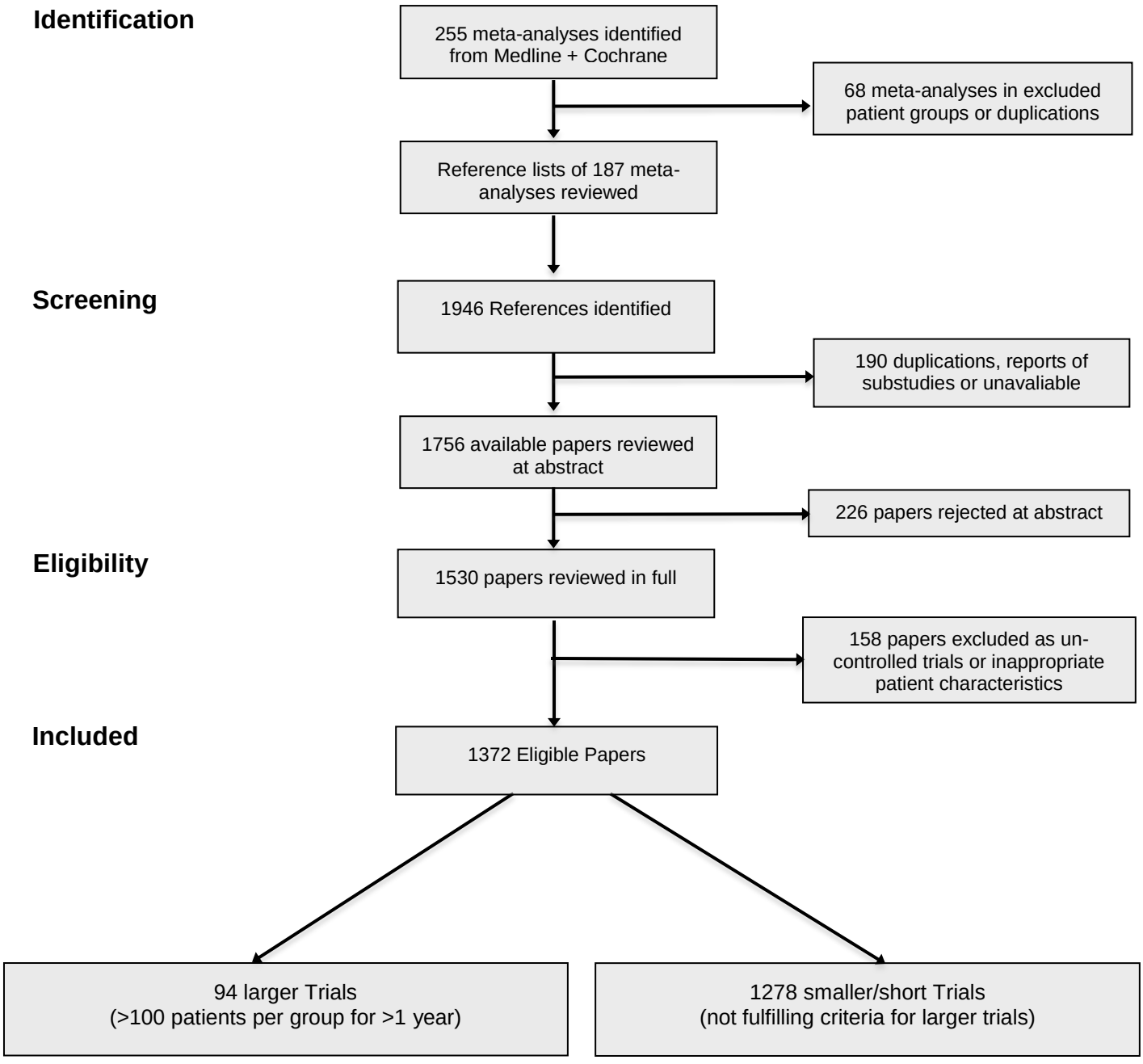
Online data supplement

Web-panel 1. Flow diagram of trial ascertainment and selection, according to PRISMA guidelines.[8]



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Webtable 1: Characteristics of included trials.

Inclusion Criteria

- Controlled trials, group allocation by randomisation, minimisation or similar
- Reported in peer-reviewed journal available in the British Library.
- Groups differ by class of agent given or drug versus control (placebo or less intensive treatment).
- >2 weeks of follow-up.
- English language.

Exclusion Criteria

- Trials requiring a recent acute cardiovascular event (within 3 months of a stroke, myocardial infarction or chest pain requiring intervention)
- Trials requiring patients with: active left ventricular failure (symptomatic or ejection fraction <40%), portal hypertension, severe liver disease, pulmonary hypertension, dialysis dependent renal failure, major life-limiting disease or disease causing significant functional impairment (excluding stroke more than 3 months prior to randomisation), pregnancy, age under 18 years.
- Trials requiring a hypertensive 'crisis' at initiation of treatment.
- Trials assessing impact of antihypertensive agents on depression, dementia and cognitive function.

Data Collection

- Trial validity: Randomisation, blinding, intention-to-treat analysis, length of follow-up.
- Inclusion/exclusion criteria
- Demographic characteristics: Number of patients, age, gender, ethnicity and disease characteristics.
- Treatment: Dose, frequency and duration of treatment with trial agents, pre-existing and maintained medications affecting blood pressure and any add-on antihypertensives during the trial.
- Results: The baseline and follow-up measures of systolic and diastolic blood pressure and the associated distribution at each timepoint recorded in the trial (numerical and graphical approaches). Any measure of intra-individual variability was searched for.

Webtable 2 . Randomised controlled trials (RCTs), comparing different antihypertensive drugs.

A) **Active treatment vs placebo**

Treatment	Treatment comparison (experimental vs reference)	n	Entry criteria	Follow-up (years)	BP reported on FU*	Med. reported on FU†	Antihyper-tensive medication
Diuretics vs placebo							
- ANBPS[w11]	Chlorothiazide vs placebo	3427	HBP, 30-39 ys	4.0	No	5	Add-on
- OSLO[w64]	Hydrochlorothiazide vs no treatment	785	HBP, 40-49 ys	5.5	No	No	No
- EWPHE[w32]	Hydrochlorothiazide+triamterene vs placebo	840	HBP, ≥60 ys	4.6	A	3	Add-on
- SHEP[w78]	Chlorthalidone vs placebo	4736	HBP, ≥60 ys	4.5	A	1	Add-on
- USPHS[w91]	Chlorothiazide vs placebo	389	HBP, <55 ys	6.5-9	B, C	4	No
- TOMHS[w86]	Chlorthalidone vs placebo	370	HBP, 45-69 ys	4.4	No	3	Add-on
- PATS[w66]	Indapamide vs placebo	665	CVA	2	A	6	No
- VACS-2[w93]	Hydrochlorothiazide vs placebo	374	HBP, men, ≥21 ys	1.2	C	6	No
β-Blocker and/or Diuretics vs placebo							
- Coope[w22]	Atenolol or bendroflurazide vs no treatment	884	HBP, ≥60 ys	4.4	No	1	Add-on
- STOP-1[w80]	β-Blocker or diuretic vs placebo	1627	HBP, ≥70 ys	2.0	A	4	No
- MRC-1[w58]	Bendroflurazide or propranolol vs placebo	17354	HBP, 35-64 ys	5.0	No	1	Add-on
- MRC-2[w59]	Bendroflurazide or propranolol vs placebo	4396	HBP, 65-74 ys	5.8	No	5	Add-on
- TOMHS[94w86]	Acebutolol vs placebo	366	HBP, 45-69 ys	4.4	No	3	Add-on
- TEST[w84]	Atenolol vs placebo	720	HBP, CVA, >40 ys	2.3	No	6	No
- BCAPS[25w17]	β-Blocker vs placebo	793	PLS right CA, 49-70 ys	3	No	6	No
- Dutch TIA[w26]	Atenolol vs placebo	1473	CVA	2.6	No	2	No
- VACS-2[w93]	Atenolol vs placebo	362	HBP, men, ≥21 ys	1.2	C	6	No
ACEI vs placebo							
- HOPE[w39]	Ramipril vs placebo	9297	CHD, CVD, or DM+CVRF, ≥55 ys	4.5	No	2	No
- PART-2[w65]	Ramipril vs placebo	617	CHD or CVD, ≤75 ys	4.7	No	3	No
- SCAT[w75]	Enalapril vs placebo	460	CHD, ≥21 ys	4.0	No	No	No
- PEACE[75w68]	Trandolapril vs placebo	8290	CHD + LVEF >40%, ≥50 ys	4.8	C	2	No
- QUIET[w73]	Quinapril vs placebo	1750	CHD, 18-75 ys	2.3	No	5	Add-on
- EUROPA[w31]	Perindopril vs placebo	12218	CHD, ≥18 ys	4.2	No	4	No
- CAMELOT[w19]	Enalapril vs placebo	1328	CHD, 30-79 ys	2.0	No	5	AH-Com.
- DIABHYCAR[w24]	Ramipril vs placebo	4912	DM + proteinuria, >50 ys	3.9	No	2	No
- BENEDICT[w18]	Trandolapril vs placebo	601	HPB + DM, ≥40 ys	3.6	No	5	AH-Com.
- TOMHS[w86]	Enalapril maleate vs placebo	369	HBP, 45-69 ys	4.4	No	3	Add-on
- DREAM[w25]	Ramipril vs placebo	24592	Impaired glucose tolerance or fasting glucose levels, >30 ys	3	No	2	No
- EUCLID[w30]	Fosinopril vs placebo	530	IDDM, 20-59 ys	2	No	No	No
- Maschio[w55]	Benazepril vs placebo	583	NP, 18-70 ys	3	No	No	No
- VACS-2[w93]	Captopril vs placebo	374	HBP, men, ≥21 ys	1.2	C	6	No
- FOSIDAL[w35]	Fosinopril vs placebo	397	NP	2	B	No	No

Treatment	Treatment comparison (experimental vs reference)	n	Entry criteria	Follow-up (years)	BP reported on FU*	Med. reported on FU†	Antihyper-tensive medication
- PREVEND IT[w69]	Fosinopril vs placebo	864	MA, 28-75 ys	3.8	A	3	No
ARB vs placebo							
- SCOPE[w76]	Candesartan vs placebo	4937	HBP, 70-89 ys	3.7	B	5	Add-on
- RENAAL[w74]	Losartan vs placebo	1513	DM + NP, 31-70 ys	3.4	No	5	AH-Com.
- IDNT[w43]	Irbesartan vs placebo	1148	HBP + DM + NP, 30-70 ys	2.6	No	No	No
- IRMA-2[w49]	Irbesartan vs placebo	590	HBP + DM + MA, 30-70 ys	2.0?	No	3	AH-Com.
- TROPHY[w88]	Candesartan vs placebo	409	Stage1 hypertension, 30-65 ys	3.6	No	No	No
- PROFESS[w71]	Telmisartan vs placebo	20332	CVA	2.5	No	1	AH-Com.
- TRANSCEND[w87]	Telmisartan vs Placebo	5926	HBP, CHD, CVA, PVD, NP, LVH, DM	4.6	No	3	AH-Com.
CCB vs placebo							
- PREVENT[w70]	Amlodipine vs placebo	825	CHD, 30-80 ys	3.0	No	5	AH-Com.
- ACTION[w6]	Nifedipine vs placebo	7665	CHD	4.9	No	6	No
- STONE[w79]	Nifedipine vs placebo	1632	HBP, ≥60 ys	2.5	C	No	No
- FEVER[w34]	Felodipine vs placebo	9711	HBP, ≥50 ys	3.3	B	3	Add-on
- Syst-Eur[w82]	Nitrendipine vs placebo	4695	HBP, ≥60 ys	2.0	C	1	AH-Com.
- Syst-China[w83]	Nitrendipine vs placebo	2394	HBP, ≥60 ys	3.0	C	1	AH-Com.
- NICOLE[w60]	Nisoldipine vs placebo	646	CHD, <75 ys	3.0	No	No	No
- IDNT[w43]	Amlodipine vs placebo	1136	HBP + DM + NP, 30-70	2.6	No	No	No
- CAMELOT[w19]	Amlodipine vs placebo	1318	CHD, 30-79 ys	2.0	No	5	AH-Com.
- BENEDICT[w18]	Verapamil vs placebo	603	HPB + DM, ≥40 ys	3.6	No	5	AH-Com.
- TOMHS[w86]	Amlodipine vs placebo	265	HBP, 45-69 ys	4.4	No	3	Add-on
- VACS-2[w93]	Diltiazem vs placebo	368	HBP, men, ≥21 ys	1.2	C	6	No
- INTACT[w45,w46]	Nifedipine vs Placebo	348	CHD, <65 ys	3.0	B	No	No
Combination vs placebo							
- PROGRESS[w72]	Perindopril (+/- indapamide) vs placebo(s)	6105	CVA	3.9	No	4	No
- ADVANCE[w7]	Perindopril + indapamide vs placebo	11140	DM, CVRF, CHD, CVD, ≥55 ys	3.	No	3	AH-Com.
- BENEDICT[w18]	Verapamil + trandolapril vs placebo	600	HPB + DM, ≥40 ys	4.3	No	5	AH-Com.
- HYVET[w42]	Indapamide + perindopril vs placebo	3845	HBP, ≥80 ys	1.8	C	3	Add-on
Others versus placebo							
- TOMHS[w86]	Doxazosin vs placebo	268	HBP, 45-69 ys	4.4	No	3	Add-on
- VA-NHLBI[1w95]	Hydrochlorothiazide (+/- reserpine +/- propranolol)	1012	HBP, 21-50 ys	2	No	2	Add-on
- HSCSG[w41]	Deserpidine+methylchlothiazide vs placebo	452	HBP, <70 ys	3.0	D	No	No
- VACS-1[w92]	Hydrochlorothiazide/reserpine vs placebo	380	HBP, men	3.2	C	6	No
- VACS-2[w93]	Clonidine vs placebo	363	HBP, men, ≥21 ys	1.2	C	6	No
- VACS-2[w93]	Prazosine vs placebo	372	HBP, men, ≥21 ys	1.2	C	6	No

B) **Active treatment vs control regimens**

CCB vs control treatment							
CCB vs diuretics							
- MIDAS[w56]	Isradipine vs hydrochlorothiazide	883	HBP	3.0	No	1	AH-Com.
- ALLHAT II[w9]	Amlodipine vs chlorthalidone	24303	HBP + CVRF, ≥55 ys	4.9	A	1	Add-on
- INSIGHT[w44]	Nifedipine GITS vs Hydrochlorothiazide+amiloride	6321	HBP + CVRF, 55-80 ys	3.5	No	1	Add-on
- NICS-EH[w61]	Nicardipine vs trichlormethiazide	429	HBP, ≥60 ys	4.3	A	1	Add-on
- SHELL[w77]	Lacidipine vs chlorthalidone	1882	HBP, ≥60 ys	2.6	No	6	No
- VHAS[w96]	Verapamil vs chlorthalidone	1414	HBP, 40-65 ys	2.0	No	3	Add-on
CCB vs β-Blocker							
- ASCOT[w13,w14]	Amlodipine vs atenolol	19257	HBP + CVRF, 40-79 ys	5.5	B, C	3	Add-on
- AASK[w1,w2]	Amlodipine vs metoprolol	658	HBP + NP, Afr, 18-70 ys	3.0	No	5	Add-on
- ELSA[w28]	Lacidipine vs atenolol	2334	HBP, 45-75 ys	3.75	No	5	Add-on
- TIBET[w85]	Nifedipine vs atenolol	458	Chronic stable angina	2.0	No	No	No
- APSIS[w12]	Verapamil vs metoprolol	809	Stable angina, <70 ys	3.4	No	4	No
CCB vs β-Blocker and/or diuretics							
- STOP-2[w81]	Felodipine or isradipine vs atenolol or metoprolol or pindolol or Hydrochlorothiazide+amiloride	4409	HBP, 70-84 ys	5.0	No	4	No
- INVEST[w47]	Ca-Antagonist vs non-Ca-antagonist	22576	HBP + CHD, ≥50 ys	2.7	C	1	Add-on
- NORDIL[w62]	Diltiazem vs β-blocker or diuretic	10881	HBP, 50-74 ys	4.5	A	3	Add-on
- CONVINCE[w21]	COER Verapamil vs hydrochlorothiazide or atenolol	16476	HBP + CVRF, ≥55 ys	3.0	No	1	Add-on
CCB vs ACEI							
- AASK[w1,w2]	Amlodipine vs ramipril	653	HBP + NP, Afr, 18-70 ys	3.0	No	5	Add-on
- ALLHAT II[17w9]	Amlodipine vs lisinopril	18102	HBP + CVRF, ≥55 ys	4.9	A	1	Add-on
- JMIC-B[w50]	Nifedipine vs ACEI	1650	HBP + CHD, <75 ys	3.0	No	6	No
- ABCD-H[w3]	Nisoldipine vs enalapril	470	HBP + DM, 40-74 ys	5.3	No	5	AH-Com.
- CAMELOT[w19]	Amlodipine vs enalapril	1336	CHD, 30-79 ys	2.0	No	5	AH-Com.
- BENEDICT[w18]	Verapamil vs trandolapril	601	HPB + DM, ≥40 ys	3.6	No	5	AH-Com.
- FACET[w33]	Amlodipine vs fosinopril	380	HBP + DM	2.5	No	Only com.	Add-on
- STOP-2[w81]	Felodipine or isradipine vs enalapril or lisinopril	4401	HBP, 70-84 ys	5.0	No	4	No
- ESPIRAL[w29]	Nifedipine vs fosinopril	241	HBP + NP, 18-75 ys	3	C	2	No
- J-MIND[w51]	Nifedipine vs enalapril	436	HBP, Diabetes, <75 ys	2	No	3	Add-on
- AVER[w15]	Amlodipine vs enalapril	263	NP, Non-diabetics, 18-80 ys	2.9	No	1	Add-on
CCB vs ARB							
- VALUE[w94]	Amlodipine vs valsartan	15245	CHD + CVRF, ≥50 ys	4.2	A	3	Add-on
- MOSES[w57]	Nitrendipine vs losartan	1352	HBP + CVA, ≤85 ys	2.5	B	3	Add-on
- IDNT[w43]	Amlodipine vs irbesartan	1146	HBP + DM + NP, 30-70 ys	2.6	No	No	No
CCB vs Combination							
- BENEDICT[w18]	Verapamil vs verapamil + trandolapril	603	HPB + DM, ≥40 ys	3.6	No	5	AH-Com.
- TIBET[w85]	Nifedipine vs nifedipine+atenolol	456	Chronic stable angina	2.0	No	No	No
β-Blocker vs control regimens							
- HAPPY[w36]	Atenolol or metoprolol vs diuretics	6659	HBP, men, + CVRF, 40-64 ys	3.75	No	3	Add-on

- IPPPSH[w48]	Oxprenolol vs Control	6357	HBP, 40-64 ys	3-5	No	5	Add-on
- Yurenev[w97]	β-Blocker vs control	304	HBP, LVH	4	C	No	No
- TIBET[w85]	Atenolol vs atenolol + nifedipine	450	Chronic stable angina	2.0	No	No	No
Alpha-Blocker vs control regimens							
- ALLHAT I[w8]	Doxazosin vs chlorthalidone	24335	HBP + CVRF, ≥55 ys	3.3	A	1	Add-on
ACEI vs control treatment							
ACEI vs diuretics							
- ALLHAT II[w9]	Lisinopril vs chlorthalidone	24309	HBP + CVRF, ≥55 ys	4.9	A	1	Add-on
- ANBP-2[w10]	Enalapril vs hydrochlorothiazide	6083	HBP, 65-84 ys	4.1	No	3	Add-on
- PHYLLIS[w68]	Fosinopril vs hydrochlorothiazide	508	HBP, Hchol, PLS, 45-70 ys	2.6	No	3	Add-on
ACEI vs β-Blocker							
- AASK[w1,w2]	Ramipril vs metoprolol	877	HBP + NP, Afr, 18-70 ys	4.1	No	5	Add-on
- UKPDS39[w91]	Captopril vs atenolol	758	HBP + DM, 40-74 ys	8.4	No	1	Add-on
- Himmelmann[w38]	Cliazepril vs atenolol	260	HBP	2	C	6	No
ACEI vs β-Blocker and/or diuretics							
- STOP-2[w81]	Enalapril or lisinopril vs atenolol or metoprolol or Pindolol or hydrochlorothiazide + amiloride	4418	HBP, 70-84 ys	5.0	No	4	No
- CAPPP[w20]	Captopril vs β-blocker or diuretic	10985	HBP, 25-66 ys	6.1	No	No	No
ACEI vs Combination							
- BENEDICT[w18]	Trandolapril vs verapamil + trandolapril	601	HPB + DM, ≥40 ys	3.6	No	5	AH-Com.
ARB vs control treatment							
ARB vs β-Blocker							
- LIFE[w54]	Losartan vs atenolol	9193	HBP + LVH, 55-80 ys	4.8	B, C	3	Add-on
- LAARS[w53]	Losartan vs atenolol	280	HBP, IMT of CCA, 35-65 ys	2	No	5	AH-Com.
ARB vs ACEI							
- DETAIL[w23]	Telmisartan vs enalapril	250	HBP + DM, 35-80 ys	5.0?	No	5	AH-Com.
- ONTARGET[w63]	Telmisartan vs ramipril (ev. telmisartan)	25620	CHD, CVD, PVD, DM with EOD, ≥55 ys	4.7	No	2	No
- E-COST[w27]	Candesartan vs conventional treatment	1630	HBP, 35-79 ys	3.1	A	5	Add-on
- Kondo[w52]	Candesartan vs control treatment	406	CHD	2.0	A	No	No
Combination vs combination							
- ACCOMPLISH[w5]	Benazepril-amlodipine vs benazepril-hydrochlorothiazide	11506	HBP, CHD, CVA, PVD, NP, LVH, DM	2.9	No	3	AH-Com.

C) **More intensive vs less intensive regimes**

- AASK[w1,w2,o]	MAP ≤ 92 vs 102-107 mmHg	1094	HBP + NP, Afr, 18-70 ys	3.8	No	1	Add-on
- ABCD-H[w3]	DBP ≤ 75 vs ≤ 90 mmHg	470	HBP + DM, 40-74 ys	5.3	No	5	AH-Com.
- ABCD-N[w4]	DBP 10 below baseline vs 80-89 mmHg	480	DM, 40-74 ys	5.3	D	Only com.	Add-on
- HOT[w40]	DBP ≤ 80 vs ≤ 85 or ≤ 90 mmHg	18790	HBP, 50-80 ys	3.8	No	3	AH-Com.
- UKPDS38[w89]	DBP < 85 vs < 105 mmHg	1148	HBP + DM, 25-65 ys	8.4	No	1	Add-on
- HDFP[w37]	Steeped versus referred care	10940	HBP, 30-69 ys	Not known	No	No	No
- BBB[w16]	DBP < 80 vs unchanged therapy	2127	HBP, 45-67 ys	3.3	No	No	No

Classification:
***** = Table 1a; † = Table 1b; **°**: The results of the patients with low BP goal were published separately;

Abbreviations:
ACEI: Angiotensin-Converting-Enzyme Inhibitor; **Add-on**: Add-on antihypertensive medication; **Afr**.: African American; **AH-Com**.: Antihypertensive Comedication; **CA**: Carotid artery; **CHD**: Coronary heart disease; **COER**: Controlled-onset extended release; **CVA**: Cerebrovascular accident; **CVD**: Cardiovascular disease; **CVRF**: Cardiovascular risk factors; **DBP**: Diastolic blood pressure; **DM**: Diabetes mellitus; **EOD**: End organ damage; **GITS**: gastrointestinal therapeutic system; **HBP**: High blood pressure (definition according to the study investigators); **Hchol**: Hypercholesterolemia; **IDDM:** Insulin dependent diabetes mellitus; **IMT**: Intima-Media-Thickness; **LVEF**: Left ventricular ejection fraction; **LVH**: Left ventricular hypertrophy; **MA**: Microalbuminuria; **MAP**: Mean arterial pressure; **n**: number of patients in the RCTs; **NP**: Nephropathy (definition according to the study investigators); **Only com**.: reporting comedication only; **PLS**: Plaques; **PVD**: Peripheral vascular disease; **ys**: years.

Webappendix

A) Information on the time point at which mean BP during follow-up is provided.

The time point during follow-up at which mean BP was reported varied: 23 (24.5%) papers[w(1,2,4,5,7,11,16,18,19,21,22,23,28,31,40,43,44,48,49,55,72,75,89,90)] reported mean BP averaged over the whole follow-up period, of which 16 also showed the course of BP in a figure. Nine studies (9.6%)[w(3,6,20,51,58,59,64,68,88)] presented the course of mean BP in a figure without reporting exact values; 32 (34.0%) studies [w(13,14,26,30,33-35,41,42,45-47,50,53,54,56,57,63,67,70,71,76,77,79,82-86,91,92,93,96,97)] reported mean BP at a given time point during follow-up, of which 16 also reported time course of mean BP in a figure. Only 27 (28.7%) studies [w(8-10,15,17,24,25,27,29,32,36-39,52,61,62,65,66,69,74,78,80,81,87,94,95)] provided mean BP at more than one follow-up visit.

B) Reporting of medication in larger trials

Use of BP lowering medication during follow-up was inconsistently reported (Figure 2). Sixteen studies (17.0%)[w(8,9,15,21,22,44,47,56,58,61,71,78,82,83,89,90)] reported the initial medication and comedication at different time points during follow-up (**Definition 1**), of which 13[w(8,9,15,21,22,44,47,58,61,71,78,89,90)] indicated whether the comedication was used specifically as add-on antihypertensive medication. Eight trials (8.5%)[w(24-26,29,39,63,67,95)] reported data consistent with **Definition 2**, 21 (22.3%)[w(5,7,10,13,14,32,34,36,40,42,49,51,54,57,62,65,68,69,86,87,94,96)] with **Definition 3**, six (6.4%)[w(12,31,72,80,81,91)] with **Definition 4**, 15 (15.9%)[w(1-3,11,18,19,23,27,28,48,53,59,70,73,74,76)] with **Definition 5**, nine (9.6%)[w(6,17,38,50,66,77,84,92,93)] with **Definition 6** and two (2.1%)[w(4,33)] reported the comedication without mentioning the adherence to the initial medication. Seventeen trials (18.1%)[w(16,20,30,35,37,41,43,45,46,52,55,60,64,75,79,85,88,97)] reported no information on medication.

C) Quantification of visit-to-visit variability in BP

Visit-to-visit BP variability refers to variability between BP measurements taken on different days, with intervals of days, weeks or months between consecutive measurements. Intra-individual variability in such measurements will be comprised of contributions from both short-term and medium-term fluctuations in BP and longer-term underlying trends. Intra-individual visit-to-visit variability in BP can be estimated indirectly from group data on the distribution of BP values at single follow-up visits or can be calculated using individual patient data on actual BP values from repeated visits.

1. Use of group variability in BP at individual follow-up visits to estimate effects on intra-individual variability

Variance in group BP at a single follow-up will be partly attributable to intra-individual visit-to-visit variation as well as differences between individuals in underlying mean BP. The expected inter-individual group variance of BP values at a single follow-up can therefore be estimated as the sum of the following variance components: inter-individual variance in mean BP, intra-individual visit-to-visit variance in BP and inter-individual variance in intra-individual visit-to-visit BP.

Table 1 shows an analysis of group and individual variability in SBP in which the observed levels of variance in group SBP at a single follow-up (taken as the average over several visits during two years of follow-up) is compared with expected levels in each of several cohorts based on the above model. The proportion of observed inter-individual group variance of SBP values at a single follow-up which could be attributed to intra-individual variability is estimated as the sum of the latter two variance components divided by the total variance and ranges from 41 to 51% depending on the cohort.[1] Effects of randomised treatment on group SD BP at single follow-ups has been shown to correlate well with effects on intra-individual variability in BP in randomised controlled trials of antihypertensive drugs,[2] and to reveal consistent drug-class effects across all available trials.[3,4]

2. Quantification of intra-individual variability visit-to-visit variability in BP

Although a number of methods have been proposed for quantifying variability in BP over a 24-hour period on ambulatory blood pressure monitoring (ABPM),[5-8] different issues arise in the appropriate quantification of visit-to-visit variability. First, the longer time-scale involved increases the potential impact on measured variability of contributions from any trends over time. Second, the relationship between mean levels and intra-individual variability may be different from that observed on ABPM. Further, there will typically be fewer measurements available with which to quantify variability. Careful consideration therefore needs to be given as to the most appropriate measure of variability to use.

Standard deviation (SD)
The most commonly used index of variability in a set of BP measurements is the standard deviation (SD), which provides a global measure of the spread of BP measurements around the mean value (Table 2). Being independent of the order in which the measurements were taken, SD will be related to the extent of both systematic and random variability. However, although SD is widely used and understood as a measure of variability, there are some situations in which it may not be the most appropriate measure to use. Specifically, if there is an underlying trend in BP over time, or if variability is highly correlated with mean levels (which it usually is), then alternative measures may be more appropriate.

Residual standard deviation (RSD)
Where BP measurements are taken over a period of weeks or months, there may be an underlying trend over time, for example a trend for BP to decrease over time in relation to the initiation of anti-hypertensive treatment in a randomised trial. In such cases, using SD as a measure of variability may over-estimate the extent of variability, with large SD values resulting from changes over time and not necessarily as a consequence of variability. If the relationship between BP and time is approximately linear, variability over and above that due to a trend can be estimated as the residual mean square after fitting a linear regression to BP against time. Residual standard deviation (RSD) can then be defined as the square root of this value (Table 2). Figure 1 shows example BP measurements for two real patients; one with a trend for decreasing BP over time and the second with no underlying trend in BP. In the first case, the RSD is substantially smaller than the SD, suggesting that much of the observed variability (as measured by SD) is due to the

trend. In the second case, the values of SD and RSD are very similar. One disadvantage of this approach is the assumption of a linear trend, which may not accurately reflect the nature of changes over time. Although it would be possible to fit a more complicated function, this would require specifying the parametric form of the relationship.

Average real variability (ARV)
Average real variability (ARV), calculated as the average absolute difference between consecutive measurements (Table 2), was proposed as an alternative measure to SD for quantifying variability on ABPM.[9] Cited advantages of this measure are that it takes into account the order of individual BP measurements and is less sensitive to relatively low frequency sampling of non-invasive monitoring. It has been suggested that ARV is a more appropriate measure of variability and a more useful predictor of outcome.[10] ARV can also be usefully applied to visit-to-visit measurements. In the presence of an underlying trend, ARV will tend to be less than the corresponding SD, and can be estimated without making any assumptions regarding the shape of the relationship between BP values and time (Figure 1). ARV therefore provides a computationally simple way of estimating variation about a trend. ARV will be greater than SD when there is a tendency for BP measurements to have an alternating pattern of increases and decreases between adjacent measurements (Figure 1b).

Successive variation (SV)
Successive variation (SV) is another measure of variability that has been applied to ABPM data.[11] It is conceptually similar to ARV, being defined as the square root of the average squared difference between successive BP measurements (Table 2). SV will be highly correlated with ARV, tending to be larger in absolute value (Figure 1) and influenced to a greater extent by large discrepancies between successive measurements.

Variation independent of mean (VIM)
Absolute levels of variability in BP are often positively correlated with mean levels. By expressing SD relative to mean levels, CV is often considered to correct for correlations between mean levels and SD; indeed, CV was found to be only weakly correlated with mean levels for ABPM data.[12] However, in the case of visit-to-visit variability, this is not always a sufficient correction, with CV also being positively correlated with mean levels in most cohorts.[1,2,13] In order to determine the prognostic value of variability, independently of mean levels, it may be useful to derive a measure of variability that is uncorrelated with mean levels. Variation independent of mean (VIM) is a transformation of SD that is defined to be uncorrelated with mean levels.[1,2,13] It is calculated by fitting a curve of the form $y = kx^p$ through a plot of SD SBP (y-axis) against mean SBP (x-axis), for all individuals in the cohort. The parameter *p* is estimated from the data and *k* is a constant which can be chosen such that the values of VIM are on the same scale as values of SD. For example, if M is the average value of mean SBP in the cohort, then $k = M^p$ and the value of VIM for any individual is given by VIM SBP = (k SD/ $\bar{x}^p$) (Table 2). Since the form of the relationship between mean and SD may differ in different cohorts, the estimated value of *p* will be specific to the cohort. Figure 2 shows example BP patterns in two patients with differing levels of mean BP. Although variability as measured by SD is higher in the patient with the higher mean level, CV is similar in the two patients and VIM is greater in the patient with lower mean. This indicates that the second example has greater variability (after correcting for the effect of mean levels on variability) than the first. Use of VIM as an index of variability may therefore help to overcome some of the difficulties associated with modelling correlated variables.

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Appendix Table 1. Percentage of variance in SBP at a single follow-up that is attributable to intra-individual visit-to-visit variation. The expected inter-individual group variance of SBP values at a single follow-up was estimated as the sum of the following variance components: inter-individual variance in mean SBP, intra-individual visit-to-visit variance in SBP and inter-individual variance in intra-individual visit-to-visit SBP. Observed levels of variance in SBP values at a single follow-up (taken as the average over the first 2 years of follow-up) is compared with expected levels in each of the cohorts based on the above model. The proportion of observed inter-individual group variance of SBP values at a single follow-up which could be attributed to intra-individual variability is estimated as the sum of the latter two variance components divided by the total variance. See reference 1 for details of cohorts.

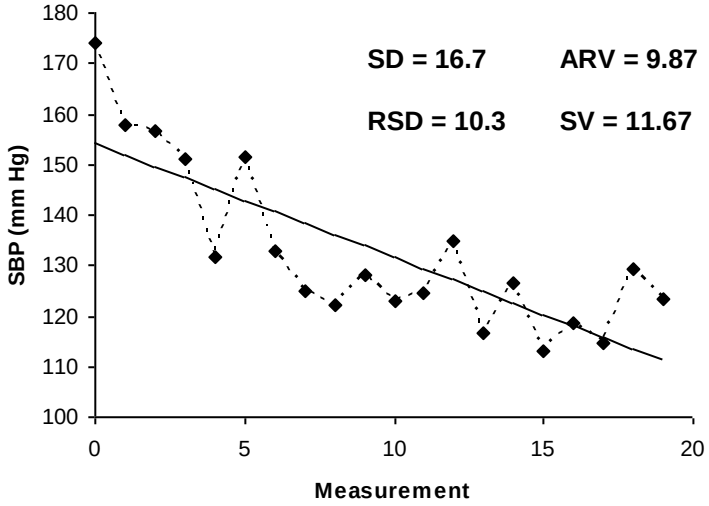
Measure	UK-TIA trial	ESPS-1	Dutch TIA trial	ASCOT trial Atenolol group	ASCOT trial Amlodipine group
Mean SBP	146.7	155.3	152.5	141.8	139.1
Inter-individual SD SBP	18.6	18.6	17.3	13.0	11.1
Mean intra-individual SD SBP	14.2	14.6	14.9	13.4	11.0
SD intra-individual SD SBP	6.6	6.8	6.4	5.8	4.8
Group SD (expected)	24.3	24.6	23.7	19.6	16.3
Group SD (observed)	23.3	22.9	22.8	19.1	15.7
% group variance attributable to intra-individual variation	41.5	42.9	46.8	55.8	53.8

Appendix Table 2. Measures of variability for a set of n BP measurements $x_1, x_2, ...x_n$

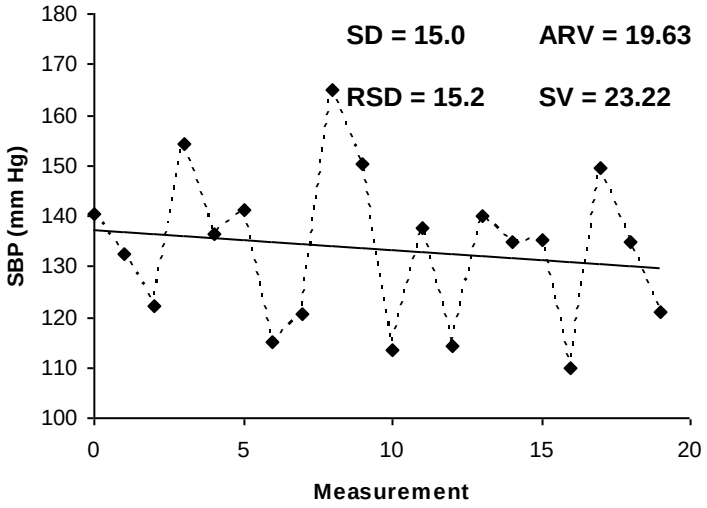
Measure		
Mean		$\bar{x} = \sum_{i=1}^{n} x_i / n$
SD	Standard deviation	$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{(n-1)}}$
CV	Coefficient of variation	100 x SD/ $\bar{x}$
VIM	Variation independent of mean	k x SD/ $\bar{x}^m$
RSD	Residual standard deviation ($\hat{x}_1, \hat{x}_2, ..., \hat{x}_n$ are the fitted values from a linear regression of BP against time)	$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \hat{x}_i)^2}{(n-2)}}$
ARV	Average real variability	$\frac{1}{n-1}\sum_{i=1}^{n-1}\lvert x_{i+1} - x_i \rvert$
SV	Successive variation	$\sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}(x_{i+1} - x_i)^2}$

Appendix Figure 1. Example of RSD vs SD in a) patient with significant linear trend and b) patient with no significant linear trend

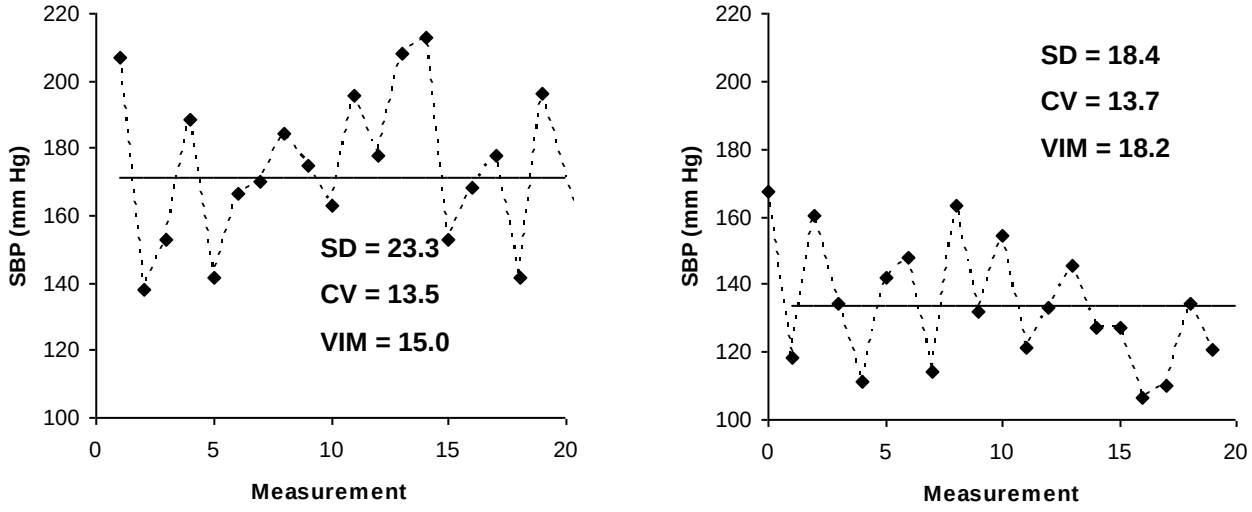
a)

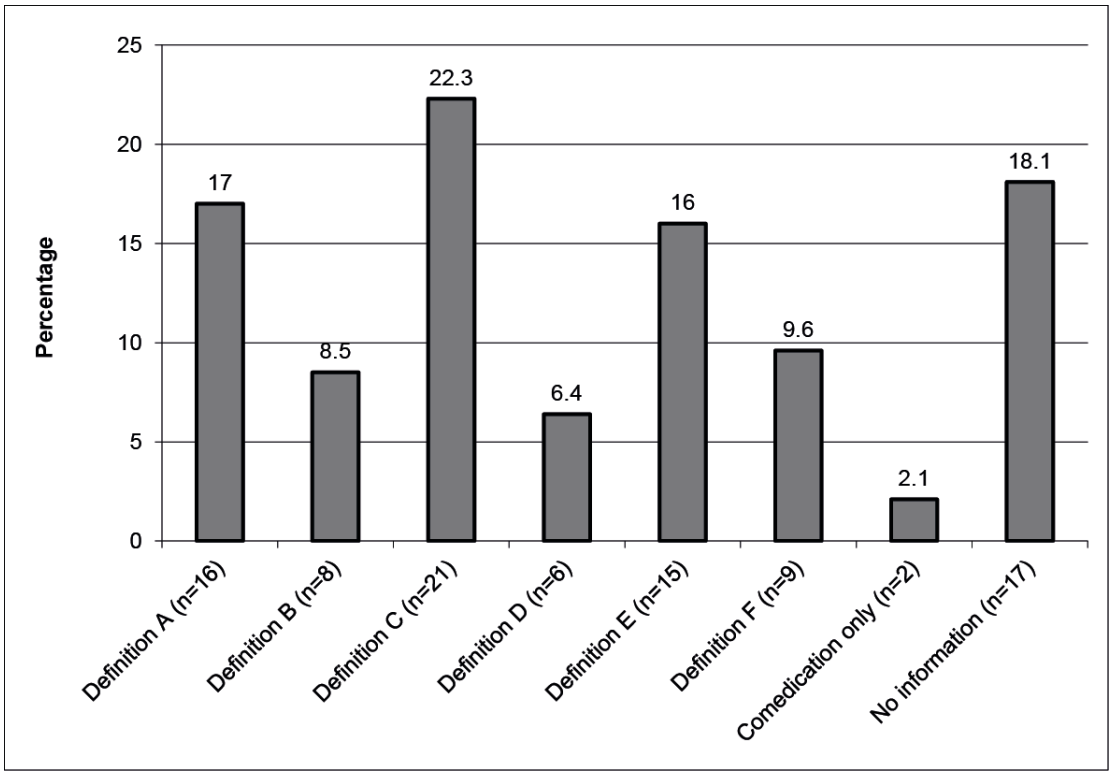


b)



Appendix Figure 2.





Appendix Figure 3. Reporting of medication during follow-up according to the different definitions in larger trials (see table 1b).