Antihypertensive withdrawal for the prevention of cognitive decline (Protocol)

Jongstra S, Harrison JK, Quinn TJ, Richard E


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Antihypertensive withdrawal for the prevention of cognitive decline (Protocol)

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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.
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 (Benots 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 (Skooog 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 (Skooog 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 Abell 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 middle-age 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 an 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 anti-hypertensive 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 antihypten-
sive medication in certain older adult populations may have benefi-
cial effects on cognition and/or rate of dementia. A cost saving in-
tervention (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 in-
terventions, or will identify the evidence gaps that require further
original research. In general, studies that address the effect of with-
drawal 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: random-
dised controlled trials (RCTs) comparing withdrawal of antihy-
pertensive medications with continuation of the medications. We
will also include controlled clinical trials (CCTs) that meet other in-
clusion 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 re-
striction 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 as-
seessment instrument, for example (but not limited to) Folstein’s Mi-
mini Mental State Examination (MMSE) (Folstein 1975), Montreal Cog-
nitive Assessment (MoCA) (Nasreddine 2005), more extensive neu-
rropsychological testing, or formal clinical diagnosis of dementia ac-
cording to current internationally accepted guidelines, for example
(but not limited to) International Classification of Diseases and Re-
lated 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 remain-
ing 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. Includ-
ing 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 rele-
vant 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 CD-
CIG, 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 infor-
mation 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 compre-
hensive 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.
In the first instance we will present a narrative description of study conclusions might be affected if studies at high risk of bias are added to the analysis. 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.

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 1, 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.

**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 I² 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-
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).
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

Beishon 2014

Benetos 2015

Chow 2013

Cohen 2011

den Abeelen 2014

Di Bari 2001

Folstein 1975

Folstein 2015

Referenced software

GRADEproGDT 2015 [Computer program]

Higgins 2011

Karachalios 2005

Kennelly 2009

Law 2009

Lewington 2002

Moher 2009

Musini 2009

Nasreddine 2005

Nilsson 2007
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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, lercanidine, levamlodipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, bamilodipine, lacidipine, aranidipine, azelnidipine, bendidine, clevidine, darodipine, efonidipine, manidipine, nifudipine, 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

Norton 2014

Peters 2008

Qiu 2009

RevMan 2014 [Computer program]

Schunemann 2011a

Schunemann 2011b

Shah 2009

Skoog 1996

Skoog 2005

Tinetti 2014

Tzourio 2003

WHO 2015

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.
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 Fosinopril/
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.
61 nimodipine\textit{.ti,ab.}
62 verapamil\textit{.ti,ab.}
63 alprenolol\textit{.ti,ab.}
64 atenolol\textit{.ti,ab.}
65 metoprolol\textit{.ti,ab.}
66 nadolol\textit{.ti,ab.}
67 oxprenolol\textit{.ti,ab.}
68 pindolol\textit{.ti,ab.}
69 propranolol\textit{.ti,ab.}
70 labetalol\textit{.ti,ab.}
71 prazosin\textit{.ti,ab.}
72 spironolactone\textit{.ti,ab.}
73 triamterene\textit{.ti,ab.}
74 bumetanide\textit{.ti,ab.}
75 furosemide\textit{.ti,ab.}
76 indapamide\textit{.ti,ab.}
77 frusemide\textit{.ti,ab.}
78 diazoxide\textit{.ti,ab.}
79 eplerenone\textit{.ti,ab.}
80 amiloride\textit{.ti,ab.}
81 clonidine\textit{.ti,ab.}
82 methyldopa\textit{.ti,ab.}
83 isradipine\textit{.ti,ab.}
84 xipamide\textit{.ti,ab.}
85 barnidipine\textit{.ti,ab.}
86 lacidipine\textit{.ti,ab.}
87 aranidipine\textit{.ti,ab.}
88 azelnidipine\textit{.ti,ab.}
89 benidipine\textit{.ti,ab.}
90 clevadipine\textit{.ti,ab.}
91 darodipine\textit{.ti,ab.}
92 efonidipine\textit{.ti,ab.}
93 manidipine\textit{.ti,ab.}
94 niguldipine\textit{.ti,ab.}
95 nilvadipine\textit{.ti,ab.}
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.
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.

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Internal sources

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External sources

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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