Hypertension Compendium

Randomized Controlled Trials of Blood Pressure Lowering in Hypertension
A Critical Reappraisal

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Abstract: **Sixty-eight blood pressure (BP)–lowering randomized controlled trials (defined as randomized controlled trials comparing active treatment with placebo, or less active treatment, achieving a BP difference, performed between 1966 and end 2013 in cohorts with ≥40% hypertensive patients, and exclusive of trials in acute myocardial infarction, heart failure, acute stroke, and dialysis) were identified and meta-analyzed grouping the randomized controlled trials on the basis of clinically relevant questions: (1) does BP lowering reduce all types of cardiovascular outcome? (2) Is prevention of all outcomes proportional to the extent of systolic, diastolic, and pulse BP? (3) Have all classes of BP-lowering drugs been shown capable of reducing all types of cardiovascular outcome? (4) Is BP lowering beneficial when intervention is initiated at any grade (or stage) of hypertension? (5) Do BP-lowering randomized controlled trials provide evidence about systolic BP and diastolic BP targets of treatment? (6) Should BP-lowering treatment be preferentially addressed to patients in higher risk categories promising larger absolute treatment benefits? The results of these meta-analyses provide further support to current hypertension treatment guidelines by showing that BP lowering can significantly reduce major cardiovascular outcomes largely independent of the agents used, significant risk reduction is found at all hypertension grades (stages), and when systolic BP is lowered below a cut off of 140 mm Hg with some further reduction limited to stroke at systolic BP values just <130 mm Hg. Absolute risk reduction progressively increases higher is total cardiovascular risk, but this greater benefit is associated with a progressively higher residual risk, ie, higher treatment failures. (*Circ Res*. 2015;116:1058-1073. DOI: 10.1161/CIRCRESAHA.116.303641.)**

Key Words: antihypertensive drugs ■ cardiovascular death ■ coronary disease ■ heart failure ■ randomized controlled trial ■ stroke

Nonstandard Abbreviations and Acronyms	
BP	blood pressure
BPLTTC	Blood Pressure Lowering Trialists' Collaboration
CHD	coronary heart disease
DBP	diastolic blood pressure
HF	heart failure
PP	pulse pressure
RCT	randomized controlled trial
RR	risk ratio
SBP	systolic blood pressure

Historical Perspective

Therapy of hypertension was undoubtedly one of the major achievements of medicine during the second half of the 20th century. This is not only because pharmacological agents capable of reducing blood pressure (BP) have been successfully developed starting from the 1950s but also because, in the same time window, the effects of drug-induced BP lowering have rigorously been tested by means of the best evidence-providing approach, ie, through large randomized controlled trials (RCTs). Indeed, hypertension experts can be proud that antihypertensive therapy has been the first among cardiovascular therapies, several years before therapies of myocardial infarction and chronic heart failure (HF), that has been tested by this approach, using so-called hard end points, ie, outcomes that can be easily diagnosed and the diagnosis of which can be easily verified.[1,2] The need of solid evidence in favor of therapeutic lowering of BP was particularly impelling because prejudice prevailing among clinicians and investigators until the mid 20th century was that "hypertension may be an important compensatory mechanism, which should not be tampered with, even were it certain we could control it."[3] This prejudice was, so to say, a heritage of the old ontological concept of medicine, by which changes in body functions were simply compensatory mechanisms to preserve some other functions of the body: in the case of hypertension to preserve perfusion of vital organs, especially the kidney. Hence, the term essential by which arterial hypertension has long been baptized, as was fever in the 18th century, on the basis of the same ontological interpretation of its beneficial compensatory action: "la fièvre essentielle est une affection de la vie qui s'efforce d'éloigner la mort" (essential fever is an affection of life that endeavors to postpone death).[4] Still in 1957, an author could write on the Lancet "Even in the case of true arterial hypertension neither product of test tube or crucible halts, nor delays materially, the unfavorable course of the disease."[5]

When the first antihypertensive agents became available during the 1950s, they were tested on the most severe form of hypertension, malignant hypertension. These early studies were uncontrolled, and the benefits of BP lowering were established by a historical comparison of the lengthened survival of a cohort of treated patients with the bad survival of cohorts of patients followed-up in the previous years when effective drugs were not available. A study published in 1959 by Leishman[6] showed that although ≈90% of treated patients had died within 5 years, among treated patients, 5 year-death was of <30%.

A subsequent study by Hamilton et al[7] was the first controlled study, in which half of the patients were actively treated, whereas the other half was left untreated, but assignment was not randomized, namely patients were assigned alternatively to one or the other treatment. Nonetheless, this relatively small study (61 patients with initial systolic BP/diastolic BP [SBP/DBP] values of ≈230/130 mm Hg but no clinical signs of cardiovascular disease) produced some convincing evidence that BP lowering could significantly reduce the incidence of cardiovascular outcomes also in nonmalignant hypertension.

The first randomized trial was a small one by Wolff and Lindeman,[8] immediately followed by a slightly larger one by the Veterans Administration Cooperative Study Group on antihypertensive agents,[9] which included patients with markedly elevated DBP (115 through 129 mm Hg), but it was able to show that BP lowering by drugs could prevent as many as 24 morbid or mortal events for every 100 severely hypertensive patients treated for 1 year. Because this trial was terminated prematurely for ethical reasons, it could not provide evidence on the specific efficacy of drug therapy of severe hypertension on strokes and coronary events, respectively.

Between 1966 and 1992, 17 trials, including 47 653 hypertensive patients, were completed, all comparing active BP-lowering drug treatment with placebo or, more rarely, no drug treatment or less active treatment, to answer the crucial question as to whether drug-induced BP lowering was indeed beneficial.[2] These trials were meta-analyzed by Collins and MacMahon in 1994[10] with the demonstration that BP lowering by drugs significantly reduced both strokes and coronary events, although the former more markedly and also significantly reduced cardiovascular mortality.

Most of the placebo-controlled trials in hypertension were initiated and conducted in the period from 1965 to 1985, and therefore, the antihypertensive drugs used in the active treatment arm were those drugs widely used at that time, namely thiazide or thiazide-like diuretics, β-blockers, methyldopa, reserpine, and hydralazine. Starting from about 1980, however, new classes of antihypertensive agents became increasingly used, namely calcium antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. It was important, therefore, to test whether BP lowering by these new drugs was also effective in reducing incidence of cardiovascular events. The real question at stake was whether the benefits of antihypertensive therapy exclusively resided in the lowering of elevated BP independently of the drugs used or whether some drug classes had some additional benefits independent of that related to BP lowering.[1,2] The previous demonstration that BP lowering by diuretics, β-blockers, and other older drugs did reduce cardiovascular event incidence made it difficult to test the new agents with the traditional design of using an entirely untreated (placebo) control group, unless patients were selected in a clinical context yet unexplored (old age, previous cardiovascular outcomes, etc). A favorite design was that of adding either the new agent or placebo on a background of preexisting antihypertensive therapy, although it must be recognized that a large number of these studies were not intended to investigate the effects of BP lowering but were

rather searching for BP-independent benefits of some of the new agents.

Another large series of RCTs approached the problem of the effects of new antihypertensive agents by head-to-head comparison of new and traditional agents, and sometimes of agents belonging to 2 different new classes, with the assumption that, for similar BP reductions, similar or different incidences of cardiovascular events could indicate similarities or differences in the beneficial effects of the compared compounds.[2]

Despite the large number of RCTs devoted to antihypertensive treatment, it must be recognized that several important issues of practical importance in the management of hypertension have not been investigated, or have rarely been investigated, or investigated according to diagnostic criteria or definitions hardly applicable today.[11] Among these problems are the BP levels at which drug treatment should be initiated, the target BP levels to be aimed at by treatment, and whether either treatment initiation and target BP levels are influenced by assessment of total cardiovascular risk, with earlier and more intense treatment to be reserved to higher risk patients.[11,12] The lack of definitive trial evidence on these issues is acknowledged in recent guidelines for the management of hypertension.[13,14]

Critical Reappraisal of Available Evidence

The large body of data provided by the numerous RCTs of antihypertensive drugs has been an obvious target of several meta-analyses, starting from the seminal one by Collins et al[15] in 1990. Among available comprehensive meta-analyses of antihypertensive treatment RCTs, those of the Blood Pressure Lowering Trialists' Collaboration (BPLTTC)[16–18] deliberately included only trials posterior to the time the BPLTTC protocol was prepared[19] and preferentially considered those RCTs the individual data of which were available to the collaboration. The largest meta-analysis available until now is the one by Law et al,[20] which included 147 trials published within 2007 but considered together trials testing antihypertensive agents in hypertension and under different clinical conditions, such as myocardial infarction, left ventricular dysfunction, and HF, where drugs belonging to antihypertensive pharmaceutical classes were not administered with the intention of lowering BP, and their effects were probably independent of, or even hindered by, BP lowering. These important limitations of meta-analysis of Law et al[20] have been appropriately underlined by Bangalore et al.[21]

Meta-analyses are known to have limitations being by definition post hoc analyses and being fraught with problems, the major one relating to criteria chosen for trial selection[22]: loose criteria may introduce confounding factors from poorly designed or conducted trials, but tight criteria are likely to cause an even greater bias favoring preconceptions and expectations of the authors of meta-analysis.[2,22] Although meta-analyses should not be considered the ultimate level of evidence, nonetheless, they are a powerful statistical method of estimating the average effect (and its confidence limits) of a given treatment, especially when the results of several RCTs are available.[21] Furthermore, when structured around a relevant clinical question, they may provide a tentative answer to this question,

with the caution that meta-analyses are hypothesis-generating instruments rather than a body of proof.[22]

With these considerations in mind, we have reviewed all RCTs of antihypertensive treatment performed from 1966 to the end of 2013 with the objective to provide some answers to the following major questions:

1. Does drug-induced BP lowering reduce incidence of all major types of fatal and nonfatal cardiovascular outcomes to a similar extent or are some types of cardiovascular events particularly susceptible to the beneficial effects of BP lowering?
2. Is prevention of all types of cardiovascular outcomes proportional to the extent of SBP, DBP, or pulse pressure (PP) reduction?
3. Is there evidence available that BP lowering produced by drugs belonging to any of the major classes of antihypertensive agents is effective in reducing all or part of cardiovascular outcomes?
4. Do BP-lowering RCTs provide some evidence whether all grades (or stages) of hypertension are worth being treated with BP-lowering drugs, treatment being accompanied by significant relative and absolute reduction in the incidence of some major cardiovascular outcomes?
5. Do BP-lowering RCTs provide some evidence about the levels to which SBP or DBP should be brought by treatment so as to maximize outcome reduction?
6. Are relative and absolute reductions of the risk of different cardiovascular outcomes by BP-lowering treatment similar or different at different levels of baseline cardiovascular risk and should BP-lowering treatment be preferentially addressed to patients in risk categories promising larger absolute treatment benefits?

The above questions have been approached in a series of meta-analyses we have recently published in 4 separate articles.[23–26] Their major results are here summarized and discussed together as an integrated critical reappraisal of the data provided by RCTs of BP-lowering treatment. The original articles should be consulted for methodological procedures and more detailed data presentation. Briefly, it can be mentioned that data from each RCT were weighted by patient numbers and follow-up duration. Risk ratios (RRs) and their 95% confidence intervals were calculated using the Mantel–Haenszel method and, when useful, standardized to a SBP/DBP difference of 10/5 mm Hg. A random-effects model was used for all analyses. Five-year absolute risk reductions of standardized BP lowering and the number of patients needed to treat for 5 years were also calculated.

Effects of BP Lowering on Outcome Incidence in Hypertension

A critical reappraisal of BP-lowering RCTs required first to establish clear criteria for defining this type of trials among the large number of those that tested drugs classified as antihypertensive. In our recent overview,[23] we have defined as BP-lowering RCTs all those in which (1) any antihypertensive drugs were compared with placebo or no treatment with the intention to investigate the consequences of BP differences on cardiovascular outcomes or mortality or (2) a more intense BP-lowering treatment was compared with a less intense one with the intention to investigate outcome difference associated with BP difference. These

trials were defined as intentional BP-lowering RCTs. To widen the body of evidence, we have also separately analyzed what we have defined nonintentional BP-lowering RCTs, ie, those trials in which BP-lowering drugs were compared with placebo and a between-group difference of ≥2 mm Hg in either SBP or DBP occurred, although the design of the trials was not that of investigating the effects of BP differences.

Furthermore, we have considered only RCTs in which BP-lowering drugs were studied in cohorts of hypertensive patients, and, in a wider approach, in cohorts in which at least a consistent proportion of hypertensive patients were present (defined as ≥40%). All trials in which drugs with BP-lowering properties were tested under conditions, such as myocardial infarction, HF, and acute stroke, and patients on dialysis were excluded. Further inclusion criteria were measurement of ≥1 type of cardiovascular

events as primary or secondary end point, BP values measured at baseline and during follow-up, ≥5 events during follow-up, follow-up of ≥6 months, and randomized allocation to treatment.

Literature search according to PRISMA (Preferred Reporting Items for Systematic Meta-Analyses) statement recommendations[27] led to the identification of 68 trials[8,9,28–96] with a total of 245 855 participants followed-up for a mean of 4.3 years (1 058 177 patient-years). Forty-seven trials (153 825 participants)[2,8,9,28–74] were of intentional BP lowering, and 21 (92 060 participants) were classified as nonintentional BP-lowering trials[75–96] (Table).

In the primary analysis, restricted to the 47 intentional BP-lowering RCTs, all considered outcomes were significantly reduced by BP lowering,[23] with the risk of stroke and HF being reduced to the greatest extent (36% and 43%, respectively, for a standardized SBP/DBP difference between active and

Table.   Characteristics of All BP Lowering Treatment Trials Included

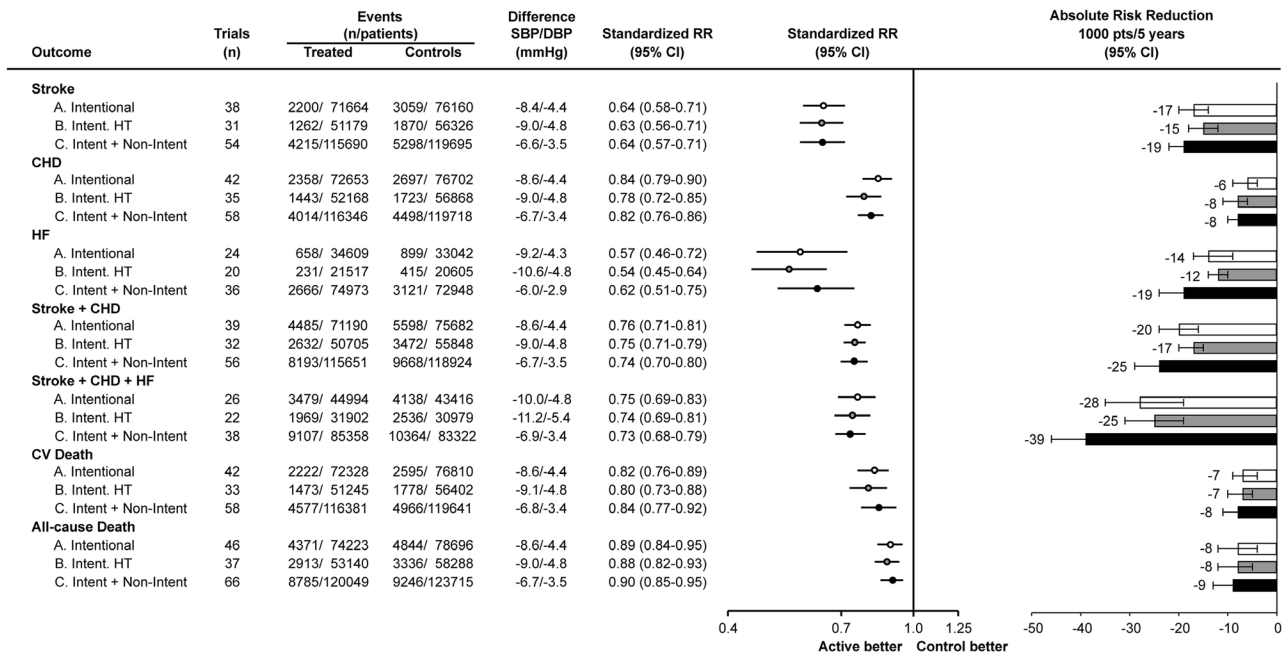| Trial Acronym	Patient Number	Follow-Up, y	Hypertensive Patients, %	SBP/DBP Difference, mm Hg	Baseline BP-Lowering Drugs	Quality Assessment vScore
Intentional, placebo (or no treatment) controlled trials						
ACTION[28]	7665	4.9	52%	−5.4/−3	Yes	5/6
ADVANCE[29]	11 140	4.3	>75%	−5.6/−4.2	Yes	6/6
AUSTRALIAN-Mild[30]	3427	4.0	100%	NR/−5.6	No	5/6
Barraclough[31]	116	2.0	100%	NR/−14.4	No	4/6
CAMELOT[32]	1991	2.0	60%	−4.9/−3.2	Yes	4/6
CARTER[33]	99	4.0	100%	−17/−9	No	4/6
EWPHE[34]	840	4.7	100%	−21.7/−8.3	No	4/6
FEVER						
All[35]	9711	3.3	100%	−4.7/−2.3	Yes, low	6/6
<153 mm Hg[36]	4855	3.3	100%	−3.7/−2.2	Yes, low	
HDFP						
All[37]	10 940	5.0	100%	−10/−5.3	No	5/6
Stratum 90–94[38]	2043	5.0	100%	−10/−7	No	
Stratum 1[37,38]	7825	5.0	100%	−10/−5	No	
Stratum 2–3[37]	3115	5.0	100%	−10/−7	No	
HEP[39]	884	4.4	100%	−18/−11	No	4/6
HSCSG[40]	452	2.3	100%	−15/−12	No	5/6
Hunan province[41]	2080	4.7	100%	−8.2/−5.3	No	3/6
HYVET pilot[42]	1283	1.1	100%	−22.2/−10.9	No	4/6
HYVET[43]	3845	2.1	100%	−13.3/−4.9	No	5/6
MRC-mild[44]	17 354	5.0	100%	−11.5/−6	No	4/6
MRC-old[45]	4396	5.8	100%	−14/−7.8	No	4/6
OSLO[46]	785	5	100%	−16.7/−9.8	No	4/6
PATS[47]	5665	1.8	84%	−5.3/−3.4	No	3/6
PROGRESS[48]	6105	3.9	>48%	−9/−4	Yes	5/6
SCOPE[49]	4937	3.7	100%	−3.3/−1.7	Yes	6/6
SHEP pilot[50]	551	2.8	100%	−16.9/−3.9	No	4/6
SHEP[51]	4736	4.5	100%	−13/−3.9	No	6/6
Sprackling[52]	120	5.0	100%	−16.5/−4.3	No	2/6
STOP[53]	1627	2.1	100%	−22.3/−9.5	No	5/6
SystChina[54]	2394	3.0	100%	−7.8/−4	No	4/6
SystEur[55]	4695	2.6	100%	−8.8/−5.6	No	5/6
						(Continued)

Table.   Continued

Trial Acronym	Patient Number	Follow-Up, y	Hypertensive Patients, %	SBP/DBP Difference, mm Hg	Baseline BP-Lowering Drugs	Quality Assessment vScore
TEST[56]	720	2.3	100%	−4/−4	No	5/6
TOMHS[57]	902	4.4	100%	−6.8/−3.6	No	4/6
USPHS[58]	389	7.0	100%	−15.9/−10	No	4/6
VA1[9]	143	1.5	100%	−39.4/−26.9	No	5/6
VA2[59]	380	3.8	100%	−34.4/−18.3	No	5/6
VA-NHLBI[60]	1012	1.5	100%	NR/−5.9	No	4/6
Wolff[8]	87	1.4	100%	−32.9/−19.8	No	5/6
Intentional, more vs less intense BP-lowering trials						
AASK[61]	1094	4.0	100%	−13/−7	Yes	3/6
ABCD-HT[62]	470	5.0	100%	−6/−8	No	3/6
ACCORD[63]	4733	4.7	87%	−14.2/−6.4	Yes	6/6
BBB[64]	2127	4.9	100%	−11/−8	Yes	5/6
Cardio-SIS[65]	1111	2.0	100%	−3.8/−1.5	Yes	3/6
Fogari[66]	309	4.0	100%	−8.9/−4.6	No	4/6
HOT[67]	18990	3.8	100%	−2.8/−3.1	No	5/6
JATOS[68]	4418	2.0	100%	−9.6/−3.3	Yes	5/6
MDRD[69]	840	2.2	86%	−10.7/−6.9	Yes	3/6
REIN-2[70]	335	1.6	60%	−4/−2	Yes	2/6
SANDS[71]	499	3.0	100%	−7/−6	Yes	4/6
SPS-3[72]	3020	3.7	75%	−12.1/NR	Yes	5/6
UKPDS[73]	1148	8.4	100%	−10/−5	Yes, low	5/6
VALISH[74]	3260	2.9	100%	−5.4/−1.7	Yes	5/6
Nonintentional blood pressure lowering trials						
ACTIVE-I[75]	9016	4.1	88%	−2.9/−1.9	Yes	6/6
AIPRI[76]	583	3.0	82%	−10.1/−6.2	Yes	4/6
BENEDICT-A[77]	1204	3.6	57%	−2.3/−2	Yes	3/6
DEMAND[78]	380	3.8	44.2%	−1.4/−2.0	Yes	3/6
DIABHYCAR[79]	4912	3.9	56%	−2/−0.7	Yes	5/6
DIRECT-2[80]	1905	4.7	62%	−3.9/−2	Yes	5/6
DREAM[81]	5269	3.0	43.5%	−4.2/−2.4	Yes	5/6
GISSI-AF[82]	1442	1.0	85.4%	−3/NR	Yes	3/6
HOPE[83]	9297	5.0	46.9%	−4.4/−1.7	Yes	5/6
MICROHOPE[84]	3577	4.5	56%	−3.3/−1.6	Yes	
IDNT[85]	1715	2.6	100%	−3.5/−3	Yes	5/6
IRMA-2[86]	590	2.0	100%	−2/0	No	4/6
I-PRESERVE[87]	4128	4.1	88%	−2.6/−2	Yes	6/6
Lewis[88]	409	3.0	75.5%	−2/−2.5	Yes	3/6
NAVIGATOR[89]	9306	6.5	77.5%	−3/−2	Yes	6/6
NICOLE[90]	819	3.0	40%	−8/−3	No	3/6
ORIENT[91]	577	3.2	93%	−4.5/−1	Yes	5/6
PEACE[92]	8290	4.8	45.5%	−2/−1.2	Yes	5/6
PROFESS[93]	20332	2.5	74%	−4.6/−2.2	Yes	6/6
RENAAL[94]	1513	3.4	93%	−2.7/−1	Yes	5/6
ROADMAP[95]	4447	3.2	82%	−3/−1.9	Yes	6/6
TRANSCEND[96]	5926	4.7	76.4%	−4.6/−2.2	Yes	6/6

In all RCTs in which randomization was to >2 groups, comparisons are between the average of all treatment groups and placebo[32,44,45,57,77,78,85] or between combination therapy and average of monotherapies.[66] In HOT[50] comparison is between groups randomized to DBP target <80 vs DBP targets <85 and <90 mm Hg together. BP indicates blood pressure; DBP, diastolic blood pressure; NR, not reported; and SBP, systolic blood pressure.

Outcome	Trials (n)	Events (n/patients) Treated	Events (n/patients) Controls	Difference SBP/DBP (mmHg)	Standardized RR (95% CI)	Standardized RR (95% CI)	Absolute Risk Reduction 1000 pts/5 years (95% CI)
Stroke							
A. Intentional	38	2200/ 71664	3059/ 76160	-8.4/-4.4	0.64 (0.58-0.71)		-17
B. Intent. HT	31	1262/ 51179	1870/ 56326	-9.0/-4.8	0.63 (0.56-0.71)		-15
C. Intent + Non-Intent	54	4215/115690	5298/119695	-6.6/-3.5	0.64 (0.57-0.71)		-19
CHD							
A. Intentional	42	2358/ 72653	2697/ 76702	-8.6/-4.4	0.84 (0.79-0.90)		-6
B. Intent. HT	35	1443/ 52168	1723/ 56868	-9.0/-4.8	0.78 (0.72-0.85)		-8
C. Intent + Non-Intent	58	4014/116346	4498/119718	-6.7/-3.4	0.82 (0.76-0.86)		-8
HF							
A. Intentional	24	658/ 34609	899/ 33042	-9.2/-4.3	0.57 (0.46-0.72)		-14
B. Intent. HT	20	231/ 21517	415/ 20605	-10.6/-4.8	0.54 (0.45-0.64)		-12
C. Intent + Non-Intent	36	2666/ 74973	3121/ 72948	-6.0/-2.9	0.62 (0.51-0.75)		-19
Stroke + CHD							
A. Intentional	39	4485/ 71190	5598/ 75682	-8.6/-4.4	0.76 (0.71-0.81)		-20
B. Intent. HT	32	2632/ 50705	3472/ 55848	-9.0/-4.8	0.75 (0.71-0.79)		-17
C. Intent + Non-Intent	56	8193/115651	9668/118924	-6.7/-3.5	0.74 (0.70-0.80)		-25
Stroke + CHD + HF							
A. Intentional	26	3479/ 44994	4138/ 43416	-10.0/-4.8	0.75 (0.69-0.83)		-28
B. Intent. HT	22	1969/ 31902	2536/ 30979	-11.2/-5.4	0.74 (0.69-0.81)		-25
C. Intent + Non-Intent	38	9107/ 85358	10364/ 83322	-6.9/-3.4	0.73 (0.68-0.79)		-39
CV Death							
A. Intentional	42	2222/ 72328	2595/ 76810	-8.6/-4.4	0.82 (0.76-0.89)		-7
B. Intent. HT	33	1473/ 51245	1778/ 56402	-9.1/-4.8	0.80 (0.73-0.88)		-7
C. Intent + Non-Intent	58	4577/116381	4966/119641	-6.8/-3.4	0.84 (0.77-0.92)		-8
All-cause Death							
A. Intentional	46	4371/ 74223	4844/ 78696	-8.6/-4.4	0.89 (0.84-0.95)		-8
B. Intent. HT	37	2913/ 53140	3336/ 58288	-9.0/-4.8	0.88 (0.82-0.93)		-8
C. Intent + Non-Intent	66	8785/120049	9246/123715	-6.7/-3.5	0.90 (0.85-0.95)		-9

Active better   Control better   -50 -40 -30 -20 -10   0

Figure 1. Relative and absolute risk reduction of various outcomes in trials of blood pressure (BP) lowering. A, Intentional BP-lowering trials. **B**, Intentional BP-lowering trials exclusively in hypertensive (HT) patients. **C**, Intentional and nonintentional BP-lowering trials together. All major types of cardiovascular (CV) events and death are significantly reduced by BP-lowering treatment, the effects being particularly large for stroke and heart failure (HF). Absolute risk reductions are also substantial. There are no major differences in the effects when only intentional BP-lowering trials are considered (**A**, primary analysis), only intentional trials exclusively enrolling hypertensive patients are analyzed (**B**, sensitivity analysis), and both intentional and nonintentional trials are considered together (**C**, secondary analysis). Standardized Mantel–Haenszel risk ratio (RR) is to a systolic BP (SBP)/diastolic BP (DBP) difference of 10/5 mmHg. The column absolute risk reduction reports the number and 95% confidence interval (CI) of events prevented for every 1000 patients treated for 5 years with a standardized RR. CHD indicates coronary heart disease (Data derived from Thomopoulos et al[23]).

control groups of 10/5 mmHg) and risks of coronary heart disease (CHD) events and cardiovascular and all-cause mortality being also significantly reduced but to a lesser extent (16%, 18%, and 11%, respectively; Figure 1, row: intentional). After excluding those intentional RCTs in which not all enrolled patients were hypertensives,[28,29,32,47,48,63,69,70,72] only slightly increased relative risk reductions were found (Figure 1, intent. hypertensive). Inclusion of nonintentional BP-lowering trials (Figure 1, intent+nonintent) did not substantially change the relative risk reductions either. Figure 1 also shows that absolute reduction of the risk of all outcomes was significantly and substantially reduced by a standardized SBP/DBP reduction of 10/5 mmHg: for example, in intentional BP-lowering RCTs, 28 major cardiovascular events (composite of stroke, CHD, and HF) could be prevented for every 1000 patients treated for 5 years, with a number of patients needed to treat of only 36.[23]

The relationship of different outcome reductions to the extent of BP reductions was investigated by metaregression analyses of the 47 RCTs of intentional BP lowering.[23] The natural logarithm of the RR of stroke was significantly related to the extent of SBP, DBP, and PP reductions and that of cardiovascular mortality to SBP and PP reductions. However, RRs of CHD and all-cause mortality did not show significant relationships with any BP reduction.[23] When metaregressions were calculated by using percent changes in BP, which were similar for SBP, DBP, and PP (maximum reductions of 22%, 22%, and 25%, respectively), regression coefficients were

similar for all types of BP (Figure 2),[23] indicating no preferential relationship of outcome reduction with any BP parameter. The finding that the relationships of the BP reductions were with the logarithm of the outcome RRs adds the information that progressively greater BP reductions result in progressively lower increments of risk reductions. This parallels the semilogarithmic relationship between BP and cardiovascular event rates in observational studies.[97]

Effects of BP Lowering Produced by Drugs Belonging to Different Classes of Antihypertensive Agents

In the 68 RCTs used to estimate quantitatively the efficacy of BP lowering in preventing different types of cardiovascular outcomes, the BP lowering was obtained by administering drugs belonging to different pharmacological classes. There is an obvious interest in further investigating whether BP lowering by any of the major classes of antihypertensive therapy can be shown to be effective in reducing all or part of cardiovascular outcomes. Several meta-analyses have approached this problem in the past,[16–20,98–106] but none of them has been comprehensive of all BP-lowering RCTs from 1966 to the end of 2013 and simultaneously exclusive of RCTs comparing different active regimens (the latter type of trials aim at avoiding, instead of inducing, a between-group BP difference) and of RCTs investigating antihypertensive drugs in the treatment of conditions different from hypertension (such as myocardial infarction and HF).
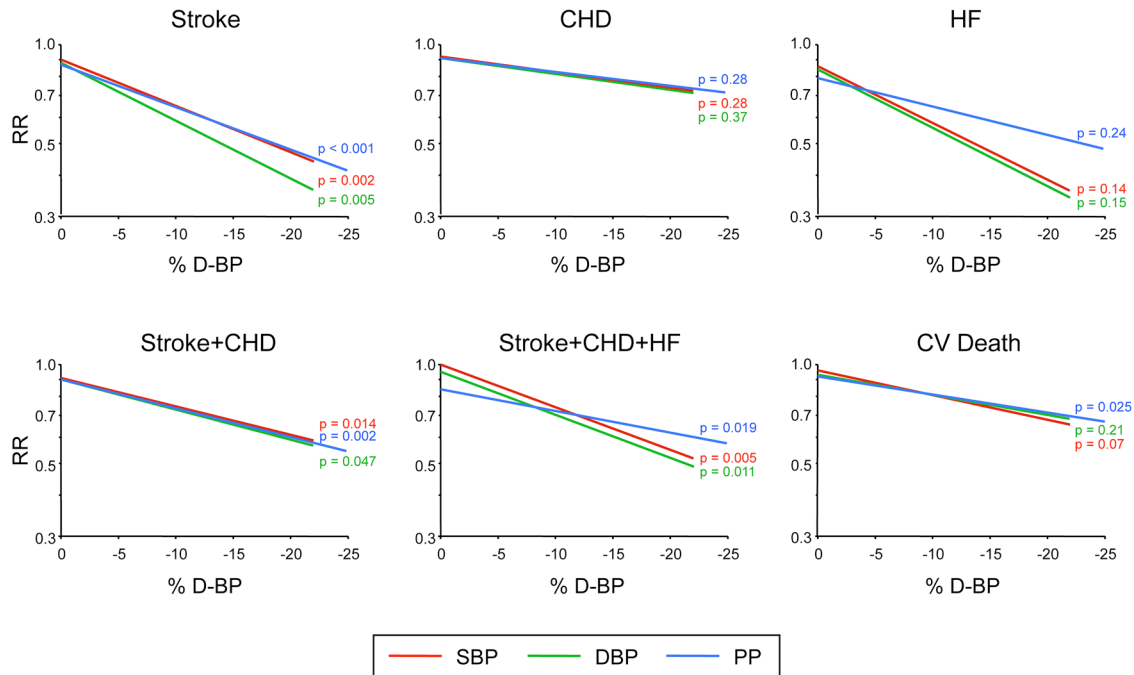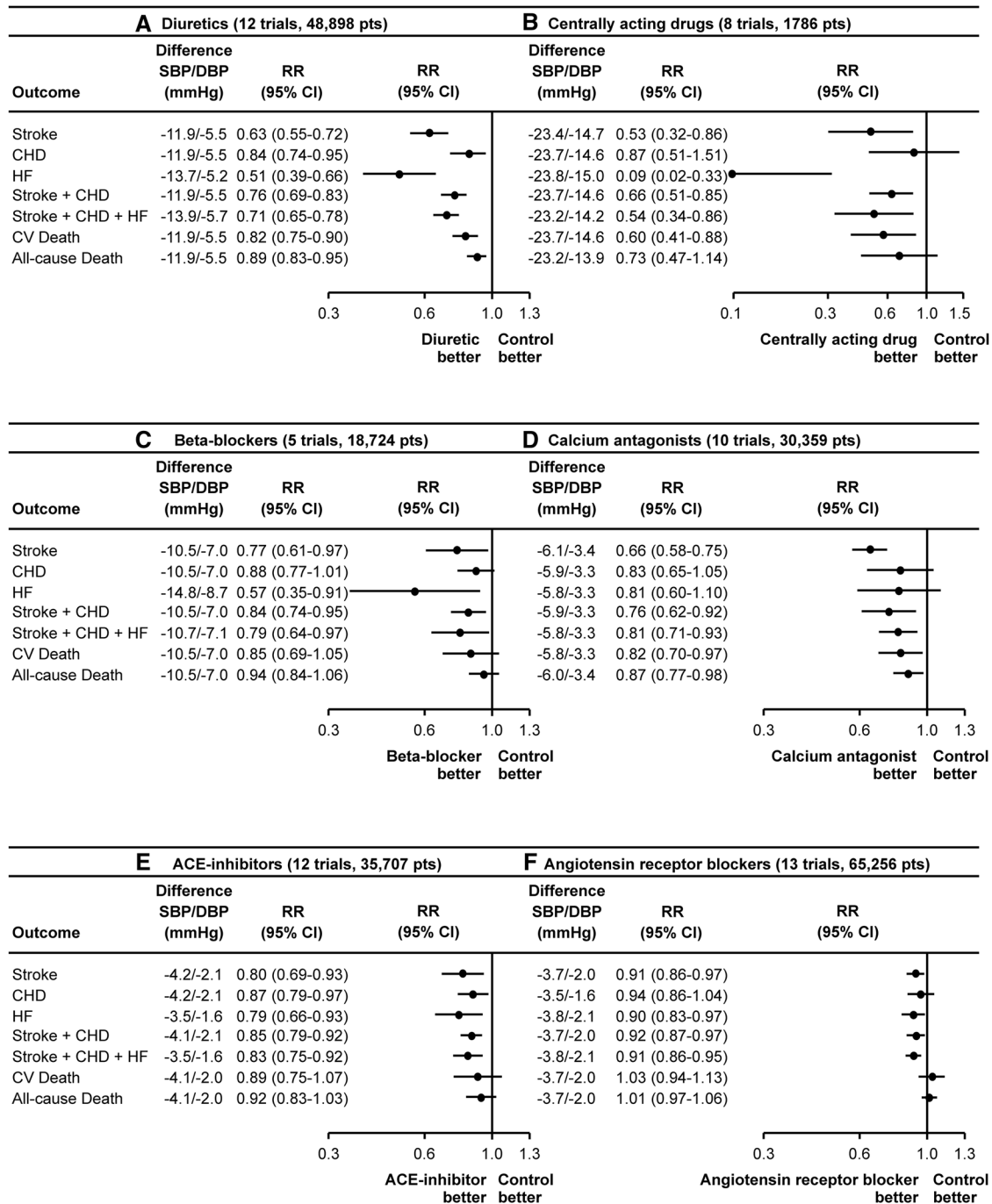
Figure 2. Relationships of outcome reductions to percent blood pressure (BP) reductions. Metaregressions of Mantel–Haenszel risk ratios (RR) on percent BP differences (BP differences of active group minus placebo or less active group as percentage of on-treatment BP in the placebo or less active group). Regressions relative to systolic BP (SBP) are in red, those relative to diastolic BP (DBP) in green, those relative to pulse pressure (PP) are in blue. Reductions in stroke, composite of stroke and coronary heart disease (CHD), composite of stroke, CHD, and heart failure (HF), and cardiovascular (CV) death are proportional to the reductions of SBP, DBP, and PP, with no closer relationship to any type of BP. Note that the logarithmic nature of the relationship implies that risk reduction increases to a progressively smaller extent the larger the BP reduction. D-BP indicates blood pressure difference (Reprinted from Thomopoulos et al[23] with permission of the publisher. Copyright ©2014, Wolters Kluwer Health).

Of the 68 BP-lowering RCTs we have identified, 55 were suitable for drug-class meta-analyses.[26] Twelve RCTs[30,34,37,38,42–47,50,51,60] (48 898 patients) compared a diuretic with no treatment. SBP/DBP differences of ≈−12/−5 mm Hg were accompanied by significant reductions of all outcomes, including mortality (Figure 3A). The same results were obtained by limiting analyses to 8 RCTs using low-dose diuretics,[34,42,43,45–47,50,51] as currently prescribed. Eight small RCTs (1786 patients)[8,9,31,33,40,52,58,59] that used a choice of centrally acting drugs (reserpine and methyldopa) often in combination with thiazide or hydralazine were analyzed together and provided evidence of significant reductions of stroke, HF, major cardiovascular events, and cardiovascular mortality[26] (Figure 3B). Five RCTs[39,44,45,56,73] (18 724 individuals) provided evidence that BP lowering by β-blockers (SBP/DBP difference, −10/−5 mm Hg) can significantly reduce stroke, HF, and major cardiovascular events (Figure 3C). Evidence of significant reduction in cardiovascular mortality was achieved only when the Swedish Trial in Old Patients with Hypertension (STOP) trial[53] using a choice between β-blockers and diuretics as active drugs was included.[26]

The design of BP-lowering RCTs comparing calcium antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers with placebo (with tested drugs and placebo often being added on a background of pre-existing antihypertensive therapy) was such that smaller SBP/DBP differences were achieved. Nonetheless, evidence of significant reductions of stroke, major cardiovascular events, and cardiovascular and all-cause deaths by 10 RCTs

(30 359 patients) comparing calcium antagonists with placebo[28,32,35,41,54,55,66,70,85,90] (Figure 3D), evidence of significant reductions of stroke, CHD, HF, and major cardiovascular events by 12 RCTs (35 707 patients) using angiotensin-converting enzyme inhibitors[32,42,48,66,73,76,77,79,81,83,88,92] (Figure 3E), and evidence of significant reductions in stroke, HF, and major cardiovascular events by 13 RCTs (65 256 patients) using angiotensin receptor blockers[49,75,80,82,85–87,89,91,93–96] (Figure 3F) were obtained.[26] Among calcium antagonist RCTs, it was possible to separately analyze, in a sensitivity meta-analysis, 4 RCTs[35,41,54,55] enrolling exclusively hypertensive patients without or with minimal background treatment (in this way, more similar to RCTs testing diuretics or β-blockers versus placebo), and this meta-analysis also showed significant reductions of CHD and HF. Similar sensitivity analyses could not be done for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers because of the absence of large RCTs done in exclusively hypertensive patients without background therapy.[26]

In conclusion, BP lowering by all classes of antihypertensive drugs is accompanied by significant reductions of stroke and major cardiovascular events. This supports the concept that reduction of these events is because of BP lowering per se rather than specific drug properties, a concept shared by the European Society of Hypertension–European Society of Cardiology hypertension guidelines,[13] which, on this basis, recommend all major classes of antihypertensive agents to initiate treatment. However, evidence of risk reduction of other cardiovascular events and, particularly, mortality has

A   Diuretics (12 trials, 48,898 pts)

Outcome	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)
Stroke	-11.9/-5.5	0.63 (0.55-0.72)	
CHD	-11.9/-5.5	0.84 (0.74-0.95)	
HF	-13.7/-5.2	0.51 (0.39-0.66)	
Stroke + CHD	-11.9/-5.5	0.76 (0.69-0.83)	
Stroke + CHD + HF	-13.9/-5.7	0.71 (0.65-0.78)	
CV Death	-11.9/-5.5	0.82 (0.75-0.90)	
All-cause Death	-11.9/-5.5	0.89 (0.83-0.95)	

0.3   0.6   1.0   1.3

Diuretic better   Control better

B   Centrally acting drugs (8 trials, 1786 pts)

Outcome	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)
Stroke	-23.4/-14.7	0.53 (0.32-0.86)	
CHD	-23.7/-14.6	0.87 (0.51-1.51)	
HF	-23.8/-15.0	0.09 (0.02-0.33)	
Stroke + CHD	-23.7/-14.6	0.66 (0.51-0.85)	
Stroke + CHD + HF	-23.2/-14.2	0.54 (0.34-0.86)	
CV Death	-23.7/-14.6	0.60 (0.41-0.88)	
All-cause Death	-23.2/-13.9	0.73 (0.47-1.14)	

0.1   0.3   0.6   1.0   1.5

Centrally acting drug better   Control better

C   Beta-blockers (5 trials, 18,724 pts)

Outcome	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)
Stroke	-10.5/-7.0	0.77 (0.61-0.97)	
CHD	-10.5/-7.0	0.88 (0.77-1.01)	
HF	-14.8/-8.7	0.57 (0.35-0.91)	
Stroke + CHD	-10.5/-7.0	0.84 (0.74-0.95)	
Stroke + CHD + HF	-10.7/-7.1	0.79 (0.64-0.97)	
CV Death	-10.5/-7.0	0.85 (0.69-1.05)	
All-cause Death	-10.5/-7.0	0.94 (0.84-1.06)	

0.3   0.6   1.0   1.3

Beta-blocker better   Control better

D   Calcium antagonists (10 trials, 30,359 pts)

Outcome	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)
Stroke	-6.1/-3.4	0.66 (0.58-0.75)	
CHD	-5.9/-3.3	0.83 (0.65-1.05)	
HF	-5.8/-3.3	0.81 (0.60-1.10)	
Stroke + CHD	-5.9/-3.3	0.76 (0.62-0.92)	
Stroke + CHD + HF	-5.8/-3.3	0.81 (0.71-0.93)	
CV Death	-5.8/-3.3	0.82 (0.70-0.97)	
All-cause Death	-6.0/-3.4	0.87 (0.77-0.98)	

0.3   0.6   1.0   1.3

Calcium antagonist better   Control better

E   ACE-inhibitors (12 trials, 35,707 pts)

Outcome	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)
Stroke	-4.2/-2.1	0.80 (0.69-0.93)	
CHD	-4.2/-2.1	0.87 (0.79-0.97)	
HF	-3.5/-1.6	0.79 (0.66-0.93)	
Stroke + CHD	-4.1/-2.1	0.85 (0.79-0.92)	
Stroke + CHD + HF	-3.5/-1.6	0.83 (0.75-0.92)	
CV Death	-4.1/-2.0	0.89 (0.75-1.07)	
All-cause Death	-4.1/-2.0	0.92 (0.83-1.03)	

0.3   0.6   1.0   1.3

ACE-inhibitor better   Control better

F   Angiotensin receptor blockers (13 trials, 65,256 pts)

Outcome	Difference SBP/DBP (mmHg)	RR (95% CI)	RR (95% CI)
Stroke	-3.7/-2.0	0.91 (0.86-0.97)	
CHD	-3.5/-1.6	0.94 (0.86-1.04)	
HF	-3.8/-2.1	0.90 (0.83-0.97)	
Stroke + CHD	-3.7/-2.0	0.92 (0.87-0.97)	
Stroke + CHD + HF	-3.8/-2.1	0.91 (0.86-0.95)	
CV Death	-3.7/-2.0	1.03 (0.94-1.13)	
All-cause Death	-3.7/-2.0	1.01 (0.97-1.06)	

0.3   0.6   1.0   1.3

Angiotensin receptor blocker better   Control better

Figure 3. Relative risk reduction of various outcomes in trials of blood pressure (BP) lowering by different classes of drugs. A, Diuretics. **B**, Centrally acting drugs. **C**, β-blockers. **D**, Calcium antagonists. **E**, Angiotensin-converting enzyme (ACE) inhibitors. **F**, Angiotensin receptor blockers. BP lowering by all classes of antihypertensive drugs is accompanied by significant reductions of stroke and composite cardiovascular (CV) events, but evidence of risk reduction of coronary heart disease (CHD) and heart failure (HF) and particularly mortality has been found to date with some drug classes only. Note, however, that BP differences between active and placebo treatments have been much smaller with more recent classes of drugs (**D–F** versus **A–C**). CI indicates confidence intervals; DBP, diastolic blood pressure; pts, patients; RR, Mantel–Haenszel risk ratios; and SBP, systolic blood pressure (Data derived from Thomopoulos et al[26]).

been obtained to date with some drug classes only. There were marked differences in trial design (in older trials, treatment was initiated by either the active drugs being tested or placebo, whereas in more recent trials, the active drugs being tested or placebo were added as the last drug on a background of pre-existing antihypertensive therapy), total cardiovascular risk (from a minimum of 3.7% cardiovascular deaths in 5 years in β-blocker RCTs to a maximum of 7.9% in angiotensin receptor blocker RCTs), SBP/DBP differences between active and placebo groups (from −3.7/−2.0 mm Hg in angiotensin receptor blocker RCTs to −23.5/−14.5 mm Hg in RCTs using centrally active drugs), and sample size (from as few

as 1786 patients in whom centrally active compounds were studied up to as many as 65 256 patients in whom angiotensin receptor blockers were studied).[26] Therefore, comparisons of meta-analyses of different class-specific placebo-controlled RCTs seem unwarranted. The relative effectiveness of different drug classes can only be estimated by their head-to-head comparison in the same trial. In concluding our recent meta-analyses of class-specific placebo-controlled RCTs, we have remarked that these meta-analyses must be considered a necessary background for the interpretation of the results of trials comparing head-to-head different active therapeutic regimens and their meta-analyses. Often similar incidences of a given outcome in active regimens comparative trials are interpreted as similar benefits of the 2 active regimens, but the data we have reported are a warning that similar outcome incidences can be defined as benefits only when ≥1 of the agents tested has been shown to significantly reduce risk of that outcome in placebo-controlled trials.[26]

Effects of BP-Lowering Treatment on Various Outcomes in Individuals at Different Levels of High BP

Untreated hypertensive patients are usually stratified in hypertension grades (stages in the US style) according to SBP/DBP levels to guide therapeutic decisions.[13,107,108] However, trials of antihypertensive therapy were rarely designed by stratifying patients in this way, and it is no surprise that guidelines markedly differ in their recommendations especially about initiation of antihypertensive drug treatment in grade 1 hypertension.[13,14,108,109] Some placebo-controlled trials, mostly in the 1970s and 1980s, were focused on so-called mild hypertension,[30,37,44,57,58] but its definition was different from the current one of grade 1 (or stage 1) hypertension.[11,12]

In lack of specific trials, meta-analyses can follow 2 different approaches to estimate and compare the effects of BP-lowering treatment in patients at different levels of initial BP: (1) to identify individuals with different hypertension grades in each trial and meta-analyze their data separately according to baseline hypertension grade and (2) to classify and meta-analyze trials according to average baseline SBP and DBP as grade 1, 2, or 3 trials. The major limitation of the first approach, in addition to being an analysis of subgroups defined post hoc, is the need to have individual patient data available, which markedly limits the number of trials that can be analyzed by any group of investigators with the loss of statistical power and possible selection bias. A Cochrane collaboration meta-analysis[110] limited to individuals in mild hypertension trials matching the BP values now defining grade 1 hypertension had indeed limited statistical power to detect significant risk reductions, although stroke reduction came close to statistical significance. A meta-analysis by Czernichow et al[111] of a larger number of trials including individuals at different baseline BP levels showed significant risk reductions at all BP levels, but a large proportion of the individuals were receiving background antihypertensive treatment at the trial beginning and were therefore different from the individuals for whom decisions on initiation of drug treatment are taken. Inclusion of patients under antihypertensive treatment at baseline and patients with cardiovascular conditions different from

hypertension (mostly acute myocardial infarction and HF) makes the meta-analyses by Law et al[20] and Thompson et al[112] scarcely contributing to the issue of BP levels at which drug treatment should be initiated. A most recent meta-analysis of the BPLTTC has used individual data of patients with SBP/DBP in the grade 1 range from 10 BP-lowering RCTs and reported that BP lowering induced a significant reduction of the risk of stroke and cardiovascular and total mortality, but most of the patients had diabetes and mortality reduction lost statistical significance after patients under baseline antihypertensive treatment were excluded.[113]

The second approach has the advantage of allowing the inclusion of all BP-lowering trials provided that no antihypertensive treatment was present at randomization; so that the average SBP/DBP baseline values can be used for classifying each trial in a given hypertension grade. In this way, a large number of trials can be analyzed; statistical power is high, and selection bias is avoided. The limitation is that by using the mean BP values for defining hypertension grade, the analyses are going to include a number, although a minority, of patients whose BP are out of the ranges defining a particular hypertension grade.

Of the 68 BP-lowering RCTs we have considered, 32 could be analyzed to evaluate the effect of baseline BP levels because no antihypertensive treatment was present at baseline (minimum treatment in 3).[24] Six RCTs (16 036 individuals) were classified as grade 1[37(stratum 1)46,47,57,58,62]; 17 (75 816 individuals) as grade 2,[8,30,35,40,41,43,44,49–51,54–56,59,66,67,73]; and 9 (12 507 individuals) as grade 3 hypertension.[9,33,34,37(stratum 2-3),39,42,45,52,53] Between-treatment SBP/DBP differences tended to be larger in grade 3 RCTs, all RRs in Figure 4 were standardized to a SBP/DBP difference of 10/5 mm Hg. Even in grade 1 hypertension, BP lowering was associated with significant relative risk reductions of stroke, CHD, the composite of stroke and CHD, and cardiovascular and all-cause mortality. Only a marked reduction in the risk of HF did not reach statistical significance owing to the extremely wide confidence intervals because of the fact that data on HF were available in 2 grade 1 RCTs only. Figure 4 also shows that relative risk of all outcomes was significantly reduced by BP lowering in grade 2 hypertensives, and the same was true in grade 3, with the only exception of all-cause death. Trend analysis demonstrated that relative risk reduction of all outcomes did not significantly change at different levels of baseline BP (*P* always >0.05).[24]

This is the first demonstration that all grades of hypertension (correctly defined in the absence of concomitant treatment) are similarly susceptible to the beneficial effect of BP lowering. Evidence of BP-lowering benefits in grade 1 hypertensives is particularly important because nowadays, these hypertensives are by far the most prevalent among those seeking counseling about drug treatment initiation. Because of the current debate about indications for BP-lowering drug treatment in grade 1 hypertensives, when their total cardiovascular risk is in the low-moderate range, a secondary analysis was done including trials or trial subgroups with mean baseline SBP/DBP values in the grade 1 range and a low-moderate total cardiovascular 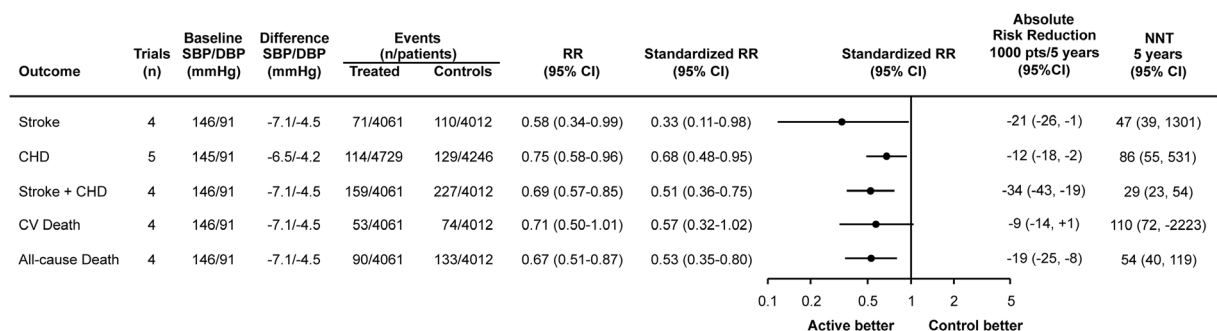risk, as indicated by a cardiovascular death incidence <5% in 10 years in the control groups[36,38,46,57,58]: risk of stroke, CHD,

Outcome	Trials (n)	Events (n/patients) Treated	Events (n/patients) Controls	Baseline SBP/DBP (mmHg)	Difference SBP/DBP (mmHg)	Standardized RR (95% CI)	Standardized RR (95% CI)
HT grade (stage) 1							
Stroke	4	218/7343	312/7321	153/ 95	-8.7/-5.3	0.64 (0.51-0.78)	
CHD	6	368/8248	403/7788	152/ 95	-8.6/-5.3	0.88 (0.77-0.99)	
HF	2	0/599	3/575	153/ 98	-16.4/-9.9	0.46 (0.14-1.57)	
Stroke + CHD	4	544/7343	689/7321	153/ 95	-8.7/-5.3	0.80 (0.72-0.88)	
Stroke + CHD + HF	2	15/599	24/575	153/ 98	-16.4/-9.9	0.76 (0.53-1.08)	
CV Death	4	218/7343	274/7321	153/ 95	-8.7/-5.3	0.78 (0.65-0.95)	
All-cause Death	5	402/7580	487/7554	153/ 95	-8.6/-5.4	0.82 (0.72-0.94)	
HT grade (stage) 2							
Stroke	17	879/35131	1322/40685	165/ 96	-7.6/-4.3	0.58 (0.50-0.69)	
CHD	16	720/34091	847/39645	165/ 96	-7.6/-4.2	0.83 (0.74-0.93)	
HF	11	159/16176	297/15250	164/ 89	-9.4/-4.2	0.45 (0.34-0.61)	
Stroke + CHD	16	1562/34091	2080/39645	165/ 94	-8.2/-4.4	0.71 (0.65-0.79)	
Stroke + CHD + HF	12	1384/24876	1788/23904	163/ 92	-10.2/-4.9	0.69 (0.62-0.76)	
CV Death	16	889/34091	1085/39645	165/ 94	-8.2/-4.4	0.79 (0.69-0.89)	
All-cause Death	17	1750/35131	2048/40685	165/ 95	-8.2/-4.4	0.85 (0.77-0.94)	
HT grade (stage) 3							
Stroke	8	255/6392	376/5995	185/100	-18.1/-8.6	0.73 (0.64-0.82)	
CHD	8	339/6392	455/5995	185/100	-18.1/-8.6	0.83 (0.75-0.91)	
HF	4	60/1720	100/1774	192/102	-21.8/-10.3	0.80 (0.69-0.93)	
Stroke + CHD	8	604/6392	831/5995	184/100	-18.1/-8.6	0.76 (0.70-0.83)	
Stroke + CHD + HF	6	508/3963	665/4047	188/ 96	-17.4/-8.8	0.86 (0.78-0.94)	
CV Death	8	410/6392	478/5995	184/100	-18.3/-8.7	0.87 (0.74-0.98)	
All-cause Death	9	774/6452	828/6055	185/100	-18.3/-8.7	0.93 (0.86-1.01)	

0.3   0.6   1.0   1.5
Active better   Control better

Figure 4. Effects of blood pressure (BP) lowering in trials stratified by mean hypertension (HT) grade (stage) at randomization. Cardiovascular (CV) outcomes are significantly reduced at all grades of HT with no significant difference in relative risk reduction between different grades (*P* for trend always >0.05). Standardized Mantel–Haenszel risk ratio (RR) is to a systolic BP (SBP)/diastolic (DBP) difference of 10/5 mm Hg. CHD indicates coronary heart disease; CI, confidence intervals; HF, heart failure; and n, number (Data derived from Thomopoulos et al[24]).

major cardiovascular events, and all-cause death were significantly reduced by BP-lowering treatment (Figure 5),[23] thus providing further support to those guidelines[13,14] favoring, at least as a prudent approach, the prescription of BP-lowering drugs to all adult individuals whose BP values remain ≥140/90 mm Hg despite adequate lifestyle interventions.

Effects of BP-Lowering by Treatment to SBP and DBP Levels Below Versus Above Predetermined Cut Offs

Prominent among practical questions of antihypertensive drug management is that about the level to which BP should be brought by treatment to maximize outcome reduction. In spite of the importance of the question, only few BP-lowering RCTs have investigated the problem. Most of these trials have

tested the effects of more or less intense lowering, however, without a precise BP target; others have used only DBP targets; others have used noncardiovascular outcomes (such as renal function or left ventricular hypertrophy) as primary end point; none of them had sufficient statistical power to answer the question. Because of the practical importance of the question, a large number of authors have exercised themselves in post hoc analyses of RCT data by correlating the incidences of cardiovascular outcomes with individual levels of treatment achieved SBP or DBP. These analyses have usefully contributed to raising 2 opposite hypotheses, namely (1) the lower is the achieved BP the better is the treatment outcome and (2) the J-curve hypothesis suggesting that at low BP values, cardiovascular risk may be less effectively prevented than at intermediate BP levels.[114] It is obvious, however, that the

Outcome	Trials (n)	Baseline SBP/DBP (mmHg)	Difference SBP/DBP (mmHg)	Events (n/patients) Treated	Events (n/patients) Controls	RR (95% CI)	Standardized RR (95% CI)	Standardized RR (95% CI)	Absolute Risk Reduction 1000 pts/5 years (95%CI)	NNT 5 years (95% CI)
Stroke	4	146/91	-7.1/-4.5	71/4061	110/4012	0.58 (0.34-0.99)	0.33 (0.11-0.98)		-21 (-26, -1)	47 (39, 1301)
CHD	5	145/91	-6.5/-4.2	114/4729	129/4246	0.75 (0.58-0.96)	0.68 (0.48-0.95)		-12 (-18, -2)	86 (55, 531)
Stroke + CHD	4	146/91	-7.1/-4.5	159/4061	227/4012	0.69 (0.57-0.85)	0.51 (0.36-0.75)		-34 (-43, -19)	29 (23, 54)
CV Death	4	146/91	-7.1/-4.5	53/4061	74/4012	0.71 (0.50-1.01)	0.57 (0.32-1.02)		-9 (-14, +1)	110 (72, -2223)
All-cause Death	4	146/91	-7.1/-4.5	90/4061	133/4012	0.67 (0.51-0.87)	0.53 (0.35-0.80)		-19 (-25, -8)	54 (40, 119)

0.1   0.2   0.5   1   2   5
Active better   Control better

Figure 5. Effects of blood pressure (BP) lowering in trials with average baseline BP in grade 1 and average low-moderate cardiovascular (CV) risk. Note significant reductions of relative and absolute risk of stroke, coronary heart disease (CHD), composite of stroke and CHD, and all-cause death. Standardized Mantel–Haenszel risk ratio (RR) is to a systolic BP (SBP)/diastolic BP (DBP) difference of 10/5 mm Hg. The column absolute risk reduction reports number (n; and 95% confidence interval [CI]) of events prevented for every 1000 patients (pts) treated for 5 years with a standardized RR. Numbers needed to treat (NNT) are numbers (and 95% CI) of patients needed to treat for 5 years to prevent 1 event. CV death rate in the control group (index of CV risk) was 4.5% in 10 years (Reprinted from Thomopoulos et al[24] with permission of the publisher. Copyright ©2014, Wolters Kluwer Health).

approach of analyzing RCTs by classifying individual data on the basis of BP values achieved during treatment independent of treatment assignment leads to the loss of randomization, and any meta-analysis of these studies becomes one of the observational rather than randomized studies.[114]

To preserve randomization, a meta-analysis investigating the effects of different SBP (or DBP) levels achieved by treatment on cardiovascular outcomes should (1) analyze RCTs in their entirety without recourse to individual data; (2) classify them according to average SBP (or DBP) levels separately achieved in the active (or more active) and placebo (or less active) treatment arms; and (3) group the different RCTs according to clinically meaningful SBP (or DBP) cut offs when average achieved BP values of the placebo (or less active) arm are above and those of the active (or more active) arm are below that particular cut off.

In 32 of the 68 BP-lowering RCTs we have identified,[23] treatment lowered BP across 3 predeterminate SBP cut offs (140–149 versus ≥150; 130–139 versus ≥140; <130 versus ≥130 mmHg) and in 29 across 2 predeterminate DBP cut offs (<90 versus ≥90; <80 versus ≥80 mmHg). As illustrated in Figure 6, the meta-analysis of 8 trials (13 841 individuals)[9,34,40,43,50,51,64,73] allowing comparison of SBP values across the cut off of 150 mmHg showed that all outcomes (stroke, CHD, HF, and cardiovascular and all-cause mortality) were significantly reduced by lowering SBP below 150 mmHg[24]; the meta-analysis of 16 RCTs (82 421 individuals)[29,35,37,44,46,48,58,59,65–68,74,76,77,84] allowing comparison of SBP values across the cut off of 140 mmHg also showed that all outcomes, with the only exception of HF, were significantly reduced by lowering SBP below 140 mmHg,[24] whereas the

meta-analysis of 8 RCTs (31 970 individuals)[38,57,61,63,69,72,81,92] allowing comparison of SBP values across the cut off of 130 mmHg showed that only stroke and all-cause death were significantly reduced by lowering SBP below 130 mmHg.[24] Furthermore, trend analysis showed that absolute risk reductions of stroke, HF, major cardiovascular events, and cardiovascular death became progressively smaller, the lower were the achieved SBP values being compared.[24]

Meta-analysis of 13 RCTs (41 790 individuals)[30,31,34,37,40–42,44,46,53,58,59,64] allowing comparison of DBP values across the cut off of 90 mmHg and a separate meta-analysis of 16 RCTs (65 875 individuals)[39,43,45,48,49,55,57,61,62,65,69,81,85,88,89,93] allowing comparison of DBP values across the cut off of 80 mmHg showed similar reduction of cardiovascular outcomes independently of the chosen cut off. However, when RCTs with a baseline DBP of <90 mmHg (predominantly isolated systolic hypertension) were excluded from RCTs with achieved DBP across the cut off of 80 mmHg, lowering DBP to <80 mmHg was associated only with significant reductions in stroke and composite cardiovascular events including stroke.

Although meta-analyses are not substitutes for trials directly investigating a clinical question (in this case, the optimal SBP and DBP targets), the results of the meta-analyses summarized above provide support to present opinion-based recommendations[13,14,108] aiming treatment at SBP/DBP targets of <140/90 mmHg, with SBP values just <130 and DBP values just <80 mmHg being safe and potentially beneficial particularly about stroke.
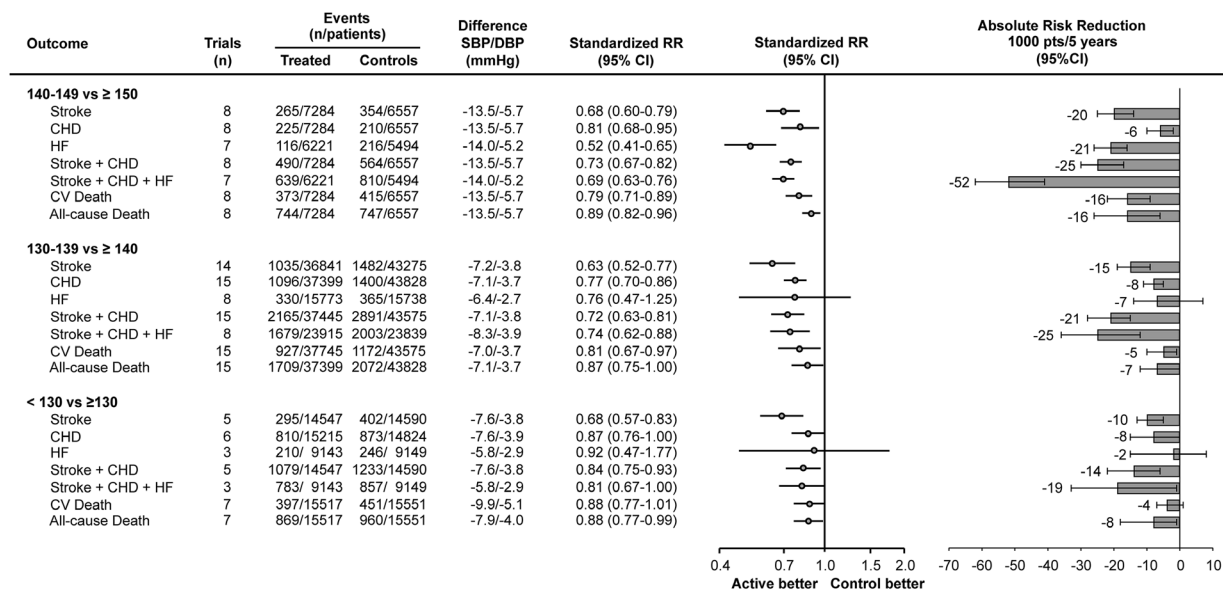
Figure 6. Effects of blood pressure (BP) lowering in trials with mean on-treatment systolic BP (SBP) below and above different cut offs. Mean SBP/diastolic BP (DBP) achieved on treatment were for SBP cut off 150, 143.3/76.4 (active) and 157.1/82.2 (control), cut off 140, 137.2/81.1 and 144.3/84.8; cut off 130, 126.8/78.7 and 136.8/83.7 mmHg. Lowering SBP just below when compared with just above the cut offs of 150 or 140 mmHg is able to reduce almost all types of outcomes, whereas lowering SBP just below when compared with just above the 130 mmHg cut off only stroke and all-cause death is significantly reduced. Standardized Mantel–Haenszel risk ratio (RR) is to a SBP/DBP difference of 10/5 mmHg. The column absolute risk reduction reports number and 95% confidence interval (CI) of events prevented for every 1000 patients (pts) treated for 5 years with a standardized RR. CHD indicates coronary heart disease; CV, cardiovascular; and HF, heart failure (Data derived from Thomopoulos et al[24]).

Influence of Different Levels of Cardiovascular Risk on the Effects of BP-Lowering Treatment on Cardiovascular Outcomes

An additional question of practical medical importance is whether the effects of BP-lowering treatment on fatal and nonfatal outcomes are similar or different at different levels of baseline cardiovascular risk and whether BP-lowering treatment should be preferentially addressed to patients in risk categories promising larger absolute treatment benefits. This question can hardly be approached within a single RCT, but it is particularly well suited to be addressed by meta-analysis of a large number of RCTs, each enrolling hypertensive patients at different cardiovascular risks.

In a recent set of meta-analyses,[25] we have classified the 68 BP-lowering RCTs (245 885 individuals) in 4 strata of increasing 10-year incidence of cardiovascular death in the control (placebo or less active treatment) group: (1) low-moderate risk (<5%; 23 RCTs[30,32,44,46,57,58,60,64–68,71,74,76–78,81,82,87,89,91,95]; 81 675 individuals); (2) high risk (5% to <10%; 11 RCTs[28,35,37 (stratum 1),41,61,63,70,72,86,90,92]; 46 162 individuals); (3) very high risk (10% to <20%; 19 RCTs[8,29,37(stratum 2-3),44,47–51,54,55,62,69,73,79,83,88,93,96]; 91 152 individuals); (4) very very high risk (≥20%; 16 RCTs[9,31,33,34,39,40,42,45,52,53,56,59,85,87,94,95]; 26 881 individuals). Relative

reductions of all outcomes did not significantly differ in risk strata, but absolute risk reductions significantly increased with the increasing level of cardiovascular risk (*P* for trend always <0.001 except for CHD; Figure 7). For example, a SBP/DBP reduction of 10/5 mm Hg reduced the incidence of major cardiovascular events (composite of stroke, CHD, and HF) by 7 (95% confidence interval, 3–10), 32 (9–50), 56 (35–76), and 87 (52–112) events for every 1000 patients treated for 5 years, with numbers needed to treat for 5 years to prevent 1 event of 152, 33, 18, and 11, respectively.[25]

The influence of different levels of cardiovascular risk (calculated by a risk equation) on the relative and absolute risk reduction has recently been explored also by the BPLTTC in 11 RCTs of antihypertensive treatment (51 917 individuals) in which individual data were available to the collaboration,[115] with findings similar to ours, namely similar relative reduction and increasing absolute reductions of the incidence of major cardiovascular events with increasing baseline cardiovascular risk (the 11 RCTs could not provide sufficient statistical power for finding significant differences in specific outcome).

Both the BPLTTC meta-analysis[115] and ours[25] obviously suggest that the cost-effectiveness ratio of antihypertensive treatment becomes progressively more and more favorable the
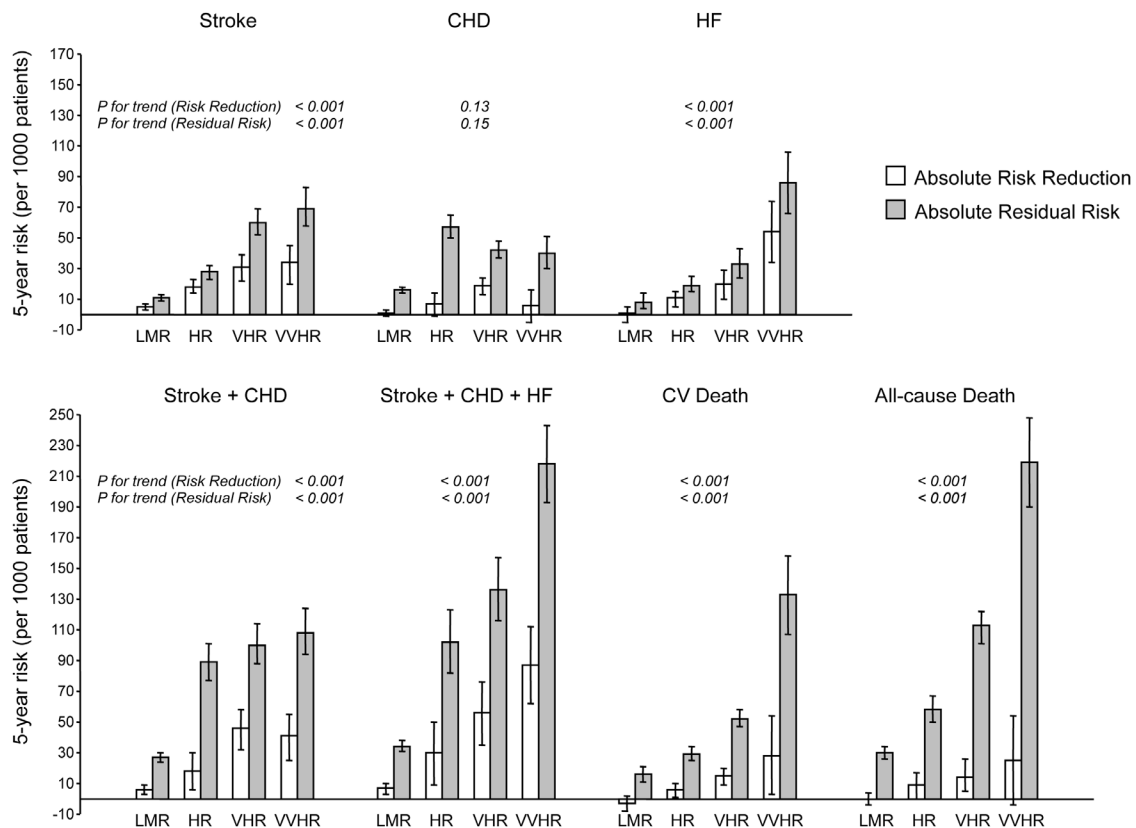
Figure 7. Absolute risk reduction by blood pressure (BP) lowering treatment (standardized to a SBP/DBP of 10/5 mm Hg) and residual risk in trials stratified by the increased level of cardiovascular (CV) risk in the control group. BP lowering produces greater absolute risk reduction (except for coronary heart disease [CHD]) the higher the level of CV risk, but a high level of risk is also associated with a higher absolute residual risk, measuring the failure of BP lowering. Absolute risk reductions (empty rectangles) and residual risk (shaded rectangles) are expressed as the number of events prevented or residual for every 1000 patients treated for 5 years. Vertical bars are 95% confidence intervals (CI). It is apparent that both benefits (risk reduction) and failures (residual risk) progressively increase with the increasing level of risk, but residual risk, particularly of mortality, increases more markedly. HF indicates heart failure; HR, high risk; LMR, low-moderate risk; VHR, very high risk; and VVHR, very very high risk (Reprinted from Thomopoulos et al[25] with permission of the publisher. Copyright ©2014, Wolters Kluwer Health).

higher the baseline risk of the patients being treated (in our meta-analysis, 11 rather than 152 patients to be treated for 5 years to prevent 1 major cardiovascular event). However, any enthusiasm for basing antihypertensive treatment decisions only on a risk-based approach, targeting those at the greatest cardiovascular risk, should be tempered by another important finding of our analyses.[25] Figure 7 also shows that, notwithstanding the increasingly greater absolute risk reduction by BP lowering the higher was the baseline cardiovascular risk, the rates of all outcomes (CHD excluded) occurring in the actively or more actively treated groups of patients despite treatment (residual risk) remained progressively higher the higher the risk level in the control group. This means that, if the success of BP lowering is measured not only by the absolute reduction in outcome it achieves, but also by the absolute level of treatment failures (residual risk),[116] it is undoubted that the greatest success of BP lowering is achieved in low-moderate risk patients, before some irreversible or scarcely reversible organ damage occurs.

There is another finding in our analyses that deserves some comment. CHD is the only outcome whose absolute reduction is not progressively greater higher is the risk of cardiovascular death, and whose residual risk does not increase with a progressive increase of cardiovascular death risk.[25] Taken together with our observation that CHD events and all-cause death are the only outcomes whose reductions by BP lowering have not been found to be significantly proportional to the extent of BP lowering,[23] these findings suggest that either CHD is less tightly associated with BP than other outcomes, such as stroke and HF, or the benefits of BP lowering on CHD prevention may be partly balanced by untoward effects when cardiovascular risk is very high or when lower BP values are achieved.

Conclusions

A critical reappraisal of the morbidity and mortality effects shown by BP-lowering RCTs has been done first by establishing a precise definition of BP-lowering trials (trials comparing active treatment with placebo, no treatment or less active treatment, achieving a BP difference, performed in cohorts with ≥40% hypertensive patients, and exclusive of trials in acute myocardial infarction, HF, acute stroke, and dialysis). This has led to the identification of 68 RCTs, involving 245 888 patients and 1 058 177 patient-years. Then, the results of these RCTs have been meta-analyzed grouping the RCTs on the basis of a series of clinically relevant questions, with the following conclusions:

1. All major types of cardiovascular events (stroke, CHD, HF, and cardiovascular death) and death by any cause are significantly reduced by BP-lowering treatment, the effects being particularly large for stroke and HF. Absolute risk reductions are also substantial, amounting to the prevention of ≈29 major cardiovascular events for every 1000 patients treated for 5 years.
2. Reductions of stroke, major cardiovascular events, and cardiovascular death are proportional to the reduction of SBP, DBP, and PP (with no closer relationship to any type of BP), but the logarithmic nature of the relationship implies that risk reduction increases to a progressively smaller extent the larger the BP reduction.
3. BP lowering by all classes of antihypertensive drugs is accompanied by significant reductions of stroke and major cardiovascular events. This supports the concept that reduction of these events is because of BP lowering per se. However, evidence of risk reduction of other cardiovascular events (CHD and HF) and, particularly, mortality has been found to date with some drug classes only. This cannot be taken to infer that some drug classes are inferior to others, unless differences between the effects of different drug classes are confirmed in RCTs with head-to-head comparison of the drugs.
4. Cardiovascular outcomes are significantly reduced in RCTs with average baseline SBP/DBP values within all grades (or stages) of hypertension, with no significant difference in relative risk reduction between different grades. Relative and absolute cardiovascular risks of most major outcomes are significantly reduced by BP-lowering treatment also in predominantly grade 1 trials with low-moderate cardiovascular risk.
5. Lowering SBP to <140 mm Hg is able to reduce all types of cardiovascular outcomes (with the possible exception of HF) and cardiovascular and all-cause mortality. Lowering SBP to <130 mm Hg seems safe, but it only adds some further reduction in stroke to the benefits of lowering SBP to <140 mm Hg.
6. BP-lowering treatment produces greater absolute risk reduction the higher the level of cardiovascular risk, but a higher level of risk is also associated with a higher absolute residual risk, measuring the failure of BP-lowering treatment. Targeting BP-lowering treatment to those with the greatest cardiovascular risk seems unwarranted because the reduction in the number of patients needing treatment to obtain a given benefit is counterbalanced by the dramatic increase in the number of patients in whom BP lowering fails to prevent fatal and nonfatal events.

On the whole, the conclusions of this reappraisal of BP-lowering RCTs agree with the recommendations provided by some of the recent hypertension guidelines[13,14,108] but give these recommendations a support stronger than that of experts' opinion.

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