. Exclusion of the four RCTs in normal or high-normal BP individuals did not alter the results.

A more stringent comparison of hypertensive patients with and without diabetes was done as a sensitivity analysis by limiting the comparison to those RCTs providing

TABLE 1. Blood pressure-lowering trials reporting outcome data separately for patients with and without diabetes

Trial acronym	Treatment		Patients (n)		Baseline SBP/DBP (mmHg)		Achieved SBP/DBP (mmHg)	
	Active	Control	DM	No DM	DM	No DM	DM	No DM
Hypertension								
AASK [34]	More	Less	–	1094	–	NA	–	128/78
ABCD-H [35]	More	Less	470	–	155/98	–	132/78	–
ACCORD [36]	More	Less	4733	–	NA	–	119.2/64.7	–
ACTION [37,38]	CA	Placebo	1113	6552	NA	NA	130.3/76.2	130.3/76.2
ADVANCE [39,40]	ACEI+D	Placebo	11140	–	NA	–	134.7/74.8	–
Australian-Mild [41]	D	Placebo	–	3427	–	157.4/100.5	–	NR/88.4
BENEDICT [42]	ACEI or CA or ACEI + CA	Placebo	1204	–	NA	–	139.7/81	–
CAMELOT [43,44]	CA or ACEI	Placebo	363	1628	NA	NA	124.4/75	124.4/75
CARDIO-SIS [45]	More	Less	–	1111	–	NA	–	136/79.2
DEMAND [46]	ACEI or ACEI + CA	Placebo	380	–	NA	–	138.1/80.8	–
DIABHYCAR [47]	ACEI	Placebo	4912	–	NA	–	143.5/81.3	–
DIRECT Protect 2 [48]	ARB	Placebo	1905	–	NA	–	136/76	–
DREAM [49]	ACEI	Placebo	–	5269	–	NA	–	127.9/78.6
EUROPA [50,51]	ACEI	Placebo	1502	10716			132.8/77.4	127.4/78.1
EWPHE [52]	D	Placebo	111	729	186.8/101.2	181.8/101.0	149.5/86.4	149.5/86.4
FEVER [53,54]	CA	Placebo	1241	8470	155.3/90.2[a]	154.2/91.3[a]	139/82.3	137.9/82.7
Fogari [55]	CA + ACEI	CA or ACEI	309	–	160.3/99.3	–	132.4/82.3	–
HDPF [56,57]	D	Little treatment	772	10168	158.8/101.5	158.8/101.5	131.5/86	131.5/86
HEP [58]	BB		–	884	–	196.1/98.5	–	162.1/77
HOPE [59,60]	ACEI	Placebo	3577	5720	NA	NA	138.4/77.2	135.7/76.2
HOPE-3H [29]	ARB + D	Placebo	–	4240	–	154.1/ -	–	135.6/-
HOT [4,61]	More	Less	1501	17289	174.1/105.3	169.3/105.4	143.7/81	139.4/81.1
HSCG [62]	Central + D	Placebo	162	290	164/100.5	164/100.5	141/88	141/88
Hunan [63]	CA	No treatment	–	2080	–	160.5/98.5	–	140.7/85.2
IDNT [64,65]	ARB or CA	Placebo	1715	–	NA	–	140.5/77	–
I-PRESERVE [66,67]	ARB	Placebo	1134	2991	NA	NA	133.2/76.9	133.2/76.9
IRMA-2 [68]	ARB	Placebo	590	–	153/90.3	–	142/83	–
JATOS [69,70]	More	Less	521	3897	NA	NA	NR	135.9/74.8
MRC-mild [71]	D or BB	Placebo	–	17354	–	161.3/98.3	–	138.1/87
MRC-old [72]	D or BB	Placebo	–	4396	–	185/90.6	–	153/77.7
NAVIGATOR [73]	ARB	Placebo	–	9306	–	NA	–	133/78
NICOLE [74]	CA	Placebo	85	741	NA	NA	139/78	128/78
ORIENT [75]	ARB	Placebo	566	–	NA	–	132.5/73	–
OSLO [76]	D	No treatment	–	785	–	155.8/96.8	–	131/88
PEACE [77]	ACEI	Placebo	1384	6906	NA	NA	NR	129.6/74.4
PROFESS [78]	ARB	Placebo	5743	14589	NA	NA	135.4/79.2	135.4/79.2
PROGRESS [79,80]	ACEI or ACEI + D	Placebo	761	5344	NA	NA	137/78	133/79
REIN-2 [81]	More	Less	–	335	–	NA	–	129.6/79.5
RENAAL [82,83]	ARB	Placebo	1513	–	–	NA	143.5/71.7	–
ROADMAP [84]	ARB	Placebo	4447	–	–	NA	125.7/74.3	–
SANDS [85]	More	Less	499		–	NA	117/67	–
SCOPE [86,87]	ARB	Placebo	599	4338	166.2/90.3[a]	166.2/90.3[a]	143.5/77.6	144.1/79.2
SHEP [88,89]	D	Placebo	583	4149	170.2/75.8	170.3/76.7	146/68.5	142/68.2
SPRINT [90]	More	Less	–	9361	–	NA	–	121.5/75.4
SPS-3 [91,92]	More	Less	1106	1914	NA	NA	125.8/69	125.8/68.5
STOP [93]	D/BB or ACEI or CA	Placebo	142	1485	191.6/101	195/102.1	166.1/87.2	166/87.2
Syst-China [94,95]	CA	Placebo	98	2296	172.5/93	170.2/93	150.6/81.1	150.6/81.1
Syst-Eur [96,97]	CA	Placebo	492	4203	175.3/84.5	173.9/85.6	153.2/77.7	150.6/78.9
TOMHS [98]	Active	Placebo	–	902	–	140.4/90.6	–	124.2/78.3
TRANSCEND [99,100]	ARB	Placebo	2118	3808	NA	–	134.1/77.1	134.1/77.1
UKPDS-38 [5]	More (BB or ACEI)	Less	1148	–	160/94[a]	–	144/82	–
USPHS [101]	Central + D	Placebo	–	389	–	146.9/98.9	–	131.5/88.4
VALISH [102]	More	Less	399	2861	NA	NA	136.6/74.8	136.6/74.8
Total			61038	182017				
Normal and high-normal BP								
ABCD-N [30]	More	Less	480	–	131.4/84.4	–	128/75	–
ABCD-2V [31]	More	Less	129	–	126/84	–	118/75	–
HOPE-3N [29]	ARB + D	Placebo	–	8463	–	129.9/-	–	123.7/NR
PHARAO [32]	ACEI	No treatment	135	873	135.5/84.1	134.2/83.5	127.2/78	127.2/78
Total general			61772	191353				

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CA, calcium antagonists; D, diuretics; DBP, diastolic blood pressure; DM, diabetes mellitus; NA, not available, because of background antihypertensive treatment; NR, not reported, SBP, systolic blood pressure.
[a]Under low-dose therapy.

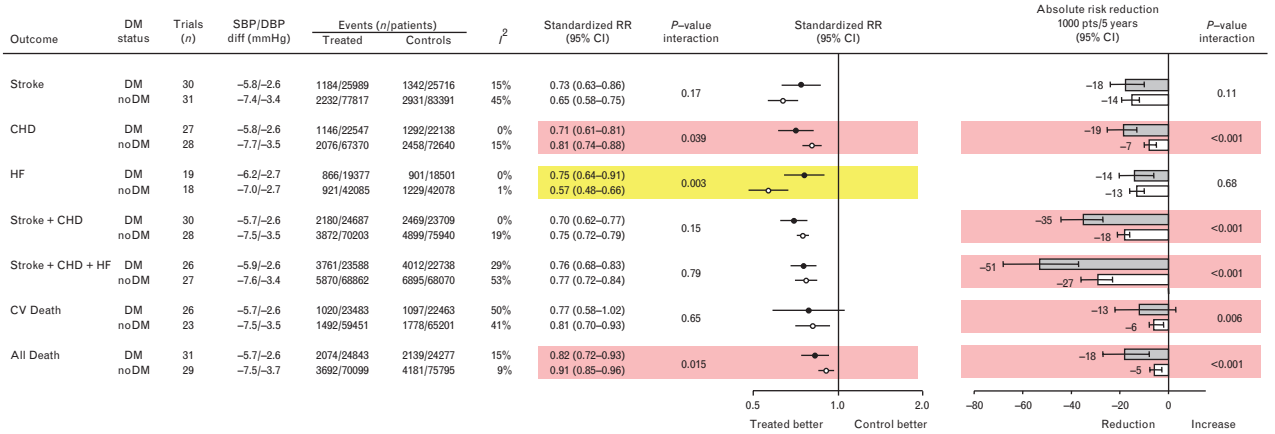

FIGURE 1 Relative risk and absolute risk reduction of various cardiovascular morbidity and mortality outcomes in patients with diabetes mellitus (DM) and without diabetes mellitus (no DM). Risk ratios (RR) standardized to a SBP/DBP difference of 10/5 mmHg. Rectangles at the right represent absolute risk reductions expressed as number (and 95% confidence interval) of events prevented every 1000 patients treated for 5 years with a standardized RR. *P* values for interaction refer to differences in standardized risk ratios, and, respectively, absolute risk reductions between patients with and without diabetes. The pink-shaded areas indicate the outcomes for which relative or absolute risk reduction was significantly greater in presence than in absence of diabetes. The yellow-shaded area indicates the outcome for which risk reduction was significantly greater in absence of diabetes. CHD, coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; DM, diabetes mellitus; HF, heart failure; RR, risk ratio; SBP, systolic blood pressure.

separate data both in individuals with and without diabetes, thus reducing influence of other variables (Fig. 2). This sensitivity analysis confirmed the significantly greater relative risk reduction of CHD events and all-cause death in hypertensive patients with diabetes, whereas the lower relative risk reduction in heart failure was not confirmed. A significantly greater absolute risk reduction for most cardiovascular outcomes and all-cause death in patients with diabetes was also confirmed by this sensitivity analysis.

Another sensitivity analysis was done excluding all trials published before the year 2000 (leaving 31 trials with patients with diabetes and 24 with patients without diabetes) in order to provide specific evidence on patients more similar to contemporary ones: the results of these meta-analyses were strictly super-imposable to those of Fig. 1 (see eFig. S1, http://links.lww.com/HJH/A729).

Linear regression of the logarithm of the risk ratios of all outcomes on the extent of systolic, diastolic, and pulse pressure (PP) reductions were calculated by meta-regression analyses. When separately calculated for patients with diabetes and without diabetes the meta-regressions were seldom significant (exceptions: regression of stroke from SBP, DBP, PP reduction in patients with diabetes, regression of stroke from DBP reduction and cardiovascular death from PP reduction in patients without diabetes). No differences could be detected between the slopes calculated in presence and absence of diabetes (*P* values for interaction between 0.20 and 0.97).

Effects on cardiovascular outcomes of blood pressure lowering in patients with and without diabetes at different grades of hypertension

As indicated in Table 1, too few data were available to carry out reliable comparative analyses on pre-hypertensive individuals and patients with grade 1 and 3 hypertension. Comparative analyses were therefore limited to patients

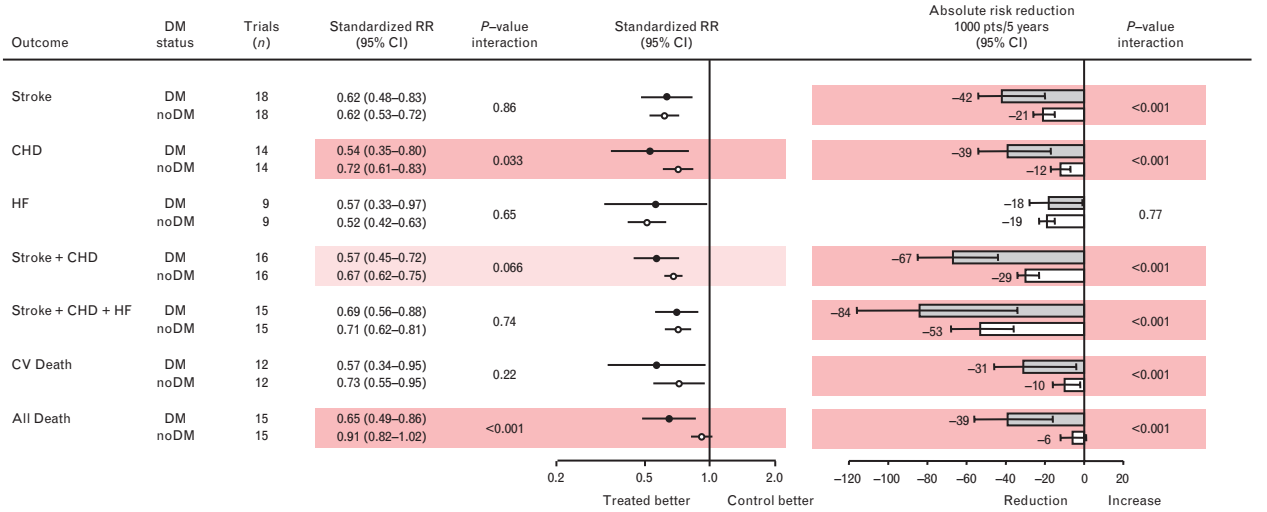

FIGURE 2 Relative risk and absolute risk reduction of various cardiovascular morbidity and mortality outcomes in patients with diabetes mellitus (DM) and without diabetes mellitus (no DM). Only trials for which separate data both on patients with and without diabetes were available. The pink-shaded areas indicate the outcomes for which relative or absolute risk reduction was significantly (deep pink) or borderline significantly (faint pink) greater in presence than in absence of diabetes. Other explanations and abbreviations as in Fig. 1.

belonging to grade 2 hypertension, for which data on individuals with diabetes were available from 10 RCTs (6905 individuals), and data on hypertensive patients without diabetes from 11 RCTs (67 748 individuals). Also in this subset of patients, the risk of all outcomes was significantly reduced both in patients with and without diabetes, with relative risk reductions numerically greater in the group with diabetes, although the test of interaction never attained statistical significance (*P* values for interaction between 0.14 and 0.87) (see eTable S1, http://links.lww.com/HJH/A729).

Effects on cardiovascular outcomes of blood pressure lowering to different systolic and diastolic levels in patients with and without diabetes

As indicated in Table 1, among RCTs providing data on hypertensive patients with diabetes, there were 13 trials, including 13 566 individuals, in which SBP in the active or more actively treated group was lowered to values no less than 140 mmHg (average SBP 143.9 mmHg, DBP 79.7 mmHg); 19 RCTs (including 34 940 individuals), in which SBP (active group) was lowered to between 130 and 140 mmHg (average SBP 135.2 mmHg, DBP 77.0 mmHg); and 6 RCTs (including 12 532 individuals), in which SBP (active group) was lowered to values less than 130 mmHg (average SBP 123.3 mmHg, DBP 70.0 mmHg). The data reported in Fig. 3a indicate that the relative risk reduction by a standardized SBP/DBP reduction of 10/5 mmHg becomes progressively smaller, the lower is the SBP value achieved on treatment (trend statistically significant for CHD events, heart failure, composite events, cardiovascular death; borderline significance for all-cause death). For cardiovascular death and all-cause death, the point estimate at achieved SBP values below 130 mmHg becomes higher than 1 (although not statistically significant). For all outcomes, absolute risk reduction also shows a significant trend to become progressively smaller, the lower is the achieved SBP (for further details see eTable S2a, http://links.lww.com/HJH/A729).

A similar trend is not observed in RCTs on hypertensive patients without diabetes (stratum SBP $\geq$140 mmHg: 10 RCTs, 24 850 individuals, average SBP 148.8, DBP 78.4 mmHg in active group; stratum SBP 130–140 mmHg: 17 RCTs, 11 487 individuals, average SBP 135.6, DBP 80.5 mmHg in active group; stratum SBP $<$130 mmHg: 10 RCTs, 38 866 individuals, average SBP 126.2, DBP 76.3 mmHg in active group). As illustrated in Fig. 3b, in patients without diabetes, the risk of most outcomes is significantly reduced even at achieved SBP values below 130 mmHg, and there is no significant trend for relative risk reduction to become smaller at lower SBP targets, the trend being rather for relative risk reduction to become slightly greater at lower SBP targets, particularly for CHD and mortality. Except for stroke, absolute risk reduction does not show any trend to decrease at lower SBP target, whereas this is the case in patients with diabetes (for further details see eTable S2b, http://links.lww.com/HJH/A729).

Interaction analyses of risk reductions in patients with and without diabetes at different levels of achieved SBP (Fig. 4) show that, at achieved SBP no less than 140 mmHg, relative and absolute risk reductions of most outcomes were significantly greater in patients with diabetes, at SBP between 130 and 140 mmHg relative risk reductions were mostly similar in diabetes and non-diabetes, whereas at achieved SBP level below 130 mmHg, the effects of BP reduction reversed with greater relative and absolute risk reductions of a number of outcomes in patients without diabetes. A sensitivity analysis also including the RCTs in individuals with high-normal blood pressure in the stratum with achieved SBP below 130 mmHg (8 RCTs, 13 276 patients with diabetes, 12 RCTs, 48 202 patients without diabetes) did not substantially change the results.

Stratification of BP-lowering RCTs in patients with diabetes by on-treatment achieved DBP no less than 80 or below 80 mmHg in the active group and identified 13 RCTs (including 12 570 individuals) with average achieved DBP 82.0 mmHg (SBP 141.8 mmHg) and 25 RCTs (including 48 468 individuals) with average achieved DBP 74.7 mmHg (SBP 132.9 mmHg). For patients without diabetes, 12 RCTs (including 64 762 individuals) were identified with average achieved DBP 84.5 mmHg (SBP 138.6 mmHg) and 26 RCTs (including 117 255 individuals) with average achieved DBP 76.9 mmHg (SBP 133.7 mmHg). Figure 5a illustrates that, in patients with diabetes, achieving a DBP level less than 80 mmHg was accompanied by significantly smaller relative and absolute risk reductions than in patients achieving a DBP level no less than 80 mmHg (further details in eTable S3a, http://links.lww.com/HJH/A729). This was not the case among patients without diabetes (Fig. 5b), in whom relative risk reduction of most outcomes was not significantly different in RCTs achieving a DBP no less than 80 and in those achieving a DBP less than 80 mmHg. Furthermore, in absence of diabetes, absolute risk reduction of several outcomes was greater at the lower than at the higher achieved DBP values (further details in eTable S3b, http://links.lww.com/HJH/A729).

When directly comparing patients with and without diabetes, achieving a DBP at least 80 mmHg was associated with significantly greater relative and absolute risk reductions of several outcomes in patients with rather than without diabetes, whereas in RCTs achieving DBP less than 80 mmHg relative and absolute risk reductions of most outcomes were not significantly different in patients with or without diabetes (Fig. 6). Inclusion in the meta-analysis of RCTs in individuals with high-normal blood pressure did not change the results.

Effects of blood-pressure lowering randomized controlled trials on renal failure in patients with and without diabetes

Outcome data for renal failure were available for a more limited number of BP-lowering RCTs: 14 with data on 33 313 patients with diabetes, and 10 with data on 36 599 patients without diabetes. In patients with diabetes, 1031 cases of ESRD were reported with a significant relative risk reduction of 21% (95% CI 5–34%) when the SBP/DBP reduction was standardized to 10/5 mmHg (absolute risk reduction 8 ESRD cases every 1000 patients treated for 5 years). In patients without diabetes the reported cases of ESRD were quite fewer (300), with no evidence of a risk

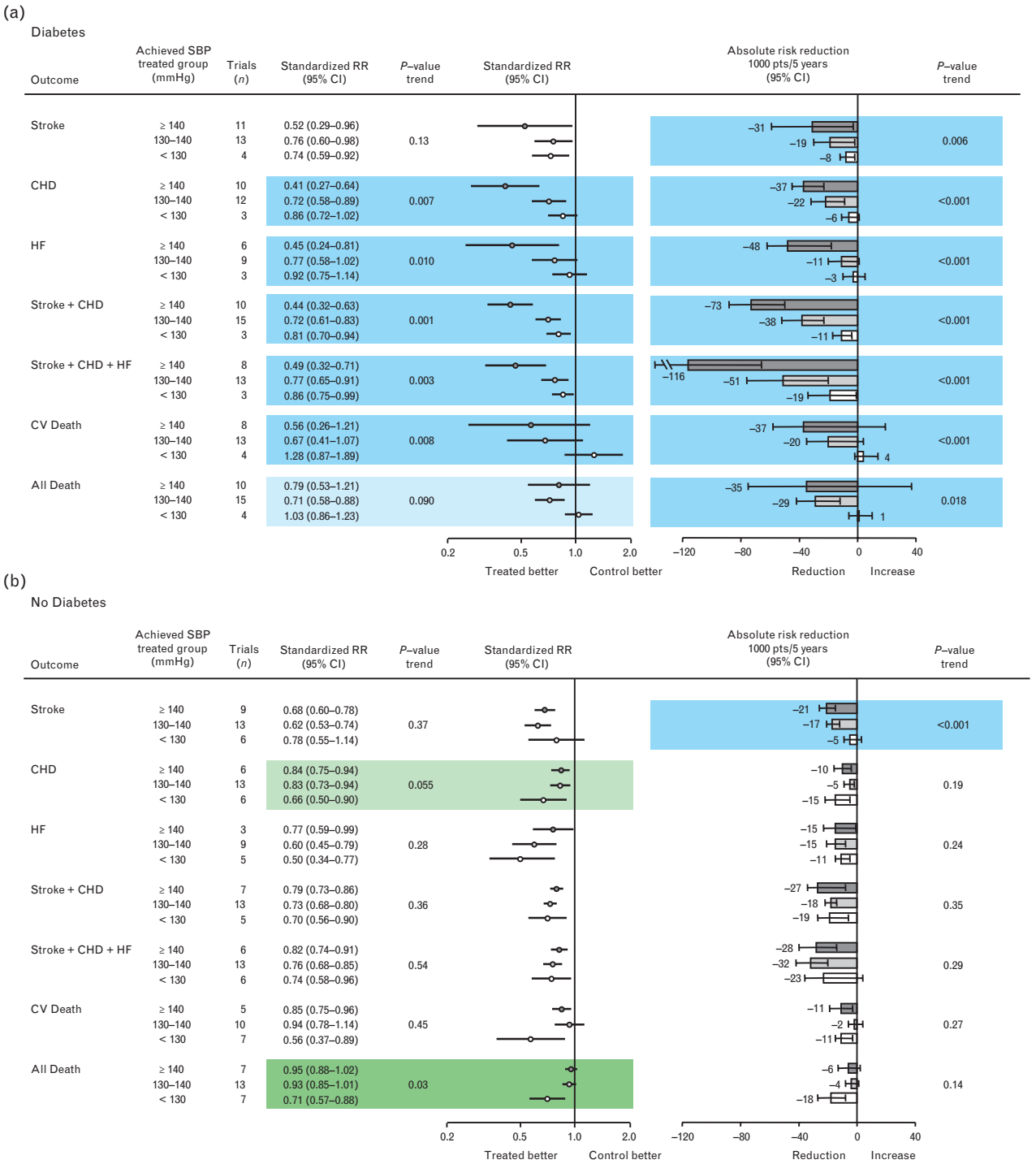

FIGURE 3 Relative risk and absolute risk reduction of various cardiovascular morbidity and mortality outcomes, according to SBP values achieved in the groups with active (or more active) BP-lowering treatment. Upper part (a): patients with diabetes; lower part (b): patients without diabetes. *P* values for trend refer to differences between standardized RR or, respectively, absolute risk reductions at the three different achieved SBP levels. The blue-shaded areas indicate the outcomes for which relative or absolute risk reduction showed a significant (deep blue) or borderline significant (faint blue) trend to decrease with decrease in achieved SBP. The green-shaded areas indicate a significant (deep green) or a borderline significant (faint green) trend of the risk reduction to increase with decreasing SBP. Other explanations and abbreviations as in Fig. 1.

reduction by BP lowering (risk ratio 1.01, 95% CI 0.82–1.24) (Fig. 7). Figure 7 also reports the effects of a standardized SBP/DBP reduction on cardiovascular outcomes to test the sensitivity of these two smaller sets of RCTs to detect the cardiovascular effects of BP lowering: most cardiovascular outcomes were significantly reduced by BP lowering both in patients with and without diabetes, with no significant interaction; the only significant interaction was that regarding ESRD.

The bottom part of Fig. 7 additionally illustrates the effects on ESRD of lowering SBP to different levels. In patients with diabetes, a marked and significant benefit

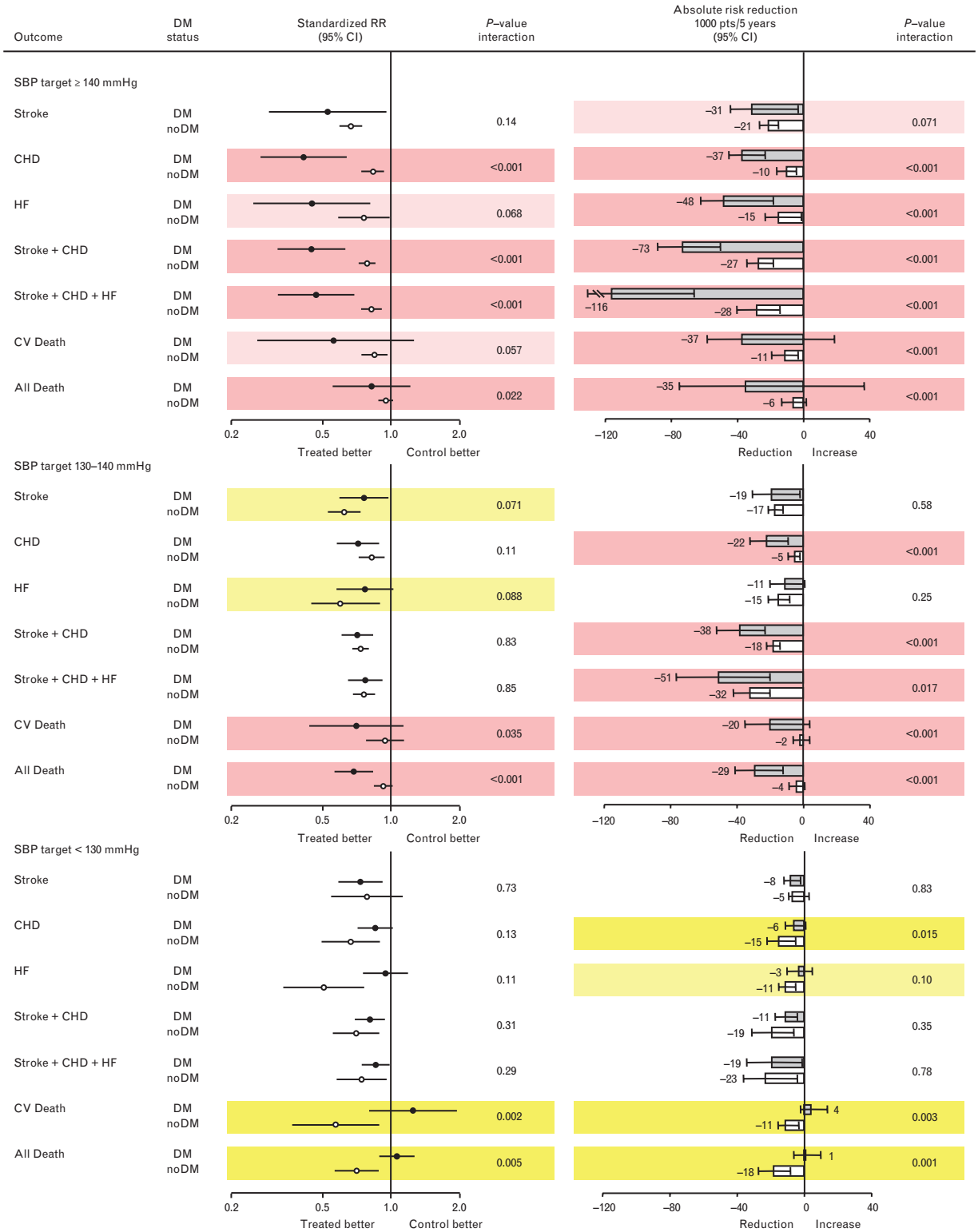

FIGURE 4 Differences between patients with diabetes mellitus (DM) and without diabetes mellitus (no DM) in standardized RR and, respectively, absolute risk reductions at each of three different levels of achieved SBP: no less than 140 mmHg (upper panel), 130–140 mmHg (middle panel) and less than 130 mmHg (lower panel). *P* values for interaction refer to differences in patients with and without diabetes. The pink-shaded areas indicate the outcomes for which relative or absolute risk reduction was significantly (deep pink) or borderline significantly (faint pink) greater in presence than in absence of diabetes. The yellow-shaded areas indicate a significant (deep yellow) or borderline significant (faint yellow) greater reduction in absence of diabetes. Other explanations and abbreviations as in Fig. 1.

could only be detected when achieved SBP was higher than 140 mmHg (44% relative risk reduction, and 45 ESRD cases avoided every 1000 patients treated for 5 years). No significant ESRD reduction was found at lower achieved SBP values, but the point estimates did not suggest increased risk. No similar analysis could be done for

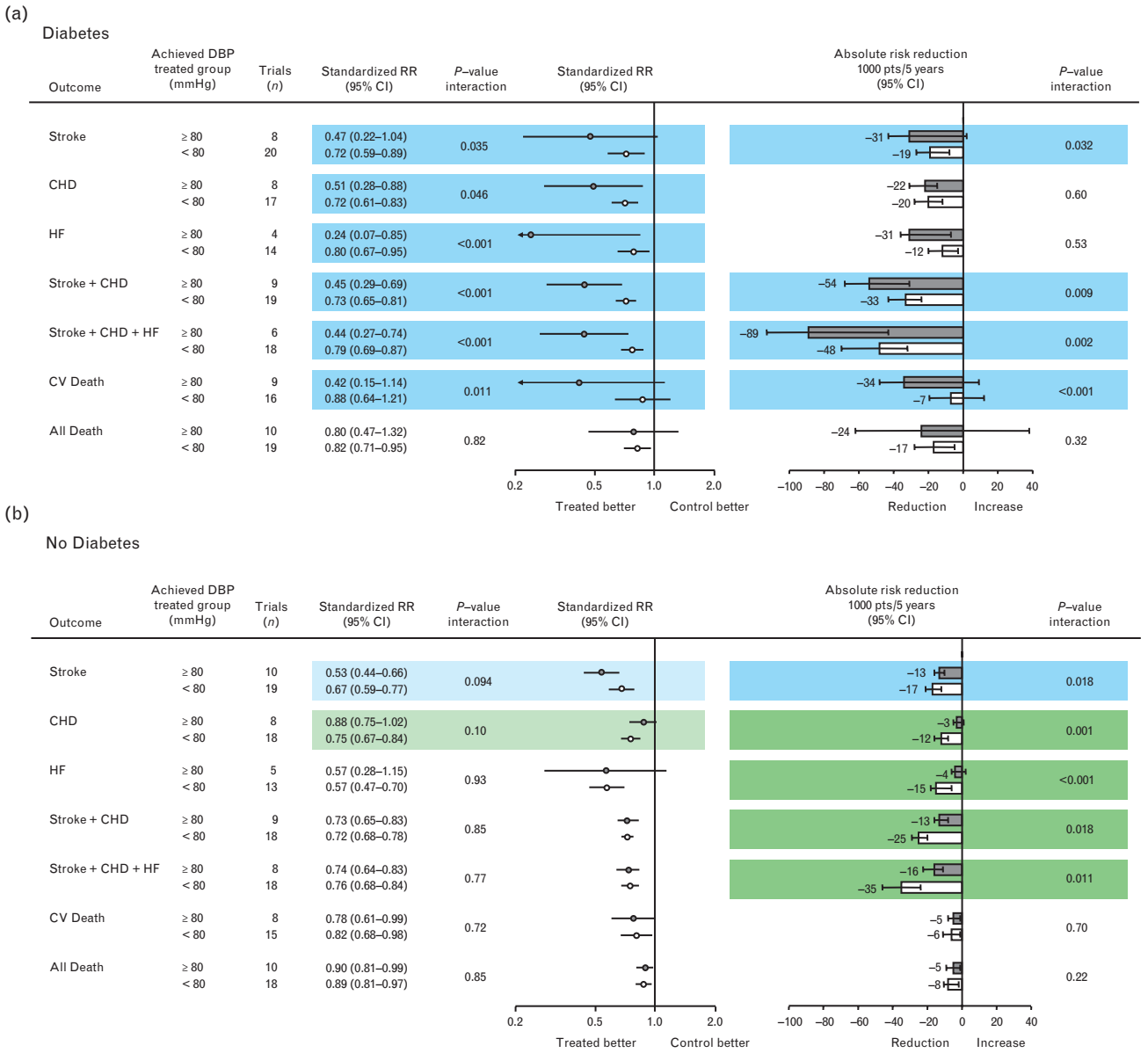

FIGURE 5 Relative risk and absolute risk reduction of various cardiovascular morbidity and mortality outcomes, according to DBP values achieved in the groups with active (or more active) BP-lowering treatment. Upper part (a): patients with diabetes; lower part (b): patients without diabetes. *P* values for trend refer to differences between standardized RR or, respectively, absolute risk reductions at the two different achieved DBP levels. The blue-shaded areas indicate the outcomes for which relative or absolute risk reduction was significantly (deep blue) or borderline significantly (faint blue) smaller at lower DBP. The green-shaded areas indicate a significantly (deep green) or borderline significantly (faint green) greater reduction at lower DBP. Other explanations and abbreviations as in Fig. 1.

patients without diabetes because of too few data and ESRD events in the two upper SBP strata.

Effects of blood pressure lowering by different classes of drugs in patients with and without diabetes

These effects have been investigated by grouping available RCTs according to the class of the drug compared with placebo (or no treatment). For the comparison of diuretics with placebo, there were three RCTs on 1466 patients with diabetes and seven RCTs on 35 503 patients without diabetes; for the comparison of beta-blockers with placebo there was only one RCT on 790 patients with diabetes and three RCTs on 17 256 patients without diabetes; for the comparison of calcium antagonists with placebo there were seven RCTs on 4371 patients with diabetes and seven RCTs on 24 677 patients without diabetes; for the comparison of angiotensin-converting enzyme (ACE) inhibitors with placebo there were eight comparisons in seven RCTs on 13 576 patients with diabetes and four RCTs on 28 611 patients without diabetes; for the comparison of angiotensin receptor blockers with placebo there were ten RCTs on 19 763 patients with diabetes and five RCTs on 35 032 patients without diabetes (Table 1).

Because the drug class-based groups were often small and not all RCTs investigated all cardiovascular outcomes, Fig. 8 only reports data on major cardiovascular events (the

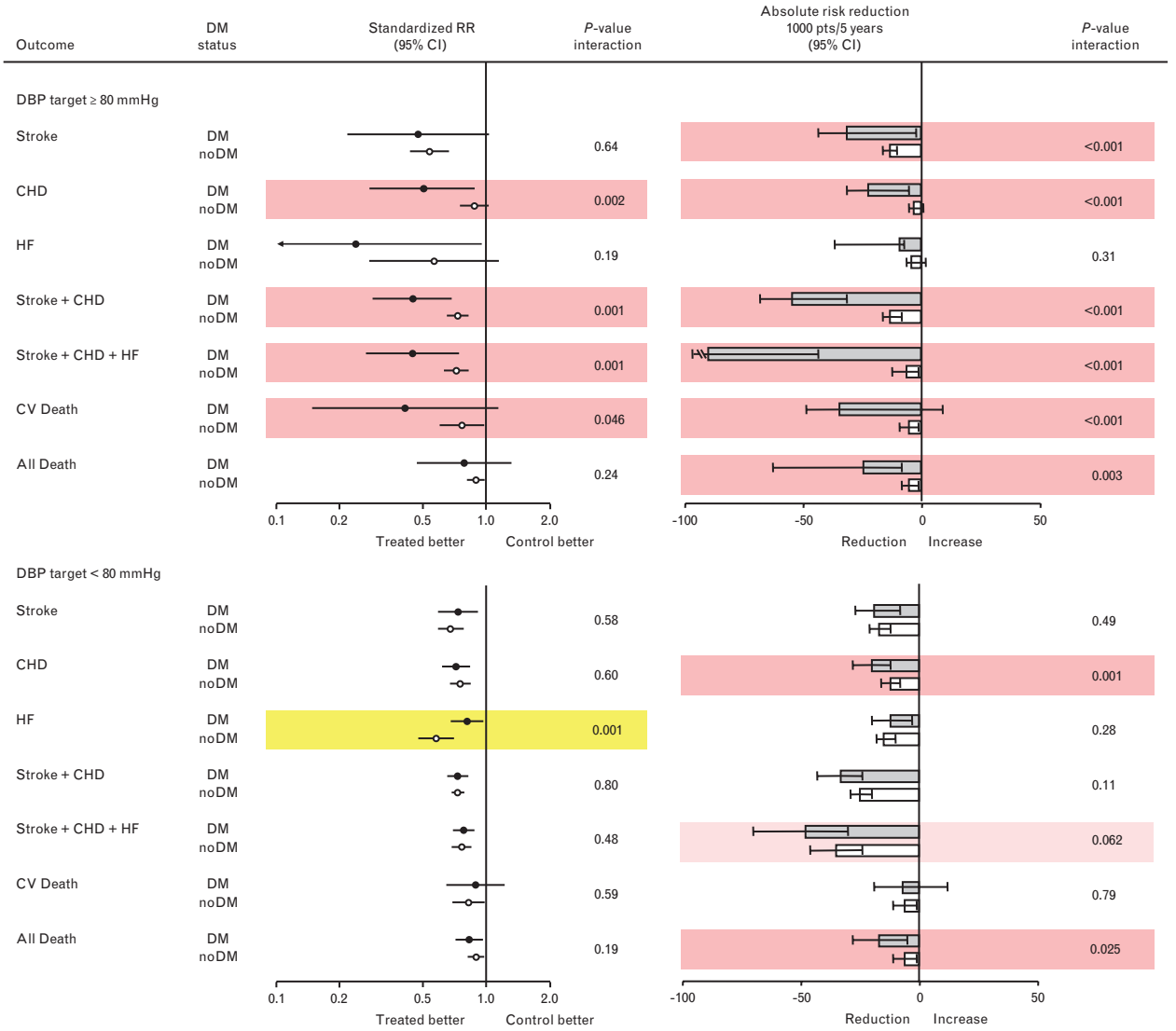

FIGURE 6 Differences between patients with diabetes mellitus (DM) and without diabetes mellitus (no DM) in standardized RR and, respectively, absolute risk reductions (*P* value for interaction) at the two different levels of achieved DBP: no less than 80 mmHg (upper panel), and less than 80 mmHg (lower panel). *P* values for interaction refer to differences in patients with and without diabetes. The pink-shaded areas indicate the outcomes for which relative or absolute risk reduction was significantly (deep pink) or borderline significantly (faint pink) greater in presence than in absence of diabetes. The yellow-shaded area indicates a significant greater reduction in absence of diabetes. Other explanations and abbreviations as in Fig. 1.

composite of stroke and CHD or the composite of stroke, CHD and heart failure, whichever available with more data), and all-cause mortality. Diuretics significantly reduced major cardiovascular events both in patients with and without diabetes, with no significant interaction, and reduced all-cause mortality in both patient groups with similar point estimates (*P* value for interaction 0.92), though statistical significance was attained only in the larger group of patients without diabetes. No comparison between patients with and without diabetes was possible for beta-blockers, vs. placebo, since only one RCT was available with data on beta-blockers in patients with diabetes. In patients without diabetes, however, beta-blockers proved effective in lowering the composite of stroke and CHD, but not cardiovascular and all-cause death. Anyway, the available data were few. Calcium antagonists significantly reduced the composite of stroke, CHD and heart failure both in patients with and without diabetes, with similar point estimates and no significant interaction. Also, cardiovascular and all-cause mortalities were reduced, though not significantly, by calcium antagonists, to a similar extent both in patients with and without diabetes. ACE inhibitors appear to be the only class of BP-lowering drugs that reduced major cardiovascular events (both the composite of stroke, and CHD and the composite of stroke, CHD and heart failure) and all-cause mortality to a significantly greater extent in patients with diabetes than in those without. On the contrary, angiotensin receptor blockers reduced major cardiovascular events to the same extent in patients with and without diabetes, whereas comparisons for the effects on cardiovascular and all-cause death could not be assessed, since only one RCT reported these events in patients without diabetes. Analysing ACE inhibitors and angiotensin receptor blockers together (RAS

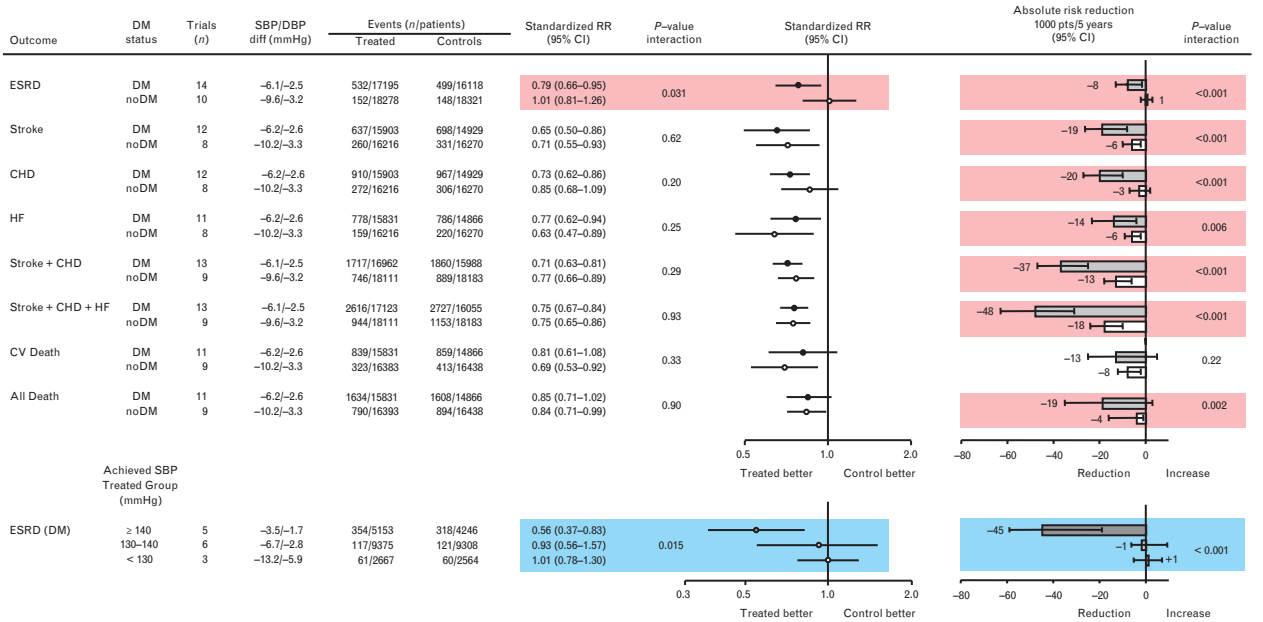

FIGURE 7 Relative risk and absolute risk reduction of end-stage renal disease (ESRD) in patients with diabetes mellitus (DM) [5,32,36,39,40,43,44,47,52,59,60,64,65,69,75,79,80,82,83,99,100] and without diabetes mellitus (no DM) [29,34,41,52,58,69,81,90,92,99–101]. For comparison, effects on cardiovascular morbidity and mortality outcomes are also shown. At bottom, the effects of standardized risk ratios are also stratified according to three levels of achieved SBP. *P* values for interaction refer to differences in patients with and without diabetes, except for the bottom set of analyses, in which *P* values for interaction refer to differences between ESRD risk ratios and, respectively, absolute ESRD risk reductions in patients with diabetes at the three different levels of achieved SBP. The pink-shaded areas indicate the outcomes for which the relative or absolute risk reduction was significantly greater in the presence than the absence of diabetes. In the bottom set the blue-shaded areas indicate a significant trend of risk reduction to decrease with decreasing achieved SBP. Other explanations and abbreviations as in Fig. 1.

blockers) showed a greater efficacy of these compounds in patients with diabetes, limited to the composite of stroke and CHD (for further details see eTable S4, http://links.lww.com/HJH/A729).

No comparison could be done of the effects on renal failure of the different drug classes, because almost no data on ESRD were available in each class for patients without diabetes. On the contrary, for patients with diabetes, sufficient data were available for RCTs comparing angiotensin receptor blockers [64,75,82,99] and RAS blockers vs. placebo, showing a marked reduction of ESRD risk in both comparisons (Fig. 8 and eTable S4, http://links.lww.com/HJH/A729). Unfortunately, too few data were available for ACE inhibitors [5,47,60].

Comparative effects of various classes of antihypertensive drugs in patients with and without diabetes as estimated by head-to-head comparative randomized controlled trials

As indicated in Table 2, the 50 RCTs head-to-head comparing different classes of antihypertensive drugs we previously surveyed [26] included seven comparisons of diuretics with any other drug class in 23 721 patients with diabetes, and 12 comparisons in 55 684 patients without diabetes; four comparisons of beta-blockers with any other drug class in 13 490 patients with diabetes, and 10 comparisons in 57 248 patients without diabetes; 21 comparisons of calcium antagonists with any other drug class in 49 620 patients with diabetes, and 18 comparisons in 108 561 patients without diabetes; 17 comparisons of ACE inhibitors with any other drug class in 26 113 patients with diabetes, and 14 comparisons in 54 661 patients without diabetes; and six comparisons of angiotensin receptor blockers with any other drug class in 16 435 patients with diabetes, and seven comparisons in 33 768 patients without diabetes.

When separately meta-analysed for presence and absence of diabetes, the heterogeneity of the data was low or moderate, with a single exception (the composite of stroke and CHD in patients with diabetes treated with angiotensin receptor blockers) (eTable S5, http://links.lww.com/HJH/A729). As illustrated in Fig. 9, comparison of each drug class with all the other classes showed that the previously described [26] similar effects of all drug classes on most cardiovascular outcomes, provided that BP was equally reduced, were also similar in patients with and without diabetes. Likewise, in those cases in which the previous meta-analyses had shown the effectiveness of a class of drugs differed from the other classes [26], these differences were similarly found in patients with and without diabetes: this was the case of the greater effectiveness of diuretics in preventing risk of heart failure, the lesser effectiveness of beta-blockers in preventing stroke, the greater effectiveness of calcium antagonists in preventing stroke and their lesser effectiveness in preventing heart failure (Fig. 9a). There are some relevant exceptions, however, in which the effectiveness of a given class vs. all other classes differed between patients with and without diabetes. The exceptions substantially regard the blockers of the RAS (Fig. 9b). As compared with all other drug classes, ACE inhibitors were found to be more effective in reducing risk of CHD events and major cardiovascular events (composite of stroke and CHD) in patients with rather than without diabetes, with *P* values for interaction of 0.028 and 0.044,

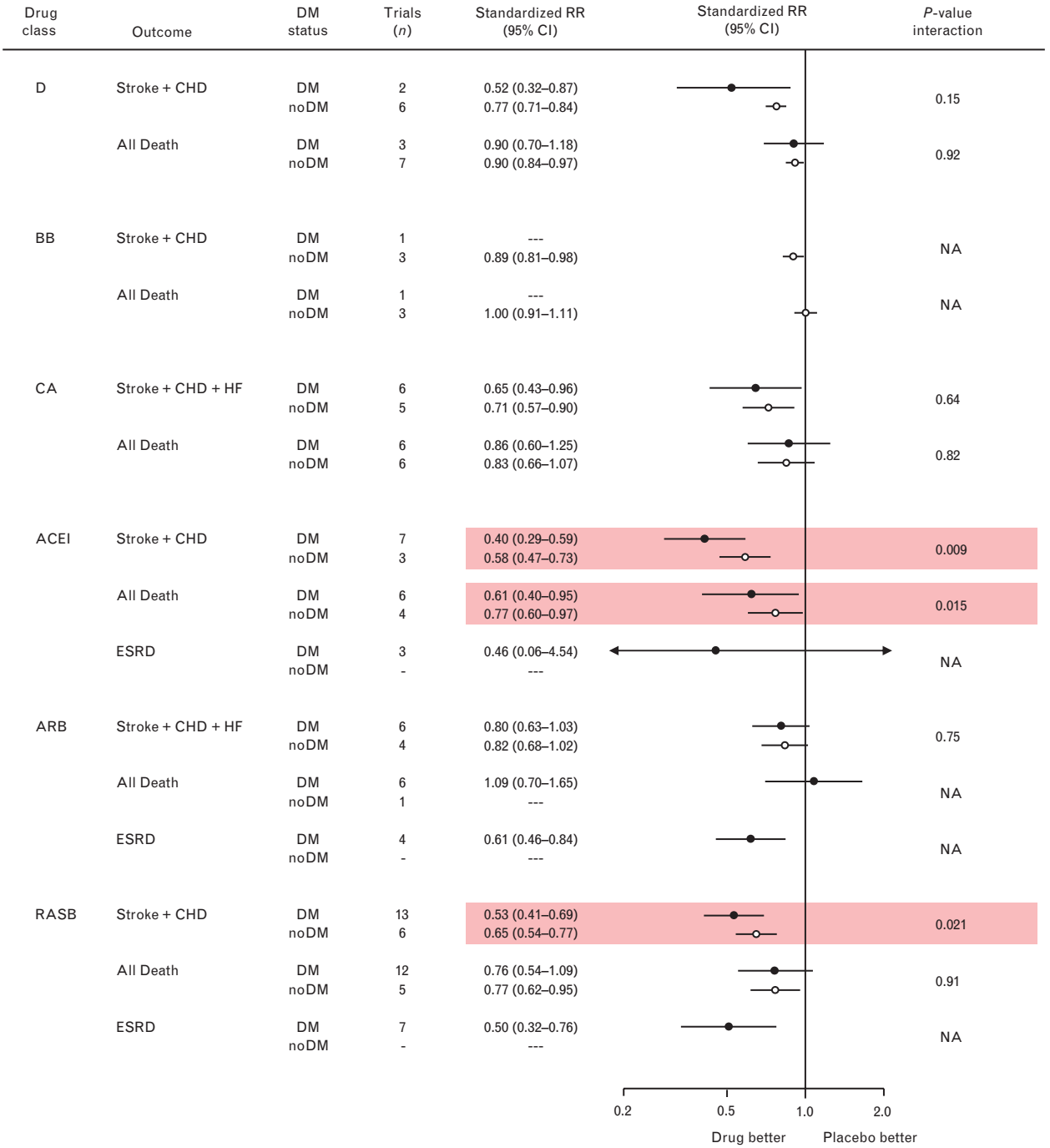

FIGURE 8 Relative risk of major cardiovascular events, all death and end-stage renal disease (ESRD) in trials of BP lowering by different classes of drugs (vs. placebo). Differences between patients with diabetes mellitus (DM) and without diabetes mellitus (no DM) (as assessed by *P* values for interaction). Risk ratios (RRs) standardized to a SBP/DBP difference of 10/5 mmHg. The pink-shaded areas indicate the cases in which relative risk reduction was significantly greater in presence than in absence of diabetes. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta-blockers; BP, blood pressure; CA, calcium antagonists; CHD, coronary heart disease; D, diuretics; DBP, diastolic blood pressure; DM, diabetes mellitus; HF, heart failure; RASB, renin–angiotensin system blockers; RR, risk ratio; SBP, systolic blood pressure.

respectively. Angiotensin receptor blockers also showed a greater effectiveness than other drugs in preventing heart failure in the presence rather than absence of diabetes (with borderline significance *P* value for interaction = 0.085). Considering all RAS blockers together, and restricting the analyses to the 11 RCTs including both patients with (n = 23 474) and without diabetes (n = 63 846), RAS blockers were found to be more effective than other drug classes in reducing the risk of CHD (*P* value for interaction = 0.016), the composite of stroke, CHD and heart failure (*P* value for interaction = 0.087) and all-cause death (*P* value for interaction = 0.06) in presence than in absence of diabetes (for further details see eTable S5a and b, http://links.lww.com/HJH/A729).

TABLE 2. Trials with head-to-head comparisons of blood-pressure-lowering drugs of different classes reporting outcome data separately for patients with and without diabetes

Classes compared	Trial	Patients (n)				Classes compared	Trial	Patients (n)			
		DM		No DM				DM		No DM	
		Drug 1	Drug 2	Drug 1	Drug 2			Drug 1	Drug 2	Drug 1	Drug 2
D vs. CA	ACCOMPLISH [103,104]	3468	3478	2293	2266	CA vs. D	INSIGHT [112,113]	649	653	2508	2511
D vs. CA	ALLHAT [105,106]	5994	3597	8419	4958	CA vs. BB	INVEST [119,120]	3169	3231	8098	8078
D vs. ACEI	ALLHAT [105,106]	5994	3510	8419	5034	CA vs. ACEI	JMIC-B [130,131]	199	173	629	649
D vs. ACEI	ABNP-2 [107,108]	212	229	2827	2815	CA vs. ACEI	JMIND [132]	228	208	–	–
D vs. BB	Berglund [109]	–	–	53	53	CA vs. D	NICS-EH [115]	–	–	204	210
D vs. CA	COLM [110]	678	684	1895	1884	CA vs. D/BB	NORDIL [133]	351	376	5375	5095
D vs. BB	HAPPHY [111]	–	–	3272	3297	CA vs. D/BB	STOP-2 [134,135]	231	253	1964	1960
D vs. CA	INSIGHT [112,113]	653	649	2511	2508	CA vs. ACEI	STOP-2 [134,135]	231	235	1964	1970
D vs. BB	MRC-mild [71]	–	–	4297	4403	CA vs. ARB	VALUE [136,137]	2428	2395	5168	5254
D vs. BB	MRC-old [72]	–	–	1081	1102						
D vs. ACEI	NESTOR [114]	283	286	–	–	ACEI vs. BB	AASK [34]	–	–	436	441
D vs. CA	NICS-EH [115]	–	–	210	204	ACEI vs. CA	AASK [34]	–	–	436	217
D vs. BB	VA-COOP [116]	–	–	177	125	ACEI vs. CA	ABCD-H [124]	235	235	–	–
						ACEI vs. D	ALLHAT [105,106]	3510	5994	5034	8419
						ACEI vs. CA	ALLHAT [105,106]	3510	3597	5034	4958
BB vs. CA	AASK [34]	–	–	441	217	ACEI vs. D	ANBP-2 [107,108]	229	212	2815	2827
BB vs. ACEI	AASK [34]	–	–	441	436	ACEI vs. CA	BENEDICT [42]	301	303	–	–
BB vs. CA	ASCOT [117,118]	2572	2565	7046	7074	ACEI vs. CA	CAMELOT [43,44,125]	118	115	555	548
BB vs. D	Berglund [109]	–	–	53	53	ACEI vs. D/BB	CAPPP [138,139]	309	263	5183	5230
BB vs. D	HAPPHY [111]	–	–	3297	3272	ACEI vs. ARB	DETAIL [140]	130	120	–	–
BB vs. CA	INVEST [119,120]	3231	3169	8078	8098	ACEI vs. CA	FACET [129]	189	191	–	–
BB vs. ARB	LIFE [121,122]	609	586	3979	4019	ACEI vs. CA	Fogari [55]	102	103	–	–
BB vs. D	MRC-mild [71]	–	–	4403	4297	ACEI vs. CA	JMIC-B [130,131]	173	199	649	629
BB vs. D	MRC-old [72]	–	–	1102	1081	ACEI vs. CA	JMIND [132]	208	222	–	–
BB vs. ACEI	UKPDS-39 [123]	358	400	–	–	ACEI vs. D	NESTOR [114]	286	283	–	–
BB vs. D	VA-COOP [116]	–	–	125	177	ACEI vs. ARB	ONTARGET [141]	3453	3550	5122	4992
						ACEI vs. Conv.	REIN-str. 1 [142]	–	–	99	87
CA vs. BB	AASK [34]	–	–	217	441	ACEI vs. Conv.	REIN-str. 2 [143]	–	–	78	88
CA vs. ACEI	AASK [34]	–	–	217	436	ACEI vs. ARB	ROAD [144]	–	–	180	180
CA vs. ACEI	ABCD-H [124]	235	235	–	–	ACEI vs. D/BB	STOP-2 [134,135]	235	253	1970	1960
CA vs. D	ACCOMPLISH [103,104]	3478	3468	2266	2293	ACEI vs. CA	STOP-2 [134,135]	235	231	1970	1964
CA vs. D	ALLHAT [105,106]	3597	5994	4958	8419	ACEI vs. BB	UKPDS-39 [123]	400	358	–	–
CA vs. ACEI	ALLHAT [105,106]	3510	5994	5034	8419						
CA vs. BB	ASCOT [117,118]	2565	2572	7074	7046	ARB vs. CA	CASE-J [126,127]	1011	1007	1343	1342
CA vs. ACEI	BENEDICT [42]	303	301	–	–	ARB vs. ACEI	DETAIL [140]	120	130	–	–
CA vs. ACEI	CAMELOT [43,44,125]	115	118	548	555	ARB vs. CA	IDNT [64,65]	579	567	–	–
CA vs. ARB	CASE-J [126,127]	1007	1011	1342	1343	ARB vs. Conv.	E-COST [145]	–	–	1053	995
CA vs. D	COLM [110]	684	678	1884	1895	ARB vs. Conv.	E-COST-R [146]	–	–	69	72
CA vs. D/BB	CONVINCE [128]	1616	1623	6563	6674	ARB vs. BB	LIFE [121,122]	586	609	4019	3979
CA vs. ACEI	FACET [129]	191	189	–	–	ARB vs. ACEI	ONTARGET [141]	3550	3453	4992	5122
CA vs. ACEI	Fogari [55]	103	102	–	–	ARB vs. ACEI	ROAD [144]	–	–	180	180
CA vs. ARB	IDNT [64,65]	567	579	–	–	ARB vs. CA	VALUE [136,137]	2395	2428	5254	5168

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CA, calcium antagonists; Conv., conventional treatment; D, diuretics; DM, diabetes mellitus.

Only a limited number of RCTs head-to-head comparing different classes of antihypertensive drugs considered renal failure (ESRD) as an outcome. The only analysis based on a sufficient number of RCTs and patients was the comparison of RAS blockers vs. the other classes (seven comparisons in 22 316 patients with diabetes [64,65,68,105,106,123,124,126, 127,136,137] and seven comparisons in 22 465 patients without diabetes [34,105,106,126,127,141,142]). There were 205 cases of ESRD among 8130 patients with diabetes treated with either an ACE inhibitor or an angiotensin receptor blocker, and 372 ESRD cases among 14 186 patients with diabetes treated with diuretics, beta-blockers or calcium antagonists with a non-significant reduction in ESRD by RAS blockers as compared to non-RAS blockers (risk ratio 0.91, 95% CI 0.67–1.25). Among patients without diabetes there were 244 cases of ESRD in 6964 patients treated with RAS blockers and 382 ESRD cases in 15 501 patients treated with non-RAS blockers, with a non-significant excess of ESRD among non-diabetes patients treated with non-RAS blockers (risk ratio 1.20, 95% CI 0.91–1.60). The differences between risk ratios did not attain statistical significance, however (P value for interaction = 0.17).

DISCUSSION

Clinical significance of our findings

Ours' are the most extensive and most specific meta-analyses comparing the effects of antihypertensive

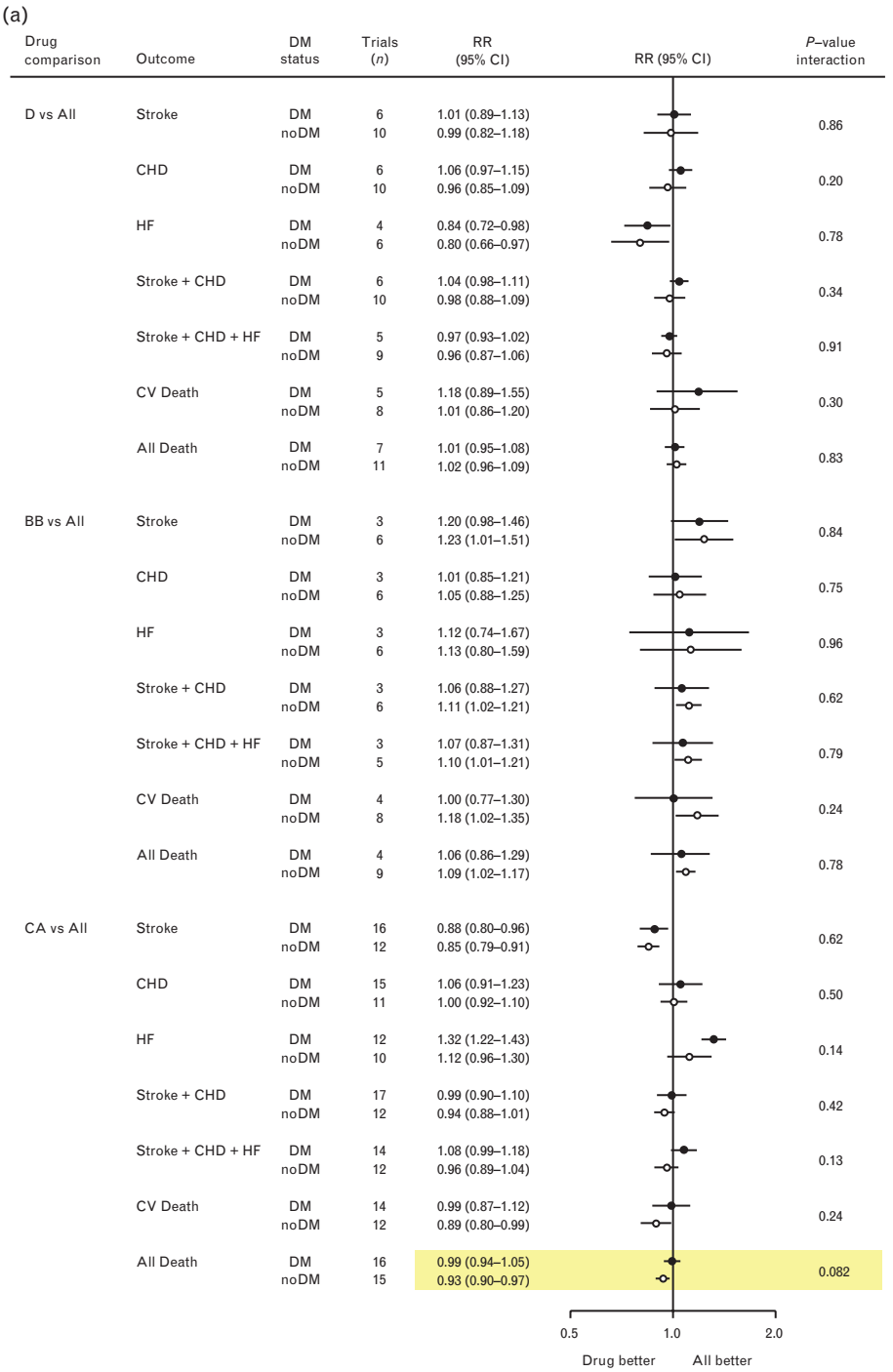

FIGURE 9 Relative risk of various cardiovascular morbidity and mortality outcomes in trials of head-to-head comparisons of one class of BP-lowering drugs with all other classes. Differences between patients with diabetes mellitus (DM) and without diabetes mellitus (no DM) (as assessed by *P* values for interaction). The pink-shaded areas indicate the cases in which a class of BP-lowering drugs was significantly (deep pink) or borderline significantly (faint pink) more effective in presence than absence of diabetes when compared to all other classes. The yellow-shaded area indicates greater effectiveness in absence of diabetes (faint yellow, borderline significance). All other explanations and abbreviations as in Fig. 8.

treatment in patients with or without type 2 diabetes. They are the most extensive ones because they include 57 BP-lowering RCTs with 61 772 patients with diabetes presenting 7773 major cardiovascular events, and 191 353 patients without diabetes presenting 12 765 major cardiovascular events and 38 drug comparison RCTs with 59 116 patients with diabetes presenting 9159 major cardiovascular events and 163 589 patients without diabetes presenting 14 146 major cardiovascular events. They are the most specific ones because they exclude RCTs on type 1 diabetes mellitus (mostly on younger patients with much lower cardiovascular risk), RCTs on patients with acute or recent myocardial infarction or heart failure (in which some drugs with BP-lowering properties may be beneficial independently

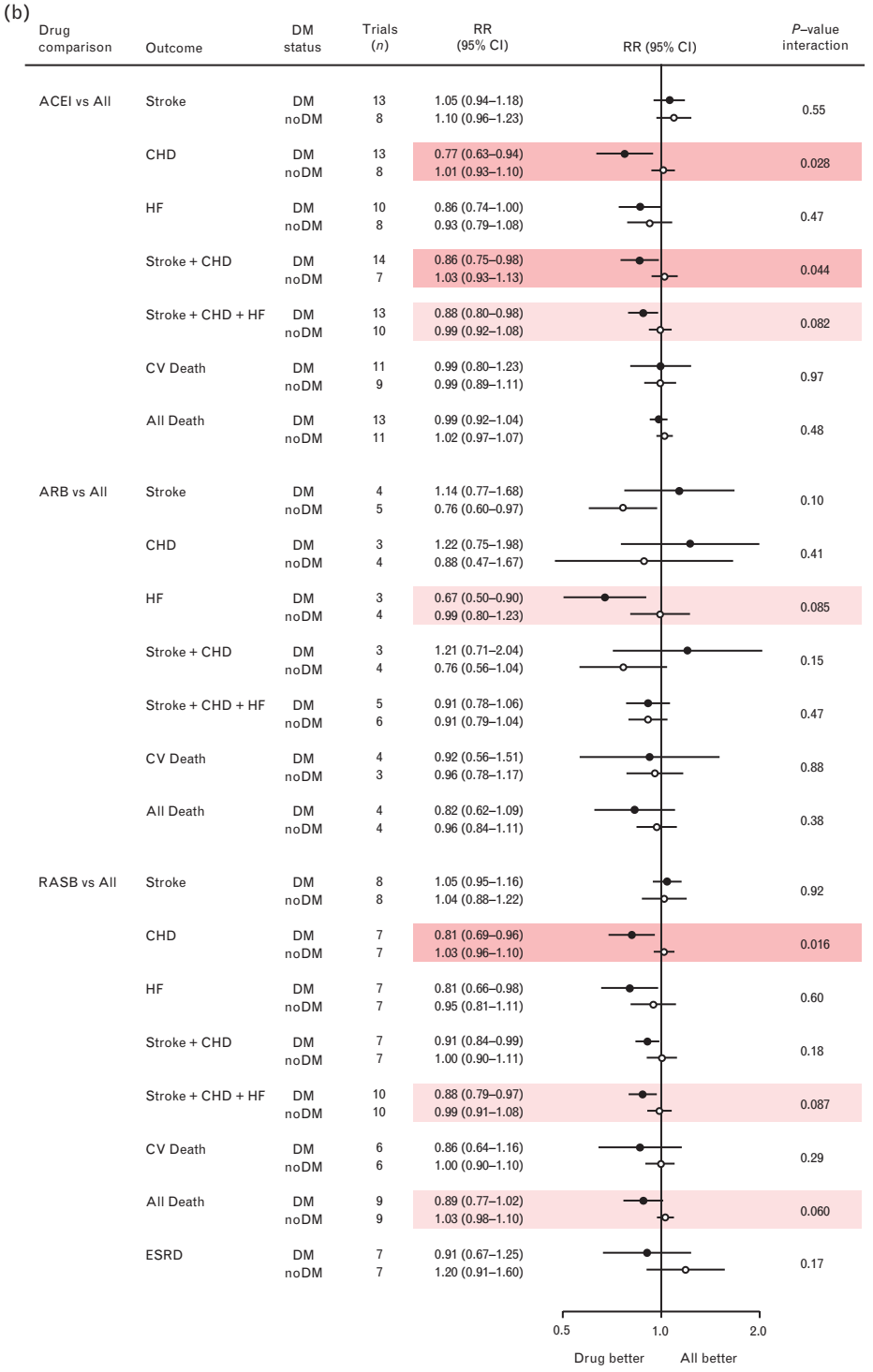

FIGURE 9 *(Continued)*

of, or even in spite of, BP lowering), and RCTs in which the combination of two RAS blockers was tested (because the demonstrated untoward effects of dual RAS blockade is likely to have obscured the beneficial effects of BP lowering).

Thanks to the large body of collected data and to their analyses based on clinically oriented questions, we have been able to show, for the first time, the following findings of practical clinical relevance:

1. Although BP lowering is capable of significantly reducing all types of cardiovascular outcomes both in hypertensive patients with and without diabetes, relative risk reductions of CHD events and all-cause

death are significantly greater in patients with than without diabetes. As expected from the higher cardiovascular risk in patients with diabetes [147,148], absolute risk reduction is about twice as large in patients with diabetes as in those without.
2. Risk of ESRD is the only outcome that BP-lowering treatment appears to favourably influence only in presence of diabetes, with a significant relative risk reduction of 21%, whereas no reduction at all is found in patients without diabetes (*P* value for interaction 0.044).
3. The effects of BP lowering more markedly differ between hypertensive patients with or without diabetes when the RCTs are stratified according to the BP levels achieved by treatment. For achieved SBP levels higher than 140 mmHg, reductions of most cardiovascular outcomes are significantly greater in hypertensive patients with rather than without diabetes, whereas for achieved SBP values lower than 130 mmHg, the difference between the effects in diabetic and non-diabetic patients disappears and often reverses, risk reduction becoming much smaller and non-significant in presence of diabetes (although it never indicates a significant harm). Also, for achieved DBP higher than 80 mmHg, risk reduction by BP lowering is significantly greater in diabetic patients, but the difference disappears at DBP values lower than 80 mmHg.
4. All classes of antihypertensive drugs, when compared with placebo, can reduce risk of cardiovascular events both in patients with and without diabetes. However, the large body of comparative data we have been able to analyse show that blockers of the RAS, with evidence particularly significant for ACE inhibitors, have some advantage in patients with diabetes, being more effective in preventing the composite of major cardiovascular events (vs. placebo) in presence than in absence of diabetes. Likewise, though most of head-to-head comparisons of different classes of drugs do not show significant differences between their effects both in diabetic and in non-diabetic patients, RAS blockers, and particularly ACE inhibitors, appear significantly more effective than other classes in preventing cardiovascular events in the presence of diabetes, whereas they are equally effective as the other classes in absence of diabetes.
5. RAS blockers, and particularly angiotensin receptor blockers, when compared with placebo, are markedly effective in reducing ESRD risk in patients with diabetes, but information on other drug classes is practically absent. However, in head-to-head comparative RCTs on diabetes ESRD prevention by RAS blockers was not significantly greater than that by other drugs, and a tendency of RAS blockers to be more effective than the other drug classes in diabetic than non-diabetic patients did not attain statistical significance.

The practical consequences of the findings of our meta-analyses are the following:

1. Despite the greater absolute cardiovascular risk reduction occurring in hypertensive patients with diabetes, the relative and absolute benefits of BP reduction are also quite consistent in hypertensive patients without diabetes (23% reduction in major cardiovascular events and 27 major cardiovascular events prevented every 1000 patients treated for 5 years). Therefore, BP-lowering treatment must be strongly recommended to hypertensive patients also in absence of diabetes.
2. Contrary to what was recommended by most guidelines until 2013, and substantiating a suggestion given by one of us on the basis of the review of a more limited number of trials [149], there is little or no additional benefit in lowering SBP below 130 mmHg in diabetes mellitus, whereas there are further significant benefits below 130 mmHg SBP in absence of diabetes. Therefore, forthcoming hypertension guidelines may recommend a SBP target between 130 and 140 mmHg for diabetic patients, and below 130 mmHg in non-diabetic patients.
3. Blood pressure lowering in patients with diabetes is not only effective in reducing risk of cardiovascular mortality and morbidity, but has also proved to be effective in reducing the risk of ESRD, whereas no evidence is available of prevention of renal insufficiency in hypertensive patients without diabetes. Hence, in hypertensive patients with diabetes prevention of progression to ESRD can be considered among the goals of antihypertensive therapy, though absolute reduction of ESRD risk (−8 cases every 1000 patients treated for 5 years) is about half of that of stroke (−18 cases), CHD (−19 cases) and heart failure (−13 cases). However, when data are stratified by level of achieved SBP, we have found that reduction of ESRD risk is particularly concentrated in the stratum with the higher SBP target ($\geq$140 mmHg), in which a standard SBP/DBP lowering did reduce relative ESRD risk by 44% and prevented about 45 ESRD cases every 1000 diabetic patients treated for 5 years. Little or no further benefit is achieved by further SBP reduction.
4. Blocking of the RAS should be recommended as initial BP-lowering therapy in hypertensive patients with diabetes, because of a moderately, but significantly greater reduction of cardiovascular events than with other drugs in diabetes. Also, for prevention of ESRD RAS blockers have proven effectiveness vs. placebo in diabetic patients, although head-to-head comparison with other classes shows only a non-significant advantage.

Comparison with other analyses

There are similarities and differences in the findings and conclusions of the present meta-analyses with respect to other recent ones.

Our results are hardly comparable to those of two recent meta-analyses [20,150], which were restricted to the few RCTs purposefully aiming at specific BP goals, and are therefore very rigorous, but scarcely informative. More

relevant to our data are the extensive meta-analyses of RCTs in patients with diabetes published by Emdin *et al.* [21], and further enlarged in 2016 by Brunström and Carlberg [22]. As we had done in 2014 for all BP-lowering RCTs, also Emdin *et al.* [21] and Brunström and Carlberg [22] stratified their meta-analyses according to SBP values achieved by treatment. Once the RCTs we have deliberately excluded for the reasons detailed above are not considered, Emdin *et al.* [21] included 15 RCTs in which average attained SBP was 130 mmHg or higher and only four RCTs in which it was lower than 130 mmHg, and Brunström and Carlberg [22] included 13, 15 and seven RCTs in the three strata with average achieved SBP greater than 140, between 130 and 140, and below 130 mmHg, whereas we have been able to further enlarge the size of our meta-analyses to include 14, 19 and eight RCTs, respectively, in the three achieved SBP strata. As in our meta-analyses, both Emdin *et al.* [21] and Brunström and Carlberg [22] have shown that in patients with diabetes BP-lowering treatment has a decreased effectiveness or loses its effectiveness in further reducing risk of a number of cardiovascular outcomes and mortality when SBP achieves values lower than 130 mmHg. We have also shown that a standard SBP/DBP lowering of 10/5 mmHg tends to progressively decrease its preventing effectiveness lower is the SBP achieved by treatment. However, if the preventive benefit of further SBP lowering tends to disappear, the effect of SBP lowering never turns to harm, at least down to values of about 123 mmHg.

As Emdin *et al.* [21] and Brunström and Carlberg [22] did not analyse BP-lowering RCTs in patients without diabetes, they could not conclude whether the attenuation of the preventive effectiveness of a standard BP lowering was typical of diabetes or a more general phenomenon. Our meta-analyses, having been focused on a comparison of BP-lowering RCTs in patients with and without diabetes, are the first to provide the evidence that the SBP levels to be attained for optimizing the benefits of BP lowering may be higher in hypertensive patients with than without diabetes. Our data also show that even for achieved DBP levels below 80 mmHg, the beneficial effects of BP-lowering treatment attenuate, though persisting, in the presence but not in the absence of diabetes.

The difference between the effects of BP lowering in patients with and without diabetes could not be observed in two previous sets of meta-analyses that compared responses in presence and absence of diabetes. The BPLTTC in 2005 could only include 14 RCTs in patients with diabetes and 10 in patients without diabetes [17], and the more recent analyses by Ettehad *et al.* [23, sensitivity analyses reported in the web supplement] included 23 RCTs in diabetic patients and 19 in patients without diabetes (to be compared to 41 and 40 RCTs in our present meta-analyses). Furthermore, neither of these two meta-analyses stratified the two sets of data by achieved BP levels. The BPLTTC meta-analyses [17], with the limited data available by 2005, did not find significant differences between responses to BP-lowering treatment in patients with or without diabetes. Ettehad *et al.* [23] underline a somewhat smaller reduction of major cardiovascular events in presence than absence of diabetes, but the more detailed data provided in the web supplement show interaction did not attain significance for any other outcomes.

One of the most relevant findings of our meta-analyses, however, has been that the relative cardiovascular risk reduction produced by a standard BP reduction (and, consequently, the absolute cardiovascular risk reduction as well) changes according to the BP levels achieved by treatment in presence of diabetes, whereas it does not in its absence. Therefore, when the achieved SBP targets remain higher than 140 mmHg, the same SBP/DBP reduction provides a better cardiovascular prevention in diabetic patients, whereas at lower SBP targets the benefits in diabetes tend to decrease until for targets below 130 mmHg, there are no or little further benefits in diabetic patients, whereas these are still present in non-diabetic patients. Whereas the greater risk reduction at higher achieved SBP values in diabetic patients appears to mean that hypertension plays an important role in the high cardiovascular risk accompanying diabetes, it seems unlikely that its attenuation at lower attained SBP values only results from a lower level of cardiovascular risk. Indeed, the 5-year risk of most outcomes was similar in the control groups of the two upper strata ($\geq$140 mmHg and 130–140 mmHg), being 5.6 and 6.0% for stroke, 5.7 and 6.9% for CHD, 11.5 and 11.9% for the composite of stroke and CHD, 19.7 and 18.0% for the composite of stroke, CHD and heart failure and, nonetheless, relative and absolute risk reductions by a standard BP-lowering were significantly smaller in the 130–140 mmHg stratum than in the $\geq$140 mmHg one. Likewise, the smaller risk reductions in diabetes patients achieving DBP below 80 mmHg occurred despite the control risk of most outcomes was similar or even higher than in diabetes patients achieving DBP values at least 80 mmHg. The most reasonable explanation is that the greater cardiovascular risk resulting from hypertension in patients with diabetes makes them more responsive to the benefits of a moderate BP reduction, but also raises the point of inflection of the J-curve relating the achieved BP with the response to treatment.

Another aspect by which our meta-analyses differ from the previous ones is the effect of BP lowering on risk of ESRD. Emdin *et al.* [21] and Ettehad *et al.* [23] were unable to show a significant reduction of ESRD risk in patients with diabetes, but they analysed a limited number of RCTs and also included trials in which the simultaneous use of two RAS blockers may mask the beneficial renal effects of BP-lowering. Brunström and Carlberg [22] found a significant reduction, but to a smaller extent, than in our meta-analysis, probably because of inclusion of RCTs using dual RAS blocker treatment. Our meta-analysis, systematically comparing the effects of BP-lowering treatment in presence or absence of diabetes, is the first showing a preferential prevention of ESRD risk in diabetes, although we cannot exclude that a small preventive effect in absence of diabetes may have escaped detection because of the low ESRD risk in patients with diabetes and the small number of RCTs that measured ESRD as an outcome.

The other major finding of the meta-analyses here presented, namely a significantly greater effectiveness of RAS blockers, and particularly ACE inhibitors, as compared to other BP-lowering agents in preventing cardiovascular

outcomes in hypertensive patients with diabetes (but not in those without diabetes), also requires some discussion. Ours' is the only available comparison of the cardiovascular and renal effects of various classes of antihypertensive agents in presence or absence of diabetes, apart from the earlier one by the BPLTTC group limited to RCTs published before July 2005 [17]. Data from other recent meta-analyses are restricted to patients with diabetes and have provided conflicting results. Emdin *et al.* [21] and Bangalore *et al.* [151] do not describe differences in the cardiovascular effects of ACE inhibitors or RAS blockers compared to other classes, whereas Cheng *et al.* [152] report a greater effectiveness of ACE inhibitors in preventing mortality, myocardial infarction and heart failure. The two meta-analyses [21,151] denying a greater cardiovascular effectiveness of RAS blockers in diabetes do not include all the data we have been able to extract, and one of them [151] avoids the most sensitive analysis, that of all major cardiovascular events together. On the contrary, the demonstration of a greater cardiovascular effectiveness of RAS blockers in diabetes, as provided by Cheng *et al.* [152], is weakened by the pooling of BP-lowering, placebo-controlled RCTs (with a BP difference in favour of RAS blockers), together with head-to-head comparative RCTs (obviously aiming at no BP difference between RAS blockers and the control drugs). Admittedly, the specific benefits of BP lowering by RAS blockers are rather small (about 10% greater reduction in major cardiovascular events and all-cause death, and 20% greater reduction in CHD events than non-RAS blockers), but their significance is further enhanced by the comparison we have done with the effects in patients without diabetes, providing evidence of significant interaction between the effects in presence and absence of diabetes. For prevention of the renal outcome we have measured, risk of ESRD, RAS blockers and particularly angiotensin receptor blockers are significantly more effective than placebo in diabetes; in drug-comparative RCTs the point estimates are also in favour of the use of RAS blockers in diabetes, but the test of interaction (presence vs. absence of diabetes) does not attain significance. However, our findings should not be taken to mean that classes of BP-lowering drugs different from RAS blockers are not effective in outcome prevention in diabetes: on the contrary, all other classes have been shown to be effective in prevention of major cardiovascular events when compared to placebo, and also in head-to-head comparative RCTs diuretics have shown particular effectiveness in preventing heart failure and calcium antagonists in preventing stroke.

Strengths and limitations

The major strengths of our meta-analyses are the number of trials and of patients included, as summarized previously; the selection criteria for inclusion and stratification of RCTs based on clinically relevant questions, namely as to whether the cardiovascular and renal effects of BP-lowering treatment, the target BP levels to be attained by treatment and the effects of BP-lowering treatment based on different classes of drugs differ in presence or absence of type 2 diabetes; the exclusion of RCTs in conditions such as a recent myocardial infarction and heart failure, in which drugs with BP-lowering potential are administered in search of benefits occurring independently of, or despite BP lowering; the exclusion of studies on type 1 diabetes. An additional strength is that within each separate group of meta-analyses (those including patients with diabetes and those including patients without), heterogeneity, as judged by the I^2 index, was commonly low or moderate.

Our analyses also had limitations. Despite the very large number of RCTs and patients considered for the analyses, their multiple subdivisions in subgroups according to baseline or achieved SBP and DBP or the drug classes used for BP lowering reduced their number, especially among patients with diabetes (who were about one-third of the patients without diabetes). Also, the renal outcome of ESRD was investigated in a much smaller number of RCTs and patients than cardiovascular outcomes, and the statistical power of their analyses was obviously lower. Furthermore, although most of the differences in patients with and without diabetes we have described were large and highly statistically significant, a few (e.g. those between the different effectiveness of different drug classes) were small, and sometimes of borderline statistical and clinical significance. Furthermore, meta-analyses depend on the number, size and design of the various RCTs, and this may have influenced, for example, our findings that, among benefits of RAS blockers in patients with diabetes, those on cardiovascular outcomes appeared to depend on ACE inhibitors, whereas those on ESRD appeared to depend on angiotensin receptor blockers. Finally, as usually occurs with meta-analyses, a large number of comparisons were made without correction for multiple testing, and it cannot be ruled out that some of the 'significant' differences may be due to chance.

A further limitation is that stratification of RCTs according to achieved BP could not be restricted to those few RCTs whose design was to achieve that particular BP level (as shown by the insufficient statistical power of two previous meta-analyses [20,149]), but was based on the average BP level achieved with active treatment group, independent of the authors' intention to attain that particular BP level. Furthermore, the separate stratification by SBP and DBP values is obviously artificial, and, as indicated in the 'Results' section, the three strata of SBP also differed by DBP, and the two strata of DBP differed by SBP as well.

In conclusion, although we are well aware of the limitations intrinsic in meta-analyses [16], even when, as in the present ones, these were careful in preserving the randomized nature of the included trials, we believe that the systematic comparisons we have done of the effects of antihypertensive treatment in presence and absence of type 2 diabetes provide important support to the following recommendations:

1. Blood-pressure-lowering treatment is indicated to reduce risk of cardiovascular disease in hypertensive patients both in presence and in absence of diabetes.
2. Systolic BP targets should be somewhat higher in presence than absence of diabetes, between 130 and 140 mmHg in patients with diabetes and below 130 mmHg in patients without diabetes, as in presence of diabetes bringing SBP a few mmHg below 130 mmHg does not add further benefit (though apparently it does not increase cardiovascular risk).

3. Diastolic BP targets below 80 mmHg can be recommended both in presence and absence of diabetes, but in diabetes most of the cardiovascular risk reduction occurs by lowering DBP values between 80 and 90 mmHg.
4. Blood-pressure-lowering treatment can be recommended in patients with diabetes also to reduce risk of renal insufficiency: for ESRD risk most of the benefit occurs at relatively high SBP values (a few mmHg above 140 mmHg), but lower values do not increase ESRD risk. In absence of diabetes we have been unable to find evidence that BP-lowering treatment reduces renal insufficiency risk, but we cannot exclude that this may result only from the low risk of ESRD in patients without diabetes.
5. All BP-lowering drugs are effective and therefore can be used in patients with and without diabetes, but the guidelines opinion to include a RAS blocker among the drugs given in the presence of diabetes is supported by the evidence provided by the present meta-analyses that these agents have some greater cardiovascular preventive action in the presence of diabetes. RAS blockers are the only drug class for which evidence is available of a significant reduction of diabetic ESRD risk in comparison with placebo (though evidence of their superiority in ESRD prevention over other drugs in direct comparative RCTs is weak).

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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 and Recordati SpA.

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Reviewer's Summary Evaluation

Referee 1

Whether hypertension should be treated more or less aggressively in patients with type 2 diabetes than in those without diabetes remains a topic of discussion, especially after the publication of the ACCORD and SPRINT trials. In this important meta-analysis, an enormous work has been done to compile and analyse the data of 82 randomized controlled trials involving more than 250 000 patients with or without diabetes. The analysis clearly demonstrates the benefits of lowering BP in both patients with and without diabetes, but it also shows significant differences such as, for example, in the benefits of lowering systolic BP < 130 mmHg which seems to be beneficial only in nondiabetics. Moreover, a specific analysis is done regarding the progression of renal disease towards ESRD and the data clearly show the benefits of lowering BP in patients with diabetes to prevent ESRD. In this latter analysis, one limitation is the rather limited number of patient without diabetes reaching ESRD to make a valuable comparison between the two groups. At last the analysis confirms the clinical benefits of using blockers of the renin-angiotensin system to reduce the risk of cardiovascular and renal events in patients with diabetes. The findings of this meta-analysis support some of the actual recommendations and might actually influence some of the future guidelines.

Referee 2

The authors analyzed a very large database comprising 82 RCTs to compare the effects of different target blood pressure levels on cardiovascular and renal prognosis. Triggered by the SPRINT study, the recommended target blood pressure has been questioned. In that respect this meta-analysis provides clear evidence that lowering systolic blood pressure <130 mmHg is of no further benefit in patients with type 2 diabetes. These data are consistent with the results of the ACCORD study. In contrast, this huge meta-analysis suggests that lowering systolic blood pressure <130 mmHg in patients without diabetes may provide additional benefit. However, a word of caution is necessary: this kind of meta-analysis, although rigorously and excellently conducted, cannot give definitive answers or provide solid evidence to generate a class I recommendation. Prospective RCTs with different target BP strata are required, with a clear description of the BP measurement modalities.