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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
23 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.

78 It is clear from the above that generic guidelines for management of hypertension may
79 require some interpretation in patients with dementia. What is not clear is how the
80 uncertainty surrounding treatment in this group influences practitioner decisions. It is
81 possible, for instance, that those concerned about potential side effects of antihypertensives
82 might advise against treatment or use less stringent target blood pressures¹⁵, while others
83 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,
108 and medication use. Participants were followed up with monthly telephone interviews for 6
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

113 Individuals with documented diagnoses of hypertension and dementia were potentially
114 eligible for this study. In those recruited through general practice, practice databases were
115 searched for individuals coded as having these two conditions on the practice database. In
116 those recruited through memory services, clinics used recorded medical histories of
117 hypertension and dementia to identify potential participants. Hypertension and dementia
118 diagnoses were not re-evaluated during screening for this study and prescription of
119 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
133 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
136 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
142 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
145 taking and not taking antihypertensive agents were explored using: the t-test for continuous
146 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
149 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 (IQR 1-2) 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
167 score was 23 (IQR 18-26). Alzheimer's dementia was the most common dementia diagnosis
168 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
171 infarction were also frequently reported (28 (16%), 23 (13%) respectively). The baseline
172 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
177 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 $R^2=0.008$ $P=0.248$, diastolic blood pressure $R^2=0$
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
186 associated with a higher proportion of participants having a blood pressure at or below their
187 specified target ($p= 0.952$) (table 2).

188

189 Table 2 The number of antihypertensive agents prescribed and mean blood pressure and
190 proportion 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
200 those on treatment during 6 months follow up, 71 participants (46%) reported at least one fall
201 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
203 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
217 findings are likely to be applicable across the whole of the UK. The most important limitation
218 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 dementia¹⁸ 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
232 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
236 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
238 and colleagues in another UK cohort study of people with mild to moderate dementia due to
239 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
241 impaired older people (1023 per 1000 patient-years)²³ and in community dwelling older
242 women (1003 per 1000 patient-years)²⁴. The fracture rate (41 per 1000 patient-years) was
243 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'
245 findings that falls and fractures are more common in people with cognitive impairment²⁵⁻²⁷.

246 The rates of events such as heart failure (65 (95% CI 58-71) per 1000 patient-years), stroke
247 (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 HiD 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
265 clinicians currently do not regard this group as being sufficiently different from patients
266 without dementia to recommend specific treatment approaches. The higher rate of adverse
267 health events experienced by this population compared to the findings of the large scale
268 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
272 currently do so, or if they do, that this understanding changes practice.

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

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- 283 1. NICE. Hypertension - Clinical management of primary hypertension in
284 adults. In: NHS, ed. Vol NICE clinical guideline 127.
285 www.nice.org.uk/guidance/CG127: NICE; 2011:1-16.
- 286 2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for
287 the management of high blood pressure in adults: report from the panel
288 members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*
289 : *the journal of the American Medical Association*. 2014;311(5):507-520.
- 290 3. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Practice
291 Guidelines for the Management of Arterial Hypertension. *Blood pressure*.
292 2014;23(1):3-16.
- 293 4. Shah SM, Carey IM, Harris T, Dewilde S, Cook DG. Quality of chronic
294 disease care for older people in care homes and the community in a
295 primary care pay for performance system: retrospective study. *Bmj*.
296 2011;342:d912.
- 297 5. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for
298 hypertension in the elderly. *Cochrane database of systematic reviews*.
299 2009(4):CD000028.
- 300 6. Cohen DL, Townsend RR. Update on pathophysiology and treatment of
301 hypertension in the elderly. *Current hypertension reports*.
302 2011;13(5):330-337.
- 303 7. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind
304 comparison of placebo and active treatment for older patients with
305 isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-
306 Eur) Trial Investigators. *Lancet*. 1997;350(9080):757-764.
- 307 8. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the
308 management of arterial hypertension: The Task Force for the
309 management of arterial hypertension of the European Society of
310 Cardiology and the European Society of Hypertension: The Task Force for
311 the management of arterial hypertension of the European Society of
312 Cardiology and the European Society of Hypertension. *J Hypertens*.
313 2018;36(10):1953-2041.
- 314 9. Whelton PK, Carey RM, Aronow WS, et al. 2017
315 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for
316 the Prevention, Detection, Evaluation, and Management of High Blood
317 Pressure in Adults: Executive Summary: A Report of the American College
318 of Cardiology/American Heart Association Task Force on Clinical Practice
319 Guidelines. *Circulation*. 2018;138(17):e426-e483.
- 320 10. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in
321 patients 80 years of age or older. *N Engl J Med*. 2008;358(18):1887-
322 1898.
- 323 11. Ogliari G, Westendorp RG, Muller M, et al. Blood pressure and 10-year
324 mortality risk in the Milan Geriatrics 75+ Cohort Study: role of functional
325 and cognitive status. *Age and ageing*. 2015;44(6):932-937.
- 326 12. Benetos A, Labat C, Rossignol P, et al. Treatment With Multiple Blood
327 Pressure Medications, Achieved Blood Pressure, and Mortality in Older
328 Nursing Home Residents: The PARTAGE Study. *JAMA internal medicine*.
329 2015;175(6):989-995.
- 330 13. Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during
331 antihypertensive treatment is associated with higher all-cause mortality

- 332 and accelerated cognitive decline in the oldest-old-data from the Leiden
333 85-plus Study. *Age Ageing*. 2018.
- 334 14. Mossello E, Pieraccioli M, Nesti N, et al. Effects of low blood pressure in
335 cognitively impaired elderly patients treated with antihypertensive drugs.
336 *JAMA Intern Med*. 2015;175(4):578-585.
- 337 15. Morley JE. Systolic Hypertension Should Not Be Treated in Persons Aged
338 80 and Older Until Blood Pressure Is Greater than 160 mmHg. *Journal of*
339 *the American Geriatrics Society*. 2013;61(7):1197-1198.
- 340 16. Aronow WS. Treatment of hypertension in the elderly. *Journal of the*
341 *American Medical Directors Association*. 2013;14(11):847.
- 342 17. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild
343 hypertension. *Cochrane database of systematic reviews*.
344 2012;8:CD006742.
- 345 18. Welsh TJ, Gladman JR, Gordon AL. The treatment of hypertension in
346 people with dementia: a systematic review of observational studies. *BMC*
347 *Geriatr*. 2014;14:19.
- 348 19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical
349 method for grading the cognitive state of patients for the clinician. *Journal*
350 *of psychiatric research*. 1975;12(3):189-198.
- 351 20. Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical
352 disability? *International disability studies*. 1988;10(2):64-67.
- 353 21. Knott C, Mindell J. The Health Survey for England. In. Vol 3. London: The
354 Health and Social Care Information Centre; 2012.
- 355 22. Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in
356 England: a serial cross-sectional study from 1994 to 2011. *Lancet*.
357 2014;383(9932):1912-1919.
- 358 23. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of
359 falls in dementia: a prospective study in older people. *PLoS One*.
360 2009;4(5):e5521.
- 361 24. Bergland A, Wyller TB. Risk factors for serious fall related injury in elderly
362 women living at home. *Inj Prev*. 2004;10(5):308-313.
- 363 25. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly
364 persons living in the community. *N Engl J Med*. 1988;319(26):1701-1707.
- 365 26. Kallin K, Gustafson Y, Sandman PO, Karlsson S. Factors associated with
366 falls among older, cognitively impaired people in geriatric care settings: a
367 population-based study. *Am J Geriatr Psychiatry*. 2005;13(6):501-509.
- 368 27. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment
369 in fall risk among older adults: a systematic review and meta-analysis.
370 *Age Ageing*. 2012;41(3):299-308.

371

372 Figure Legend

373 Figure 1 Participant flow diagram

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