SUPPLEMENTARY MATERIAL

Investigating the stratified efficacy and safety of pharmacological blood pressure-lowering: An overall protocol for individual patient-level data meta-analyses of over 300,000 randomised participants in the new phase of the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC)

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***Supplementary table*** ***1.*** Search strategy to be used in MEDLINE, covering indexed entries between 01 Jan 1966 to 01 Jun 2018.

|  |
| --- |
| Search (((((( "Hypertension/drug effects"[Mesh] OR "Hypertension/drug therapy"[Mesh] ))) AND (( "Blood Pressure/drug effects"[Mesh] OR "Blood Pressure/therapy"[Mesh] ))) AND ( ( Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase III[ptyp] ) AND Humans[Mesh] AND adult[MeSH]))) AND ((((((((((("Antihypertensive Agents" [Pharmacological Action]) OR "Antihypertensive Agents/therapeutic use"[Mesh])) OR ((("Vasodilator Agents" [Pharmacological Action])) OR ( "Vasodilator Agents/therapeutic use"[Mesh] OR "Vasodilator Agents/therapy"[Mesh] ))) OR (("Adrenergic alpha-Antagonists/therapeutic use"[Mesh]) OR "Adrenergic alpha-Antagonists" [Pharmacological Action])) OR (("Adrenergic beta-Antagonists" [Pharmacological Action]) OR "Adrenergic beta-Antagonists/therapeutic use"[Mesh])) OR (("Sodium Chloride Symporter Inhibitors" [Pharmacological Action]) OR "Sodium Chloride Symporter Inhibitors/therapeutic use"[Mesh])) OR "Angiotensin-Converting Enzyme Inhibitors/therapeutic use"[Mesh]) OR (("Angiotensin II Type 1 Receptor Blockers" [Pharmacological Action]) OR "Angiotensin II Type 1 Receptor Blockers/therapeutic use"[Mesh])) OR (("Calcium Channel Blockers" [Pharmacological Action]) OR "Calcium Channel Blockers/therapeutic use"[Mesh])) AND ( ( Clinical Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase III[ptyp] ) AND Humans[Mesh] AND adult[MeSH])) Filters: Clinical Trial; Controlled Clinical Trial; Randomized Controlled Trial; Clinical Trial, Phase III; Meta-Analysis; Systematic Reviews; Humans; Adult: 19+ years |

***Supplementary table 2***. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist for the Blood Pressure Lowering Treatment Trialists' Collaboration protocol for individual patient-level data meta-analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Section and topic | Item No | Checklist item | | Location in the manuscript |
| ADMINISTRATIVE INFORMATION |  | |
| Title: |  |  | |  |
| Identification | 1a | Identify the report as a protocol of a systematic review | | Title page |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | | NA |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | | Page 5 |
| Authors: |  |  | |  |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | | Title page (email address in Supplementary material title page) |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | | Page 10 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | | NA |
| Support: |  |  | |  |
| Sources | 5a | Indicate sources of financial or other support for the review | | Page 10 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | | Page 10 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | | Page 10 |
| INTRODUCTION |  | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | | Page 3 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | | Page 4 |
| METHODS |  | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | | Pages 4 to 5 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | | Page 5 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | | Supplementary table 1 |
| Study records: |  |  | |  |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | | Page 5 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | | Pages 5 to 6 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | | Page 6 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | | Supplementary table 3 (Protocols for each meta-analysis will be developed and published which will include specific definitions of relevant variables) |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | | For each meta-analysiss (to address each specific objectives), specific protocol will be developed and published which will include a definition of the outcome of interest |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | | Page 6 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | | Pages 8 to 9 |
| 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall’s τ) | | Pages 8 to 9 (more detailed analytical plans will be described in separate protocols for each meta-analysis) |
| 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | | Pages 8 to 9 |
| 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | | NA |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | | Pages 6 and 9 (specific assessments will be described in the protocol for each planned meta-analysis) |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | | Page 9 |

Reference: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647.

***Supplementary table 3***. Blood pressure lowering randomized trials eligible for BPLTTC individual patient-level data meta-analysis.

|  |  |  |  |
| --- | --- | --- | --- |
| Study name or author | Publication year | Total N | Intervention/Comparisons |
| **AASK** (African American Study of Kidney Disease and Hypertension)1 | 2006 | 1094 | Intensive BP lowering, moderate BP lowering, ACEi, CCB and BB (factorial design) |
| **ABCD** (Appropriate Blood Pressure Control in Diabetes Trial)2 | 1998 | 1900 | BP lowering to different targets |
| **ACCOMPLISH** (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension)3 | 2008 | 11,506 | CCB + ACEi vs diuretic |
| **ACCORD** (Action to Control Cardiovascular Risk in Diabetes)4 | 2010 | 4733 | Intensive vs standard BP lowering |
| **ACTION** (A Coronary Disease Trial Investigating Outcome with Nifedipine GITS)5 | 2004 | 7665 | CCB vs placebo |
| **ACTIVE I** (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events)6 | 2011 | 9016 | AARB vs placebo |
| **ADVANCE** (Action in Diabetes and Vascular Disease)7 | 2007 | 11,140 | ACEi + diuretic vs placebo |
| **ALLHAT** (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attacks Trial)8 | 2002 | 42,418 | Diuretic vs CCB vs ACEi vs alpha-adrenergic blocker |
| **ALTITUDE** (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints)9 | 2012 | 8561 | Renin inhibitor vs placebo |
| **ANBP** (The Australian National Blood Pressure Study)10 | 1980 | 3427 | Diuretic ± alpha-adrenergic agonist/BB vs placebo |
| **ANBP2** (Second Australian National Blood Pressure Study)11 | 2003 | 6083 | ACEi vs diuretic |
| **APSIS** (Angina Prognosis Study in Stockholm)12 | 1996 | 809 | BB vs CCB |
| **ASCOT-BPLA** (Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm)13 | 2005 | 19,257 | BB vs CCB |
| **ATTEMPT-CVD** (A Trial of Telmisartan Prevention of Cardiovascular Diseases)14 | 2016 | 1228 | ARB vs non-ARB |
| **BBB** (Behandla Blodtryck Battre)15 | 1994 | 2127 | Intensive vs usual BP lowering |
| **BCAPS** (β-Blocker Cholesterol-Lowering Asymptomatic Plaque Study)16 | 2001 | 793 | BB vs placebo |
| **BENEDICT** (Bergamo Nephrologic Diabetes Complications Trial)17 | 2004 | 1808 | ACEi, CCB or combination vs placebo; ACEi vs CCB |
| **CAMELOT** (The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis)18 | 2004 | 3327 | CCB or ACEi vs placebo; CCB vs ACEi |
| **CAPPP** (Captopril Prevention Project)19 | 1999 | 10,985 | ACEi vs diuretic + BB |
| **Cardio-Sis** (CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica)20 | 2009 | 1111 | Tight vs usual BP lowering |
| **CASE-J** (Candesartan Antihypertensive Survival Evaluation in Japan)21 | 2008 | 4703 | ARB vs CCB |
| **CHIEF** (Chinese Hypertension Intervention Efficacy study)22 | 2012 | 13,080 | CCB + diuretic vs CCB + ARB |
| **COLM** (Combination of OLMesartan and calcium channel blocker or diuretic)23 | 2014 | 5141 | CCB + ARB vs diuretic + ARB |
| **CONVINCE** (Controlled Onset Verapamil Investigation of Cardiovascular End Points)24 | 2003 | 16,476 | CCB vs BB or diuretic |
| **Coope J**, et al25 | 1986 | 884 | BB ± diuretic |
| **COPE** (Combination Therapy of Hypertension to Prevent Cardiovascular Events)26 | 2011 | 6586 | BB + CCB vs ARB + CCB; ARB + CCB vs diuretic + CCB; BB + CCB vs diuretic + CCB |
| **DIABHYCAR** (Non-insulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril)27 | 2004 | 4912 | ACEi vs placebo |
| **DIME** (Diuretics in the Management of Essential hypertension study)28 | 2014 | 1130 | Diuretic vs non-diuretic |
| **DIRECT-Prevent 1** (Effect of candesartan on prevention)29 | 2008 | 1421 | ARB vs placebo |
| **DIRECT-Protect 1** (Effect of candesartan on progression)29 | 2008 | 1905 | ARB vs placebo |
| **DIRECT-Protect 2** (Effect of candesartan on progression and regression of retinopathy in type 2 diabetes)30 | 2011 | 1905 | ARB vs placebo |
| **DREAM** (Diabetes REduction Assessment with ramipril and rosiglitazone Medication)31 | 2006 | 5269 | ACEi vs placebo |
| **Dutch TIA Trial** (Dutch Transient Ischemic Attack Trial)32 | 1993 | 1473 | BB vs placebo |
| **E-COST** (Efficacy of Candesartan on Outcome in Saitama Trial)33 | 2005 | 2048 | ARB vs conventional drug (other than ACEi or ARB) |
| ELSA (Efficacy of Candesartan on Outcome in Saitama Trial)34 | 2002 | 2334 | BB vs CCB |
| **EUROPA** (European trial on reduction of cardiac events with perindopril in stable coronary artery)35 | 2003 | 12,218 | ACEi vs placebo |
| **EWPHE** (European Working Party on High Blood Pressure in the Elderly)36 | 1985 | 840 | Diuretic vs placebo |
| **FEVER** (Felodipine Event Reduction Study)37 | 2005 | 9711 | CCB + diuretic vs diuretic |
| **HAPPHY** (Heart Attack Primary Prevention in Hypertension Trial)38 | 1987 | 6569 | Diuretic vs BB |
| **HDFP** (Hypertension Detection and Follow Up Program)39 | 1979 | 10,940 | Intensive (stepped care) vs usual (referred care) BP lowering |
| **HIJ-CREATE** (Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Heart Disease)40 | 2009 | 2049 | ARB vs non-ARB |
| **HOMED-BP** (Hypertension Objective Treatment based on Measurement by Electrical Devices of Blood Pressure Study)41 | 2012 | 3518 | Tight BP control, usual BP control, ACEi, CCB and ARB (factorial design) |
| **HOPE** (Heart Outcomes Prevention Evaluation Study)42 | 2000 | 9297 | ACEi vs placebo |
| **HOPE-3** (Heart Outcomes Prevention Evaluation-3)43 | 2016 | 12,705 | ARB + diuretic vs placebo |
| **HOT** (Hypertension Optimal Treatment Study)44 | 1998 | 18,790 | DBP lowering to ≤80, ≤85 and ≤90 mmHg |
| **HYVET** (Hypertension in the Very Elderly Trial)45 | 2008 | 3845 | Diuretic vs placebo |
| **IDNT** (Irbesartan Diabetic Nephropathy Trial)46 | 2001 | 2861 | ARB or CCB vs placebo; ARB vs CCB |
| **INSIGHT** (International Nifedipine GITS Study: Intervention as a Goal for Hypertension Therapy)47 | 2000 | 6321 | CCB vs diuretic |
| **INVEST** (International Verapamil-Trandolapril Study)48 | 2003 | 22,576 | CCB vs BB |
| **IPPSH** (International Prospective Primary Prevention Study in Hypertension)49 | 1985 | 6357 | BB vs non-BB |
| **JATOS** (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients)50 | 2008 | 4418 | Strict vs mild BP lowering |
| **JMIC-B** (Japan Multicenter Investigation for Cardiovascular Diseases-B)51 | 2004 | 1650 | CCB vs ACEi |
| **LIFE** (Losartan Intervention for Endpoint Reduction in Hypertension Study)52 | 2002 | 9193 | ARB vs BB |
| **LIT** (Lopressor Intervention Trial)53 | 1987 | 2395 | BB vs placebo |
| **MIDAS** (Multicenter Isradipine Diuretic Atherosclerosis Study)54 | 1996 | 883 | CCB vs diuretic |
| **MOSES** (Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention)55 | 2005 | 1352 | ARB vs CCB |
| **MRC-1** (Medical Research Council Treatment of Mild Hypertension)56 | 1985 | 26,054 | Diuretic or BB vs placebo |
| **MRC-2** (Medical Research Council Treatment of Hypertension in Older Adults)57 | 1992 | 6579 | Diuretic or BB vs placebo; Diuretic vs BB |
| **Multicentre International Study**58 | 1975 | 3038 | BB vs placebo |
| **NAVIGATOR** (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)59 | 2010 | 9306 | ARB vs placebo |
| **NICOLE** (Nisoldipine in Coronary Artery Disease in Leuven Study)60 | 2001 | 819 | CCB vs placebo |
| **NICS-EH** (National Intervention Cooperative Study in Elderly Hypertensives)61 | 1999 | 414 | CCB vs diuretic |
| **NORDIL** (Nordic Diltiazem Study)62 | 2000 | 10,881 | CCB vs diuretic |
| **ONTARGET** (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial)63 | 2008 | 34,196 | ARB + ACEi vs ACEi; ARB vs ACEi |
| **OSCAR** (OlmeSartan and calcium antagonists randomized study)64 | 2012 | 1164 | ARB vs ARB + CCB |
| **The Oslo Study**65 | 1980 | 785 | Diuretic ± alpha-adrenergic agonist or BB vs placebo |
| **PART-2** (Prevention of Atherosclerosis with Ramipril Trial)66 | 2000 | 617 | ACEi vs placebo |
| **PATE-Hypertension** (The Practitioner’s Trial on the Efficacy of Antihypertensive Treatment in the Elderly with Hypertension)67 | 2000 | 1748 | ACEi vs CCB |
| **PATS** (Post-stroke Antihypertensive Treatment Study)68 | 2009 | 5665 | Diuretic vs placebo |
| **PEACE** (Prevention of Events with Angiotensin Converting Enzyme Inhibition)69 | 2004 | 8290 | ACEi vs placebo |
| **PHARAO** (Prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure)70 | 2008 | 1008 | ACEi vs placebo |
| **PREVEND IT** (Prevention of Renal and Vascular Endstage Disease)71 | 2004 | 864 | ACEi vs placebo |
| **PREVENT** (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial)72 | 2000 | 825 | CCB vs placebo |
| **PRoFESS** (Prevention Regimen For Effectively Avoiding Second Strokes)73 | 2008 | 20,332 | ARB vs placebo |
| **PROGRESS** (Perindopril Protection Against Recurrent Stroke Study)74 | 2001 | 6105 | ACEi ± diuretic vs placebo |
| **QUIET** (Quinapril Ischaemic Event Trial)75 | 2001 | 1750 | ACEi vs placebo |
| **RENAAL** (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study)76 | 2001 | 1513 | ARB vs placebo |
| **ROADMAP** (Randomized Olmesartan And Diabetes Microalbuminuria Prevention Study)77 | 2011 | 4447 | ARB vs placebo |
| **SCOPE** (Study on Cognition and Prognosis in the Elderly)78 | 2003 | 4937 | ARB vs placebo |
| **SHELL** (Systolic Hypertension in the Elderly Long-term Lacidipine Trial)79 | 2003 | 1882 | CCB vs diuretic |
| **SHEP** (Systolic Hypertension in the Elderly Program)80 | 1991 | 4736 | Diuretic ± BB vs placebo |
| **SPRINT** (Systolic Blood Pressure Intervention Trial)81 | 2015 | 9361 | Intensive vs standard BP lowering |
| **SPS3** (Secondary Prevention of Small Subcortical Strokes)82 | 2013 | 3020 | SBP lowering to <120 and <140 mmHg |
| **STONE** (Shanghai trial of nifedipine in the elderly)83 | 1996 | 1632 | CCB vs placebo |
| **STOP Hypertension** (Swedish Trial in Old Patients with Hypertension)84 | 1991 | 1627 | BB + diuretic vs placebo |
| **STOP Hypertension-2** (Swedish Trial in Old Patients with Hypertension-2)85 | 1999 | 13,228 | ACEi vs conventional drug; CCB vs conventional drug; ACEi vs CCB |
| **Sun M**, et al86 | 1997 | 2080 | CCB vs placebo |
| **Syst-China** (Systolic Hypertension in China)87 | 1988 | 2394 | CCB ± ACEi and/or diuretic vs placebo |
| **Syst-Eur** (Systolic Hypertension in Europe)88 | 1997 | 4695 | CCB ± ACEi and/or diuretic |
| **Taylor SH**, et al89 | 1982 | 1103 | BB vs placebo |
| **TEST** (Ternormin after stroke and TIA)90 | 1995 | 720 | BB vs placebo |
| **TOMHS** (Treatment of Mild Hypertension Study)91 | 1993 | 902 | Multi-drug class combination vs placebo |
| **TRANSCEND** (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease)92 | 2008 | 5926 | ARB vs placebo |
| **TROPHY** (Trial of Preventing Hypertension)93 | 2006 | 772 | ARB vs placebo |
| **UKPDS** (UK Prospective Diabetes Study)94 | 1998 | 1906 | Strict vs less strict BP lowering; ACEi vs BB |
| **VA NEPHRON-D** (Veterans Affairs Nephropathy in Diabetes)95 | 2013 | 1448 | ACEi + ARB vs ARB |
| **VALISH** (Valsartan in Elderly Isolated Systolic Hypertension Study)96 | 2010 | 3079 | Strict vs moderate BP lowering |
| **VALUE** (Valsartan Antihypertensive Long-Term Use Evaluation)97 | 2004 | 15,245 | ARB vs CCB |
| **VHAS** (Verapamil in Hypertension and Atherosclerosis Study)98 | 1997 | 1414 | Diuretic vs CCB |
| **Wei Y**, et al.99 | 2013 | 724 | Intensive vs standard BP lowering |

BPLTTC – Blood Pressure Lowering Treatment Trialists' Collaboration; ACEi – Angiotensin-converting enzyme inhibitor; ARB – Angiotensin receptor blocker; BB – Beta-blocker; CCB – Calcium channel blocker; BP – blood pressure; SBP – Systolic BP; DBP – Diastolic BP.

**Supplementary table 3 references:**

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***Supplementary table 4.*** Variables to be sought from participating trials.

|  |  |
| --- | --- |
| Data | Variables |
| Study level data | Region  Treatment/Comparison groups  Study period / Duration of follow-up  Randomisation method/Treatment allocation  Outcome ascertainment  Early stopping and reasons  Funding source |
| Participant level data | Baseline characteristics  Sex, age, ethnicity, lifestyle (e.g. smoking, alcohol intake), past medical history (e.g. diabetes, cardiovascular disease, chronic renal disease), drug treatment (e.g. hypertension, dyslipidaemia, cardiovascular disease) weight, height, systolic and diastolic blood pressure, blood and urine measurements (e.g. lipids, glucose homestasis, renal function)  Follow-up variables (after randomisation)  Outcomes and relevant dates (e.g. cardiovascular events, acute renal injury / renal replacement therapy, cancer, fractures, diabetes, retinopathy, neurodegenerative conditions, serious adverse events)  Vital status (and cause of death) on last follow-up  Clinical measures and relevant dates (e.g. weight, height, systolic and diastolic blood pressure, blood and urine measurements)  Changes in treatment (e.g. discontinuation) and date |