Preparatory review of studies of withdrawal of anti-hypertensive medication in older people

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Abstract

Introduction
Since 2012 we have undertaken a programme of research into the management of hypertension in people with dementia[1]. As part of this we are studying the feasibility of withdrawing antihypertensive drugs in people with dementia and well-controlled hypertension, with the aim of them remaining normotensive but avoiding some of the burdens and side-effects of antihypertensive medications. We decided to undertake a preliminary examination of the literature to examine the evidence and safety of antihypertensive withdrawal (not restricted to those with dementia) to determine whether this has already been extensively reviewed, to provide an approximate estimate of the likelihood of success of antihypertensive withdrawal, and to prepare for a systematic review of this literature if required and feasible.

Method
For this rapid review, we undertook a search for existing reviews and examined the relevant papers identified, and briefly updated the search once we found that the most recent review was in 2008.

Results
One appropriate review (from 2008) yielding seven relevant articles, and one further article were identified, giving eight articles which were examined. Seven of the eight were published more than ten years ago. Six of the eight studies had follow-up data for 1 year or longer. Successful long term (1 year or more) withdrawal of antihypertensive medication was reported in 20-52% of patients.

Conclusion
Our review indicates that 22-50% of patients whose blood pressures are currently adequately controlled might be able to withdraw medication without return of long term hypertension. The rapid review approach we took may have missed articles of relevance and so we propose that a systematic review of withdrawal is undertaken. Because much of the data will be old, it should seek data not only on the proportions of patients who remained normotensive at long term follow up using the standards of the day, but should seek data on findings relevant to current guidelines. Only data reporting long
term follow up (≥ 1 year) should be included. Data referring to old or discontinued medications should be distinguished.

**Introduction**

Our research group is undertaking a programme of research into the management of hypertension in people with dementia. We recognise that it is now widely accepted that advanced age alone is not a contra-indication to the treatment of hypertension. UK guidelines produced by the National Institute for Health and Care Excellence (NICE) for the management of hypertension and European guidelines for the management of arterial management of hypertension differ according to age (above and below 80) and the presence of diabetes[2 3]. The guidelines advise that co-pathology is taken into account in those aged over 80, but there is no specific guidance about how to amend treatment in the context of co-morbidity other than adjustment of pharmacotherapy in those with clinical features of symptomatic orthostatic hypotension. There is no specific guidance for the treatment of hypertension in people with dementia.

The management of hypertension in those with dementia is uncertain. Although hypertension increases the risk of dementia[4] it is still unclear if it affects dementia progression[5 6]: lowering blood pressure levels could protect against ischaemic damage but could also increase the risk of hypo-perfusion damage. There is very little evidence of treatment benefit in people with dementia[6] largely because such people were excluded from most trials of antihypertensive therapy. People with dementia may be at higher risk of the adverse effects of antihypertensive therapy[7].

Given this uncertainty, it may be helpful to ensure that all people with dementia given antihypertensive therapy actually need them to control their hypertension: if the drugs can be removed or reduced, the risks from them can be abolished or diminished. This might be possible because some patients may have been spuriously diagnosed with essential hypertension due to the “white coat” effect. There is also a tendency for blood pressure levels to fall with the development of dementia so some of those who were previously hypertensive may become normotensive over time[8].

For these reasons our research programme examined the feasibility of a large controlled study of the withdrawal of antihypertensive medication in people with dementia. As part of this work, we sought to determine from previous literature what proportion of people
with hypertension can successfully withdraw anti-hypertensive medication without return of hypertension. We undertook a preliminary examination of the literature to examine the evidence and safety of antihypertensive withdrawal (not restricted to those with dementia) to determine whether this has already been extensively reviewed, to provide an approximate estimate of the likelihood of success of antihypertensive withdrawal, and to prepare for a systematic review of this literature if required and feasible.

Method

Our initial rapid review approach was to conduct a “review of reviews” by searching for existing reviews – which saves the time taken to undertake primary searches – and to select and examine papers from those reviews. As the only suitable review we found was in 2007, reflecting practice of at least a decade ago, we briefly searched for more recent articles using the search strategy reported in the 2007 review.

The primary outcome measure for the review was the proportion of participants who could successfully withdraw their anti-hypertensive medications. Secondary outcomes included the definitions of normotension, safety of antihypertensive withdrawal, predictors of successful withdrawal and identification of clinical protocols used to withdrawn medications and monitor participants.

Identification and selection of reviews

The following databases were searched for reviews:

- Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid Medline (R) 1946 to April 2014
- PubMed
- Database of Abstracts on Reviews and Effectiveness
- Scopus
- Web of Science
- Cochrane Library

The following terms were combined: antihypertensive.mp or antihypertensive agents AND withdrawal.mp AND review.pt AND english.lg and applied to each database in turn. Figure 1 outlines the searching procedure employed and process of study selection.
The following criteria were used to select reviews for examination:

**Inclusion criteria**
- review articles that quantify the success or failure of specific antihypertensive drug withdrawal regimes
- including studies reporting on participants aged 65 years and older

Titles and abstracts of published reviews were reviewed by two reviewers. Consensus was reached on review studies to exclude: full-text articles of the reviews were sought when abstracts were unclear or absent. Quality assessment of retained review papers was then undertaken independently by the pair of reviewers using the Critical Appraisal Skills Programme (CASP) Checklist for Review Articles[9]. The CASP tool for systematic reviews consists of 10 questions, of which seven or eight (depending on whether or not there was a meta-analysis) can be scored 0/1/2, giving a maximum score per paper of 14-16 marks. We assigned a percentage rating to each review paper to allow for differences in the scoring system, and papers scoring above 50% that met the selection criteria were included in the present study.

**Selection of primary research articles from reviews papers**
Primary research articles were included where they presented data specific to our research question of interest. They had to report data specific to the older adult population, reporting on the rates of successful withdrawal. It was also necessary for them to report the effects of withdrawal of treatment for essential hypertension specifically, rather than just the effects of stopping these classes of medications prescribed for other reasons, e.g. ankle swelling, heart failure etc.

**Data extraction and analysis from included research articles**
Data were extracted to allow demographic characterisation of the recruited sample, including age and gender plus the healthcare setting where the study was performed. Data were then extracted for the pre-specified outcomes of interest. These were tabulated and a narrative synthesis performed.

**Results**
Figure 1 shows the search results and selection process. 23 reviews were identified, of which only eight were relevant and only one met our quality criteria, a review by Iyer and colleagues published in 2008[10].

Iyer et al. presented the results of 13 withdrawal studies, the full-texts of which were obtained for review. Four of the studies were randomised, double-blind, placebo-controlled studies which looked at the withdrawal of diuretics[11-14] and the remaining nine were prospective observational studies[15-23]. Six of the 13 withdrawal studies were not suitable for our purposes as they concerned withdrawal of diuretics prescribed for ankle oedema[12], exclusion of participants who were prescribed loop diuretics for hypertension [11] and a lack of included data on the successful withdrawal of medication for the treatment of essential hypertension[13 14 21 23].

As the retained review only searched the literature until 2007, we replicated Iyer et al.’s search strategy[10] for the period January 2007 – May 2014, to establish if any studies had been published since the review was published, combining the search terms: ‘withdrawal OR stop OR cessation OR discontinue AND anti-hypertensive’. We limited this search to studies conducted on human subjects including adults >65 years and excluded case reports.

This search resulted in 229 results in PubMed and 88 in Ovid MEDLINE (Figure 2). The titles were reviewed by two reviewers and two articles were retained and reviewed, Hajjar and van Duijn[24 25]. However, although van Duijn et al. included participants up to the age of 75, they did not present withdrawal results specifically for the older adult population and so it was excluded[25].

Thus, in total we examined eight primary research studies.

Study characteristics
The studies were published between 1983 and 2013. The studies reported upon a total of 7989 participants. The mean age of participants ranged from 71-75 years and all comprised a female-predominant population. Follow-up ranged from three weeks to five years, with a mean follow-up period of 1.6 years. Five of the studies were conducted as part of run-in or preparatory phases before the onset of a new clinical trial of antihypertensive medication [15 17 19 20 24]. The largest study Nelson (b) accounted for 86% of participants and followed-up participants for a median of four weeks[20].
The studies were conducted in a range of healthcare settings, recruiting from general practice, hospital inpatients, and outpatient clinics but not institutional care (care homes). Studies tended to recruit a highly selected study population, with one (Ekbom) necessitating that participants be healthy and independent[15] and another (Lernfelt) that they have no evidence of cardiovascular disease[17]. Study findings are summarised in Tables 1, 2 & 3.

**Successful anti-hypertensive withdrawal**

The proportions of participants who had anti-hypertensive medication successfully withdrawn are tabulated in Table 2, comparing the follow-up and definition of normotension applied in each study.

Two studies provided data on short term withdrawal only (Hajar, Nelson b). Despite such short follow-up, Nelson and colleagues (Nelson b) only found that 9.4% of patients remained with a blood pressure of 140/80 or less after a median of four weeks follow up.

The other six studies provide follow-up of at least one year and reported successful withdrawal of 27-52% of participants at one to three years, using criteria for success that varied from a systolic BP of 160 to 230.

In summary, successful long term (1-3 years) withdrawal of antihypertensive medication was reported in 27-52% of patients. A discrepant finding was Nelson b,[20] who showed only a 9-18% successful withdrawal rate (depending upon the cut off for success used) by four weeks: this was by far the largest study in our review.

**Safety of anti-hypertensive withdrawal**

The safety data relating to anti-hypertensive withdrawal was varied and summarised in Table 3. No standard approach to reporting safety data was identified across the included studies, and so we included any descriptive or quantitative data relating to adverse events. One study defined pre-specified end-points (e.g. myocardial infarction, stroke etc.)[18] but there were no such events; a second study defined serious adverse events, including myocardial infarction, angina and left ventricular failure and reported a 2.3% adverse event rate. The remaining studies which reported safety data simply present the total numbers of participants who either died or experienced an adverse event without reporting which intervention they received[17 19].
One study modelled the likelihood of adverse events and survival following antihypertensive withdrawal[15]. It reported that 22.2% of participants died in the study period. However, those who had withdrawn from medication were at lower risk of cardiovascular events and death than those who remained on them[15].

**Predictive factors for successful withdrawal**

Three of the studies reported that participants were more likely to have their antihypertensive therapy successfully withdrawn if they were on monotherapy[15 19 20]. Lower age was also identified as a predictor of more successful withdrawal in two of the studies with those aged 65-74 more successful than older participants[19 20]. A low baseline blood pressure was also a predictor of successful withdrawal[15].

One study identified that withdrawal of α- and β-blockers were associated with higher rates of withdrawal failure[20]. However, a second study identified more likelihood of successful withdrawal among male compared to female participants and identified male participants were most commonly prescribed β-blockers[18].

**Timing of return of hypertension**

The early return of hypertension was a common feature, with three studies reporting a higher rate of developing hypertension within the first few weeks/month compared to later follow-up progressed[15 16 19]. The most marked difference was found by Nelson (a) who reported 50% returned to hypertension in the first 70 days, compared to 11% from days 200-400[19].

**Use of clinical protocols**

Half of the studies explicitly stated their procedure for anti-hypertensive withdrawal, of which one specified this was done ‘gradually under supervision of a research nurse’[19] and one described ‘a wash-out over a three month period’[15]. The other two specified the precise regime for dose reduction[20 24] and one expressed a preference for holding the withdrawal of β-adrenoceptor blockers or diuretics until last if the patient is on multiple medications[20].

One study supplemented researcher-recorded blood pressure measurements with participant automated measurements twice daily[24]. This procedure appeared to be feasible and rate of BP diary recording was 74%[24]. Two studies required the agreement and active participation of the participant’s primary care physician in completion of the withdrawal programme[20 24] or in monitoring after withdrawal[16 19].
Discussion

Using this rapid review technique we found eight studies that reported on the success of antihypertensive drug withdrawal, six of which presented long term data. The studies we examined gave a mixed picture: long term studies showed a successful withdrawal rate of 27-52% yet a single but very large study showed short term success rates of 9-18%. We found no evidence that successful withdrawal of antihypertensive therapy was unsafe, and some evidence that successful withdrawal was more likely in those on fewer agents and lower baseline blood pressures. Several months of follow-up is required to determine whether withdrawal has been successful, as half of those who become hypertensive after withdrawal do so after 10 weeks.

There are considerable drawbacks to this rapid review technique, and we cannot claim that it will have identified all the potentially relevant information. We propose that a formal systematic review is undertaken given that no adequate and up to date one has yet been conducted. The experience gained from this rapid review can guide the development of the protocol for a systematic review and can be used to check the adequacy of any future search strategy. Most papers identified in this review reported on practice from more than 10 years ago. The fact that treatment thresholds were higher in the past than they are today should not affect the proportion of patients who can withdraw and so this fact alone does not invalidate the relevance of the findings to modern practice. However, older studies will have used different drugs and different methods for the determination of blood pressure than used currently (such as ambulatory BP measurements) and so the findings may not directly apply to current practice.

Given the limitations of the review and the uncertainty of the findings, we recommend that a formal systematic review is conducted. Widespread searching will be required, particularly looking at the preparatory phases of trials of newer antihypertensive agents. Data should be sought from such studies that define how blood pressure was measured, the agents in use, the actual follow up blood pressures over time, and precise definitions of successful withdrawal. Another approach that could shed light upon the degree to which antihypertensive medication can be withdrawn without the return of hypertension might be afforded by new primary studies of GP databases, since we are aware that many people withdraw antihypertensive treatment as part of clinical practice (for example due to poor compliance, decline of consent, or adverse drug reactions) –
although this would not represent the effects of a systematic programme of withdrawal of antihypertensive medications in the absence of a clinical indication.

From the perspective of our research programme into the management of hypertension in people with dementia, these observations remind us that a primary problem is that we are still not sure if the benefits of treating hypertension outweigh the risks in people with dementia. Given that it is unlikely that adequately powered placebo controlled trials of antihypertensive therapy in this group will be feasible, we recommend that further studies in this area seek to perform epidemiological studies using large databases of existing practice of to examine the relationships between patient and medication factors and adverse outcomes including death, and vascular events but also other events of importance to people with dementia such as falls and institutionalisation. Modelling studies, informed by information from epidemiological studies might be able to identify clinical subgroups in which the risks of treatment offset or outweigh its benefits. Given the uncertainty of the benefit to risk ratio, it will also be useful to continue to work on means of reducing the risks of antihypertensive therapy and identifying those at high risk of an adverse drug reaction, for example by using ambulatory or home blood pressure monitoring to detect excessive blood pressure variability, or episodes of significant hypotension.

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**Competing interests**

None of the authors have any conflicts of interest that might bias this work.
Figure 1 Summary of search and selection process

554 records identified through database searching
OVID Medline = 97
PubMed = 292
DARE = 3
Scopus = 149
Web of science = 13
Cochrane Library = 0

556 records screened

2 additional records identified through other sources

533 records excluded

15 full text reviews excluded
13 - described symptoms of drug withdrawal
1 - did not report success/failure of withdrawal regimes
1 - diuretic withdrawal review for indications not limited to essential hypertension

23 full-text review articles assessed for eligibility

8 review articles underwent quality assessment

7 review articles excluded due to insufficient quality

1 review article included
(Reported 7 relevant included studies of anti-hypertensive withdrawal)
Figure 2 Update search

229 records from PubMed

88 records from Ovid Medline

317 records screened

305 excluded on basis of title alone

10 abstracts excluded
[Duplicate entries, not about antihypertensive withdrawal, discussion of cardiovascular risk, analysis of reasons for patient discontinuation of antihypertensive medications]

12 abstracts obtained and read

2 full-text articles read

1 excluded due to lack of data specific to population >65 years

1 full-text article added to review
Table 1 Antihypertensive withdrawal study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Country</th>
<th>Healthcare Setting</th>
<th>Study Design</th>
<th>Number of Participants Withdrawal Attempted</th>
<th>Other Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekbom[15]</td>
<td>1994</td>
<td>Sweden</td>
<td>Community</td>
<td>Prospective observational cohort</td>
<td>333</td>
<td>Mean age 75.2 years; 68% female &lt;br&gt; Participants recruited were relatively healthy and independent</td>
</tr>
<tr>
<td>Hajjar[24]</td>
<td>2013</td>
<td>USA</td>
<td>Community</td>
<td>‘Taper phase’ of randomised controlled trial (before randomisation)</td>
<td>53</td>
<td>Mean age 71 years; 64% female</td>
</tr>
<tr>
<td>Hansen[16]</td>
<td>1983</td>
<td>Denmark</td>
<td>Inpatients &amp; outpatients</td>
<td>Prospective observational cohort</td>
<td>105</td>
<td>Mean age 75 years &lt;br&gt; No gender data presented for cohort</td>
</tr>
<tr>
<td>Lernfelt[17]</td>
<td>1990</td>
<td>Sweden</td>
<td>Community</td>
<td>Prospective observational cohort</td>
<td>25</td>
<td>All aged &gt;70 years; 60% female &lt;br&gt; Treatment for 4-30 years (mean 11.6)</td>
</tr>
<tr>
<td>Nadal[18]</td>
<td>1994</td>
<td>Sweden</td>
<td>Outpatients</td>
<td>Prospective observational cohort</td>
<td>86</td>
<td>Mean age 74 years; 62% female &lt;br&gt; Treatment for 3-36 years (mean 20) &lt;br&gt; BP at start of follow-up SBP160 +/-3 in males, 169 +/-3 in females. DBP 91 +/-1</td>
</tr>
<tr>
<td>Nelson (a)[19]</td>
<td>2002</td>
<td>Australia</td>
<td>General practice</td>
<td>Prospective observational cohort</td>
<td>503</td>
<td>Median age 71 years; 83% female</td>
</tr>
<tr>
<td>Nelson (b)[20]</td>
<td>2003</td>
<td>Australia</td>
<td>General practice</td>
<td>Prospective observational cohort</td>
<td>6833</td>
<td>Mean 71.9 years; 56% female &lt;br&gt; Mean SBP 146.7 DBP 80.6</td>
</tr>
<tr>
<td>van Kraaij[22]</td>
<td>1997</td>
<td>The Netherlands</td>
<td>Inpatients &amp; outpatients</td>
<td>Retrospective analysis of case records and 1-year follow-up</td>
<td>51</td>
<td>Withdrawal in 218 participants of whom 72% female, all over 75 years of age &lt;br&gt; 51 of 218 withdrawn for hypertension</td>
</tr>
</tbody>
</table>

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Table 2 Successful withdrawal by follow-up and BP criteria

<table>
<thead>
<tr>
<th>Study Name &amp; Date</th>
<th>Proportion withdrawn successfully</th>
<th>Time of follow-up</th>
<th>BP Criteria Used</th>
<th>Mean End of Study BP (Off-AHT Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekbom 1994[15]</td>
<td>40% / 20%</td>
<td>1 year / 5 years</td>
<td>SBP 180-230 with DBP of at least 90 OR DBP 105-120 on three occasions</td>
<td>169/88</td>
</tr>
<tr>
<td>Hajjar 2013[24]</td>
<td>100%</td>
<td>3-4 weeks</td>
<td>&gt;180/100 on two occasions</td>
<td>Up by 12/6</td>
</tr>
<tr>
<td>Hansen 1983[16]</td>
<td>41%</td>
<td>1 year</td>
<td>DBP ≥110</td>
<td>160/90</td>
</tr>
<tr>
<td>Lernfelt 1990[17]</td>
<td>32%</td>
<td>2 years</td>
<td>SBP ≥200 OR DBP ≥105</td>
<td>Up by 23.8/9.6</td>
</tr>
<tr>
<td>Nadal 1994[18]</td>
<td>60%</td>
<td>1 month / 3 years</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>27% (of those withdrawn successfully at 1 month)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson (a) 2002[19]</td>
<td>36%</td>
<td>1 year</td>
<td>SBP ≥160 OR DBP ≥90 where SBP ≥140</td>
<td>SBP &lt;160 and DBP &lt;90</td>
</tr>
<tr>
<td>Nelson (b) 2003[20]</td>
<td>18% (Using 160/90mmHg) / 9.4% (Using 140/90mmHg)</td>
<td>Median 4 weeks (Range: 0-76)</td>
<td>SBP ≥160 OR DBP ≥90 where SBP ≥140</td>
<td>Not reported</td>
</tr>
<tr>
<td>van Kraaij 1997[22]</td>
<td>52%</td>
<td>1 year</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Table 3 Further results of withdrawal studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Safety</th>
<th>Drugs</th>
<th>Timing of Return of Hypertension</th>
<th>Withdrawal Protocol</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekbom[15]</td>
<td>74/333 (22.2%) died during study period</td>
<td>Monotherapy associated with successful withdrawal</td>
<td>10% restarted medication within the first month</td>
<td>Wash-out of medications over a 3-month period</td>
<td>Successful withdrawal associated with blood pressure before withdrawal</td>
</tr>
<tr>
<td></td>
<td>Lower rate of cardiovascular events in those without treatment</td>
<td></td>
<td>60% restarted medication within the first year</td>
<td>Exclusion criteria/failure if supine SBP on 3 separate occasions was 180-230mmHg with a DBP of at least 50 OR if DBP was between 105-120mmHg</td>
<td>Cohort of participants recruited for STOP Hypertension study</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hajjar[24]</td>
<td>No participants experienced headaches, dizziness, visual changes or focal weakness</td>
<td>No specific class effects identified</td>
<td>No data provided</td>
<td>Dose reduction and cessation over 3 weeks</td>
<td>Preparation for participation in The Antihypertensives and Vascular, Endothelial and Cognitive Function Trial AVEC</td>
</tr>
<tr>
<td></td>
<td>Mean BP increase 12/6mmHg in 4 weeks</td>
<td></td>
<td></td>
<td>Week 1: reduction 25-50%, Week 2: reduction 50-75%, Week 3: off all medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2% of readings exceeded 180/100mmHg</td>
<td></td>
<td></td>
<td>Participants completed automated home BP monitoring</td>
<td></td>
</tr>
<tr>
<td>Hansen[16]</td>
<td>No safety data reported</td>
<td>No specific class effects identified</td>
<td>Most developed hypertension within 3 weeks of withdrawal</td>
<td>Protocol not described</td>
<td>Target used was DBP of &lt;110mmHg</td>
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<tr>
<td>Lernfelt[17]</td>
<td>One death at 2 months due to MI; one episode of AF and heart failure at 4 months</td>
<td>Majority of participants prescribed ACE-i or diuretics</td>
<td>Three developed significant hypertension within 6 months of withdrawal</td>
<td>Protocol not described</td>
<td>Conducted as part of longitudinal population study of ‘70-year-old people in Gothenburg, Sweden’ Only withdrew from those with ‘no signs of cardiovascular disease’</td>
</tr>
<tr>
<td>Nadal[18]</td>
<td>No primary endpoints (MI, stroke or heart failure) occurred during study</td>
<td>Most males were prescribed β-blockers, females were prescribed β-blockers and diuretics</td>
<td>No data provided</td>
<td>In first month BP was checked fortnightly Monthly over following three months and twice yearly thereafter No drug withdrawal protocol provided</td>
<td>More males remained normotensive than females (62 vs. 11%)</td>
</tr>
<tr>
<td>Nelson (a)[19]</td>
<td>Four participants died (two with vascular events)</td>
<td>Single drug treatment associated with more successful withdrawal</td>
<td>Most returned to hypertension within the first 100 days</td>
<td>Treatment ‘gradually withdrawn under supervision of a research nurse’. Seen weekly during withdrawal until a minimum of two weeks after cessation of all medications Normotension: sitting SBP &lt;160mmHg and DBP &lt;90mmHg Medications re-initiated by participant’s own GP</td>
<td>Participants drawn from those volunteers who participate in the second Australian National Blood Pressure Study Those aged 65-74 were more likely to remain normotensive than those 75-84yrs</td>
</tr>
<tr>
<td>Nelson (b)[20]</td>
<td>2.3% of participants experienced a serious adverse event. 2.5% of normotensive group vs. 1.5% who became hypertensive vs. 9.6% who exited during withdrawal</td>
<td>Monotherapy associated with successful withdrawal</td>
<td>No data provided</td>
<td>Family physicians given guidance Stepwise withdrawal (i.e. one drug at a time, half doses at weekly intervals to the lowest usual therapeutic dose then cease and withdrawal of β-adrenoceptor blockers or diuretics last if patient on more than one medication)</td>
<td>Run-in phase of Second Australian National Blood Pressure Study Definition of hypertension revised to modern cut-point of 140 latterly and data presented for both</td>
</tr>
<tr>
<td>van Kraaij[22]</td>
<td>Data not specific for AHT withdrawal</td>
<td>Data not specific for AHT withdrawal</td>
<td>Protocol not described</td>
<td>101/218 (46%) indication for diuretic therapy was unclear</td>
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<tr>
<td></td>
<td>Study nurse monitored BP at weekly intervals</td>
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<tr>
<td></td>
<td>Hypertension defined ≥160mmHg systolic or ≥90mmHg diastolic (if SBP ≥140mmHg).</td>
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<tr>
<td></td>
<td>Younger participants more likely to remain normotensive</td>
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</table>
References