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Deprescribing of Antihypertensive Medications and Cognitive Function in Nursing Home Residents

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IMPORTANCE Antihypertensive medication deprescribing is common among nursing home residents, yet its association with cognitive decline remains uncertain.

OBJECTIVE To investigate the association of deprescribing antihypertensive medication with changes in cognitive function in nursing home residents.

DESIGN, SETTING, AND PARTICIPANTS This cohort study using a target trial emulation approach included VA long-term care residents aged 65 years or older with stays of at least 12 weeks from 2006 to 2019. Residents who were not prescribed antihypertensive medication, with blood pressure greater than 160/90 mm Hg, or with heart failure were excluded. Eligible residents with stable medication use for 4 weeks were classified into deprescribing or stable user groups and followed for 2 years or until death or discharge for intention-to-treat (ITT) analysis. Participants switching treatment groups were censored in the per-protocol analysis. Cognitive function measurements during follow-up were analyzed using an ordinal generalized linear mixed model, adjusting for confounders with inverse probability of treatment weighting. Per-protocol analysis included inverse probability of censoring weighting. Data analyses were performed from May 1, 2023, and July 1, 2024.

EXPOSURES Deprescribing was defined as a reduction in the total number of antihypertensive medications or a decrease in medication dosage by 30%, sustained for a minimum of 2 weeks.

MAIN OUTCOMES AND MEASURES Cognitive Function Scale (CFS) was classified as cognitively intact (CFS = 1), mildly impaired (CFS = 2), moderately impaired (CFS = 3), and severely impaired (CFS = 4).

RESULTS Of 45 183 long-term care residents, 12 644 residents (mean [SD] age 77.7 [8.3] years; 329 [2.6%] females and 12 315 [97.4%] males) and 12 053 residents (mean [SD] age 77.7 [8.3] years; 314 [2.6%] females and 11 739 [97.4%] males) met eligibility for ITT and per-protocol analyses, respectively. At the end of the follow-up, 12.0% of residents had a worsened CFS (higher score) and 7.7% had an improved CFS (lower score) with 10.8% of the deprescribing group and 12.1% of the stable user group showing a worsened CFS score. In the per-protocol analysis, the deprescribing group had a 12% reduction in the odds of progressing to a worse CFS category per 12-week period (odds ratio, 0.88; 95% CI, 0.78-0.99) compared to the stable user group. Among residents with dementia, deprescribing was associated with 16% reduced odds of cognitive decline (odds ratio, 0.84; 95% CI, 0.72-0.98). These patterns remained consistent in the ITT analysis.

CONCLUSIONS AND RELEVANCE This cohort study indicates that deprescribing is associated with less cognitive decline in nursing home residents, particularly those with dementia. More data are needed to understand the benefits and harms of antihypertensive deprescribing to inform patient-centered medication management in nursing homes.

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Supplemental content

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Polypharmacy is common among older adults, with more than 40% taking 5 or more medications.[1,2] Antihypertensive medications are important contributors to polypharmacy, with the prevalence notably high at 70%.[3] While antihypertensive medications reduce cardiovascular risks, they also pose risks of adverse effects such as falls, orthostatic hypotension, and drug-drug interactions.[4-9] The risk to benefit ratio of antihypertensive medication is unclear in adults with multimorbidity who are institutionalized given that they have been largely excluded from clinical trials. Considering that this population is at high risk for adverse effects, deprescribing—the strategic reduction or discontinuation of medications that may no longer be beneficial or could be associated with harm—may be clinically appropriate.[1,10]

The relationship between antihypertensive medication management and cognitive function in older adults is complex. While elevated blood pressure (BP) in midlife is a well-documented risk factor for cognitive decline, the optimal BP targets for older adults—especially those in nursing homes—remain unclear.[11-14] Randomized clinical trials (RCTs) have shown mixed evidence on the effect of intensive BP control in reducing cognitive decline and the incidence of dementia.[15,16] First, most trials enrolled relatively healthier older adults, specifically excluding nursing home residents and individuals with dementia who comprise a substantial segment of the aging population and who are at higher risk for cognitive decline. Second, several observational studies have observed an association between higher BP and less cognitive decline in older adults, especially among those with poor functional status.[17-20] Therefore, a substantial knowledge gap persists regarding the long-term cognitive impact of antihypertensive treatment in frail older individuals, particularly those in nursing homes or those with dementia.

Our study aims to fill this gap by estimating the association of antihypertensive deprescribing with change in cognitive function of older nursing home residents, using a target trial approach using data from the US Department of Veteran's Affairs (VA). We carried out a prespecified subgroup analysis based on dementia status given the paucity of data in this population and the potentially distinct responses to antihypertensive medications.[21,22]

Key Points

Question What is the association of deprescribing antihypertensive medication with cognitive function in older residents in nursing homes?

Findings This target trial emulation approach including 12 644 nursing home residents found that deprescribing antihypertensive medication was associated with less cognitive decline, particularly among those with dementia.

Meaning These findings suggest the importance of patient-centered approaches to deprescribing antihypertensive medication, ensuring that regimens for older adults are optimized to preserve cognitive function and minimize potential harm.

Methods

This study received institutional review board approval from Stanford University and the VA Palo Alto Health Care System, with a waiver of informed consent because the research posed minimal risk and had procedures to protect confidentiality. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Target Trial Protocol Overview

We emulated a target trial to estimate the association of antihypertensive deprescribing on changes in cognitive function among veterans residing in a Community Living Center (CLC)—the VA term for nursing homes. The protocol is outlined in eTable 1 in Supplement 1. We identified residents as antihypertensive deprescribing users or stable users and recorded their cognitive function from time 0 to the final assessment of cognitive function or the end of the follow-up period. Subsequent analyses, emulating intention-to-treat (ITT) and per-protocol analyses, were executed to contrast the variations in the odds of worsening cognitive function between different treatment groups. Because protocol deviation is common in both RCTs and observational studies, we designated the per-protocol analysis as our primary approach to estimate the associations of deprescribing for patients who adhered to their assigned deprescribing or control groups.

Eligibility Criteria

Eligible candidates included residents aged 65 years and older from 2006 to 2019 who had a minimum CLC stay of 12 weeks (to ensure that residents were not short-term rehabilitation patients). To identify a population in which there was clinical uncertainty regarding antihypertensive medication use, we excluded residents whose admission systolic/diastolic BP exceeded 160/90 mm Hg, those diagnosed with heart failure, or those not taking any antihypertensive medications at admission (**Figure 1**).

Treatment (Deprescribing) Strategies and Assignment

We used VA Barcode Medication Administration data to extract daily antihypertensive regimens for residents. Antihypertensive medications included β-blockers, calcium channel-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor-blockers, loop diuretics, thiazide diuretics, α-blockers, vasodilators, and potassium-sparing diuretics. Medications were converted into weekly standard doses.[23] Deprescribing was defined as either a reduction in the overall number of antihypertensive medications or a 30% decrease in medication dosage compared to the previous week and sustained for at least 2 weeks. Residents who did not undergo these medication changes were considered to be stable users of antihypertensive medications.

Outcomes and Follow-Up

The primary outcome was the Cognitive Function Scale (CFS), collected through the Minimum Dataset (MDS). This scale encompasses the Brief Interview for Mental Status assessment, which includes self- and staff-reported cognitive data.[24] CFS is

a 4-level ordinal variable, characterized as cognitively intact (CFS = 1), mildly impaired (CFS = 2), moderately impaired (CFS = 3), and severely impaired (CFS = 4). It was collected at least quarterly throughout the nursing home stay. For the ITT analysis, we collected residents' CFS measurements from the event week to a maximum of 2 years (104 weeks). Residents were censored at either death or discharge within the 2-year follow-up period. For the per-protocol analysis, candidates were censored if medication intensification occurred in the deprescribing group (eg, eFigure 1 resident C in Supplement 1), or if medication deprescribing occurred in the stable user group within the 2 years (eg, eFigure 1 resident D in Supplement 1).

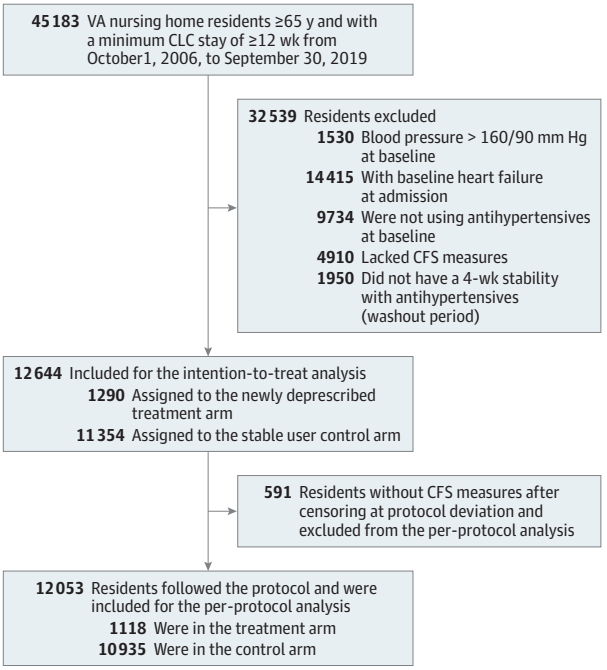
Covariates

For both the ITT and per-protocol analyses, we collected the following covariates for potential confounding and modeling: sociodemographic covariates collected from the electronic health record including age, sex, race and ethnicity, and US region of residence; admission comorbidity indicators based on codes from the *International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revision (ICD)* for acute kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, cerebrovascular disease, depression, kidney failure, peripheral vascular disease, coronary heart disease, dementia, diabetes, any malignant neoplasm, metastatic cancer, ischemic or unspecified stroke, osteoarthritis; vital signs and health history covariates including systolic/diastolic BP, activities of daily living (ADL), number and median daily dose of antihypertensive medications, weight, smoking status, history of falls, and insulin use indicator; laboratory values including blood urea nitrogen, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glycated hemoglobin, serum albumin, total cholesterol, carbon dioxide, estimated glomerular filtration rate, serum glucose, serum potassium, serum sodium, triglycerides, and serum creatinine; and Steinman Indices, composite measurements of multimorbidity for risk assessment, including ADL, instrumental ADL, hospitalization, death.[25] Dementia was ascertained using *ICD* codes during 1 year before CLC admission (eTable 3 in Supplement 1). Covariates were sourced from the VA Corporate Data Warehouse.

Statistical Analysis

To estimate the association of deprescribing compared to the stable user, we used the ordinal logistic generalized linear mixed model (GLMM) to analyze the longitudinal CFS outcome. The proportional odds ratio (OR) assumption was examined via the Brant-Wald test, with $P > .05$ suggesting this assumption was upheld. We incorporated a random intercept to account for intrapatient heterogeneity and used the cumulative logit function to model the ordinal CFS with the covariates. For the estimation of the fixed-effects, the Gauss-Hermite quadrature method was applied to estimate the marginal likelihood function using 10 quadrature points.[26,27] The unadjusted model included follow-up time (modeled per 12 weeks), treatment (deprescribing), and the interaction (time × treatment). We analyzed the entire population before stratifying by dementia status (dementia vs nondementia) to investigate possible effect modification.

Figure 1. Cohort Flowchart for Target Trial Study Participants Exclusion and Censorship



CFS indicates Cognitive Function Scale; CLC, community living center; and VA, US Department of Veterans Affairs.

To emulate the randomization process, we used the inverse probability of treatment weighting (IPTW) method, adjusting for potential confounders. Specifically, we calculated the propensity for deprescribing, converted this into weights, and used these weights in the outcome model. For the per-protocol analysis, we further modeled the probability of censoring due to protocol deviations and applied the inverse probability of censoring weighting (IPCW). We designated the per-protocol approach as our primary analysis which would estimate the effects of deprescribing if the patients remained in their deprescribing and stable user groups. We used the SuperLearner algorithm to model the probability of treatment and censoring, integrating a variety of algorithms such as the mean model, logistic regression, least absolute shrinkage and selection operator, interaction model, classification and regression tree, neural network, random forest, and gradient boosting. The balance of the covariates before and after applying IPTW and IPCW weighting is illustrated in eFigure 4 in Supplement 1. To account for residual confounding, we adjusted for the following covariates: age, sex, race, baseline ADL, systolic/diastolic BP, weight, median daily medication dose, falls within 30 days, depression, diabetes, peripheral vascular disease, presence of malignant and/or metastatic tumors, end-stage renal disease, and Steinman risk indices in the ordinal GLMMs. The weighting approach was implemented in both the unadjusted and the fully adjusted models.

We conducted sensitivity analyses using 2 outcomes, hearing ability and pain intensity level, as negative control studies. Both outcomes were ordinal variables with 4 naturally or-

dered levels, derived from the MDS. The results of these analyses are presented in eTable 5 in Supplement 1. eFigure 7 in Supplement 1 reports the weekly changes in systolic BP compared with baseline systolic BP across different treatment groups from time 0 to per-protocol censoring.

We present treatment effects as ORs with 95% CIs. The E-value, which assesses the robustness of an estimated effect against potential unmeasured confounding, was reported alongside ORs. A higher E-value indicates that the association is more robust to potential unmeasured confounding.[28,29] Additionally, we displayed the predicted probabilities across various CFS levels between treatment groups. For the construction of the ordinal GLMMs, we used SAS, 9.4 (SAS Institute Inc) and for SuperLearner execution, we used R, version 4.1.1 (The R Foundation for Statistical Computing). Data analyses were performed from May 1, 2023, and July 1, 2024.

Results

In all, 12 644 CLC residents (mean [SD] age, 77.7 [8.3] years; 12 315 [97.4%] males and 329 [2.6%] females; 49 [0.4%] American Indian, 155 [1.2%] Asian or Pacific Islander, 2207 [17.5%] Black, and 9247 [73.1%] White individuals, with 592 [4.7%] of Hispanic ethnicity) met the eligibility criteria and were included in the ITT analysis (**Table 1**). Of these, 1290 residents (10.2%) experienced deprescribing episodes and 11 354 (89.8%) remained stable users. Median (range) follow-up duration was 23 (9-65) weeks for the deprescribing group and 21 (5-77) weeks for the stable users. Within 2 years of follow-up, 383 participants (29.7%) in the deprescribing group and 2592 participants (22.8%) in the stable user group had died; 769 participants (59.6%) in the deprescribing group and 7342 participants (64.7%) in the stable user group were discharged from the CLC. Within these groups, 586 residents (45.4%) from the deprescribing group and 4551 stable users (40.1%) deviated from their assigned treatment group and were censored in the week of deviation. We excluded 591 residents (4.7%) without CFS measures between time 0 and the censored week; therefore, the per-protocol analysis included 12 053 residents (95.3%; Figure 1).

Residents in the control group had higher baseline BP, lower median ADL difficulty counts, and were taking fewer antihypertensive medications compared to the deprescribing group (Table 1). Residents in the deprescribing group had an elevated weekly average systolic BP compared to stable users (eFigure 7 in Supplement 1). No significant cognitive differences were observed at baseline. Stable users had a lower proportion of laboratory test result changes, with a creatinine increase of 50% or greater and potassium counts less than 3.5 mEq/L (to convert to mmol/L, multiply by 1) compared to the deprescribing group. Residents in the deprescribing group had a slightly higher Steinman index for mortality, indicating higher mortality risk. The standardized mean differences were all within 0.1, indicating balanced covariates after weighting (eFigure 4 in Supplement 1).[30]

Compared to their CFS at the beginning of the follow-up, 12.0% of the residents had a worsened CFS (higher score), while 7.7% had an improved CFS (lower score) by the end of the follow-up. Additionally, 10.8% of the residents in the deprescribing group and 12.1% in the stable user group had a worsened CFS score. **Table 2** presents the primary findings. In the fully adjusted per-protocol analysis, which considered only those residents who followed their assigned group, residents in the deprescribing group experienced a 12% reduction in the odds of progressing to a worse CFS category per 12-week period (odds ratio [OR], 0.88; 95% CI, 0.78-0.99; $P = .04$) compared to stable users. This association remained consistent in ITT analysis, demonstrating a protective association, albeit with an attenuated magnitude (OR, 0.94; 95% CI, 0.90-0.98).

When stratified by dementia, we noticed similar trends of cognitive decline in both groups throughout the study. This decline was statistically significant given the association between dementia status, deprescribing, and time. Among residents with dementia, those in the deprescribing group had a 16% reduced odds of cognitive function worsening per 12-week period (OR, 0.84; 95% CI, 0.72-0.98). The E-values for the interaction terms in both analyses were modest (ITT E-value = 1.32; per-protocol E-value = 1.53). The main effects of deprescribing at baseline and time are detailed in eTable 2 in Supplement 1.

Figure 2 illustrates the marginal predicted probabilities for each cognitive function category over time based on the fully adjusted per-protocol analysis. At the start of the study (baseline cognitive state), residents in the stable user group were more likely to be estimated as cognitively intact (Figure 2A) or mildly impaired (Figure 2B), whereas they had a lower probability of being moderately impaired (Figure 2C) or severely impaired (Figure 2D) when compared to the deprescribing group. Over time, both the deprescribing and stable user groups experienced a decline in cognitive function with a higher probability of residents entering categories with higher levels of cognitive impairment (ie, more residents entering the categories of moderately or severely impaired). Residents in the deprescribing group demonstrated a slower rate of decline across all cognitive function categories compared to stable users. For example, the probability of being cognitively intact and mildly impaired for the deprescribing group decreased more gradually than among stable users, implying that deprescribing was associated with a slower transition to more severe states of cognitive impairment.

The analyses assessing the association between deprescribing, and 2 negative control outcomes are presented in eTable 5 in Supplement 1. Results showed that deprescribing was associated with worse hearing ability and no difference in pain intensity.

Discussion

Our study provides novel evidence regarding the association of antihypertensive deprescribing with cognitive outcomes among older nursing home residents. Based on a target trial emulation, residents who were deprescribed antihypertensive medications had slower cognitive decline when compared with residents who maintained a stable antihypertensive regimen. Notably, this association was stronger in persons with

Table 1. Baseline Characteristics of Study Cohort, Stable Use of Antihypertensive Medication (Control) Arm Compared With Newly Deprescribed Arm

Variable	Analysis arm					
	Intention to treat, No. (%)			Per protocol, No. (%)		
	Stable use	Newly deprescribed	SMD	Stable use	Newly deprescribed	SMD
Participants, No.	11 354	1290	NA	10 935	1118	NA
Demographic characteristic						
Age, mean (SD), y	77.6 (8.3)	78.0 (8.3)	0.04	77.6 (8.3)	78.0 (8.4)	0.05
Female	295 (2.6)	34 (2.6)	0.002	286 (2.6)	28 (2.5)	−0.007
Male	11 059 (97.4)	1256 (97.4)		10 649 (97.4)	1090 (97.5)	
Race						
American Indian	44 (0.4)	5 (0.4)	0.15	42 (0.4)	4 (0.4)	0.17
Asian/Pacific Islander	145 (1.3)	10 (0.8)		138 (1.3)	10 (0.9)	
Black	1998 (17.6)	209 (16.2)		1935 (17.7)	171 (15.3)	
White	8270 (72.8)	977 (75.7)		7952 (72.7)	857 (76.7)	
Multiple races	87 (0.8)	6 (0.5)		85 (0.8)	5 (0.4)	
Unknown	810 (7.1)	83 (6.4)		783 (7.2)	71 (6.4)	
Hispanic ethnicity	535 (4.7)	57 (4.4)	−0.01	517 (4.7)	49 (4.4)	−0.02
US region of residence						
Continental	1457 (12.8)	203 (15.7)	0.15	1396 (12.8)	171 (15.3)	0.12
Midwest	2679 (23.6)	308 (23.9)		2577 (23.6)	270 (24.2)	
North Atlantic	3600 (31.7)	378 (29.3)		3468 (31.7)	326 (29.2)	
Pacific	1662 (14.6)	160 (12.4)		1618 (14.8)	143 (12.8)	
Southeast	1956 (17.2)	241 (18.7)		1876 (17.2)	208 (18.6)	
Vital signs, mean (SD)[a]						
Systolic BP, mm Hg	129.6 (19.4)	124.3 (19.9)	−0.27	129.7 (19.3)	124.2 (19.9)	0.03
Diastolic BP, mm Hg	70.2 (10.8)	67.6 (10.8)	−0.24	70.3 (10.8)	67.6 (10.7)	0.04
Weight, lb	190.5 (47.4)	188.5 (45.3)	−0.05	190.7 (47.5)	188.3 (44.9)	−0.05
Nursing home admission measures						
ADL,[b] median (IQR)	12 (6-19)	13 (6-19)	0.07	13 (6-19)	13.5 (7-20)	0.21
Cognitive impairment, per CFS						
Cognition intact	3364 (29.6)	364 (28.2)	0.06	3290 (30.1)	327 (29.2)	0.10
Mildly impaired	4409 (38.8)	511 (39.6)		4219 (38.6)	427 (38.2)	
Moderately impaired	2718 (23.9)	305 (23.6)		2606 (23.8)	270 (24.2)	
Severely impaired	863 (7.6)	110 (8.5)		820 (7.5)	94 (8.4)	
Medication use						
Insulin	3844 (33.9)	438 (34)	0.002	3709 (33.9)	370 (33.1)	−0.02
Antihypertensive use, median No.						
1	5378 (47.4)	532 (41.2)	0.16	5199 (47.5)	482 (43.1)	0.13
2	3986 (35.1)	460 (35.7)		3830 (35)	399 (35.7)	
3	1525 (13.4)	231 (17.9)		1461 (13.4)	187 (16.7)	
≥4	465 (4.1)	67 (5.2)		445 (4.1)	50 (4.5)	
Antihypertensive use, mean (SD)	1.8 (1.7)	2.0 (1.8)	0.27	1.8 (1.7)	1.9 (1.7)	0.10
Comorbidities						
Acute kidney injury	2162 (19.0)	264 (20.5)	0.05	2082 (19.0)	232 (20.8)	0.04
Atrial fibrillation	2234 (19.7)	261 (20.2)	0.01	2164 (19.8)	233 (20.8)	0.03
COPD	1603 (14.1)	142 (11.0)	−0.09	1565 (14.3)	132 (11.8)	−0.07
Cerebrovascular disease	3900 (34.3)	448 (34.7)	0.008	3754 (34.3)	384 (34.3)	0
Depression	4648 (40.9)	524 (40.6)	−0.006	4470 (40.9)	451 (40.3)	−0.01
Kidney failure	2961 (26.1)	352 (27.3)	0.03	2836 (25.9)	305 (27.3)	0.03
Peripheral vascular disease	2807 (24.7)	320 (24.8)	0.002	2678 (24.5)	268 (24.0)	−0.01
Coronary heart disease	4102 (36.1)	485 (37.6)	0.03	3946 (36.1)	423 (37.8)	0.04
Dementia	5350 (47.1)	575 (44.6)	−0.05	5145 (47.1)	496 (44.4)	−0.05
Diabetes	5384 (47.4)	586 (45.4)	−0.04	5193 (47.5)	505 (45.2)	−0.05
Any malignant neoplasm	3156 (27.8)	400 (31)	0.07	3026 (27.7)	354 (31.7)	0.09
Metastatic cancer	979 (8.6)	156 (12.1)	0.11	947 (8.7)	140 (12.5)	0.13
Osteoarthritis	2935 (25.8)	349 (27.1)	0.03	2813 (25.7)	303 (27.1)	0.03
Ischemic/unspecified stroke	2103 (18.5)	236 (18.3)	0.05	2033 (18.6)	202 (18.1)	−0.01

(continued)

Table 1. Baseline Characteristics of Study Cohort, Stable Use of Antihypertensive Medication (Control) Arm Compared With Newly Deprescribed Arm (continued)

Variable	Analysis arm					
	Intention to treat, No. (%)			Per protocol, No. (%)		
	Stable use	Newly deprescribed	SMD	Stable use	Newly deprescribed	SMD
Fall and smoking history						
Fall in 30 d prior	5082 (44.8)	599 (46.4)	0.03	4869 (44.5)	517 (46.2)	0.04
Smoking history						
No	6433 (56.7)	755 (58.5)	0.05	6199 (56.7)	663 (59.3)	0.05
Yes	2789 (24.6)	300 (23.3)		2694 (24.6)	258 (23.1)	
Unknown	2132 (18.8)	235 (18.2)		2042 (18.7)	197 (17.6)	
Laboratory test results, mean (SD)						
Blood urea nitrogen, mg/dL	24.0 (11.9)	27.0 (16.1)	0.22	24.0 (11.9)	26.7 (15.9)	0.01
HDL, mg/dL	40.4 (13.4)	39.9 (13.7)	−0.04	40.5 (13.4)	39.6 (13.6)	0.01
LDL, mg/dL	76.6 (30.3)	76.6 (30.5)	0	76.6 (30.2)	76.6 (30.5)	−0.08
Total cholesterol, mg/dL	139.7 (37.1)	139.1 (38.0)	−0.02	139.7 (37.1)	138.8 (37.8)	−0.03
Glycated hemoglobin, %	6.3 (1.3)	6.2 (1.3)	−0.03	6.3 (1.3)	6.2 (1.3)	−0.24
Albumin, g/dL	3.3 (0.6)	3.1 (0.6)	−0.19	3.3 (0.6)	3.1 (0.6)	−0.002
Carbon dioxide, mEq/L	27.0 (3.5)	26.7 (3.8)	−0.09	27.0 (3.5)	26.8 (3.9)	0.05
Creatinine eGFR, mL/min/1.73 m^2	75.4 (34.2)	73.6 (35.0)	−0.05	75.6 (34.1)	74.1 (34.8)	−0.002
Glucose, mg/dL	122.4 (50.6)	123.8 (51.3)	0.03	122.5 (50.6)	123.2 (51.3)	−0.06
Potassium, mEq/L	4.2 (0.5)	4.3 (0.5)	0.05	4.3 (0.5)	4.3 (0.5)	0.02
Serum creatinine, mg/dL	1.4 (1.9)	1.5 (2.4)	0.06	1.4 (1.9)	1.5 (2.5)	−0.02
Sodium, mEq/L	138.2 (5.4)	137.7 (6.0)	−0.08	138.2 (5.5)	137.7 (6.1)	−0.04
Triglycerides, mg/dL	118.5 (63.7)	116.9 (64.3)	−0.03	118.6 (63.8)	115.4 (62.4)	0.01
Creatinine increase of 50%[c]	122 (1.1)	29 (2.2)	0.092	118 (1.1)	25 (2.2)	−0.06
Potassium counts <3.5[c]	223 (2.0)	42 (3.3)	0.08	210 (1.9)	32 (2.9)	0.08
Sodium count decline of 5[c]	416 (3.7)	58 (4.5)	0.04	397 (3.6)	46 (4.1)	−0.009
Steinman Index,[d] mean (SD)						
ADL	2.3 (1.8)	2.3 (1.8)	0.02	2.3 (1.8)	2.4 (1.9)	0.04
IADL	2.7 (1.9)	2.8 (1.9)	0.03	2.7 (1.9)	2.8 (1.9)	0.03
Hospitalization	3.0 (2.4)	3.1 (2.4)	0.03	3.0 (2.4)	3.1 (2.4)	0.03
Death	2.4 (1.7)	2.6 (1.8)	0.08	2.5 (1.7)	2.6 (1.8)	0.08

Abbreviations: ADL, activities of daily living; CFS, Cognitive Function Scale; COPD, chronic obstructive pulmonary disease; EGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; IADL, instrumental activities of daily living; LDL, low-density lipoprotein cholesterol; SMD, standardized mean difference.

[a] Measured prior to time 0.

[b] Composed of 7 items: bed mobility, transfer, walking/locomotion, dressing, eating, toilet use, and personal hygiene that were rated on a 5-level scale from 0 (totally independent) to 4 (totally dependent), making the overall ADL score range from 0 to 28.

[c] Calculated prior to time 0.

[d] Steinman Index consists of 4 indices of multimorbidity developed from Medicare claims data and is designed to assess risks associated with ADL dependency, IADL dependency, hospitalization, and mortality.

SI conversion factor: to convert blood urea nitrogen to mmol/L, multiply by 0.357; HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; glycated hemoglobin to proportion of total hemoglobin, multiply by 0.01; albumin to g/L, multiply by 10; carbon dioxide to mmol/L, multiply by 1; creatinine eGFR to mL/s/m2, multiply by 0.0167; glucose to mmol/L, multiply by 0.0555; potassium to mmol/L, multiply by 1; serum creatinine to μmol/L, multiply by 88.4; sodium to mmol/L, multiply by 1; triglycerides to mmol/L, multiply by 0.0113.

dementia. However, we interpret these results with caution because the estimates were close to null, the precision was limited, and the E-value suggests that moderate to strong unmeasured confounding could offset a potential protective effect. Our results align with emerging literature[21,31,32] and suggest caution regarding intensive BP control in older adults living in nursing homes, particularly those with cognitive impairment.

Our results complement the existing evidence found in RCTs on deprescribing in community-dwelling older adults. The OPTIMISE trial[33] randomized 569 patients (mean age, 84.8 years) to deprescribing and control arms with a primary outcome of systolic BP less than 150 mm Hg at the 12-week follow-up. Deprescribing was noninferior to usual care with an adjusted 1-sided relative risk of 0.98 (97.5% CI, 0.92 to ∞). The ECSTATIC trial[34] assessed the predicted cardiovascular disease (CVD) risk between a deprescribing cardiovascular medication arm and a usual care arm, enrolling 1067 participants with a mean age of 55 years and including 319 in the per-protocol deprescribing arm. After a 2-year follow-up, the predicted CVD risk increased by 2.0% in the deprescribing arm and 1.9% in the usual care arm. Nevertheless, neither trial examined the impact of deprescribing on cognitive function, leaving a gap in our understanding of the broader impacts of deprescribing. The DANTE trial,[35] involving 385 older adults residing in the community with mild cognitive impairment and no history of heart conditions, found no difference in cognitive or daily functional outcomes, but follow-up was limited to only 16 weeks. Most importantly, these 3 trials only included older

Table 2. Association of Deprescribing Antihypertensive Medication With Change in Cognitive Function Scale (CFS) Score, by Per-Protocol and Intention-to-Treat Analyses

Variable	Odds ratio (95% CI)[a]			
	Per-protocol analysis		Intention-to-treat analysis	
	Unadjusted[b]	Fully adjusted[c]	Unadjusted[b]	Fully adjusted[c]
All nursing home residents[d]				
Deprescribing × time (12 wk)	0.99 (0.99-1.01)	0.88 (0.78-0.99)	0.94 (0.90-0.98)	0.94 (0.90-0.98)
E-value	1.11	1.53	1.32	1.32
Residents without dementia				
Deprescribing × time (12 wk)	0.94 (0.76-1.18)	0.94 (0.75-1.17)	0.96 (0.90-1.04)	0.95 (0.89-1.02)
E-value	1.32	1.17	1.25	1.29
Residents with dementia				
Deprescribing × time (12 wk)	0.95 (0.82-1.09)	0.84 (0.72-0.98)	0.94 (0.90-0.99)	0.94 (0.89-0.98)
E-value	1.29	1.67	1.32	1.32

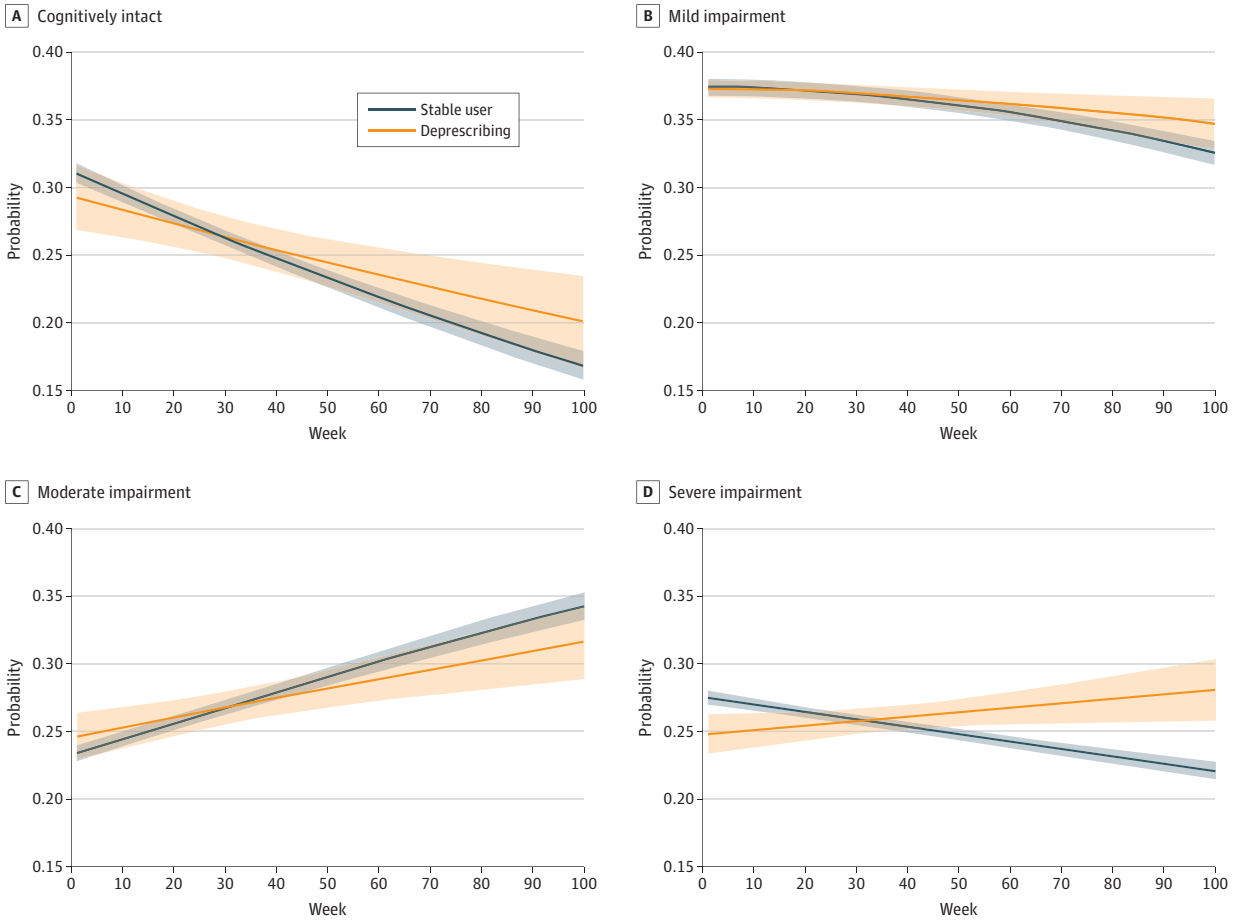
[a] An odds ratio less than 1 suggests a protective association with deprescribing over time.

[b] Unadjusted model: CFS approximate time + deprescribing + time × deprescribing.

[c] Fully adjusted model: unadjusted + age, sex, race or ethnicity, baseline activities of daily living score, systolic/diastolic blood pressure, weight, median daily medication dose, occurrences of falls within 30 days, depression, diabetes, peripheral vascular disease, presence of malignant and metastatic tumors, end-stage renal disease, and 4 Steinman risk indices.

[d] Overall, 12.1% of the residents transitioned to a worsened (higher) score on the CFS at the end of the follow-up period, 10.8% in the deprescribed group and 12.1% in the stable user group.

Figure 2. Average Predicted Probabilities Over Time for the Cognitive Function Scale Categories, With 95% CI Bands



Shading indicates 95% CI band for the predicted probabilities for each cognitive function category.

adults living in the community, who are generally healthier than older adults living in nursing homes.

Although a robust association exists between midlife hypertension and cognitive decline and dementia in later life, the association may change with aging. Two longitudinal studies, the AGE-Reykjavik[31] and the ARIC,[36] showed that individuals with midlife hypertension who later exhibited lower BP measurements in late life had poorer cognitive performance. In contrast, those without a history of midlife hypertension generally maintain consistent cognitive function, regardless of their BP levels in later years. This pattern suggests that the long-term effects of hypertension on cognitive function can vary based on when hypertension first develops and its duration. Recognizing the differential effects of hypertension across the life course could help target the optimal timing for deprescribing. Deprescribing should involve a strategic and careful reduction or discontinuation of nonessential antihypertensive medications. This process must be person-centered, considering individual risk factors and medical history of BP control.[9]

Target trial emulation is a complementary approach to RCTs and proves useful when RCTs are challenging to implement or when assessing treatment effects in populations excluded from RCTs. Both situations apply in our study.[37] However, similar to most observational studies, our study may be subject to residual confounding. Thus, to mitigate this bias, we implemented multiple methods including inverse probability weighting with SuperLearner, multivariable adjustment for residual confounding, and the evaluation of negative control outcomes, hearing loss and pain. The results from the analysis of change in hearing ability over time suggested a modest harmful effect of deprescribing; this is reassuring as it suggests that any bias of our design and analytic approach would result in a conservative bias. We used a robust and valid study design, aligning eligibility criteria, treatment assignment, and follow-up from time zero to mitigate biases, such as immortal time bias. Moreover, other studies have demonstrated that the results from well-designed target trial emulations largely align with those from RCTs, demonstrating the method's effectiveness, although not its infallibility.[38] Future studies could benefit from employing techniques such as instrumental variable analysis to better control for unmeasured confounding, especially given the robust design of our approach. Additionally, enhancing the representativeness of the sample by including more diverse populations beyond the VA, and using alternative statistical methods for further validation of the findings, could strengthen future research efforts.

Limitations

Our cohort study has additional strengths and limitations. We used a robust target trial emulation design involving a large cohort of older, co-morbid nursing home residents with a prolonged follow-up duration. We used detailed medication administered information to meticulously track medication adjustments in terms of quantity and dosage. Additionally, the use of MDS data captures a comprehensive and longitudinal view of cognitive outcomes throughout the study, offering ample repeated measurements conducive to sophisticated modeling approaches. Our study contains several limitations. First, the VA population is predominantly male and white, thus limiting the generalizability of our results to females and other racial and ethnic groups. Second, our cohort did not include patients with heart failure, limiting the generalizability of our results to this population. Third, the specificity of our dementia diagnosis is limited, as our current ascertainment lumps together various forms of dementia, such as Alzheimer disease and vascular dementia. Differentiating the impacts of deprescribing among these subgroups is challenging with the current *ICD* coding system, and the small sample sizes within each subgroup may not support valid analyses.

Conclusions

Our study suggests that deprescribing antihypertensives may protect nursing home residents from future cognitive losses, especially for those living with dementia. This work highlights the need for patient-centered approaches to deprescribing, ensuring that medication regimens for older adults are optimized to preserve cognitive function and minimize potential harms.

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