Cochrane Library

Cochrane Database of Systematic Reviews

Antihypertensive withdrawal for the prevention of cognitive decline (Protocol)

Jongstra S, Harrison JK, Quinn TJ, Richard E

Jongstra S, Harrison JK, Quinn TJ, Richard E.
Antihypertensive withdrawal for the prevention of cognitive decline.
Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD011971.
DOI: 10.1002/14651858.CD011971.

www.cochranelibrary.com

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Protocol]

Antihypertensive withdrawal for the prevention of cognitive decline

Susan Jongstra[1], Jennifer K Harrison[2], Terry J Quinn[3], Edo Richard[4]

[1]Department of Neurology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands. [2]Centre for Cognitive Ageing and Cognitive Epidemiology and the Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK. [3]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK. [4]Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands

Contact address: Terry J Quinn, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Walton Building, Glasgow Royal Infirmary, Glasgow, G4 0SF, UK. Terry.Quinn@glasgow.ac.uk.

Editorial group: Cochrane Dementia and Cognitive Improvement Group
Publication status and date: New, published in Issue 11, 2015.

Citation: Jongstra S, Harrison JK, Quinn TJ, Richard E. Antihypertensive withdrawal for the prevention of cognitive decline. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD011971. DOI: 10.1002/14651858.CD011971.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objective is to assess the effects of complete withdrawal of at least one antihypertensive medication on cognitive function in healthy and cognitive impaired adults.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Hypertension (blood pressure above a recommended value) is a common clinical condition with a well-established causal role in cardiovascular disease(Lewington 2002). Hypertension is particularly prevalent in older age; more than half of the population over the age of 50 years, and approximately 80% of the population older than 80 years have hypertension (Chow 2013; Cohen 2011). The protective effect of antihypertensive treatment against cardiovascular events and premature mortality is well established (Law 2009; Musini 2009). The evidence to support treatment of hypertension in healthy older adults is robust (Beckett 2012). Evidence for benefit of antihypertensive therapy in frail older adults with comorbidities and geriatric syndromes including cognitive and functional decline is limited, and some data suggest potential for harm, with studies describing association between antihypertensive therapy and higher mortality (Benetos 2015), and serious injuries arising from falls (Tinetti 2014).

The evidence for antihypertensive therapy in those with cognitive impairment or dementia, and the impact of this treatment on cognition is uncertain, with conflicting results in published data and no meta-analysis possible due to heterogeneity (Beishon 2014). Data have variously shown a protective, harmful or neutral effect of antihypertensives on cognition. A study with almost 5000 older adults, suggested no detrimental effect of antihypertensive treatment on cognitive function in people with existing cognitive problems (Skoog 2005). Two other large studies did not show a reduction of incident dementia in patients treated with antihypertensive medications (Di Bari 2001; Peters 2008). However, other work has suggested a protective effect of antihypertensive treatment on vascular induced dementia (Tzourio 2003), while another study reported potential for antihypertensive medication to accelerate cognitive decline (Alrawi 2013).

These seemingly conflicting trial data may be explained by the complex relationship between blood pressure and cognition over the life course. Hypertension in middle-age is a risk factor for incident dementia, driven at least in part by cerebrovascular disease (Norton 2014). However, the association between blood pressure and dementia at an older age is inverse (Kennelly 2009; Qiu 2009). Several years before dementia onset, a decrease in blood pressure can be seen (Skoog 1996), and low blood pressure is associated with cognitive decline in the years after diagnosis (Nilsson 2007), although the direction of causality is unknown. Several mechanisms have been proposed to underlie this decrease in blood pressure in the years before the diagnosis of dementia, including autonomic dysregulation as symptom of neurodegeneration (den Abeelen 2014). The arteriosclerotic and age-related changes to cerebral blood flow autoregulation in older people could also result in cerebral hypoperfusion, potentially influencing cognitive functioning (Qiu 2009).

Thus, the evidence base for cognitive benefits of hypertension treatment in midlife is compelling, but the evidence for cognitive effects of hypertension treatment in older age is less clear. The Cochrane systematic review on hypertension treatment in the elderly showed that adherence to treatment is limited and a considerable proportion of older patients discontinue treatment, due to adverse effects, in particular when the level of prescribed treatment increased (Musini 2009) . Taking all this into account, there is a concern that antihypertensive medication may have potential for harm in those with cognitive impairment/dementia and it may negatively influence cognitive functioning. There has been associated debate regarding the benefit of withdrawing antihypertensive therapy in older adults, since the risk-benefit ratio of treatment might be different at differing ages and with different classes of antihypertensive medications (Shah 2009).

It would be interesting for policymakers if withdrawal of hypertensive medications has a positive effect on cognitive functioning, since this might possibly lead to a decrease in dementia incidence and thus major health cost savings. Reducing medication use will also contribute to less healthcare expenditures.

The purpose of this systematic review is to summarise all available evidence on cognitive effects of withdrawal of antihypertensive medications and associated benefits and harms in adults (including healthy adults and those with prevalent cognitive decline).

Description of the condition

We will focus on the implications of antihypertensive medication on cognitive functioning, including cognitive decline and dementia. Cognitive decline is often accompanied by deterioration in emotional control, social behaviour, or motivation. The number of people living with cognitive impairment not classified as dementia is probably even higher, but no exact data on this exist. The term ‘dementia’ refers to a group of diseases which shares a syndrome that is typically chronic and progressive in nature. The dementia syndrome involves disturbances of multiple higher cortical functions, such as memory, thinking, orientation, perception and behaviour, which are severe enough to affect the ability to perform everyday activities. The number of people living with dementia is increasing due to the ageing world population. Currently, worldwide 47.5 million people are estimated to be affected. This number will double within the next 20 years, resulting in high costs and considerable burden to individuals and societies (WHO 2015).

Description of the intervention

In this review we will identify and appraise controlled clinical trials which evaluate the cognitive consequences of withdrawal of antihypertensive treatment in adults.

How the intervention might work

There are plausible theoretical reasons why withdrawal of antihypertensive therapy may have a beneficial effect on cognition, mostly relating to improving cerebral perfusion. Equally, withdrawal of antihypertensive therapy may accelerate cognitive decline through incident stroke or progression of small vessel disease.

Interventions to completely withdraw at least one antihypertensive medication in patients with and without cognitive problems may also reduce adverse effects and improve quality of life for the patient and carer. However, they may also cause withdrawal symptoms like “rebound” tachycardia with withdrawal of beta-blocker, headache, agitation and nausea (Karachalios 2005). We will therefore examine trials which evaluate effects of antihypertensive withdrawal, contributing to the evidence base in this area.

Why it is important to do this review

Contemporary guidelines for blood pressure management in older adults focus on indications for treatment and choice of treatment. There is ground to suspect that withdrawal of antihyperten-

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

sive medication in certain older adult populations may have beneficial effects on cognition and/or rate of dementia. A cost saving intervention (drug withdrawal) that impacts on cognition would have important individual and public health implications. A synthesis of all relevant data will move us closer to adopting evidence based interventions, or will identify the evidence gaps that require further original research. In general, studies that address the effect of withdrawal of drugs in (frail) older populations are highly relevant to prevent unnecessary and potentially harmful treatments.

OBJECTIVES

The objective is to assess the effects of complete withdrawal of at least one antihypertensive medication on cognitive function in healthy and cognitive impaired adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will select studies if they meet the following criteria: randomised controlled trials (RCTs) comparing withdrawal of antihypertensive medications with continuation of the medications. We will also include controlled clinical trials (CCTs) that meet other inclusion criteria. An outcome measure assessing cognitive function or dementia diagnosis must be clearly defined.

Types of participants

Participants must be aged 18 years and over. Participants must have been taking the antihypertensive medications for a minimum of one month irrespective of indication.

Participants may reside in any healthcare setting (including acute hospitals, nursing and residential homes and the community). We will include healthy participants and participants with all grades of severity of dementia or cognitive impairment.

Types of interventions

Withdrawal of any medication with blood pressure lowering effects (see list of relevant medications included in Appendix 1) with no restriction to duration of follow-up.

Types of outcome measures

Primary outcomes

- Cognitive impairment or rates of incident dementia in healthy and cognitive impaired adults
- Cognition in the short-term in adults with or without established cognitive impairment.

Cognitive function quantified with a recognised multidomain assessment instrument, for example (but not limited to) Folstein's Mini Mental State Examination (MMSE) (Folstein 1975), Montreal Cognitive Assessment (MoCA) (Nasreddine 2005), more extensive neuropsychological testing, or formal clinical diagnosis of dementia according to current internationally accepted guidelines, for example (but not limited to) International Classification of Diseases and Related Health Problems (ICD-10), Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

Secondary outcomes

- Effects on systolic and diastolic blood pressure.
- Adherence to withdrawal of the antihypertensive medications. We will define adherence to withdrawal as patients remaining off medication for the duration of the study or at least six months, whichever is longer.
- Rates of serious adverse events across the included studies. Including mortality, cardiovascular events, early (within first 8 weeks) and late (post-six months) adverse effects (e.g. falls and hospitalisation).

Search methods for identification of studies

We will use the electronic databases listed below to search for relevant studies regardless of language, personnel, research setting or date of publication.

Electronic searches

We will search ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialised register.

ALOIS is maintained by the Trials Search Co-ordinator for the CDCIG, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy older adult populations. The studies are identified through:

1. monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS;
2. monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the World Health Organization (WHO) portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
3. quarterly search of the Cochrane Central Register of Controlled Trials (CENTRAL); and
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see AboutALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement trials, can be viewed in the 'methods used in reviews' section within the editorial information about the Cochrane Dementia and Cognitive Improvement Group.

We will run additional searches in MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS, Web of Science core collection, ClinicalTrials.gov and the WHO Portal/ICTRP to ensure that the search is as comprehensive and as up-to-date as possible. The search strategy that we will use to retrieve reports of trials from MEDLINE (via the Ovid SP platform) can be seen in Appendix 2.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Searching other resources

In case of incomplete reports, we will conduct further searches for connected papers, or we will contact authors to retrieve missing information.

We will handsearch the reference lists of all of the relevant articles that we retrieve and search for non-MEDLINE listed journals. We will also search the Science Citation Index for articles citing key references. We will contact authors of relevant papers and relevant organisations to identify additional studies, including unpublished and ongoing studies. Finally, we will revise key original database search strategies based on the yield of the above searches and update for subsequent reviews.

Data collection and analysis

Selection of studies

Phase 1: Two review authors (SJ and JH) will perform searches and screening of identified studies independently. We will independently examine titles and abstracts of citations obtained from the searches and discard obviously irrelevant articles. At this stage, we will be overly inclusive; we will retrieve for further assessment of any article that suggests a relevant trial.

Phase 2: From the potentially relevant articles in Phase I, two review authors (SJ and JH) will independently select trials (based on the full-text format) for inclusion. We will resolve disagreement on study inclusion by consensus or third party adjudication.
We will detail the study selection process in a PRISMA flow diagram (Moher 2009).

Data extraction and management

Two independent review authors (SJ and JH) will perform data extraction using a prespecified data extraction form and enter the data into Review Manager software (RevMan 2014).

Assessment of risk of bias in included studies

At least two independent review authors (SJ and JH) will assess the internal validity of each included study. Where relevant details are unclear, we will ask for clarification and we will discuss discrepancies with a third reviewer (ER), if necessary. We will use the Cochrane 'Risk of bias' tool for assessment and we will use seven standard criteria: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; other risk of bias (Higgins 2011). We will assess every study for each of the seven criteria and report the information in a 'Risk of bias' table.

We will restrict the primary analysis to studies at low or unclear risk of bias. We will perform sensitivity analyses to determine how conclusions might be affected if studies at high risk of bias are added to the analysis.

Measures of treatment effect

In the first instance we will present a narrative description of studies and results; if data allow we will perform a meta-analysis to describe summary effects.

The meta-analysis will require the combination of data from trials that may not use the same rating scale or test to assess an outcome. The measure of the withdrawal of treatment difference for any outcome will be the weighted mean difference when the pooled trials use the same assessment instrument, and the standardised mean difference when different assessment instruments are used. For binary outcomes we will use the odds ratio (OR) to measure treatment effect and calculate a weighted estimate of the typical treatment effect across trials.

Unit of analysis issues

We will consider for each study whether groups of individuals were randomised together to the same intervention (i.e. cluster-randomised trials), whether individuals underwent more than one intervention (e.g. in a cross-over trial, or simultaneous treatment of multiple sites on each individual) or whether there are multiple observations for the same outcome (e.g. repeated measurements, recurring events).

Dealing with missing data

We will contact authors of studies if there are missing data crucial for the interpretation or the use in quantitative meta-analysis and we will report this. We will make a qualitative judgement as to whether to exclude studies if the impact of missing data is too large.

Assessment of heterogeneity

We will only perform a meta-analysis when studies are sufficiently homogeneous in terms of participants, interventions and outcomes. Statistical heterogeneity will be considered by using the I^2 test (Higgins 2011). We will consider heterogeneity of 30% to 60% as moderate, 50% to 90% as substantial and 75% to 100% as considerable. We will make a decision on the appropriateness of meta-analysis based on statistical and clinical heterogeneity.

Assessment of reporting biases

We will search for non-published as well as published studies in databases and trial registries, to avoid publication bias. To avoid language bias, we will not employ language restrictions for included studies. Where there are multiple publications from one study, we will only include the primary publication to address duplicate publication bias. To investigate the likelihood of overt publication bias, we will enter data from all identified trials into a funnel plot.

Data synthesis

We will decide on suitability of meta-analysis for each outcome by a qualitative assessment (including statistical and clinical heterogeneity) of the included studies.

We will conduct data synthesis and analyses using Review Manager software (RevMan 2014). We will use risk ratios (RRs) and a random-effects model to combine outcomes across trials for a meta-analysis. The weighting factor for each study is the inverse of the within-study variance plus a between-study variance component. If it is not possible to combine outcome data due to differences in the reporting or substantive heterogeneity, we will report a narrative summary.

Study duration of trials may vary. If the range of study duration is considered too large to pool all trials into one meta-analysis, we will divide the data into smaller time periods and conduct a separate meta-analysis for each period. Some trials may contribute da-

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ta to more than one time period if multiple assessments have been made.

Subgroup analysis and investigation of heterogeneity

If around 10 or more trials are identified that contribute to the analyses of primary outcomes, we aim to perform stratified analyses of the primary effectiveness outcome, according to the following trial characteristics: presence versus absence of dementia or cognitive impairment at baseline, age, type of antihypertensive treatment (thiazide diuretics, ACE inhibitors, etc.).

Data presentation - 'Summary of findings' tables

We will use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess the quality of the supporting evidence behind each estimate of treatment effect (Schunemann 2011a; Schunemann 2011b) . We will present key findings of the review including a summary of the amount of data, the magnitude of the effect size and the overall quality of the evidence, in a 'Summary of findings' table, created using GRADEproGDT software (GRADEproGDT 2015). We have preselected the following outcomes: cognitive impairment (1. incident dementia (clinical diagnosis) and 2. change in a validated cognitive test score); change in systolic and diastolic blood pressure; mortality; cardiovascular events; falls; hospitalisation and re-commencement of antihypertensive medications.

Sensitivity analysis

We will perform a sensitivity analysis for pooled results based on methodological quality if possible. Many issues suitable for a sensitivity analysis can only be identified during the review process when the individual peculiarities of studies under investigation are identified. We will perform sensitivity analyses without possibly included CCTs to look at the effect of these studies and to avoid risk of bias.

ACKNOWLEDGEMENTS

We would like to acknowledge the valuable input of Sue Marcus (Managing Editor, Cochrane Dementia and Cognitive Improvement Group (CDCIG)) and Anna Noel-Storr (Trials Search Co-ordinator, CDGIG).

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

Additional references

Alrawi 2013

Alrawi YA, Panerai RB, Myint PK, Potter JF. Pharmacological blood pressure lowering in the older hypertensive patients may lead to cognitive impairment by altering neurovascular coupling. *Medical Hypotheses* 2013;**80**(3):303-7.

Beckett 2012

Beckett N, Peters R, Tuomilehto J, Swift C, Sever P, Potter J, et al. HYVET Study Group. Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial. *BMJ (Clinical Research ed)* 2012;**344**:d7541.

Beishon 2014

Beishon LC, Harrison JK, Harwood RH, Robinson TG, Gladman JR, Conroy SP. The evidence for treating hypertension in older people with dementia: a systematic review. *Journal of Human Hypertension* 2014;**28**(5):283-7.

Benetos 2015

Benetos A, Labat C, Rossignol P, Fay R, Rolland Y, Valbusa F, et al. Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. JAMA Internal Medicine 2015; Vol. 175, issue 6:989-95.

Chow 2013

Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA* 2013;**310**(9):959-68.

Cohen 2011

Cohen DL, Townsend RR. Update on pathophysiology and treatment of hypertension in the elderly. *Current Hypertension Reports* 2011;**13**(5):330-7.

den Abeelen 2014

den Abeelen AS, Lagro J, van Beek AH, Claassen JA. Impaired cerebral autoregulation and vasomotor reactivity in sporadic Alzheimer's disease. *Current Alzheimer Research* 2014;**11**(1):11-7.

Di Bari 2001

Di Bari M, Pahor M, Franse LV, Shorr RI, Wan JY, Ferrucci L, et al. Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial. *American Journal of Epidemiology* 2001;**153**(1):72-8.

Folstein 1975

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;**12**(3):189-98.

GRADEproGDT 2015 [Computer program]

McMaster University (developed by Evidence Prime, Inc.). GRADEproGDT: GRADEpro Guideline Development Tool [www.guidelinedevelopment.org]. Hamilton: McMaster University (developed by Evidence Prime, Inc.), 2015.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Karachalios 2005

Karachalios GN, Charalabopoulos A, Papalimnenou V, Kiortsis D, Dimmicco P, Kostoula OK, et al. Withdrawal syndrome following cessation of antihypertensive drug therapy. *International Journal of Clinical Practice* 2005;**59**(5):562-70.

Kennelly 2009

Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. *Ageing Research Reviews* 2009;**8**(2):61-70.

Law 2009

Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ (Clinical Research ed)* 2009;**338**:b1665.

Lewington 2002

Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**(9349):1903-13.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *BMJ* 2009;**339**:2535.

Musini 2009

Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD000028.pub2]

Nasreddine 2005

Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;**53**(4):695-9.

Nilsson 2007

Nilsson SE, Read S, Berg S, Johansson B, Melander A, Lindblad U. Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older. *Aging Clinical and Experimental Research* 2007;**19**(1):41-7.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Norton 2014

Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurology* 2014;**13**(8):788-94.

Peters 2008

Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *The Lancet Neurology* 2008;**7**(8):683-9.

Qiu 2009

Qiu C, Winblad B, Fratiglioni L. Low diastolic pressure and risk of dementia in very old people: a longitudinal study. *Dementia and Geriatric Cognitive Disorders* 2009;**28**(3):213-9.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schunemann 2011a

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schunemann 2011b

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Shah 2009

Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. *American Journal of Geriatric Pharmacotherapy* 2009;**7**(5):250-61.

Skoog 1996

Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996;**347**(9009):1141-5.

Skoog 2005

Skoog I, Lithell H, Hansson L, Elmfeldt D, Hofman A, Olofsson B, et al. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). *American Journal of Hypertension* 2005;**18**(8):1052-9.

Tinetti 2014

Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA Internal Medicine* 2014;**174**(4):588-95.

Tzourio 2003

Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Archives of Internal Medicine* 2003;**163**(9):1069-75.

WHO 2015

World Health Organization. Dementia fact sheet No. 362. www.who.int/mediacentre/factsheets/fs362/en/ (accessed March 2015).

APPENDICES

Appendix 1. All medications with antihypertensive function (irrespective of indication)

Loop diuretics: bumetanide, ethacrynic acid, furosemide, torsemide

Thiazide diuretics: epitizide, hydrochlorothiazide and chlorothiazide, bendroflumethiazide, xipamide

Thiazide-like diuretics: indapamide, chlorthalidone, metolazone

Potassium-sparing diuretics: amiloride, triamterene

Dihydropyridines: amlodipine, cilnidipine, felodipine, isradipine, lercanidipine, levamlodipine, nicardipine, nifedipine, nimodipine, nitrendipine, barnidipine, lacidipine, aranidipine, azelnidipine, benidipine, clevidipine, darodipine, efonidipine, manidipine, niguldipine, nilvadipine, nisoldipine, nitrendipine, oxodipine, pranidipine

Non-dihydropyridines: diltiazem, verapamil

ACE-inhibitors: captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, benazepril, zofenopril, imidapril, cilazapril

Angiotensin II receptor antagonists: candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, azilsartan, fimasartan

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Beta blockers: atenolol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, propranolol, timolol, bisoprolol, acebutolol, celiprolol, esmolol, sotalol

Alpha blockers: doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, tolazolin, ketanserin, urapidil, fentolamin

Mixed Alpha + Beta blockers: carvedilol, labetalol

Vasodilators: hydralazine, minoxidil

Renin Inhibitors: aliskiren

Aldosterone receptor antagonists: eplerenone, spironolactone

Alpha-2 adrenergic receptor agonists: clonidine, guanabenz, guanfacine, methyldopa, moxonidine, guanethidine, mecamylamine

Other: magnesium sulfate

Appendix 2. MEDLINE search strategy

1 exp Antihypertensive Agents/

2 Hypertension/dt

3 antihypertensive*.ti,ab.

4 anti-hypertensive*.ti,ab.

5 exp Angiotensin-Converting Enzyme Inhibitors/

6 exp Angiotensin Receptor Antagonists/

7 angiotensin converting enzyme inhibitor*.ti,ab.

8 (ace adj2 inhibitor*).ti,ab.

9 (acei or ace-i).ti,ab.

10 Angiotensin II/ai [Antagonists & Inhibitors]

11 (angiotensin adj2 receptor antagonist*).ti,ab.

12 (angiotensin adj2 receptor block*).ti,ab.

13 AT 2 receptor block*.ti,ab.

14 AT 2 receptor antagon*.ti,ab.

15 (ARB or ARBs).tw.

16 exp Adrenergic beta-Antagonists/

17 exp Adrenergic alpha-Antagonists/

18 exp Diuretics/

19 adrenergic beta antagonist*.ti,ab.

20 adrenergic alpha antagonist*.ti,ab.

21 beta block*.ti,ab.

22 41. alpha block*.ti,ab.

23 diuretic*.ti,ab.

24 exp Calcium Channel Blockers/

25 calcium channel blocker*.ti,ab.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

26 (CCB or CCBs).ti,ab.

27 chlorothiazide.ti,ab.

28 Chlorothiazide/

29 chlorthalidone.ti,ab.

30 Chlorthalidone/

31 hydralazine.ti,ab.

32 Hydralazine/

33 hydrochlorothiazide.ti,ab.

34 Hydrochlorothiazide/

35 minoxidil.ti,ab.

36 Minoxidil/

37 captopril.ti,ab.

38 Captopril/

39 enalapril.ti,ab.

40 Enalapril/

41 fosinopril.ti,ab.

42 Fosinopri/

43 lisinopril.ti,ab.

44 Lisinopril/

45 ramipril.ti,ab.

46 Ramipril/

47 losartan.ti,ab.

48 Losartan/

49 irbesartan.ti,ab.

50 irbesartan /

51 candesartan.ti,ab.

52 eprosartan.ti,ab.

53 valsartan.ti,ab.

54 olmesartan.ti,ab.

55 telmisartan.ti,ab.

56 amlodipine.ti,ab.

57 diltiazem.ti,ab.

58 felodipine.ti,ab.

59 nicardipine.ti,ab.

60 nifedipine.ti,ab.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

61 nimodipine.ti,ab.

62 verapamil.ti,ab.

63 alprenolol.ti,ab.

64 atenolol.ti,ab.

65 metoprolol.ti,ab.

66 nadolol.ti,ab.

67 oxprenolol.ti,ab.

68 pindolol.ti,ab.

69 propranolol.ti,ab.

70 labetalol.ti,ab.

71 prazosin.ti,ab.

72 spironolactone.ti,ab.

73 triamterene.ti,ab.

74 bumetanide.ti,ab.

75 furosemide.ti,ab.

76 indapamide.ti,ab.

77 frusemide.ti,ab.

78 diazoxide.ti,ab.

79 eplerenone.ti,ab.

80 amiloride.ti,ab.

81 clonidine.ti,ab.

82 methyldopa.ti,ab.

83 isradipine.ti,ab.

84 xipamide.ti,ab.

85 barnidipine.ti,ab.

86 lacidipine.ti,ab.

87 aranidipine.ti,ab.

88 azelnidipine.ti,ab.

89 benidipine.ti,ab.

90 clevidipine.ti,ab.

91 darodipine.ti,ab.

92 efonidipine.ti,ab.

93 manidipine.ti,ab.

94 niguldipine.ti,ab.

95 nilvadipine.ti,ab.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

96 nisoldipine.ti,ab.

97 nitrendipine.ti,ab.

98 oxodipine.ti,ab.

99 pranidipine.ti,ab.

100 zofenopril.ti,ab.

101 imidapril.ti,ab.

102 cilazapril.ti,ab.

103 azilsartan.ti,ab.

104 fimasartan.ti,ab.

105 bisoprolol.ti,ab.

106 acebutolol.ti,ab.

107 celiprolol.ti,ab.

108 esmolol.ti,ab.

109 sotalol.ti,ab.

110 ketanserin.ti,ab.

111 urapidil.ti,ab.

112 fentolamin.ti,ab.

113 minoxidil.ti,ab.

114 magnesium sulphate.ti,ab.

115 or/1-114

116 withdraw*.mp.

117 cessat*.mp.

118 (reduce* OR reducing* OR reduct*).mp.

119 taper*.mp.

120 stop*.mp.

121 (“carr* on” OR continuation).mp.

122 (“come off” OR “taken off”).mp.

123 or/116-122

124 randomised controlled trial.pt.

125 controlled clinical trial.pt.

126 random*.ab.

127 placebo.ab.

128 drug therapy.fs.

129 trial.ab.

130 groups.ab.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

131 “double-blind*”.ti,ab.

132 “single-blind*”.ti,ab.

133 or/124-132

134 114 and 123 and 133

CONTRIBUTIONS OF AUTHORS

Susan Jongstra (SJ) prepared the protocol under the direction of Edo Richard (ER), Terence J Quinn (TQ) and Jennifer K Harrison (JH). SJ and JH will undertake the database searches and review the literature identified. ER will act as an independent co-reviewer.

DECLARATIONS OF INTEREST

SJ has no known conflicts of interest.
ER has no known conflicts of interest.
TQ has no known conflicts of interest.
JH is a named co-applicant on a UK National Institute for Health Research (NIHR) grant conducting a feasibility of antihypertensive withdrawal for people with dementia, jointly run by the University of Nottingham and the University of Leicester.

SOURCES OF SUPPORT

Internal sources

- Academic Medical Center, University of Amsterdam, Netherlands.
- Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK.
- Centre for Cognitive Ageing and Cognitive Epidemiology and The Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK.
- Alzheimers Scotland and The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, UK.

JKH is supported by a Clinical Research Fellowship funded by Alzheimers Scotland and The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/L501530/1). Funding from the Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC) is gratefully acknowledged.

External sources

- NIHR, UK.

This protocol was supported by the National Institute for Health Research, via a Cochrane Programme Grant to the Cochrane Dementia and Cognitive Improvement group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health

INDEX TERMS

Medical Subject Headings (MeSH)

*Antihypertensive Agents; *Withholding Treatment; Blood Pressure [physiology]; Cognition [drug effects]; Cognitive Dysfunction [*prevention & control]; Dementia [prevention & control]; Randomized Controlled Trials as Topic; Stroke; Time Factors

MeSH check words

Adult; Humans

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.