- 1 Abstract
- 2 Objectives
- 3 To describe the treatment of hypertension in people with dementia and collate evidence on
- 4 adverse health events whilst on treatment.
- 5 Design
- 6 A multi-centre prospective observational cohort study.
- 7 Setting and Participants
- 8 People with documented diagnoses of hypertension and dementia were recruited through
- 9 memory clinics and general practice from eight sites in the UK.
- 10 Methods
- 11 The cohort was recruited between July 2013 and October 2014. Participants underwent
- 12 face-to-face, standardised assessment of blood pressure (BP), activities of daily living,
- 13 cognitive function, and medication use. Follow up was by monthly telephone interview for 6
- 14 months to collate data on adverse health events.
- 15 Results
- 16 181 participants were recruited and 177 followed-up. 126 (70%) were female, mean age was
- 17 82 (SD6.3) years, median Mini Mental State Examination score 23 (IQR18-26) and mean BP
- 18 141/78 (SD22/12) mmHg. Antihypertensive drugs were prescribed in 157 (87%). Participants
- 19 were prescribed a median of 1 (IQR1-2) antihypertensive medication. ACE-inhibitors and/or
- 20 Angiotensin Receptor Blockers were the most frequently prescribed antihypertensives in
- 21 63% of participants. Target BP was achieved in 58% (95% CI49% 64%). Increasing
- 22 number of antihypertensives was not associated with lower systolic or diastolic BP, or with a
- higher proportion of patients attaining target BP. Participants had 214 falls, three had a
- 24 fracture, three developed symptomatic heart failure, four had cerebrovascular events and
- 25 eight died.
- 26 Conclusions and Implications
- 27 In this population of people with mild dementia, participants were treated with standard
- 28 antihypertensive medications in a similar proportion to the general population, with a similar
- 29 proportion achieving target BP. The rate of adverse health events was higher than in
- 30 randomised controlled trials of antihypertensives and raises reservations about the

- 31 assumptions underpinning antihypertensive treatment in people with dementia. These
- 32 findings may help inform clinical decision making.

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55 Introduction

56 International policies and guidelines stress the importance of the detection and treatment of 57 hypertension, which is the most important cardiovascular risk factor with the greatest impact 58 on mortality¹⁻³. High blood pressure is common amongst older adults. A reported 56.1% of 59 community dwelling older people and 43.7% of care home residents have hypertension⁴. 60 Prevalence increases with age⁵ and approximately 80% of those aged over 80 are 61 hypertensive⁶. Multiple large scale randomised controlled trials, such as the Hypertension in 62 the Very Elderly Trial (HYVET), have demonstrated health benefits from medications that 63 lower blood pressure^{5,7} and increasingly guidelines are advocating lower and lower target

64 blood pressures even amongst the oldest old⁸⁻¹⁰.

65 Current guidance on hypertension advises that co-pathology should be taken into account 66 when treatment decisions are made¹. People with dementia were not included in the large 67 scale Randomised Controlled Trials (RCTs) of antihypertensives. At present, there are no 68 condition-specific recommendations for treating hypertension in people with dementia and 69 the benefits of treatment are assumed to apply. Observational evidence, however, has 70 suggested the benefits of blood pressure lowering may be attenuated by co-existing 71 cognitive impairment. A cohort study of 1587 people over 75 years found higher systolic 72 blood pressure to be associated with reduced mortality in people with cognitive and 73 functional impairment¹¹. The PARTAGE group found an association between increased 74 mortality and a systolic BP below 130mmHg in care home residents taking two or more 75 antihypertensives¹². The Leiden 85+ study found an association between cognitive decline 76 and low blood pressure in patients taking antihypertensives¹³; a finding replicated by 77 Mossello and colleagues¹⁴.

It is clear from the above that generic guidelines for management of hypertension may require some interpretation in patients with dementia. What is not clear is how the uncertainty surrounding treatment in this group influences practitioner decisions. It is possible, for instance, that those concerned about potential side effects of antihypertensives might advise against treatment or use less stringent target blood pressures¹⁵, while others might advocate tight blood pressure control¹⁶.

84 There are limited data available on how people with cognitive impairment are affected by 85 antihypertensive-associated adverse health events¹⁷. Medication side effects are commonly 86 overlooked in dependent people with cognitive impairment¹⁸, raising the possibility of greater 87 harm from adverse health events associated with antihypertensive therapy in people with

88 dementia.

- 89 The aim of the Hypertension in Dementia (HinD) study, described in this paper, was to
- 90 describe current practice regarding treatment of hypertension in people with dementia.
- 91 Specific objectives were to (i) describe the proportion people with dementia and
- 92 hypertension that are prescribed antihypertensives, (ii) to identify what class of
- 93 antihypertensives are prescribed, (iii) to identify the proportion achieving target blood
- 94 pressure, and (iv) to describe how often they report adverse health events during 6 months
- 95 follow-up. By doing so the study aimed to provide more evidence for clinicians and patients
- 96 to use in informed decision-making.
- 97 Methods
- 98 Study design
- 99 The HinD study was an observational cohort study.
- 100 Cohort

101 The cohort involved a multi-centre prospective community-based cohort in the UK. Between 102 July 2013 and October 2014, 181 individuals with recorded diagnoses of hypertension and 103 dementia were recruited via GP practices and memory clinics from 8 sites. All participants 104 had an informant and where they lacked capacity to consent consultee advice was sought 105 regarding participation in the study. After informed consent or consultee advice was 106 obtained, participants and informants underwent a face-to-face standardised assessment 107 involving assessment of blood pressure, activities of daily living (ADLs), cognitive function, and medication use. Participants were followed up with monthly telephone interviews for 6 108 109 months to collect information on adverse health events. (Ethical approval was obtained from 110 NRES Committee East Midlands - Nottingham 1 REC ref. 13/EM/0099 and Scotland A 111 REC ref. 14/SS/0035)

112 Selection criteria

Individuals with documented diagnoses of hypertension and dementia were potentially eligible for this study. In those recruited through general practice, practice databases were searched for individuals coded as having these two conditions on the practice database. In those recruited through memory services, clinics used recorded medical histories of hypertension and dementia to identify potential participants. Hypertension and dementia diagnoses were not re-evaluated during screening for this study and prescription of

antihypertensive medication was not used to identify people with hypertension.

120

121

122 Blood pressure

- 123 Researchers measured blood pressure using a validated automatic BP machine (OMRON
- 124 M6 HEM-7211-E) with an appropriate cuff size after 10 minutes of rest when seated. The
- 125 blood pressure one minute after standing was then measured. Postural hypotension was
- 126 defined as a drop of more than 20mmHg in systolic blood pressure or of 10mmHg in diastolic
- 127 blood pressure.
- 128 Cognitive assessment and dependency for ADLs
- 129 Cognitive function was assessed using the Mini-Mental State Examination (MMSE)¹⁹.
- 130 Dependency for activities of daily living was evaluated using the modified Barthel Index²⁰.
- 131 Comorbidity
- 132 Participants and informants were asked about their medical diagnoses at baseline interview
- and these were confirmed by reference to medical records.
- 134 Medical events
- 135 Participants and informants were contacted every week for four weeks and then monthly for
- a further 5 months. A structured telephone interview with the participant and/or informant
- 137 was used to collect data on falls, falls with fractures, new cardio- or cerebrovascular events
- 138 (self-reported myocardial infarction, stroke, TIA, heart failure), or death.
- 139 Planned statistical analysis
- 140 Descriptive statistics were used to describe the study population and its antihypertensive
- 141 treatment and adverse health events in detail. The rate of reported adverse health events
- over the duration of the study was transformed into the rate per 1000patientyears and 95%
- 143 confidence interval estimates were calculated. Differences between GP and memory clinic
- 144 recruits, between those achieving and those not achieving target BP, and between those
- taking and not taking antihypertensive agents were explored using: the t-test for continuous
- and normally distributed variables; the Mann-Whitney U test for continuous and non-normally
- 147 distributed or ordinal variables and the Chi-Squared test for categorical variables.
- 148 Association between number of antihypertensives and blood pressure and achievement of
- target blood pressure was tested using regression analysis.
- 150 Results

151 Study population

- 152 1585 eligible individuals with diagnoses of hypertension and dementia were invited to
- 153 participate in the study via mail sent to clinic lists from GP practices and memory clinics from
- 154 8 sites within the UK. 181 individuals were recruited: 86 from GP practices, 95 from memory
- 155 clinics. Of these 181 individuals, one withdrew before baseline assessment could be
- 156 completed and a further three withdrew before follow-up commenced, leaving 177 to enter
- 157 follow up (Figure 1).
- 158 People recruited via GP were more likely to have fallen (30% vs 16% p=0.021), took fewer
- 159 antihypertensives (median 1 (IQR1-2) vs 2 (IQR 1-2) p=0.008), had more medical diagnoses
- 160 (median 5.5 (IQR 4-8) vs 4 (3-5) p<0.001), and were more dependent for basic ADLs
- 161 (Barthel median 19 (IQR 14.75-20) Vs 20 (IQR 17-20) p=0.028) compared to those recruited
- 162 via memory clinics.
- 163
- 164 Figure 1 Participant flow diagram
- 165

166 At baseline 126 (70%) were female, mean age was 82 years (SD 6.3), and median MMSE

- score was 23 (IQR 18-26). Alzheimer's dementia was the most common dementia diagnosis
- in 101 (56%), followed by vascular dementia 36 (20%), mixed dementia 23 (13%) and others
- 169 20 (11%). There were a median of 5 (IQR 3-7) medical diagnoses per participant. Diabetes
- 170 mellitus was the most common problem (35 (19%)) while previous stroke and myocardial
- infarction were also frequently reported (28 (16%), 23 (13%) respectively). The baseline
- variables of the HIND population are summarised in table 1.
- 173 Table 1. HIND population baseline variables
- 174
- 175 Blood pressure and treatment
- 176 High blood pressure was treated in 157 (87% (95% CI 82% 92%)); 23 (13%) were taking
- no agents, 79 (44%) were taking one, 50 (28%) were taking two, 20 (11%) were taking three,
- 178 6 (3%) were taking four and 2 (1%) were taking five agents. ACEi/ARBs were the most
- 179 frequently prescribed antihypertensive (63%), followed by calcium channel blockers (37%),
- 180 beta-blockers (34%) and diuretics (23%). An average blood pressure of 141/78 (SD 22/12)
- 181 was recorded. Increasing number of antihypertensives was not associated with lower blood

- 182 pressure (systolic blood pressure R²=0.008 P=0.248, diastolic blood pressure R²=0
- 183 P=0.907) see Table 2.
- 184 Target blood pressure (as defined by NICE 2011 guidance¹) was achieved in 58% (95% CI
- 185 49% 64%) of those on treatment. Increasing numbers of antihypertensives were not
- associated with a higher proportion of participants having a blood pressure at or below their
- 187 specified target (p= 0.952) (table 2).
- 188
- Table 2 The number of antihypertensive agents prescribed and mean blood pressure andproportion achieving target blood pressure.
- 191
- 192 Postural blood pressure
- 193 Postural blood pressures were measured in 174 individuals at baseline and were omitted in
- 194 6 where participants were unable to stand. 19 (11%) participants had a drop in blood
- 195 pressure sufficient to meet the criteria for orthostatic hypotension. Orthostatic hypotension
- 196 was more prevalent in those not prescribed antihypertensives (6 (26%) Vs 13 (8.6%)
- 197 P=0.009).
- 198 Follow up
- 199 177 participants entered follow up of whom 155 were taking at least one antihypertensive. Of
- those on treatment during 6 months follow up, 71 participants (46%) reported at least one fall
- and 30 (19%) two or more. In total 214 falls were sustained; a rate of 2760 falls per 1000
- 202 patient-years. Three participants (2%) sustained a fracture (41 per 1000 patient-years) as a
- result of falling, three (2%) experienced five episodes of heart failure (65 (95% CI 58-71) per
- 204 1000 patient-years), four (3%) experienced six strokes / TIAs (77 (95% CI 70-84) per 1000
- 205 patient-years) and eight (5%) participants died (103 (95%CI 95-111) per 1000 patient-years).
- 206 Discussion
- 207 In this study of people with mild dementia and a diagnosis of hypertension, high blood
- 208 pressure was treated in the majority of participants and standard antihypertensive
- 209 medication was used. Target blood pressure was achieved in just over half of participants
- 210 irrespective of the number of antihypertensives prescribed. The majority of those not
- 211 prescribed antihypertensives had blood pressure readings within the target range.
- 212 Presumably these individuals had become normotensive having previously been

- 213 hypertensive or had been erroneously coded. The study population largely had mild
- 214 dementia, but experienced multiple adverse health events during the six month follow up
- 215 period with falls being the most common.
- 216 The study recruited participants from a variety of settings and geographical locations so its
- findings are likely to be applicable across the whole of the UK. The most important limitation
- affecting the study was that the recruitment strategy selected a study population with mild
- 219 dementia, limiting generalisability of the findings to this group.
- 220 A systematic review of historical observational studies of the treatment of hypertension in 221 people with dementia ¹⁸ found that 73% were on at least one antihypertensive. In the current 222 study treatment rates were higher at 87% (95% CI 82% - 92%), which is in keeping with the 223 findings of a survey of the general population (Health Survey for England 2011) where the 224 reported treatment rate was also 87%²¹. The higher treatment rate, than that identified by the 225 review, may be an effect of the timing of the study, or because the HinD population were 226 mildly cognitively impaired and hence similar to the general population. The proportion 227 achieving target blood pressure (58%) was similar to that reported in both the review (55%)¹⁸ 228 and Health Survey (52%)²¹. The average blood pressure was similar to that achieved in 229 randomised controlled trials such as HYVET (140/72 (HYVET) vs 141/78 (HinD))¹⁰.The 230 Health Survey found that ACEi/ARBs were the most frequently prescribed class²² – the 231 same as in the HinD study. However, the systematic review identified diuretic
- antihypertensives as the most frequently prescribed class (64%), while calcium channel
- 233 blockers (43%), ACEi/ARBs (42%) and β -blockers (42%) were less commonly prescribed
- 234 perhaps reflecting historic prescribing trends¹⁸.
- 235 The HinD population experienced multiple adverse health events including 214 falls, of
- which 3 resulted in fractures, and one in twenty dying during the 6 month follow-up period.
- 237 The incidence of falls (2760 falls per 1000 patient-years) was similar to that reported by Allan
- and colleagues in another UK cohort study of people with mild to moderate dementia due to
- Alzheimer's disease (2486 per 1000 patient-years) and vascular disease (3135 per 1000
- 240 patient years)²³. The rate of falls was higher than has been reported in non-cognitively
- impaired older people (1023 per 1000 patient-years)²³ and in community dwelling older
- women (1003 per 1000 patient-years)²⁴. The fracture rate (41 per 1000 patient-years) was
- higher than that reported in those aged 80-85 in the Rotterdam Study (20 per 1000 patient-
- 244 years men, 30 per 1000 patient years for women). This is in keeping with other groups'
- findings that falls and fractures are more common in people with cognitive impairment²⁵⁻²⁷.
- The rates of events such as heart failure (65 (95% CI 58-71) per 1000 patient-years), stroke (77 (95% CI 70-84) per 1000 patient-years) and death (103 (95% CI 95-111) per 1000

248 patient-years) were higher than those reported in trials such as HYVET (heart failure 5.3 per 249 1000 patient-years, stroke 12.4 per 1000 patient-years, death 47.2 per 1000 patient-years 250 ¹⁰). This may reflect the higher conventional vascular risk within the HinD population where 251 the prevalence of comorbidities such as diabetes and ischaemic heart disease was higher¹⁰ 252 at baseline. Previous observational data have raised the possibility that the effect of blood 253 pressure lowering may be attenuated in the presence of co-existing cognitive impairment. 254 The Milan Geriatrics 75+ cohort study found that in participants with Mini-Mental State 255 Examination scores indicating cognitive impairment and ADL dependence, a higher systolic 256 blood pressure was associated with reduced mortality¹¹. The data from HIND therefore 257 aligns with data from generic longitudinal observational cohort studies which suggest that 258 populations recruited by RCTs, such as HYVET, were not fully representative of the patterns 259 of comorbidity and adverse outcomes seen in the real world. In HIND, as in the Milan-65+ 260 and PARTAGE studies, both were more common.

261 Conclusion and implications

262 Participants in this study had their blood pressure treated with standard antihypertensive

263 medications. Their blood pressure was treated in a similar proportion to the general

264 population and a similar proportion achieved target blood pressure. This suggests that

clinicians currently do not regard this group as being sufficiently different from patients

without dementia to recommend specific treatment approaches. The higher rate of adverse

health events experienced by this population compared to the findings of the large scale

randomised controlled trials may just reflect the relative robustness of a randomised

269 controlled trial population. However, it does raise the possibility that treatment of

270 hypertension in people with dementia may be associated with greater harm. Clinicians must

271 understand the caveats attached to treatment in this patient group – it is not clear that they

currently do so, or if they do, that this understanding changes practice.

These discussions are, at present, stymied by the limitations of observational data and in particular by the largely mildly impaired nature of participants. A randomised controlled trial examining the risk to benefit ratio of antihypertensives in people with dementia is one possible way forward but could, in practice, be very difficult to conduct. In the absence of an RCT, further observational data are required so that those writing guidelines can give appropriate consideration to the safest approach to treatment in this vulnerable group of patients.

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- 371
- 372 Figure Legend
- 373 Figure 1 Participant flow diagram

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