ORIGINAL ARTICLE

Reduction of Antihypertensive Treatment in Nursing Home Residents

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ABSTRACT

BACKGROUND

Among older adults with frailty, evidence on the benefits and risks of discontinuing antihypertensive drugs is limited.

METHODS

In a multicenter, randomized, controlled trial conducted in France, we assigned, in a 1:1 ratio, nursing home residents 80 years of age or older who were receiving more than one antihypertensive drug and had a systolic blood pressure below 130 mm Hg to a protocol-driven strategy of progressive reduction of antihypertensive treatment (step-down group) or to receive usual care (usual-care group). Patients were to be followed for up to 4 years. The primary end point was death from any cause. Secondary end points included the changes in the number of antihypertensive drugs being used from baseline to the last trial visit and the change in systolic blood pressure during the follow-up period.

RESULTS

A total of 1048 patients underwent randomization: 528 to the step-down group and 520 to the usual-care group. The estimated median potential follow-up was 38.4 months. Between baseline and the last trial visit, the mean (±SD) number of antihypertensive drugs being used decreased from 2.6±0.7 to 1.5±1.1 in the step-down group and from 2.5±0.7 to 2.0±1.1 in the usual-care group. The adjusted mean between-group difference (step-down group minus usual-care group) in the change in systolic blood pressure during the follow-up period was 4.1 mm Hg (95% confidence interval [CI], 1.9 to 5.7). Death from any cause occurred in 326 patients (61.7%) in the step-down group and in 313 (60.2%) in the usual-care group (adjusted hazard ratio, 1.02; 95% CI, 0.86 to 1.21; P=0.78). There were no apparent differences in adverse events between the trial groups.

CONCLUSIONS

Among older nursing home residents with frailty who were receiving treatment with antihypertensive agents and had a systolic blood pressure below 130 mm Hg, an antihypertensive treatment step-down strategy did not lead to lower all-cause mortality than usual care. (Funded by the French Ministry of Health and others; RETREAT-FRAIL ClinicalTrials.gov number, NCT03453268.)

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*A complete list of members of the RETREAT-FRAIL Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Older patients with hypertension are at high risk for cardiovascular complications. Owing to this increased risk, such patients may derive substantial benefits from antihypertensive drugs.[1,2] However, randomized clinical trials have generally excluded patients with clinically significant frailty, who are more likely than other patients of similar ages to have adverse effects from antihypertensive drugs.[3,4] Several observational studies have found that among patients with frailty, low blood pressure is associated with increased cardiovascular morbidity and mortality,[5,6] especially in those receiving antihypertensive treatment.[5,7-9] In the observational PARTAGE (Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population) study, which enrolled nursing home residents who were at least 80 years of age with hypertension, all-cause mortality among participants with a systolic blood pressure below 130 mm Hg who were receiving more than one antihypertensive medication was twice as high as that among other residents.[5]

This finding from the PARTAGE study raises questions regarding the management of hypertension in older patients with clinically significant frailty.[10] Recent European guidelines on hypertension management[11,12] emphasize the need to adapt therapeutic strategies according to the level of frailty and to consider gradual reduction of antihypertensive treatment in patients with low blood pressure. However, evidence on the benefits and risks of discontinuing drugs in older adults is limited, and there is consensus that clinical research should focus on populations in which uncertainty about the benefit and risk regarding the use of antihypertensive medications is greatest, such as persons with frailty, those who are older, and those who are taking multiple medications.[13]

Here, we describe the results of RETREAT-FRAIL (Reduction of Antihypertensive Treatment in Frail Patients), a pragmatic, interventional, randomized trial that evaluated the effect of a protocol-driven strategy of progressive reduction of antihypertensive therapies as compared with usual care on all-cause mortality among nursing home residents who were 80 years of age or older and had frailty, had a systolic blood pressure of less than 130 mm Hg, and were receiving at least two antihypertensive agents.

Methods

Trial Oversight

This randomized, open-label clinical trial was conducted in 108 nursing homes in France. A coordinating team provided training regarding standardized blood-pressure measurements and training and certification regarding Good Clinical Practice standards to the physicians caring for patients enrolled in the trial. The training on Good Clinical Practice standards was conducted online with Formedea software that had been set up for the training of clinicians in French public hospitals. Knowledge of these standards was assessed with multiple-choice questionnaires, and documentation regarding certification was delivered to the participant and the coordinating team, which shared it with the institutional review board, once completion of the training was validated.

The trial protocol (available with the full text of this article at NEJM.org) was approved by the ethics committee of Ile-de-France VII. Details regarding the trial organization are provided in the Supplementary Appendix (available at NEJM.org). An independent data and safety monitoring board reviewed safety data during the trial. The trial was conducted and reported according to the principles of the Declaration of Helsinki and current Good Clinical Practice guidelines. The authors had access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial and this report to the protocol.

Patients

Patients were eligible for enrollment if they were 80 years of age or older, resided in a nursing home, were being treated for hypertension with more than one antihypertensive drug, and had a systolic blood pressure below 130 mm Hg. Patients who were not receiving an antihypertensive drug that could be discontinued because of a compelling indication and those with an estimated life expectancy of less than 3 months were excluded. Additional details about inclusion and exclusion criteria are provided in the Supplementary Appendix.

Written informed consent was obtained from capable patients or from their legal representatives, as appropriate. For patients who were un-

able to consent and had no legal representative, the ethics committee of Ile-de-France VII authorized family members or other relatives to provide informed consent.

TRIAL DESIGN AND INTERVENTIONS

Patients were randomly assigned in a 1:1 ratio to a protocol-driven strategy of progressive discontinuation of antihypertensive drugs (step-down group) or to receive usual care (usual-care group). Randomization was performed with a Web-based randomization system (CleanWeb). The randomization list was generated by means of the PLAN procedure in SAS software, version 9.4 (SAS Institute), and used permuted blocks of four or eight, with stratification according to nursing home.

Patients were to be followed for up to 4 years after enrollment. At the time of enrollment, patients underwent a complete clinical evaluation, which included assessment of autonomy with the Index of Activities of Daily Living (ADL; scores range from 0 to 6, with higher scores indicating greater independence),[14] assessment of cognition with the Mini–Mental State Examination (MMSE; range, 0 to 30; higher scores indicate greater cognitive function),[15] assessment of muscular force with a hand-grip strength test,[16] assessment of mobility with a walk test (longer walking times indicate greater mobility) and the Short Physical Performance Battery (SPPB; range, 0 to 12; higher scores indicate better physical performance),[16] and assessment of quality of life with the European Quality of Life 5-Dimension 3-Level (EQ-5D-3L) questionnaire (range, 0 to 1; higher scores indicate better quality of life).[17]

The level of frailty was assessed with an algorithm that calculated a composite score. The algorithm included data on functional capacities (autonomy, mobility, and cognitive status) measured in the trial to classify frailty levels according to scores on the validated Clinical Frailty Scale (scores range from 1 to 9, with higher scores indicating greater frailty).[18,19] Additional details about the assessments at baseline and during the follow-up period are provided in Table S1 in the Supplementary Appendix.

The protocol-driven reduction of antihypertensive medications began immediately after randomization in all the patients in the step-down group. Subsequent discontinuation of treatments occurred during visits at 3 and 6 months and then every 6 months thereafter if the systolic blood pressure remained below 130 mm Hg in the absence of an acute medical illness. The methods for blood-pressure measurement are detailed in the Supplementary Appendix.

As indicated in the trial protocol, several precautionary measures were implemented in order to minimize the risks associated with discontinuing medications. Before randomization, a senior consultant reviewed the antihypertensive medications being used by each patient and determined those that could be discontinued (list 1 medications) and those that could not be discontinued owing to medical necessity (list 2 medications). For patients in the step-down group, the local investigator was responsible for the management of list 1 medications, with prior approval from the general practitioner of each patient. The sequence in which medications were discontinued was based on a prespecified trial algorithm (Fig. S1). Only one medication could be discontinued at each visit. In the case of beta-blockers, treatment was first reduced to a half dose and then withdrawn 1 week later if the systolic blood pressure remained below 130 mm Hg; the same approach was used with loop diuretics unless these drugs were being used at low doses. All other drugs were discontinued without a reduction in dose. If the patient's systolic blood pressure increased to 160 mm Hg or greater after treatment reduction, treatment with the last discontinued drug was reintroduced at a half dose (Fig. S2). In the usual-care group, the patient's general practitioner was asked to continue to manage antihypertensive treatment as usual.

END POINTS

The primary end point was death from any cause. Secondary end points included a composite of major adverse cardiovascular events (defined as the first occurrence of death from cardiovascular causes, stroke, myocardial infarction and other serious coronary artery disease events, acute heart failure, pulmonary embolism, deep-vein thrombosis, atrial fibrillation and major heart-rhythm and conduction disorders, major peripheral vascular events, or transient ischemic attack) as assessed by an independent adjudication committee, death from noncardiovascular causes, the change from baseline in systolic and diastolic blood pressure (measured while the

patient was seated), the change from baseline in functional capacity (the score on the ADL, the score on the SPPB, and the peak force on the handgrip test) assessed as the area under the curve (AUC), the change from baseline in the score on the MMSE assessed as the AUC, the number of fractures, the number of falls, the change from baseline to the last trial visit in the total number of medications, the change from baseline to the last trial visit in the number of antihypertensive drugs, the change from baseline in the score on the EQ-5D-3L questionnaire as assessed as the AUC, and death from coronavirus disease 2019 (Covid-19) (Table S2). Members of the adjudication committee and data analysts were unaware of the patient's trial-group assignment.

STATISTICAL ANALYSIS

We estimated that 550 participants per group would provide at least 80% power to detect a 25% lower risk of a primary end-point event (hazard ratio, 0.75) with the step-down strategy than with usual care, using a two-sided log-rank test at an alpha level of 0.05. This estimate was based on the assumption of a primary end-point event occurring in 30% of the patients in the usual-care group by 24 months, a 5% early withdrawal rate, an accrual period of 24 months, and a maximum follow-up period of 48 months. The sample-size calculations were conducted with nQuery 7 Pro software (Statistical Solutions).

An interim efficacy analysis was conducted after 500 participants had completed 1 year of follow-up. To preserve the overall type 1 error rate of 0.05, the primary end point was assessed at a significance level of 0.001 in the interim analysis and 0.049 in the final analysis.

The primary analysis was performed according to the intention-to-treat principle. A hierarchical testing procedure was used, in which secondary end points were to be tested without alpha adjustment only if the between-group difference with regard to the primary end point was significant. Each secondary end point was to be tested sequentially according to the prespecified sequence shown in the Supplementary Appendix, contingent on the rejection of all preceding null hypotheses. If any null hypothesis in the hierarchy was not rejected, subsequent end points were to be presented as point estimates with 95% confidence intervals; such confidence intervals were not adjusted for multiplicity and should not be used to infer treatment effect. All tests were two-sided.

The primary efficacy end point was assessed with survival analysis based on a Cox proportional-hazards regression model with nursing home as a random effect and adjustment for prespecified covariates known to affect mortality (see the Supplementary Appendix). The proportional-hazards assumption was assessed by examining the plot of Schoenfeld residuals against time and using tests based on Schoenfeld residuals.[20] The proportional-hazards assumption was satisfied for all end points.

Survival was assessed with Kaplan–Meier analysis. The associated 95% confidence intervals were calculated with the use of the bias-corrected and accelerated bootstrap interval method from 10,000 repetitions of a Cox proportional-hazards regression model or a generalized linear model bootstrap procedure, clustered at the nursing home level.

To analyze secondary end points regarding the time to event with a competing risk, the cause-specific proportional-hazards model was used. In addition, the Fine–Gray proportional subdistribution hazards analysis was conducted as a sensitivity analysis to ensure robustness (Table S3).

Secondary continuous end points with repeated measurements were assessed with mixed-model repeated-measures analysis of variance with the Kenward–Roger adjustment for degrees of freedom. The model included trial group, visit, trial-group-by-visit interaction, and nursing home as random effects. Least-squares means and 95% confidence intervals were calculated for each trial group at each time point, along with between-group differences (step-down group minus usual-care group) and corresponding 95% confidence intervals.

Prespecified exploratory subgroup analyses of primary and secondary end points were conducted for age (>90 years or ≤90 years), baseline systolic blood pressure (<105 mm Hg, 105 to 115 mm Hg, or >115 mm Hg), chronic heart failure, and baseline Clinical Frailty Scale score (1, 2, or 3; 4 or 5; 6; or 7 or 8). All tests were performed with SAS software, version 9.4. Additional information about the statistical methods is provided in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

We screened 10,596 nursing home residents. A total of 1048 residents from 108 nursing homes underwent randomization: 528 to the step-down group and 520 to the usual-care group (Fig. S3). The participating nursing homes are listed in the Supplementary Appendix. The first patient underwent randomization on April 15, 2019, and the last patient on July 1, 2022. The recruitment period lasted 1 year longer than initially scheduled, primarily because of the Covid-19 pandemic. Follow-up ended in July 2024, which was 24 months after the last patient had undergone randomization. The estimated median potential follow-up was 38.4 months (interquartile range, 30.0 to 48.0) (Table S2).

The baseline demographic and clinical characteristics of the patients are shown in Table 1 and Table S4. The mean (±SD) age of the patients was 90.1±5.0 years, and 80.7% were women. The mean MMSE score was 13.4. In the assessment of frailty, 9.5% of the patients had a Clinical Frailty Scale score of 1, 2, or 3 (fit, well, or managing well, respectively); 29.9%, a score of 4 or 5 (vulnerable or mild frailty); 22.0%, a score of 6 (moderate frailty); and 38.5%, a score of 7 or 8 (severe frailty or very severe frailty). The mean systolic blood pressure was 113±11 mm Hg in the step-down group and 114±11 mm Hg in the usual-care group; the mean diastolic blood pressure was 65±10 mm Hg in both groups. Other baseline characteristics appeared to be similar in the two groups.

At baseline, the mean number of antihypertensive medications being taken by the patients was 2.5±0.7, of which 1.8±0.8 were list 1 medications (and could potentially be discontinued) and 0.7±0.7 were list 2 medications (and could not be discontinued) (Table 2). A total of 573 patients (54.7%) were taking at least one list 2 antihypertensive medication.

END POINTS AND SAFETY

The change in systolic blood pressure during the follow-up period in the step-down and usual-care groups is shown in Figure S4. During the follow-up period, the adjusted mean between-group difference in the change in systolic blood pressure was 4.1 mm Hg (95% confidence interval [CI], 1.9 to 5.7); the adjusted mean between-group difference in the change in diastolic blood pressure was 1.8 mm Hg (95% CI, 0.5 to 3.0). Drug reintroduction because of an increase in systolic blood pressure to 160 mm Hg or higher occurred in 7 patients in the step-down group. Postural changes in blood pressure during the follow-up period are shown in Table S5.

The adjusted mean between-group difference in the number of antihypertensive medications that were stopped was −0.73 (95% CI, −0.85 to −0.66) (Fig. S5). The mean number of antihypertensive drugs (list 1 plus list 2) being used decreased from 2.6±0.7 at baseline to 1.5±1.1 at the last trial visit in the step-down group and from 2.5±0.7 to 2.0±1.1 in the usual-care group. The mean number of concomitant medications being taken at baseline was generally similar to that at the last follow-up visit in each trial group (Table 2).

Death from any cause (primary end point) occurred in 326 patients (61.7%) in the step-down group and in 313 (60.2%) in the usual-care group (adjusted hazard ratio, 1.02; 95% CI, 0.86 to 1.21; P=0.78) (Table 3 and Fig. 1). Event rates during follow-up that were estimated with the Kaplan–Meier estimator are shown in Table S6. The results of prespecified subgroup analyses of all-cause mortality are shown in Figure 2.

Death from noncardiovascular causes occurred in 284 patients (53.8%) in the step-down group and in 278 (53.5%) in the usual-care group (Table 3). Acute heart failure occurred in 67 patients (12.7%) and 57 patients (11.0%) in the step-down and usual-care groups, respectively. A total of 264 patients (50.0%) in the step-down group and 260 (50.0%) in the usual-care group had a fall. Fracture occurred in 41 patients (7.8%) in the step-down group and in 48 (9.2%) in the usual-care group. Death from Covid-19 occurred in 6 patients (1.1%) in the step-down group and in 16 patients (3.1%) in the usual-care group. A composite of major adverse cardiovascular events occurred in 102 patients (19.3%) in the step-down group and in 90 (17.3%) in the usual-care group (hazard ratio, 1.15; 95% CI, 0.84 to 1.56) (Table 3 and Table S7). Results of subgroup analyses of the composite end point of major cardiovascular events are shown in Figure S6.

The least-squares mean AUC of the changes from baseline in scores on the MMSE, SPPB, ADL,

Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Step-Down Strategy (N=528)	Usual Care (N=520)	Total (N=1048)
Age — yr	90.0±4.8	90.1±5.3	90.1±5.0
Female sex — no. (%)	423 (80.1)	423 (81.3)	846 (80.7)
Weight — kg†	64.9±14.8	65.2±15.0	65.1±14.9
Height — m‡	1.59±0.09	1.58±0.09	1.59±0.09
Body-mass index§	25.9±5.6	26.3±5.8	26.1±5.7
Systolic blood pressure — mm Hg¶	113±11	114±11	114±11
Diastolic blood pressure — mm Hg¶	65±10	65±10	65±10
Heart rate — beats/min¶	72±12	71±12	71±12
MMSE score‖	13.5±10.0	13.3±10.1	13.4±10.0
ADL score**	3.1±2.0	3.2±2.0	3.1±2.0
SPPB score††	1.2 ±1.9	1.2 ±2.0	1.2 ±1.9
EQ-5D-3L questionnaire score ‡‡	0.431±0.407	0.468±0.398	0.449±0.403
Peak muscular force — kg§§	11.7±6.4	12.0±6.8	12.0±6.8
Clinical Frailty Scale score — no./total no. (%)¶¶			
1, 2, or 3	47/525 (9.0)	52/514 (10.1)	99/1039 (9.5)
4 or 5	147/525 (28.0)	164/514 (31.9)	311/1039 (29.9)
6	118/525 (22.5)	111/514 (21.6)	229/1039 (22.0)
7 or 8	213/525 (40.6)	187/514 (36.4)	400/1039 (38.5)
Medications‖‖			
No. of list 1 and list 2 antihypertensive medications	2.6±0.7	2.5±0.7	2.5±0.7
No. of concomitant medications	6.7±3.2	6.7±2.8	6.7±3.0

* Plus–minus values are means ±SD. The intention-to-treat population comprised patients who provided written informed consent and underwent randomization. The step-down strategy was a protocol-driven progressive reduction in the number of antihypertensive medications. The estimated median potential follow-up was 38.6 months (interquartile range, 30.1 to 48.0) in the step-down group and 37.9 months (interquartile range, 29.9 to 48.0) in the usual-care group.

† Data are for 1011 patients: 508 in the step-down group and 503 in the usual-care group.

‡ Data are for 865 patients: 443 in the step-down group and 422 in the usual-care group.

§ Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters. Data are for 860 patients: 441 in the step-down group and 419 in the usual-care group.

¶ Blood pressure and heart rate were assessed while the patient was seated.

‖ Scores on the Mini–Mental State Examination (MMSE) range from 0 to 30, with higher scores indicating greater cognitive function. Data are for 989 patients: 497 in the step-down group and 492 in the usual-care group.

** Scores on the Index of Activities of Daily Living (ADL) range from 0 to 6, with higher scores indicating greater independence. Data are for 1039 patients: 525 in the step-down group and 514 in the usual-care group.

†† Scores on the Short Physical Performance Battery (SPPB) range from 0 to 12, with higher scores indicating better physical performance. Data are for 974 patients: 496 in the step-down group and 478 in the usual-care group.

‡‡ Scores on the European Quality of Life 5-Dimension 3-Level (EQ-5D-3L) questionnaire range from 0 to 1, with higher scores indicating better quality of life. Data are for 781 patients: 401 in the step-down group and 380 in the usual-care group.

§§ Peak physical force was assessed with a manual digital dynamometer (Smedley, Homecraft AbilityOne). The highest force of three measurements was used. Data are for 794 patients: 413 in the step-down group and 381 in the usual-care group.

¶¶ The level of frailty was assessed with an algorithm that calculated a composite score. The algorithm included data on functional capacities (autonomy, mobility, and cognitive status) measured in the trial to classify frailty levels according to scores on the validated Clinical Frailty Scale. Scores range from 1 to 9, with a score of 1 indicating fit, 2 well, 3 managing well, 4 vulnerable, 5 mild frailty, 6 moderate frailty, 7 severe frailty, 8 very severe frailty, and 9 terminally ill.

‖‖ List 1 antihypertensive medications are defined as antihypertensive medications that could be discontinued, list 2 antihypertensive medications as those that could not be discontinued owing to medical necessity, and concomitant medications as all medications other than antihypertensive medications. Additional information about list 1 and list 2 antihypertensive medications and the protocols for reducing and reintroducing medications is provided in the Supplementary Appendix.

Table 2. Medications at Baseline and at the Last Follow-up Visit.*

Medications	Step-Down Strategy (N=528)	Usual Care (N=520)	Total (N=1048)
At baseline — no.			
List 1 antihypertensive medications	1.8±0.8	1.8±0.7	1.8±0.8
List 2 antihypertensive medications	0.7±0.7	0.7±0.7	0.7±0.7
List 1 and list 2 antihypertensive medications	2.6±0.7	2.5±0.7	2.5±0.7
Concomitant medications	6.7±3.2	6.7±2.8	6.7±3.0
All medications	9.3±3.4	9.3±2.9	9.3±3.2
At last follow-up visit — no.			
List 1 antihypertensive medications	0.5±0.7	1.2±0.9	0.8±0.9
List 2 antihypertensive medications	1.1±1.0	0.8±0.9	0.9±0.9
List 1 and list 2 antihypertensive medications	1.5±1.1	2.0±1.1	1.8±1.1
Concomitant medications	6.8±3.7	6.6±3.5	6.7±3.6
All medications	8.3±4.1	8.6±3.8	8.5±3.9

* Plus–minus values are mean ±SD. The number of list 2 antihypertensive medications is higher at the last follow-up visit than at baseline because antihypertensive medications reintroduced by the investigator or the patient's general practitioner were moved to list 2.

and EQ-5D-3L questionnaire and in hand-grip strength were similar in the trial groups (Table S8 and Table S9). Serious adverse events other than those included in definitions of the primary and secondary end points occurred in 132 patients in the step-down group and in 128 patients in the usual-care group and were generally similar in the two groups (Table S10).

DISCUSSION

In the current trial, we evaluated the effect of a progressive reduction in antihypertensive medications as compared with usual care on all-cause mortality among older nursing home residents who had frailty and a systolic blood pressure below 130 mm Hg. The patients were generally representative of nursing home residents with low blood pressure who were taking antihypertensive medications (Table S11). Our trial did not confirm the hypothesis that the antihypertensive treatment step-down strategy would result in 25% lower all-cause mortality than usual care in this population.

The hypothesis in the current trial was supported by data from a previous observational study conducted in nursing homes[5] and was reinforced by data from several other observational studies that showed increased morbidity and mortality among very old individuals with frailty who had low blood pressure and were receiving treatment for hypertension.[7,8] Our trial showed that the mean number of antihypertensive medications used in the step-down group decreased throughout the follow-up period, leading to a moderate increase in blood pressure without an apparent increase in major cardiovascular and noncardiovascular adverse events as compared with usual care. The OPTIMISE (Optimising Treatment for Mild Systolic Hypertension in the Elderly) and DANTON (Discontinuation of Antihypertensive Treatment in Older People with Dementia Living in a Nursing Home) trials, which evaluated the effect of reducing antihypertensive treatment in older patients, enrolled patients with less severe frailty than those in our trial and did not assess death as a primary end point.[21-23] Data from our trial suggest that an antihypertensive medication step-down strategy is unlikely to have a clinically relevant effect on all-cause mortality.

The Covid-19 pandemic did not appear to affect the percentage of patients with a primary end-point event. Mortality due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was low (22 deaths among 376 infected patients). This finding is probably explained by the enrollment of 60% of the patients after February 2021, when nearly 90% of the nursing home residents in France had received at least one dose of SARS-CoV-2 vaccine.[24] The percentage of patients in the step-down group who died from

Table 3. Primary and Secondary End Points.*

End Points	Step-Down Strategy (N=528)	Usual Care (N=520)	Adjusted Effect Measure (95% CI)	P Value†
Primary end point: death from any cause				
Intention-to-treat analysis — no. (%)	326 (61.7)	313 (60.2)	1.02 (0.86–1.21)‡	0.78
Per-protocol analysis — no./total no. (%)§	311/499 (62.3)	305/497 (61.4)	1.04 (0.87–1.23)‡	
Secondary end points				
Death from noncardiovascular causes — no. (%)	284 (53.8)	278 (53.5)	1.00 (0.83–1.19)¶	
Acute heart failure — no. (%)	67 (12.7)	57 (11.0)	1.19 (0.80–1.78)‖	
Falls				
Overall — no. (%)	264 (50.0)	260 (50.0)	—	
No. of falls per year	0.81±2.08	0.71±1.91	1.14 (0.84–1.51)**	
Fractures				
Overall — no. (%)	41 (7.8)	48 (9.2)	—	
No. of fractures per year	0.03±0.17	0.04±0.17	0.80 (0.51–1.26)††	
Death from Covid-19 — no. (%)	6 (1.1)	16 (3.1)	0.38 (0.10–1.00)‡‡	
Composite of major adverse cardiovascular events — no. (%)§§	102 (19.3)	90 (17.3)	1.15 (0.84–1.56)¶¶	

* Plus–minus values are means ±SD. Confidence intervals were calculated with a bias-corrected and accelerated bootstrap method with 10,000 replications. In the analyses of secondary end points, confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing or to infer treatment effects.

† A hierarchical approach was used to control the type I error. Hypothesis testing of the secondary end points was performed sequentially in the order listed in the statistical analysis plan. When a P value of 0.05 or higher was observed for an end point, the subsequent end points in the hierarchy were not formally tested.

‡ Shown is a hazard ratio calculated with a Cox proportional-hazards regression model with adjustment for age, sex, smoking status, diabetes mellitus, coronary disease, chronic heart failure, severe renal insufficiency, cognitive disorders, a history of stroke or transient ischemic attack, and baseline systolic blood pressure and inclusion of nursing home as a random effect.

§ The per-protocol population was defined as all the patients in the intention-to-treat population who met the inclusion criteria, did not have an interval of more than 6 months between two successive nursing visits, and did not have an interval of more than 12 months between two successive physician visits.

¶ Shown is a hazard ratio calculated with a cause-specific proportional-hazards model with death from cardiovascular causes as a competing risk.

‖ Shown is a hazard ratio calculated with a cause-specific proportional-hazards model with death as a competing risk.

** Shown is the rate ratio calculated with a Poisson regression model with adjustment for baseline systolic blood pressure (measured while the patient was seated) and number of falls during the 12-month period before randomization and with inclusion of nursing home as a random effect.

†† Shown is the rate ratio calculated with a Poisson regression model with adjustment for baseline systolic blood pressure (measured while the patient was seated) and occurrence of fractures (yes or no) during the 12-month period before randomization and with inclusion of nursing home as a random effect.

‡‡ Shown is a hazard ratio calculated with a cause-specific proportional-hazards model with death from causes other than coronavirus disease 2019 (Covid-19) as a competing risk, adjustment for baseline systolic blood pressure, and inclusion of nursing home as a random effect.

§§ A composite of major adverse cardiovascular events was defined as the first occurrence of death from cardiovascular causes, stroke, myocardial infarction and other serious coronary artery disease events, acute heart failure, pulmonary embolism, deep-vein thrombosis, atrial fibrillation and major heart-rhythm and conduction disorders, major peripheral vascular events, or transient ischemic attack.

¶¶ Shown is a hazard ratio calculated with a cause-specific proportional-hazards model with death from noncardiovascular causes as a competing risk.

Covid-19 was consistent with data showing that among patients with treated hypertension, those with a systolic blood pressure between 140 and 159 mm Hg had a lower risk of death from Covid-19 than those with a systolic blood pressure below 130 mm Hg.[25]

The initial increase in systolic blood pressure in both groups soon after randomization may be explained by the enrollment only of patients with a systolic blood pressure below 130 mm Hg. However, owing to variability in blood pressure in older adults with frailty,[26] the mean systolic blood

pressure increased by approximately 10 mm Hg from baseline in both groups, a finding that indicated a regression to the mean. A clinically meaningful difference (4.1 mm Hg; step-down strategy minus usual care) in the mean systolic blood pressure between the trial groups was observed over time, but the magnitude of this difference was lower than expected on the basis of data from younger populations with less severe frailty.[27]

We also observed a decrease from baseline to the last follow-up visit in the mean number of antihypertensive medications being taken in the usual-care group, although this decrease was less pronounced than in the step-down group. This finding suggests that physicians may routinely reduce treatments as patients become older and have increasing frailty. However, the mean number of concomitant medications used at baseline was similar to that at the last follow-up visit. Thus, the decrease in the number of antihypertensive

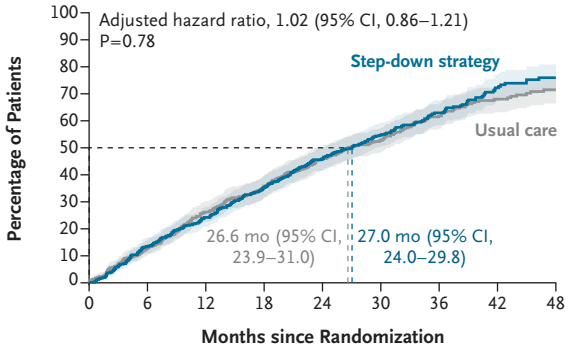

Figure 1. Kaplan–Meier Analysis of Death from Any Cause (Primary End Point).

The step-down strategy was a protocol-driven progressive reduction in antihypertensive medications. Dashed lines indicate the median time to death in each trial group. The shaded areas indicate 95% confidence intervals.

Subgroup	Step-Down Strategy	Usual Care	Hazard Ratio for Death from Any Cause (95% CI)
	no. of patients with event/total no. of patients (%)		
All patients	326/528 (61.7)	313/520 (60.2)	1.02 (0.86–1.21)
Age			
>90 yr	185/267 (69.3)	176/253 (69.6)	0.97 (0.79–1.20)
≤90 yr	141/261 (54.0)	137/267 (51.3)	1.09 (0.86–1.38)
Systolic blood pressure			
<105 mm Hg	76/104 (73.1)	71/104 (68.3)	1.18 (0.85–1.63)
105–115 mm Hg	97/168 (57.7)	88/154 (57.1)	0.95 (0.71–1.27)
>115 mm Hg	153/256 (59.8)	154/262 (58.8)	1.06 (0.84–1.32)
Chronic heart failure			
Yes	87/128 (68.0)	74/118 (62.7)	1.15 (0.84–1.57)
No	239/400 (59.8)	239/402 (59.5)	1.00 (0.84–1.20)
Clinical Frailty Scale score			
1, 2, or 3	21/47 (44.7)	19/52 (36.5)	1.42 (0.76–2.64)
4 or 5	78/147 (53.1)	80/164 (48.8)	1.16 (0.84–1.58)
6	79/118 (66.9)	76/111 (68.5)	0.95 (0.69–1.31)
7 or 8	146/213 (68.5)	134/187 (71.7)	0.89 (0.70–1.12)

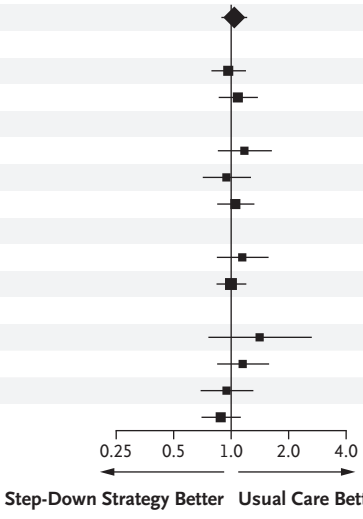

Figure 2. Subgroup Analyses of Death from Any Cause.

All the analyses except those of systolic blood pressure (measured while the patient was seated) were adjusted for baseline systolic blood pressure. The level of frailty was assessed with an algorithm that calculated a composite score. The algorithm included data on functional capacities (autonomy, mobility, and cognitive status) measured in the trial to classify frailty levels according to scores on the validated Clinical Frailty Scale. Scores range from 1 to 9, with a score of 1 indicating fit, 2 well, 3 managing well, 4 vulnerable, 5 mild frailty, 6 moderate frailty, 7 severe frailty, 8 very severe frailty, and 9 terminally ill. Clinical Frailty Scale scores were missing for three patients in the step-down group and six patients in the usual-care group.

medications being taken in the usual-care group was more likely due to an unanticipated crossover effect. Although patients in each nursing home were randomly assigned to the step-down or usual-care groups, general practitioners caring for patients in both groups may have inadvertently adopted the step-down strategy in the care of patients in the usual-care group.

Our trial has limitations. First, this pragmatic trial was open label. However, the primary end point (death from any cause) was unquestionably objective. Although general practitioners approved the reduction of antihypertensive treatment in patients in the step-down group, they may have been more likely to detect and report mild adverse events in patients in the step-down group than in those in the usual-care group. However, the percentage of patients with serious adverse events did not differ substantially between the groups. In addition, the incidence of major adverse cardiovascular events, which were adjudicated by a committee whose members were unaware of the trial-group assignments, did not differ significantly between the groups. Second, we conducted the current trial in a single country, which could theoretically limit the external validity of the trial. However, the characteristics of patients in the current trial are generally similar to those of patients in observational cohorts from other countries.[28-30] In addition, the discontinuation algorithm that is precisely described in the protocol is easy to implement and universally applicable. These factors support the generalizability of our results.

Our trial showed that a step-down strategy for reducing antihypertensive treatment did not lead to lower all-cause mortality than usual care among patients who were 80 years of age or older and had frailty, were receiving antihypertensive drugs, and had a systolic blood pressure below 130 mm Hg.

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