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

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East Midlands Research into Ageing Network (EMRAN) is a research collaboration across the East Midlands to facilitate collaborative applied clinical research into ageing and the care of older people. EMRAN was set up with support from NIHR CLAHRC East Midlands.

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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 anti-hypertensive 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 anti-hypertensive 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 anti-hypertensive 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 anti-hypertensive 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

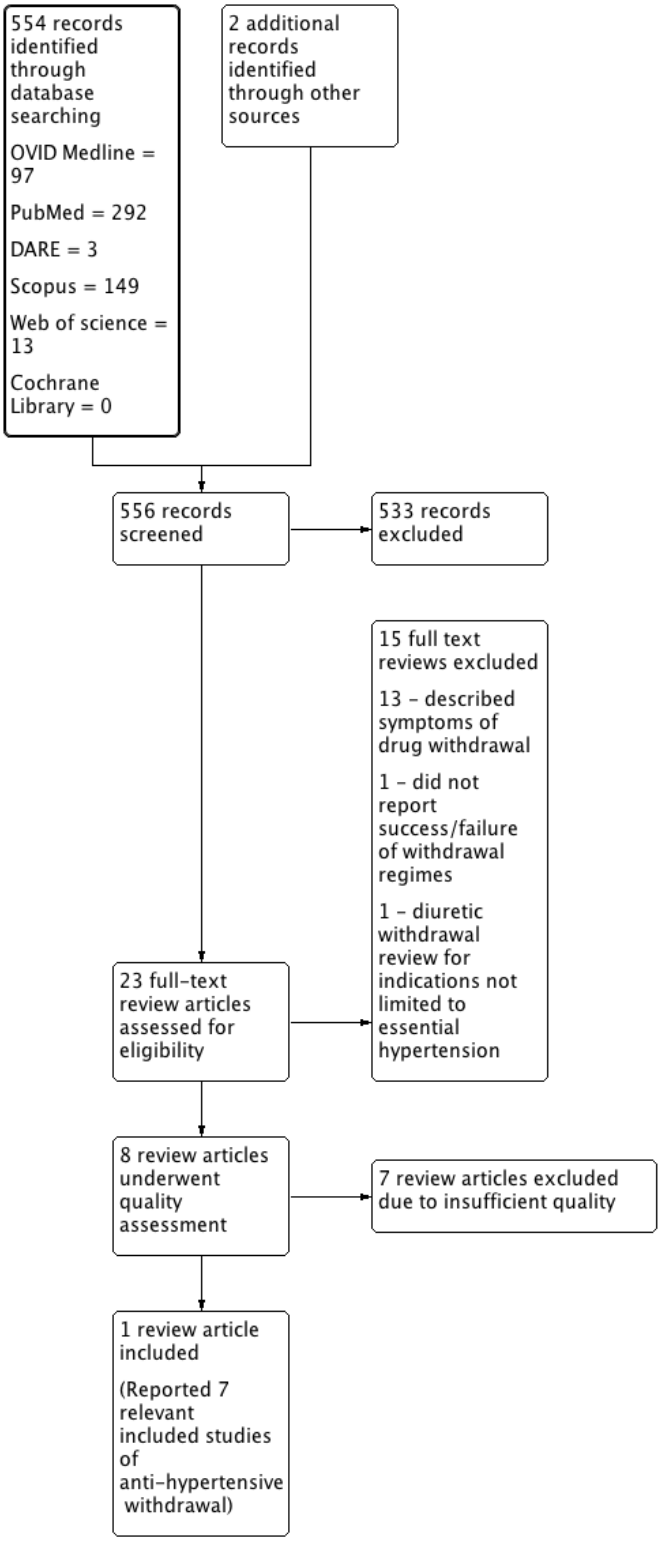

Figure 2 Update search

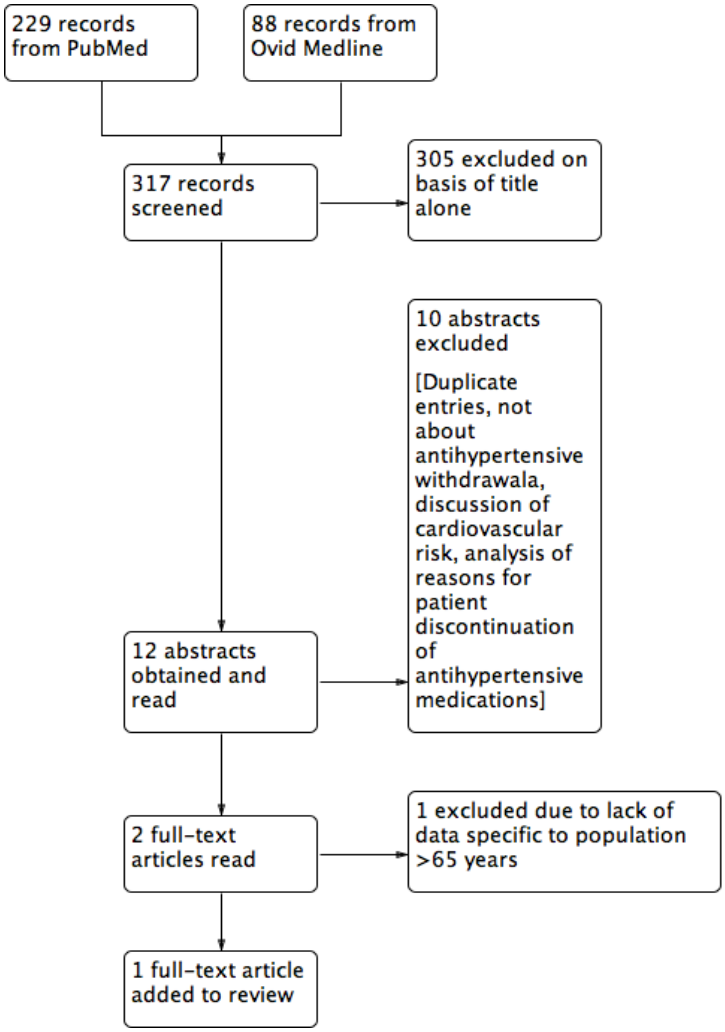

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Table 1 Antihypertensive withdrawal study characteristics

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

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Table 2 Successful withdrawal by follow-up and BP criteria

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

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Table 3 Further results of withdrawal studies

Study	Safety	Drugs	Timing of Return of Hypertension	Withdrawal Protocol	Other Comments
Ekbom[15]	74/333 (22.2%) died during study period Lower rate of cardiovascular events in those without treatment	Monotherapy associated with successful withdrawal	10% restarted medication within the first month 60% restarted medication within the first year	Wash-out of medications over a 3-month period Exclusion criteria/failure if supine SBP on 3 separate occasions was 180-230mmHg with a DBP of at least 90 OR if DBP was between 105-120mmHg	Successful withdrawal associated wit blood pressure before withdrawal Cohort of participants recruited for S Hypertension study
Hajjar[24]	No participants experienced headaches, dizziness, visual changes or focal weakness Mean BP increase 12/6mmHg in 4 weeks 2% of readings exceeded 180/100mmHg	No specific class effects identified	No data provided	Dose reduction and cessation over 3 weeks Week 1: reduction 25-50%, Week 2: reduction 50-75%, Week 3: off all medications Participants completed automated home BP monitoring	Preparation for participation in The Antihypertensives and Vascular, End and Cognitive Function Trial AVEC)
Hansen[16]	No safety data reported	No specific class effects identified	Most developed hypertension within 3 weeks of withdrawal	Protocol not described	Target used was DBP of <110mmHg
Lernfelt[17]	One death at 2 months due to MI; one episode of AF and heart failure at 4 months	Majority of participants prescribed ACE-i or diuretics No specific class effects identified as predictors	Three developed significant hypertension within 6 months of withdrawal	Protocol not described	Conducted as part of longitudinal po study of '70-year-old people in Goth Sweden' Only withdrew from those with 'no s cardiovascular disease'
Nadal[18]	No primary endpoints (MI, stroke or heart failure) occurred during study	Most males were prescribed β-blockers, females were prescribed β-blockers and diuretics	No data provided	In first month BP was checked fortnightly Monthly over following three months and twice yearly thereafter No drug withdrawal protocol provided	More males remained normotensive females (62 vs. 11%)
Nelson (a)[19]	Four participants died (two with vascular events)	Single drug treatment associated with more successful withdrawal	Most returned to hypertension within the first 100 days	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 <160mmHg and DBP <90mmHg Medications re-initiated by participant's own GP	Participants drawn from those volun participate in the second Australian N Blood Pressure Study Those aged 65-74 were more likely t normotensive than those 75-84yrs
Nelson (b)[20]	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	Monotherapy associated with successful withdrawal Use of β or α blockers associated with failure	No data provided	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)	Run-in phase of Second Australian Na Blood Pressure Study Definition of hypertension revised to modern cut-point of 140 latterly and presented for both

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		to withdraw		Study nurse monitored BP at weekly intervals Hypertension defined ≥160mmHg systolic or ≥90mmHg diastolic (if SBP ≥140mmHg).	Younger participants more likely to r normotensive
van Kraaij[22]	Data not specific for AHT withdrawal	Data not specific for AHT withdrawal	Data not specific for AHT withdrawal	Protocol not described	101/218 (46%) indication for diuretic was unclear

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