JAMDA xxx (2019) 1–5

JAMDA

journal homepage: www.jamda.com

Original Study

Treatment of Hypertension in People With Dementia: A Multicenter Prospective Observational Cohort Study

Tomas J. Welsh MBChB, PhD [a,b,c,*], Adam L. Gordon MBChB, PhD [d,e,f,g], John R.F. Gladman MBChB, DM [d,f,g]

[a] Research Institute for the Care of Older People (RICE), Bath, Somerset, United Kingdom
[b] Royal United Hospital Bath NHS Foundation Trust, Bath, Somerset, United Kingdom
[c] University of Bristol, Bristol, United Kingdom
[d] University of Nottingham, Nottingham, Nottingham, United Kingdom
[e] University Hospitals of Derby and Burton NHS Foundation Trust, Derby, Derbyshire, United Kingdom
[f] Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East Midlands, United Kingdom
[g] NIHR Nottingham Biomedical Research Centre, Nottingham, Nottinghamshire, United Kingdom

Keywords:
Dementia
hypertension
antihypertensive agents

A B S T R A C T

Objectives: To describe the treatment of hypertension in people with dementia and collate evidence on adverse health events whilst on treatment.
Design: A multicenter prospective observational cohort study.
Setting and participants: People with documented diagnoses of hypertension and dementia were recruited through memory clinics and general practice from 8 sites in the United Kingdom.
Methods: The cohort was recruited between July 2013 and October 2014. Participants underwent face-to-face, standardized assessment of blood pressure (BP), activities of daily living, cognitive function, and medication use. Follow-up was by monthly telephone interview for 6 months to collate data on adverse health events.
Results: 181 participants were recruited and 177 followed up; 126 (70%) were female, mean age was 82 [standard deviation (SD) 6.3] years, median Mini-Mental State Examination score was 23 [interquartile range (IQR) 18-26] and mean BP was 141/78 (SD 22/12) mmHg. Antihypertensive drugs were prescribed in 157 (87%). Participants were prescribed a median of 1 (IQR 1-2) antihypertensive medication. Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers were the most frequently prescribed antihypertensives in 63% of participants. Target BP was achieved in 58% (95% confidence interval 49%-64%). Increasing 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, 3 had a fracture, 3 developed symptomatic heart failure, 4 had cerebrovascular events, and 8 died.
Conclusions/Implications: In this population of people with mild dementia, participants were treated with standard antihypertensive medications in a similar proportion to the general population, with a similar proportion achieving target BP. The rate of adverse health events was higher than in randomized controlled trials of antihypertensives and raises reservations about the assumptions underpinning antihypertensive treatment in people with dementia. These findings may help inform clinical decision making.

International policies and guidelines stress the importance of the detection and treatment of hypertension, which is the most important cardiovascular risk factor with the greatest impact on mortality.[1–3] High blood pressure is common among older adults. A reported 56.1% of community-dwelling older people and 43.7% of care home residents have hypertension.[4] Prevalence increases with age,[5] and approximately 80% of those older than 80 years are hypertensive.[6]

This work was supported by a British Geriatrics Society SpR Start-up Grant and the Primary Care Research Network, United Kingdom, and by the University of Nottingham, Division of Rehabilitation and Ageing, as part of a PhD project.
The authors declare no conflict of interest.
* Address correspondence to Tomas J. Welsh, MBChB, PhD, RICE, Royal United Hospital, Combe Park, Bath, BA1 3NG, Somerset, United Kingdom.
E-mail address: tomas.welsh@nhs.net (T.J. Welsh).

https://doi.org/10.1016/j.jamda.2019.03.036
1525-8610/

Multiple large-scale randomized controlled trials (RCTs), such as the Hypertension in the Very Elderly Trial (HYVET), have demonstrated health benefits from medications that lower blood pressure,[5,7] and increasingly guidelines are advocating lower and lower target blood pressures even among the oldest old.[8–10]

Current guidance on hypertension advises that co-pathology should be taken into account when treatment decisions are made.[1] People with dementia were not included in the large-scale RCTs of antihypertensives. At present, there are no condition-specific recommendations for treating hypertension in people with dementia, and the benefits of treatment are assumed to apply. Observational evidence, however, has suggested that the benefits of blood pressure lowering may be attenuated by coexisting cognitive impairment. A cohort study of 1587 people older than 75 years found higher systolic blood pressure to be associated with reduced mortality in people with cognitive and functional impairment.[11] The PARTAGE group found an association between increased mortality and a systolic BP below 130 mmHg in care home residents taking 2 or more antihypertensives.[12] The Leiden 85+ study found an association between cognitive decline and low blood pressure in patients taking antihypertensives,[13] a finding replicated by Mossello and colleagues.[14]

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 pressures,[15] whereas others might advocate tight blood pressure control.[16]

There are limited data available on how people with cognitive impairment are affected by antihypertensive-associated adverse health events.[17] Medication side effects are commonly overlooked in dependent people with cognitive impairment,[18] raising the possibility of greater harm from adverse health events associated with antihypertensive therapy in people with dementia.

The aim of the Hypertension in Dementia (HinD) study, described in this article, was to describe current practice regarding treatment of hypertension in people with dementia. Specific objectives were to (1) describe the proportion of people with dementia and hypertension who are prescribed antihypertensives, (2) to identify what class of antihypertensives are prescribed, (3) to identify the proportion achieving target blood pressure, and (4) to describe how often they report adverse health events during 6 months' follow-up. By doing so, the study aimed to provide more evidence for clinicians and patients to use in informed decision making.

Methods

Study Design

The HinD study was an observational cohort study.

Cohort

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

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 2 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.

Blood Pressure

Researchers measured blood pressure using a validated automatic BP machine (OMRON M6 HEM-7211-E) with an appropriate cuff size after 10 minutes of rest when seated. The blood pressure 1 minute after standing was then measured. Postural hypotension was defined as a drop of more than 20 mmHg in systolic blood pressure or of 10 mmHg in diastolic blood pressure.

Cognitive Assessment and Dependency for ADL

Cognitive function was assessed using the Mini-Mental State Examination.[19] Dependency for ADL was evaluated using the modified Barthel Index.[20]

Comorbidity

Participants and informants were asked about their medical diagnoses at baseline interview, and these were confirmed by reference to medical records.

Medical Events

Participants and informants were contacted every week for 4 weeks and then monthly for a further 5 months. A structured telephone interview with the participant and/or informant was used to collect data on falls, falls with fractures, new cardio- or cerebrovascular events (self-reported myocardial infarction, stroke, transient ischemic attack, or heart failure), or death.

Planned Statistical Analysis

Descriptive statistics were used to describe the study population and its antihypertensive 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 1000 patient-years and 95% confidence interval (CI) estimates were calculated. Differences between GP and memory clinic recruits, between those achieving and those not achieving target BP, and between those taking and not taking antihypertensive agents were explored using the following: the *t* test for continuous and normally distributed variables; the Mann-Whitney *U* test for continuous and non-normally distributed or ordinal variables; and the chi-squared test for categorical variables. Association between number of antihypertensives and blood pressure and achievement of target blood pressure was tested using regression analysis.

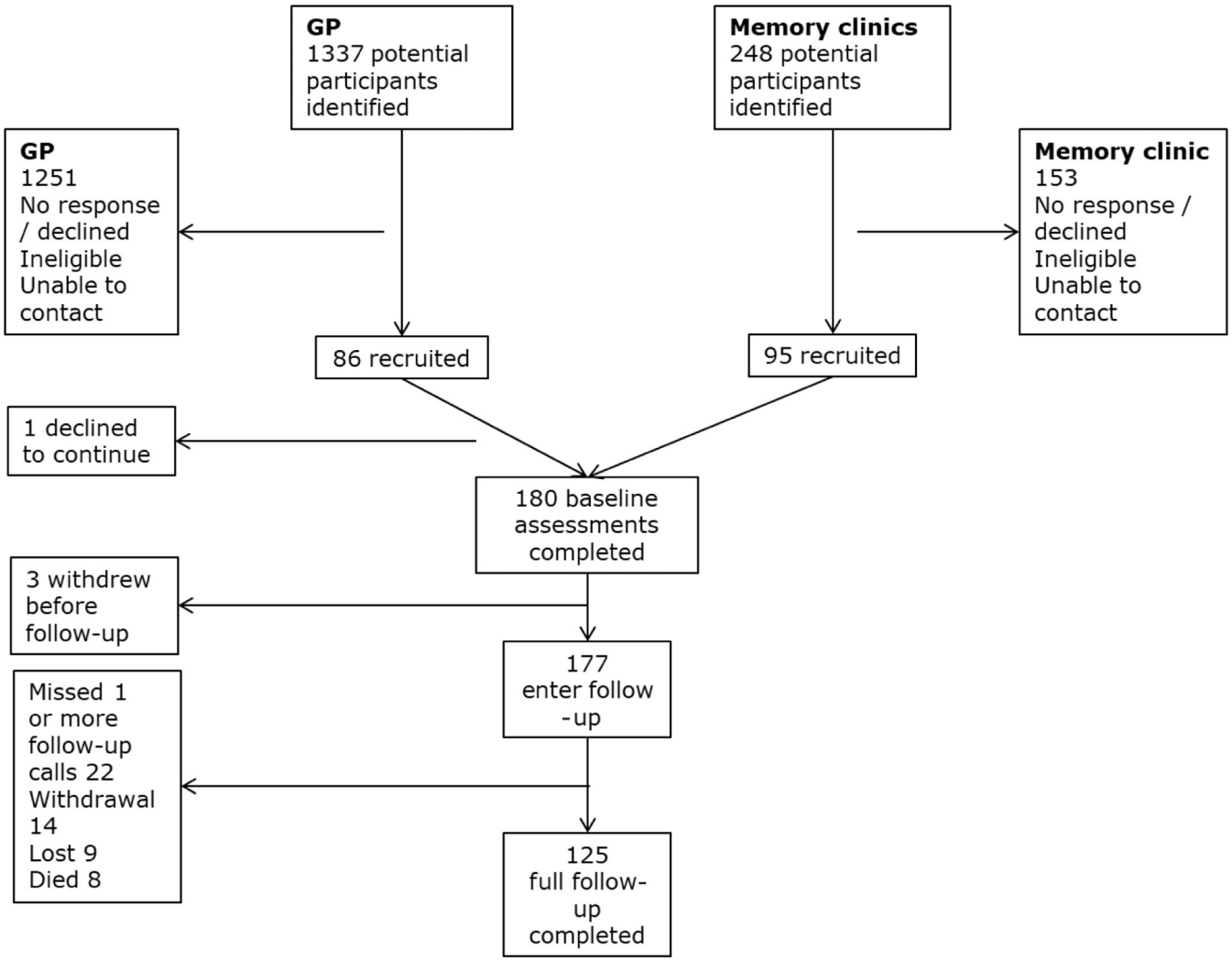

Fig. 1. Participant flow diagram.

Results

Study Population

A total of 1585 eligible individuals with diagnoses of hypertension and dementia were invited to participate in the study via mail sent to clinic lists from GP practices and memory clinics from 8 sites within the United Kingdom. Subsequently, 181 individuals were recruited: 86 from GP practices and 95 from memory clinics. Of these 181 individuals, 1 withdrew before baseline assessment could be completed and a further 3 withdrew before follow-up commenced, leaving 177 to enter follow-up (Figure 1).

People recruited via GP were more likely to have fallen (30% vs 16%, $P = .021$), took fewer antihypertensives [median 1 (IQR 1-2) vs 2 (IQR 1-2), $P = .008$], had more medical diagnoses [median 5.5 (IQR 4-8) vs 4 (3-5), $P < .001$], and were more dependent for basic ADL [Barthel median 19 (IQR 14.75-20) vs 20 (IQR 17-20), $P = .028$] compared to those recruited via memory clinics.

At baseline, 126 (70%) were female, mean age was 82 years (standard deviation 6.3), and median Mini-Mental State Examination score was 23 (IQR 18-26). Alzheimer's dementia was the most common dementia diagnosis in 101 (56%), followed by vascular dementia in 36 (20%), mixed dementia in 23 (13%), and others in 20 (11%). There were a median of 5 (IQR 3-7) medical diagnoses per participant. Diabetes mellitus was the most common problem [35 (19%)] while previous stroke and myocardial infarction were also frequently reported [28 (16%) and 23 (13%) respectively]. The baseline variables of the HIND population are summarized in Table 1.

Blood Pressure and Treatment

High blood pressure was treated in 157 (87%, 95% CI 82%-92%); 23 (13%) were taking no agents, 79 (44%) were taking 1 agent, 50 (28%) were taking 2 agents, 20 (11%) were taking 3 agents, 6 (3%) were taking 4 agents, and 2 (1%) were taking 5 agents. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were the most frequently prescribed antihypertensive (63%), followed by calcium channel blockers (37%), beta-blockers (34%), and diuretics (23%). An average blood pressure of 141/78 (standard deviation 22/12) was recorded. Increasing number of antihypertensives was not associated with lower blood pressure (systolic blood pressure $R^2 = 0.008$, $P = .248$, diastolic blood pressure $R^2 = 0$, $P = .907$; see Table 2).

Target blood pressure (as defined by NICE 2011 guidance[1]) was achieved in 58% (95% CI 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 specified target ($P = .952$) (Table 2).

Table 1
HinD Population Baseline Variables

Variable	HinD Population
Number	180
Age, mean (SD)	82 (6.3)
Sex, female, n (%)	126 (70)
Residence, n (%)	
Own home	157 (87)
Residential home	22 (12)
Nursing home	1 (1)
Blood pressure, mean (SD)	141/78 (22/12)
Prevalence of orthostatic hypotension, n (%) (n = 174)	19 (11)
MMSE, median (IQR)	23 (18-26)
Background problems, n (%)	
Diabetes mellitus	35 (19)
Stroke	28 (16)
MI	23 (13)
Atrial fibrillation/flutter	21 (12)
Heart failure	23 (13)

MMSE, Mini-Mental State Examination; SD, standard deviation.

Postural Blood Pressure

Postural blood pressures were measured in 174 individuals at baseline and were omitted in 6 where participants were unable to stand. In addition, 19 (11%) participants had a drop in blood pressure sufficient to meet the criteria for orthostatic hypotension. Orthostatic hypotension was more prevalent in those not prescribed antihypertensives [6 (26%) vs 13 (8.6%), $P = .009$].

Follow-up

A total of 177 participants entered follow-up, of whom 155 were taking at least 1 antihypertensive. Of those on treatment during the 6-month follow-up, 71 participants (46%) reported at least 1 fall and 30 (19%) reported 2 or more falls. In total, 214 falls were sustained, a rate of 2760 falls per 1000 patient-years. Three participants (2%) sustained a fracture (41 per 1000 patient-years) as a result of falling, 3 (2%) experienced 5 episodes of heart failure (65, 95% CI 58-71, per 1000 patient-years), 4 (3%) experienced 6 strokes/transient ischemic attacks (77, 95% CI 70-84, per 1000 patient-years), and 8 (5%) participants died (103, 95% CI 95-111, per 1000 patient-years).

Discussion

In this study of people with mild dementia and a diagnosis of hypertension, high blood pressure was treated in the majority of participants and standard antihypertensive medication was used. Target blood pressure was achieved in just over half of participants irrespective of the number of antihypertensives prescribed. The majority of those not prescribed antihypertensives had blood pressure readings within the target range. Presumably, these individuals had become normotensive, having previously been hypertensive or had been erroneously coded. The study population largely had mild dementia, but experienced multiple adverse health events during the 6-month follow-up period, with falls being the most common.

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 United Kingdom. The most important limitation affecting the study was that the recruitment strategy selected a study population with mild dementia, limiting generalizability of the findings to this group.

A systematic review of historical observational studies of the treatment of hypertension in people with dementia[18] found that 73% were on at least 1 antihypertensive. In the current study, treatment rates were higher at 87% (95% CI 82%-92%), which is in keeping with the findings of a survey of the general population (Health Survey for England 2011) where the reported treatment rate was also 87%.[21] The higher treatment rate (than that identified by the review) may be an effect of the timing of the study, or because the HinD population was mildly cognitively impaired and hence similar to the general population. The proportion achieving target blood pressure (58%) was similar to that reported in both the review (55%)[18] and Health Survey (52%).[21] The average blood pressure was similar to that achieved in RCTs such as HYVET [140/72 (HYVET) vs 141/78 (HinD)].[10] The Health Survey found that angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers were the most frequently prescribed class[22]—the same as in the HinD study. However, the systematic review identified diuretic antihypertensives as the most frequently prescribed class (64%), whereas calcium channel blockers (43%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (42%), and β-blockers (42%) were less commonly prescribed, perhaps reflecting historic prescribing trends.[18]

The HinD population experienced multiple adverse health events, including 214 falls, of which 3 resulted in fractures, and 1 in 20 dying during the 6-month follow-up period. 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 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 years in the Rotterdam Study (20 per 1000 patient-years for men and 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 impairment.[25–27]

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 patient-years) were higher than those reported in trials such as HYVET (heart failure 5.3 per 1000 patient-years, stroke 12.4 per 1000 patient-years, death 47.2 per 1000 patient-years[10]). This may reflect the higher conventional vascular risk

Table 2
The Number of Antihypertensive Agents Prescribed and Mean Blood Pressure and Proportion Achieving Target Blood Pressure

Number of Antihypertensive Agents	Systolic Blood Pressure, Mean (SD)	Diastolic Blood Pressure, Mean (SD)	Target Systolic Blood Pressure Achieved, n (%)	Target Diastolic Blood Pressure Achieved, n (%)	Combined Achievement, n (%)
0	141 (17)	78 (11)	16 (70)	20 (87)	16 (70)
1	139 (21)	78 (11)	52 (66)	67 (85)	48 (61)
2	142 (24)	79 (14)	29 (58)	40 (80)	28 (56)
3	146 (22)	77 (14)	12 (60)	14 (70)	9 (45)
4	138 (18)	68 (5.3)	3 (50)	6 (100)	3 (50)
5	137 (38)	65 (21)	1 (50)	2 (100)	1 (50)

SD, standard deviation.

within the HinD population, where the prevalence of comorbidities such as diabetes and ischemic heart disease was higher[10] at baseline. Previous observational data have raised the possibility that the effect of blood pressure lowering may be attenuated in the presence of coexisting cognitive impairment. The Milan Geriatrics 75+ cohort study found that in participants with Mini-Mental State Examination scores indicating cognitive impairment and ADL dependence, a higher systolic blood pressure was associated with reduced mortality.[11] The data from HinD therefore aligns with data from generic longitudinal observational cohort studies that suggest populations recruited by RCTs, such as HYVET, were not fully representative of the patterns of comorbidity and adverse outcomes seen in the real world. In HinD, as in the Milan-65+ and PARTAGE studies, both were more common.

Conclusion and Implications

Participants in this study had their blood pressure treated with standard antihypertensive medications. Their blood pressure was treated in a similar proportion to the general 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 large-scale RCTs may just reflect the relative robustness of an RCT population. However, it does raise the possibility that treatment of hypertension in people with dementia may be associated with greater harm. Clinicians must 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. An RCT examining the risk-to-benefit ratio of antihypertensives in people with dementia is 1 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.

Acknowledgments

The authors acknowledge the role of the Primary Care Clinical Research Network and the teams and participants at the study sites in Nottinghamshire, Leicestershire, Leicestershire Partnership NHS Trust, Surrey and Borders NHS Trust, NHS Fife, South Essex Partnership University NHS Trust, Southern Health NHS Trust, and Solent NHS Trust, without whom the study could not have happened.

References

1. National Institute for Health and Care Excellence. NICE Guidance. Hypertension: The clinical management of primary hypertension in adults; 2015. Available at: https://www.nice.org.uk/guidance/cg127/evidence/cg127-hypertension-full-guideline3. Accessed November 10, 2018.
2. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520.
3. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC practice guidelines for the management of arterial hypertension. Blood Pressure 2014;23:3–16.
4. Shah SM, Carey IM, Harris T, et al. Quality of chronic disease care for older people in care homes and the community in a primary care pay for performance system: Retrospective study. BMJ 2011;342:d912.
5. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. Cochrane Database Syst Rev 2009:CD000028.
6. Cohen DL, Townsend RR. Update on pathophysiology and treatment of hypertension in the elderly. Curr Hypertens Rep 2011;13:330–337.
7. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997;350:757–764.
8. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens 2018;36:1953–2041.
9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2018;138:e426–e483.
10. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887–1898.
11. Ogliari G, Westendorp RG, Muller M, et al. Blood pressure and 10-year mortality risk in the Milan Geriatrics 75+ Cohort Study: Role of functional and cognitive status. Age Ageing 2015;44:932–937.
12. Benetos A, Labat C, Rossignol P, et al. Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents: The PARTAGE study. JAMA Intern Med 2015;175:989–995.
13. Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old-data from the Leiden 85-plus Study. Age Ageing 2018;47:545–550.
14. Mossello E, Pieraccioli M, Nesti N, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med 2015;175:578–585.
15. Morley JE. Systolic hypertension should not be treated in persons aged 80 and older until blood pressure is greater than 160 mmHg. J Am Geriatr Soc 2013;61:1197–1198.
16. Aronow WS. Treatment of hypertension in the elderly. J Am Med Dir Assoc 2013;14:847.
17. Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database Syst Rev 2012:CD006742.
18. Welsh TJ, Gladman JR, Gordon AL. The treatment of hypertension in people with dementia: A systematic review of observational studies. BMC Geriatr 2014;14:19.
19. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state.” A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
20. Wade DT, Collin C. The Barthel ADL Index: A standard measure of physical disability? Int Disabil Stud 1988;10:64–67.
21. Knott C, Mindell J. The Health Survey for England, Vol 3. London: The Health and Social Care Information Centre; 2012.
22. Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in England: a serial cross-sectional study from 1994 to 2011. Lancet 2014;383:1912–1919.
23. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: A prospective study in older people. PLoS One 2009;4:e5521.
24. Bergland A, Wyller TB. Risk factors for serious fall related injury in elderly women living at home. Inj Prev 2004;10:308–313.
25. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319:1701–1707.
26. Kallin K, Gustafson Y, Sandman PO, Karlsson S. Factors associated with falls among older, cognitively impaired people in geriatric care settings: A population-based study. Am J Geriatr Psychiatry 2005;13:501–509.
27. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: A systematic review and meta-analysis. Age Ageing 2012;41:299–308.