Collaborative Medication Reviews by Geriatrician and Family Physician for Improving Health-Related Quality of Life in Older Patients: A Cluster Randomized Clinical Trial

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Key Points

Question: Can clinical assessments and medication reviews carried out by a geriatrician in cooperation with the patient's family physician have positive effects on health-related quality of life in older patients receiving polypharmacy?

Findings: In this cluster randomized clinical trial that included 70 family physicians participating with 174 patients, health-related quality of life after 16 weeks was statistically significantly better in patients randomized to receive the intervention compared to those who received usual care.

Meaning: Clinical geriatric assessments and collaborative medication reviews have the potential to improve health-related quality of life among older patients exposed to polypharmacy.

Abstract

Importance: Polypharmacy and inappropriate drug use is a major health concern among older adults. Various interventions focused on medication optimization strategies have been carried out, but the effect on patient-relevant outcomes remains uncertain.

Objective: To investigate the effect of clinical geriatric assessments and medication reviews on health-related quality of life and other patient-relevant outcomes in home-dwelling older patients receiving polypharmacy.

Design: Cluster randomized, single-blind, clinical trial.

Setting: Norwegian family physicians were recruited from March 2015 to March 2017 to participate in the trial with patients from their lists.

Participants: Home-dwelling patients aged 70 years or older, using at least 7 medications regularly, having their medications administered by the home nursing service.

Intervention: a) Clinical geriatric assessment of the patients combined with a thorough review of their medications. b) A meeting between the geriatrician and the family physician. c) Clinical follow-up. Patients in the control group received usual care. Randomization occurred at the family physician level.

Main outcomes and Measures: The primary outcome was health-related quality of life as assessed by the 15D instrument (score range 0–1, higher scores indicating better quality of life, minimum clinically important change ± 0.015) at week 16. Secondary outcomes included changes in medication appropriateness, physical and cognitive functioning, use of health services, and mortality.

Results: Among 174 patients (mean age, 83 years; 68% women, 87 intervention, 87 control) in 70 clusters (36 intervention, 34 control), 158 (90.8%) completed the trial. Mean (SD) 15D score at baseline was 0.708 (0.121) in the intervention group and 0.714 (0.113) in the control group. At week 16, mean (SD) 15D score was 0.698 (0.164) in the intervention group and 0.655 (0.184) in the control group, with an estimated between-group difference of 0.045 (95% CI, 0.004 to 0.086; p=0.033). Several secondary outcomes were also in favor of the intervention. There were more drug withdrawals, reduced dosages, and new drugs started in the intervention group.

Conclusions and Relevance: In older patients exposed to polypharmacy, clinical assessments and medication reviews carried out by a geriatrician in cooperation with the patient's family physician resulted in positive effects on health-related quality of life.

Trial registration

ClinicalTrials.gov Identifier: NCT02379455

Introduction

Older patients are prescribed an increasing number of medications.[1,2] Polypharmacy is associated with negative health outcomes[3] but, individually, many drugs may have good clinical indications. Evidence-based methods to manage complex treatment regimens in a way that ensures positive effects on clinical and patient-relevant outcomes are lacking. Thus, there is a need for strategies that can guide clinicians on how to provide the benefits of drug treatment for these patients, but at the same time avoid negative consequences.

Previous studies aimed at improving drug treatment for older patients have mainly studied effects on surrogate clinical outcomes, such as potentially inappropriate medications.[4,5] Numerous tools to assess medication appropriateness have been developed, but effects on such criteria-based outcomes do not necessarily mean that the patient has benefited from the intervention.[6] Although some studies have included clinical outcomes, the results have been inconclusive.[7,8] We hypothesize that most improvements in drug treatment – such as better pain control, better symptom control in heart failure, or less iatrogenic dehydration or sedation – have the potential to improve health-related quality of life (HRQoL). In our opinion, HRQoL is therefore an appropriate outcome measure when the aim is to improve drug treatment in an individualized manner across a broad spectrum of drug classes. Two core outcome sets for polypharmacy interventions have been developed, both highlighting HRQoL as the most important patient-related outcome to assess.[9,10] It is so far unclear whether interventions to improve pharmacotherapy actually result in clinical improvements, and there is no evidence regarding effect on HRQoL.[11]

Geriatricians are trained in assessments of multimorbidity and polypharmacy. A closer cooperation between geriatricians and family physicians (FPs), which have a key role in follow-up of patients over time, might therefore be beneficial. We investigated whether clinical assessments and comprehensive medication reviews carried out by a geriatrician in cooperation with the patient's FP could have positive effects on HRQoL and other patient-relevant outcomes in older, home-dwelling patients receiving polypharmacy.

Methods

Trial oversight

This was a cluster-randomized, single-blind, controlled trial with follow-up at 16 and 24 weeks. The trial protocol has previously been published.[12] Inclusion of patients was based upon informed, written consent. Patients unable to give a valid consent due to dementia were included based on informed consent from a close relative in combination with assent from the patient. The trial was approved by the Regional Committee for Medical and Health Research Ethics and by the Data Protection Officer at Oslo University Hospital, and was carried out in accordance with the Declaration of Helsinki.

Participants

FPs from the counties of Akershus and Oslo, Norway, were invited to participate in the trial with patients from their lists. Patients were eligible for enrollment if they were home-dwelling, had their medications administered by the home nursing service, were 70 years of age or older, and used at least 7 systemic medications taken regularly. Patients were excluded if they were expected to die or become permanently institutionalized within six months, if the FP discouraged participation, or if valid information was unavailable. See eAppendix 1 for details.

Trial procedures

Our intervention consisted of three main parts. a) Geriatric assessment consisting of a medical history, systematic screening for current problems, clinical examination of the patient, and relevant supplementary tests, as well as a detailed review of each medication in use with emphasis on indication, dosage, possible side effects, and interactions. Assessments were done by a physician trained in geriatric medicine, supervised by a senior consultant. On average, one hour was spent on each clinical consultation. b) A meeting between the geriatrician and the FP with discussion of each medication, establishing a collaborative plan for adjustments and follow-up. Approximately 15 minutes were spent discussing each patient. c) Clinical follow-up by the FP or geriatrician as agreed upon. Follow-up was in general done by the FP. Details on the various components of the intervention are provided in eAppendix 1, eFigure 1, and eFigure 2 in the Supplement. The control group received standard care.

Cluster randomization at the physician level was performed to avoid between-group contamination. To avoid large variations in cluster sizes, each FP participated with a maximum of five patients, and stratification was performed based on the number of contributing patients (1-2 versus 3-5). Randomization was computer-generated and carried out in blocks of unknown and variable size. A statistician not otherwise involved in trial procedures prepared the allocation sequence. The research assistant, who provided all assessments, was blinded with respect to allocation. The patients received three home visits from the research assistant: at baseline, 16, and 24 weeks. Detailed descriptions of trial procedures are given in eAppendix 1.

Outcomes

The primary outcome was HRQoL, measured by the 15D instrument at 16 weeks.[13,14] The 15D instrument is a generic, 15-dimensional measure assessing mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort/symptoms, depression, distress, vitality, and sexual activity. Each dimension is rated by the respondent on an ordinal scale with five levels. Single index scores are calculated by population-based utility weights and range from 0 to 1, with higher scores indicating better HRQoL.[15] A change of ± 0.015 or more is considered clinically important, and a change of more than 0.035 in the positive direction represents "much better HRQoL".[16]

Secondary outcomes were appropriateness of drug use, as assessed by the Medication Appropriateness Index (MAI) and Assessment of Underutilization (AOU)[17,18]; physical functioning, as assessed by the Short Physical Performance Battery (SPPB), gait speed, and grip strength[19,20]; cognitive functioning, as assessed by digit span, Trail Making Tests A and B, and the Five Digits Test[21-23]; physical and cognitive disability, as assessed by the Functional Independence Measure (FIM)[24]; and carer burden, as assessed by the Relative Stress Scale (RSS).[25] We also assessed orthostatic blood pressure, falls, weight, hospital admissions, the number of days the patient spent in his/her own home during follow-up, use of home nursing service, admission to permanent institutional care, and mortality. Details on secondary outcomes are provided in eTable3 in the Supplement.

Statistical analysis

Detailed power calculations are included in eAppendix 2. We planned to randomly assign 200 patients (100 per trial group), which was expected to give > 80% power to detect a difference of 0.035 in 15D score after 16 weeks, at a two-sided significance level of 5%.

In the primary analysis, all participants were kept in the treatment group to which their physician had been randomly assigned. However, a strict intention-to-treat analysis was not possible because outcome data were missing in some patients. According to protocol, an analysis of covariance (ANCOVA) model was used, with 15D score at 16 weeks as the dependent variable, randomization group as the fixed factor, and cluster size and baseline 15D score as covariates. A clustered sandwich estimator of the standard error with FP as the cluster was applied. Missing data were imputed by multiple imputation, as explained in eAppendix 2. Distributional assumptions were checked by visual inspection of residual plots. Secondary analysis of the primary outcome included adjustment for other covariates expected a priori as being prognostic of the outcome. These included age, sex, comorbidity (Cumulative Illness Rating Scale (CIRS)[26]), dementia severity (Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB)[27,28]) and use of home nursing service (hours per week), measured at baseline. If their introduction to the model changed the effect estimate for the randomization variable with ≥ 10%, they were introduced in a final model including all variables with an effect of this size. We also carried out a linear mixed model analysis, adjusting for cluster size, applying an unstructured covariance matrix, and using a clustered sandwich estimator to estimate standard errors (SE). The same analytic approach was used for 15D scores at 24 weeks. We performed multiple additional sensitivity analyses, described in eAppendix 2. Analyses of the primary outcome were carried out by a statistician blinded to group allocation.

Responder analyses, classifying all patients with an improvement of at least 0.015 on 15D as responders, were performed by logistic regression, adjusted for cluster size and covariates as described above, using the clustered sandwich estimator to estimate SE.

Secondary outcomes with repeated measurements were analyzed by linear mixed model as described above. When distributional assumptions were violated, percentile confidence intervals were estimated by

100 bootstrap replications with FP as the unit of resampling. Outcomes measured only once were analyzed by multiple linear regression or logistic regression as appropriate. The analyses were adjusted for age, sex, dementia severity and use of home nursing service at baseline, and the clustered sandwich estimator was used to estimate SE. CIRS did not affect any of the estimates, and was not included as a covariate for adjustment.

Analyses were performed with SPSS, version 25.0.0.1 (IBM) and Stata, version 15 (StataCorp).

Results

Participants

From March 2015 through March 2017, we recruited 84 FPs to participate in the study. The screening procedure (see eAppendix 1) identified 355 patients meeting the inclusion criteria. Of these, 163 were excluded, and 18 were withdrawn before randomization. Fourteen FPs did not have eligible patients. The modified intention-to-treat analysis is thus based on 70 FPs and 174 patients who underwent randomization (Figure 1). Demographic and baseline data are shown in Table 1.

Primary outcome

At week 16, mean (SD) 15D score was 0.698 (0.164) in the intervention group and 0.655 (0.184) in the control group, with an estimated between-group difference of 0.045 (95% CI, 0.004 to 0.086; p=0.033). Dementia severity, CDR-SOB, was the only pre-specified covariate that influenced the effect estimate for the randomization variable with ≥ 10%. Adjusted for CDR-SOB score, the between-group difference was 0.055 (95% CI, 0.014 to 0.096; p=0.010). Analyzed by linear mixed model, the between-group difference was 0.048 (95% CI, 0.006 to 0.090; p=0.025). All sensitivity analyses gave similar results (eTable 5 in the Supplement). The proportion of responders was higher in the intervention group (41 patients (47.7%)) compared to the control group (18 patients (21.7%)); adjusted odds ratio (OR), 3.32 (95% CI, 1.47 to 7.46; p=0.004).

Mean 15D score decreased in both groups, but at a slower pace in the intervention group (Figure 2). At week 24, mean (SD) 15D score was 0.675 (0.186) in the intervention group and 0.620 (0.216) in the control group, with an estimated between-group difference of 0.052 (95% CI, -0.002 to 0.105; p=0.060).

Adjusted for CDR-SOB, the between-group difference was 0.064 (95% CI, 0.011 to 0.116; p=0.018). Analyzed by linear mixed model, the between-group difference was 0.061 (95% CI, 0.004 to 0.118; p=0.037). The proportion of responders at week 24 was higher in the intervention group (37 patients (43.5%)) compared to the control group (19 patients (22.9%)); adjusted OR, 2.74 (95% CI, 1.13 to 6.65; p=0.025).

Secondary outcomes

Secondary outcomes are displayed in Table 2 and in eTable 6 in the Supplement. Medication appropriateness, as assessed by MAI and AOU, improved in the intervention group as compared to the control group at 16 and 24 weeks. There was also a trend towards positive effects of the intervention on several of the physical and cognitive tests (Table 2). Of those completing the study, 31 patients in the intervention group (37.8%) and 17 in the control group (22.4%) had been hospitalized during follow-up; adjusted OR, 2.03 (95% CI, 0.98 to 4.24; p=0.06). There were no statistically significant differences between groups regarding orthostatic hypotension, falls, weight, relative stress, disability (FIM), use of home nursing service, number of days the patients had spent in their own home, admissions to permanent nursing home, or mortality.

Changes in drug use from baseline to week 16 are displayed in Table 3, whereas eTable 7 in the Supplement shows drug use at baseline. There were more drug withdrawals, reduced dosages, and new drugs started in the intervention group in the period from baseline to week 16, but no statistically significant differences between groups in the period from week 16 to 24. At week 16, only one patient (1%) in the intervention group had not experienced any drug changes at all, compared to 28 patients (35%) in the control group.

Discussion

This cluster-randomized trial shows that clinical assessments and comprehensive medication reviews carried out by a geriatrician in cooperation with the patient's FP may have a positive effect on HRQoL among older patients receiving polypharmacy. Secondary outcomes indicate a trend towards positive effects also on several physical and cognitive tests. We believe that the intervention could be implemented

within the framework of a geriatric outpatient clinic. Whether comparable results can be achieved by other health professionals using a similar methodology can be the topic of future studies.

The 15D instrument assesses different dimensions of HRQoL that, in our experience, are perceived as important for older patients. Although 15D scores declined in both groups, we found a statistically significant between-group difference in favor of the intervention group. The responder analyses indicate that a higher proportion of patients in the intervention group experienced clinically significant improvements on 15D scores compared to the control group. We therefore regard our results to be clinically relevant.

Medication appropriateness improved in the intervention group as compared to the control group. Our results also indicate a positive trend on many secondary outcomes assessing physical and cognitive functioning. There were no statistically significant effects regarding orthostatic hypotension, falls, weight, relative stress, ADL functioning, or the use of formal care resources. For these outcomes, other aspects of the patients' health and social situation might be of greater importance.

There were more hospital admissions in the intervention group than in the control group. Although not statistically significant, it cannot be excluded that this was due in part to negative effects from medication changes following the intervention. However, some patients were actually hospitalized because examinations carried out during the intervention procedure identified severe illness. For these patients, being admitted to the hospital was a clearly positive event. Data on hospital admissions were incomplete for patients that withdrew consent or died, and the analysis only included patients still participating after 24 weeks. As more patients died in the control group, it is possible that they would have contributed with hospital admissions related to their terminal illness if all patients had been considered for this outcome.

The intervention group experienced more drug withdrawals, reduced dosages, and prescriptions of new drugs as compared to the control group. The number of medication changes that indicate reduced treatment intensity (e.g. withdrawals and reduced dosages) outnumbered new prescriptions. Deprescribing is a process focused on gradual withdrawal of inappropriate or unnecessary medications – a process that

becomes increasingly important the more frail the patients get.[29-31] At the same time, even in the context of polypharmacy, an optimized pharmacotherapy sometimes involves initiation of new drugs.

A possible reason for our positive results is that the medication reviews were led by a physician experienced in evaluating geriatric pharmacotherapy. Older people exposed to polypharmacy are heterogeneous, and our aim was to assess their diverse clinical problems and thereby personalize the pharmacotherapy. We presume that clinical examinations and relevant supplementary tests are necessary for medication reviews to be effective in this population. The clinician must carefully balance potential benefits and harms of all medications, while taking the patients' wishes into consideration. Our intervention was time-consuming, but the results indicate that such thorough evaluations are beneficial for patients with pronounced and complex polypharmacy. Interventions that only utilize standardized prescription tools or guidelines and do not include individual clinical assessments are less likely to provide health benefits.[32]

Another potentially important factor was the involvement of FPs, physicians with a key role in patient follow-up over time. This close cooperation between hospital specialists and the primary health care system is innovative, and combines the strengths of both specialties. Many participating FPs knew their patients well, and contributed with valuable input in the discussions on medication changes. However, most FPs had limited experience and confidence regarding performing structured evaluations of complex pharmacotherapy. Time constraints were also highlighted as a reason for why they rarely performed equally comprehensive assessments. The patients included in our trial were clinically stable, and the FPs rarely had any specific concerns about their drug use. Although the geriatrician could suggest changes to the drug regimen, the FP retained the medical responsibility for the patient, and was in charge of all medication changes. Thus, the discussion between the two physicians was important in order to reach a common understanding, achieve implementation of suggested medication changes, and ensure further follow-up.

A strength of our trial was the combination of a rigorous design with an examination of real-life scenarios involving old and multimorbid patients. Our focus on patient-related outcomes provides valuable knowledge regarding clinical effects of medication reviews.

Our use of a complex, pragmatic, and not completely standardized intervention might be viewed as a limitation with regard to replication. We have provided a detailed description of the intervention in the Supplement. The advices on medication changes are, however, inevitably dependent on the competence of the physician performing the assessments. As all interventions were carried out by one single physician, we do not know if other geriatricians would have achieved similar results. The inability to blind patients was a possible source of bias. Although we repeatedly instructed patients not to reveal their allocation group to the research assistant, this may also have happened. The recommendations resulting from the geriatric assessment were clearly focused on medication use, and not on other aspects of the patients' situation. In a few cases, however, the FP was advised to refer patients to a specialist for further investigation. In such situations, as well as when patients were admitted to hospital because of serious illness revealed by the geriatric assessment, the intervention could have led to improved HRQoL beyond our recommendations on medication use.

We conclude that in older, home-dwelling patients exposed to polypharmacy, clinical assessments and comprehensive drug reviews carried out by a geriatrician in cooperation with the patient's family physician may constitute a beneficial model of care.

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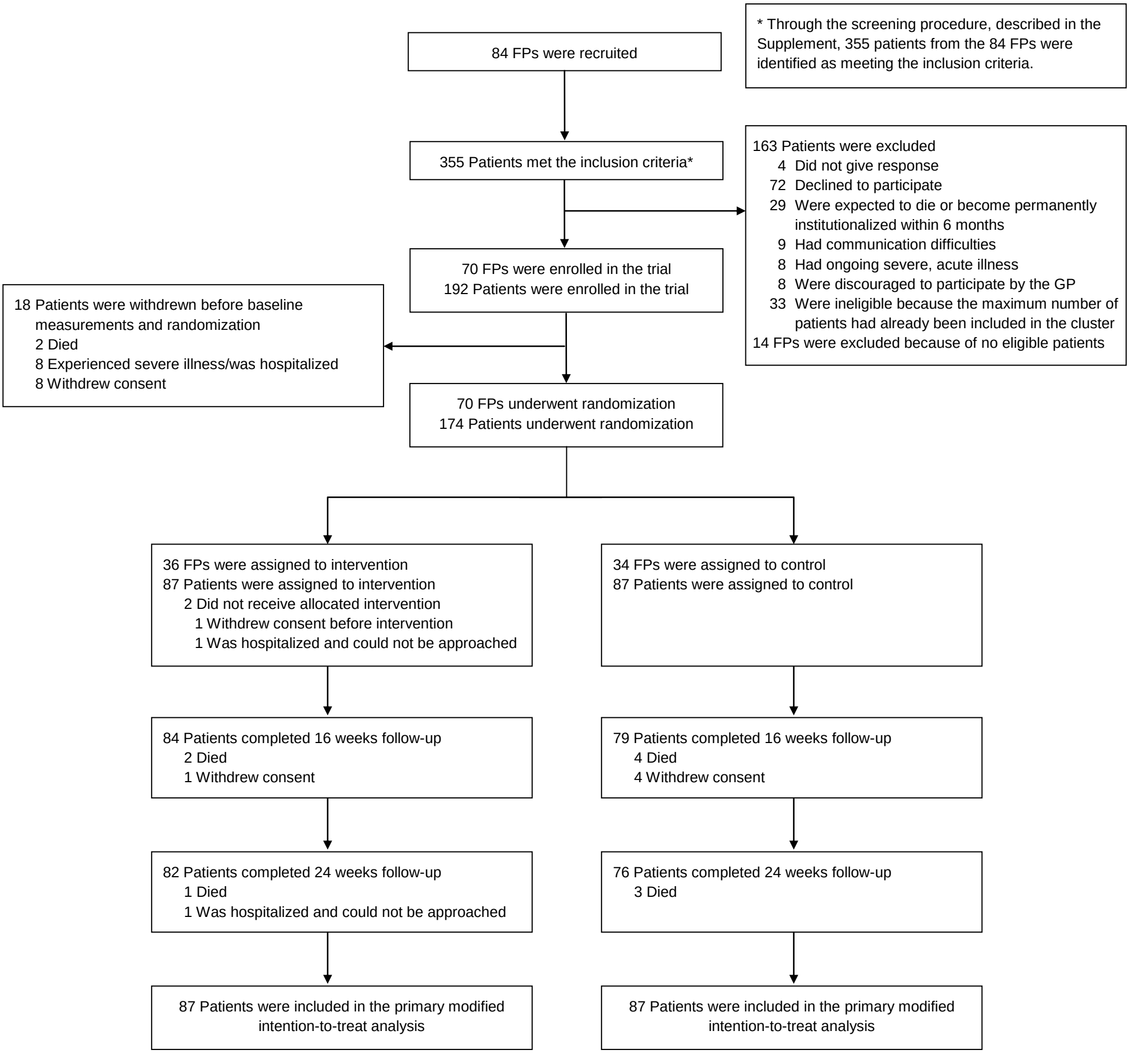
Figure Titles and Legends

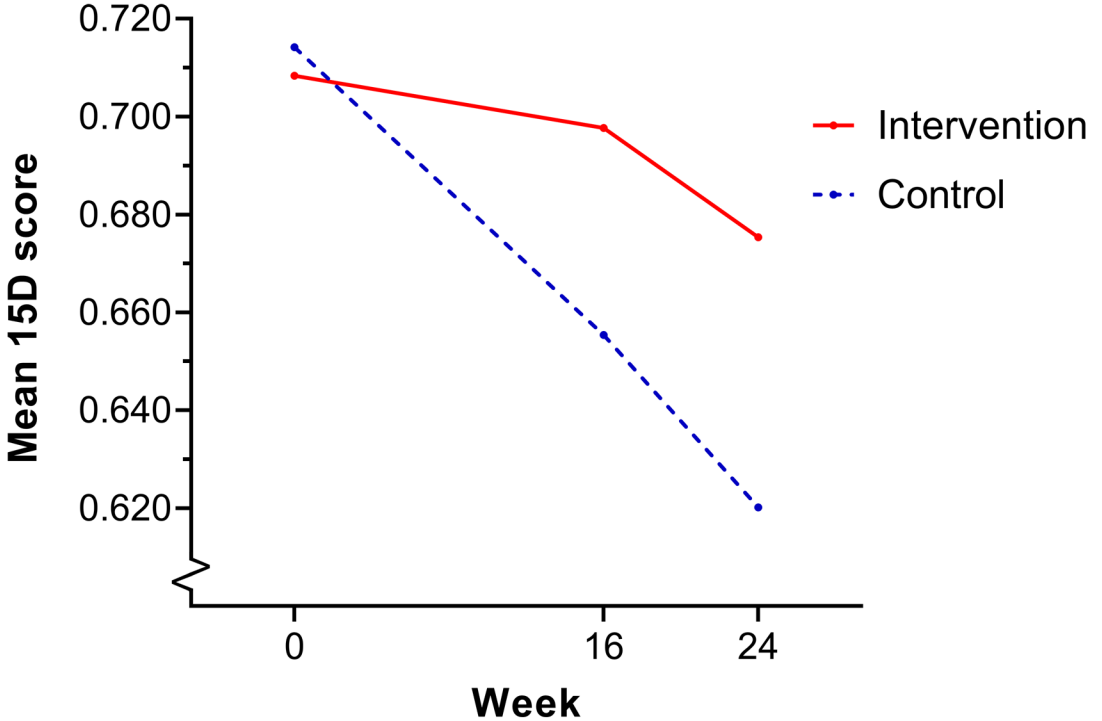
Figure 1. Flow of Patients in a Study of the Effect of Medication Reviews on Health-Related Quality of Life in Older Patients Receiving Polypharmacy

Legend: FP indicates family physician.

Figure 2. Primary End Point

Legend: Mean 15D score at baseline, week 16 and week 24.


84 FPs were recruited
* Through the screening procedure, described in the Supplement, 355 patients from the 84 FPs were identified as meeting the inclusion criteria.
355 Patients met the inclusion criteria*
163 Patients were excluded
4 Did not give response
72 Declined to participate
29 Were expected to die or become permanently institutionalized within 6 months
9 Had communication difficulties
8 Had ongoing severe, acute illness
8 Were discouraged to participate by the GP
33 Were ineligible because the maximum number of patients had already been included in the cluster
14 FPs were excluded because of no eligible patients
70 FPs were enrolled in the trial
192 Patients were enrolled in the trial
18 Patients were withdrawn before baseline measurements and randomization
2 Died
8 Experienced severe illness/was hospitalized
8 Withdrew consent
70 FPs underwent randomization
174 Patients underwent randomization
36 FPs were assigned to intervention
87 Patients were assigned to intervention
2 Did not receive allocated intervention
1 Withdrew consent before intervention
1 Was hospitalized and could not be approached
34 FPs were assigned to control
87 Patients were assigned to control
84 Patients completed 16 weeks follow-up
2 Died
1 Withdrew consent
79 Patients completed 16 weeks follow-up
4 Died
4 Withdrew consent
82 Patients completed 24 weeks follow-up
1 Died
1 Was hospitalized and could not be approached
76 Patients completed 24 weeks follow-up
3 Died
87 Patients were included in the primary modified intention-to-treat analysis
87 Patients were included in the primary modified intention-to-treat analysis


0.720
0.700
0.680
0.660
0.640
0.620
Mean 15D score
0
16
24
Week
Intervention
Control

Tables

Table 1. Baseline Characteristics of Participants

Characteristic	Intervention (n=87)	Control (n=87)
Age, mean (SD), y	82.2 (7.6)	84.4 (6.9)
Female sex, no. (%)	52 (60)	66 (76)
Cumulative Illness Rating Scale, mean (SD), sum score	16.8 (4.4)	16.6 (4.1)
CDR-SOB, mean (SD), score	2.9 (3.7)	1.8 (2.8)
Regular drugs in use, mean (SD), no.	10.1 (2.7)	9.5 (2.6)
Medication Appropriateness Index, mean (SD), score	16.3 (9.2)	14.6 (7.2)
Assessment of Underutilization, mean (SD), score	0.49 (0.70)	0.55 (0.74)
15D, mean (SD), score	0.708 (0.121)	0.714 (0.113)
Short Physical Performance Battery, mean (SD), score	4.8 (3.3)	4.3 (2.8)
Gait speed, mean (SD), m/s	0.62 (0.21) (n=81)	0.61 (0.20) (n=81)
Grip strength, mean (SD), kg	19.4 (7.7)	17.7 (8.4)
Digit span forwards, mean (SD), maximum span	4.69 (0.92)	4.57 (0.95) (n=86)
Digit span backwards, mean (SD), maximum span	2.94 (0.96)	2.96 (0.97) (n=85)
Trail Making Test A, mean (SD), s[a]	163 (138) (n=72)	130 (104) (n=70)
Trail Making Test B, mean (SD), s[a]	359 (161) (n=70)	398 (151) (n=69)
Five Digits Test 1, mean (SD), s[a]	47 (27) (n=77)	48 (43) (n=74)
Five Digits Test 2, mean (SD), s[a]	56 (62) (n=77)	51 (49) (n=73)
Five Digits Test 3, mean (SD), s[a]	108 (86) (n=76)	83 (64) (n=72)
Five Digits Test 4, mean (SD), s[a]	229 (124) (n=74)	202 (127) (n=70)
Use of home nursing service, mean (SD), min/week	155 (173)	181 (268)
Functional Independence Measure, mean (SD), score	111 (11)	111 (11)
Relative Stress Scale, mean (SD), score	14.4 (11.9) (n=81)	11.8 (10.1) (n=77)
Change in SBP after 1 min standing, mean (SD), mm Hg	-9.7 (19.3) (n=82)	-9.9 (22.8) (n=77)

SD denotes standard deviation, CDR-SOB Cumulative Illness Rating Scale Sum of Boxes, SBP systolic blood pressure.

[a] Values for patients unable to finalize the test due to cognitive difficulties were imputed as described in eTable 3.

Table 2. Change in Secondary Outcomes from Baseline to Week 16 and 24

Outcome	Change from baseline to week 16			Change from baseline to week 24		
	Intervention (n=84)	Control (n=79)	Estimated effect of intervention (95% CI)	Intervention (n=82)	Control (n=76)	Estimated effect of intervention (95% CI)
Medication Appropriateness Index, mean (SD), score	-6.6 (7.1)	-0.1 (4.3)	-6.5 (-8.6 to -4.3)	-7.2 (7.2)	-0.4 (4.9)	-6.9 (-9.1 to -4.7)
Short Physical Performance Battery , mean (SD), score	-0.15 (1.52) (n=83)	0.03 (1.28) (n=76)	-0.17 (-0.58 to 0.23)	-0.29 (1.60) (n=79)	-0.18 (1.29) (n=73)	-0.09 (-0.51 to 0.33)
Gait speed, mean (SD), m/s	0.02 (0.12) (n=74)	0.00 (0.08) (n=68)	0.01 (-0.02 to 0.05)	0.02 (0.12) (n=69)	-0.02 (0.09) (n=66)	0.04 (0.00 to 0.07)
Grip strength, mean (SD), kg	-0.4 (2.5) (n=83)	-1.3 (2.2)	0.99 (0.24 to 1.73)	-1.4 (3.1) (n=80)	-2.0 (3.9) (n=75)	0.62 (-0.41 to 1.65)
Digit span forwards, mean (SD), maximum span	-0.07 (0.91) (n=83)	-0.33 (0.62) (n=76)	0.23 (-0.01 to 0.48)	-0.08 (0.98) (n=78)	-0.41 (0.72) (n=74)	0.30 (0.03 to 0.58)
Digit span backwards, mean (SD), maximum span	0.12 (0.77) (n=83)	0.00 (0.69) (n=76)	0.12 (-0.08 to 0.33)	0.03 (0.93) (n=78)	-0.26 (0.85) (n=74)	0.27 (-0.01 to 0.56)
Change in SBP after 1 min standing, mean (SD), mm Hg	-0.3 (22.9) (n=77)	1.4 (21.2) (n=69)	-0.3 (-10.5 to 9.9)	-1.0 (21.9) (n=73)	0.4 (20.0) (n=67)	2.3 (-7.8 to 12.4)
Functional Independence Measure, mean (SD), score	-2.4 (8.5)	-1.6 (3.6)	-0.74 (-3.04 to 1.55)	-5.5 (14.2)	-3.1 (4.9)	-2.22 (-5.56 to 1.11)
Relative Stress Scale, mean (SD), score	-0.2 (6.3) (n=74)	-0.6 (4.8) (n=71)	0.4 (-1.4 to 2.2)	-1.0 (6.5) (n=75)	-0.5 (4.6) (n=67)	-0.3 (-2.2 to 1.7)
Trail Making Test A, mean (SD), s	-5.4 (55.5) (n=60)	11.0 (28.1) (n=58)	-15.0 (-31.7 to -2.9)[a]	9.3 (90.7) (n=60)	35.0 (81.5) (n=56)	-23.9 (-58.5 to 7.4)[a]
Trail Making Test B, mean (SD), s	23.6 (131.6) (n=59)	25.0 (133.1) (n=57)	-1.8 (-44.0 to 31.4)[a]	16.2 (159.3) (n=59)	35.7 (133.6) (n=57)	-19.5 (-61.1 to 24.1)[a]
Five Digits Test 1, mean (SD), s	3.7 (28.3) (n=67)	12.2 (45.1) (n=61)	-6.5 (-17.8 to 4.8)[a]	8.0 (40.0) (n=62)	18.6 (53.6) (n=59)	-6.7 (-21.4 to 8.0)[a]
Five Digits Test 2, mean (SD), s	6.2 (43.7) (n=67)	9.7 (40.7) (n=61)	-10.7 (-34.2 to 6.2)[a]	5.2 (69.1) (n=61)	18.7 (61.3) (n=59)	-26.6 (-69.5 to 6.2)[a]
Five Digits Test 3, mean (SD), s	8.3 (66.2) (n=66)	5.4 (15.3) (n=60)	-0.3 (-12.6 to 14.5)[a]	4.5 (51.7) (n=60)	14.2 (37.8) (n=58)	-8.9 (-26.4 to 10.1)[a]
Five Digits Test 4, mean (SD), s	5.2 (66.0) (n=63)	19.0 (56.0) (n=57)	-13.1 (-35.3 to 10.2)[a]	17.4 (67.5) (n=59)	41.3 (83.0) (n=55)	-24.4 (-52.6 to 3.2)[a]

Results were derived by linear mixed model, adjusted for baseline values, cluster size, age, sex, severity of dementia and use of home nursing service at baseline. CI denotes confidence interval, SBP systolic blood pressure.

[a] Bootstrap (100 replications) with percentile confidence interval. Values for patients unable to finalize the test due to cognitive difficulties were imputed as described in eTable 3.

Table 3. Changes in Drug Use from Baseline to Week 16

	No. of withdrawals		No. of reduced dosages		No. of new drugs started		No. of increased dosages	
	IG n=84	CG n=79	IG n=84	CG n=79	IG n=84	CG n=79	IG n=84	CG n=79
Total number of drug changes	**224**	**56**	**84**	**18**	**109**	**50**	**38**	**29**
Alimentary tract and metabolism (ATC group A)	53	13	17	4	47	15	6	6
Blood and blood forming organs (ATC group B)	31	7	4	1	12	5	4	0
Cardiovascular system (ATC group C)	68	14	35	5	19	3	13	5
Genitourinary system and reproductive hormones (ATC group G)	11	3	2	0	2	2	0	0
Systemic hormonal preparations, excl. reproductive hormones and insulin (ATC group H)	2	0	2	1	0	0	2	0
Antiinfectives for systemic use (ATC group J)	4	0	0	0	0	1	0	0
Antineoplastic and immunomodulating agents (ATC group L)	0	0	0	0	1	0	1	0
Musculoskeletal system (ATC group M)	5	2	1	0	1	0	0	1
Nervous system (ATC group N)	37	15	21	6	24	21	11	15
Respiratory system (ATC group R)[a]	13	2	2	1	3	2	1	2
Various (ATC group V)	0	0	0	0	0	1	0	0

IG denotes intervention group, CG control group, ATC anatomical therapeutic classification.

[a] Includes codeine used as an analgesic (in combination with paracetamol)

SUPPLEMENTARY ONLINE CONTENT

eAppendix 1. Methods

The supplementary information given in this section is based on the study protocol[1].

Recruitment of family physicians

Family physicians (FPs) from the counties of Akershus and Oslo, Norway, were invited to participate in the study with patients from their lists. There were no specific eligibility criteria for the FPs. We did not have the capacity to enroll all FPs in these areas, and municipalities in Akershus within a reasonable driving distance were prioritized. The FPs received written invitations, followed by a phone call to clarify if they were interested. When possible, information about the study was also given at FP meetings within each municipality.

Patient inclusion and exclusion criteria

We assumed that our intervention would be most relevant for the oldest and most frail patients, with relatively pronounced polypharmacy, and chose the inclusion and exclusion criteria presented in eTable 1.

Screening and recruitment of patients

The majority of home-dwelling patients with medications administered by the home nursing service have their medications prepared by multi-dose packaging systems delivered by a pharmacy, and screening of these medication lists were an efficient way of finding patients for the study.

Medication lists for patients listed with participating FPs were obtained from the pharmacy and screened by the home nursing service or by FP office staff to identify patients fulfilling the inclusion criteria. The FPs then considered the eligibility of their patients based on the exclusion criteria. Patients eligible for participation were contacted by the home nursing service or the FP's office, explaining the study and asking whether the researchers might contact them. If this was accepted, the patients received a home visit from the research assistant, who gave supplementary oral and written information, and obtained an informed consent if the patient wanted to participate. To avoid selection bias, the clusters (FPs) were randomized after all patients had been included in each cluster.

Primary outcome

15D is a generic, 15-dimensional instrument concerning different aspects of health-related quality of life (HRQoL) that has been used in similar geriatric interventions[2,3]. The dimensions are mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Each dimension is rated on an ordinal scale with five levels, and the respondent chooses the level best describing his/her present health status. Single index scores are calculated by population-based utility weights, and range from 0 to 1 (with "0" representing "dead", and higher scores indicating better HRQoL)[4].

We hypothesize that most improvements in the total drug regimen of frail older patients, such as better pain control, better symptom control in heart failure, less parkinsonian side effects, less iatrogenic dehydration or less sedation, have the potential to improve HRQoL. In our opinion, 15D is therefore an appropriate outcome measure when the aim is to improve the total drug regimen in an individualized manner across a broad spectrum of drug classes within a heterogeneous group of patients.

The patients included in our study were old, and many were not familiar with self-administration of questionnaires of this kind. 15D was therefore administered by interview. Usually, the 15D questionnaire is filled in by the individual whom it concerns, but it can also be answered by proxy raters. If the patient had moderate or severe dementia (i.e., Clinical Dementia Rating Scale > 1), or the research assistant considered that they did not understand the questionnaire, the interview was carried out with the closest proxy. To ensure that the proxy had updated knowledge on the patient's state of health, these ratings were only used if the patient and the proxy had regular contact – at least once every second week. To account for patients that might lose their ability to respond to 15D during the follow-up period, the questionnaire was administered to the closest proxy for all patients. The same source (patient or proxy) for the 15D score was used at all assessment points for each patient.

Proxy rating of the 15D questionnaire is generally accepted as valid[5] and has been successfully used in previous studies.[6] We emphasized for the proxy raters that we expected them to score the instrument as they thought the patients themselves would have done. We cannot, however, rule out a possible bias when using proxy raters. A recent study

indicates that proxy ratings on different measures of HRQoL consistently differ from ratings given by patients.[7] However, our primary outcome is the development of HRQoL over time, and the same source for the 15D score was used at all assessment points. This can be expected to reduce the impact of a potential bias in the proxy scores.

Data collection

Background information on diagnoses and comorbidity were obtained from the FP's electronic patient records. The patients received three home visits from the research assistant; at baseline, 16 and 24 weeks (±2 weeks). These visits took place where the patient was living at that moment; in the patient's own home, a nursing facility or a rehabilitation institution. All assessments directly involving the patient were performed at these visits. Proxy information was collected through telephone calls and/or questionnaires sent by mail if the proxy was not present at the home visit.

Updated medication lists were obtained at all assessment points. The research assistant checked if medications were taken as prescribed by asking the patient and the home nursing service if there had been any discrepancies. Multi-dose packages were also inspected to see if their content matched the medication lists. Nonprescription drugs and pro re nata (PRN) drugs taken regularly were counted as "regular drugs", but PRN drugs taken only occasionally were not counted. Drugs were registered according to the Anatomical Therapeutic Chemical (ATC) classification system.

See eTable 2 for study assessment procedures and timetable and eTable 3 for details on data collection for secondary outcomes.

Intervention

Our intervention consisted of three main parts: clinical geriatric assessment of the patient combined with a thorough review of their medications; a targeted meeting between the geriatrician and the FP; and clinical follow-up.

Geriatric assessment and medication review

As soon as possible after randomization, the patients were seen by a physician trained in geriatric medicine. In advance, the geriatrician obtained necessary information on the patient's medical history and actual medication from hospital records, the FP's electronic patient record, the home nursing service and other relevant sources. The geriatrician carried out a medical history from the patient (if necessary supplemented by a close relative) and a physical examination, both with focus on conditions most relevant for the patient's total medication use. Relevant blood analyses and other supplementary tests were ordered if not already available. The geriatric work-up was aimed at evaluating whether current medications were indicated, whether the relevant conditions were satisfactorily compensated, whether the dosages were appropriate, whether the patient had symptoms of adverse drug reactions, and whether drug-drug interactions or drug-disease interactions were present or likely to occur. A drug interaction database[8] , lists of anticholinergic drugs[9,10], the STOPP/START criteria[11] and the NORGEP criteria[12] were also used. See eFigure 1 and 2 for more details on the assessments carried out by the geriatrician.

Meeting between the geriatrician and FP

The main purpose of this meeting was to combine the competence and knowledge of the geriatrician with that of the FP. The geriatrician summarized the findings from the geriatric assessment and medication review, and the two physicians discussed the patient's drug list systematically. The geriatrician could suggest changes in the drug regimen, but the FP retained the medical responsibility for the patient, and was in charge of all ordinations and medication changes.

Clinical follow-up

Depending on medication changes that had been done, the two physicians arranged the necessary follow-up within the project period. The follow-up could consist of a clinical evaluation, further drug adjustments, blood tests etc., and could be carried out by the FP, the geriatrician or through telephone contact with the patient, the relative or the home nursing service, depending on the circumstances.

Control group

The control group received usual care from their FPs during the study period. The FPs in the control group were offered our assistance in performing medication reviews after the study period was completed.

eAppendix 2. Statistical Analysis

Information given in this section is based on the Statistical Analysis Plan dated 31th January 2018, published online before any unblinding of the researchers.

Power calculation

The maximum number of patients feasible to assess during the time limits of the trial was thought to be approximately 200. As each FP could participate with 1-5 patients, the number of clusters was therefore expected to be 20-100 in each group.

It was difficult to make valid assumptions on the correlation between patients within each cluster. In order to estimate the power, we chose to estimate power in a worst case (perfect correlation) and best case (no correlation) scenario. The true correlation was expected to be much closer to the latter, as the potential for intervention varies between individual patients. Based on previous studies using 15D, the standard deviation of change over time was expected to be between 0.07 and 0.08[2,3,13]. The minimum important change (MIC) for the change in 15D score is assumed to be ± 0.015[14]. A change of more than 0.035 in the negative direction is assumed to represent "much worse HRQoL" and a change of more than 0.035 in the positive direction "much better HRQoL". Based on previous studies, in addition to a pilot study, we believed that our intervention was extensive enough to potentially lead to a difference between groups of at least 0.035.

As can be seen from eTable 4, the power to detect a difference of 0.035 would then be in the range 59 to 94 %, and most probably > 80 %, provided that 100 patients were included in each treatment group.

Protocol violations

Wrongly included patients

13 patients using < 7 regular medications were included. The researchers could not check the number of medications before consent to participation was given, and in some cases it turned out that the FP or home nursing service had counted incorrectly. In other cases, medications had been discontinued in the period from inclusion to baseline. We believe that the potential for clinical improvements in the intervention group is better the more medications the patients use. We have therefore chosen to include these patients in the analysis, as it is likely that this will underestimate the effect of the intervention rather than overestimate it.

Patients not handled according to randomization

Two patients in the intervention group were not handled according to randomization. One withdrew consent before intervention, and one was hospitalized with severe acute illness and could not be approached. The patient that withdrew consent was included in the analysis and handled with multiple imputation as described in 2.3. The hospitalized patient completed the follow up-visits, and these measurements were used.

Timing of follow-up visits

Follow-up visits were 16 and 24 weeks (± 2 weeks) after baseline. However, if the date of the follow-up visit was exceeded by some days, these patients were still included in the analysis, and their measurements were used unchanged.

Missing data

Missing responses on 15D

To derive the 15D score, there must be a response to each question (dimension). If a maximum of three responses were missing, we used the imputation algorithm provided from the developers of the instrument (www.15d-instrument.net).

Lost to follow-up

Patients who died before follow-up were registered with the score "0" (worst possible HRQoL) on 15D. If patients were lost to follow-up for other reasons than death, they were included in the primary analysis, and missing values were handled with multiple imputation using the mi procedure in Stata with M=5 imputations.

The following variables were included in the imputation procedure:

- Age
- Sex

- Cumulative Illness Rating Scale (CIRS)[15]
- Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB)[16,17]
- Use of home nursing service at baseline (minutes/week)

Sensitivity analyses

We performed an analysis by linear mixed model, with FP as a random factor, time point (baseline, 16 and 24 weeks), treatment and the interaction between time and treatment as fixed factors, and cluster size as a covariate.

In addition, missing values for the primary endpoint were analyzed in different ways in order to explore their potential influence on the results:

Sensitivity analysis 1
Patients not handled according to randomization and patients that were missing (all reasons) were excluded (per-protocol analysis).

Sensitivity analysis 2
Patients missing for other reasons than death were excluded, but deceased patients were kept with the value "0" on 15D.

Sensitivity analysis 3
Patients missing for other reasons than death were handled as "last observation carried forward" (LOCF), but deceased patients were kept with the value "0" on 15D.

Variables for adjustments

Variables with believed prognostic influence upon the outcome were included in the analysis, one by one in addition to the randomization group and cluster size. If their introduction to the model changed the effect estimate for the randomization variable with 10% or more, they were introduced in a final model including all variables with an effect of this size.

The following variables were subject to such analyses:
- Age
- Sex
- Cumulative Illness Rating Scale (CIRS)
- Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB)
- Use of home nursing service at baseline (minutes/week)

Secondary outcomes

We compared the intervention group with the control group with respect to all secondary outcomes. Patients lost to follow-up were not imputed for, and results on secondary outcomes are based on patients still participating in the study. Originally, we planned to give deceased patients the "worst possible value" when reporting secondary outcomes. For some outcomes, however, this approach yielded illogical results. For the Relative Stress Scale (RSS)[18], for example, giving a deceased patient the worst possible score would mean that the nearest relative suffered a greater burden of care after the patient's death. Because of more deaths in the control group than in the intervention group, our decision of excluding these patients will underestimate the effect of the intervention rather than overestimate it.

All estimates for secondary outcomes were adjusted for age, sex, dementia severity and use of home nursing service at baseline. CIRS did not affect the estimates and was not included.

eAppendix 3. Results

The trial was stopped before reaching the planned 200 patients because of time constraints.

Primary outcome

The primary outcome, 15D at week 16, has been analyzed in various ways. All analyses conclude with a statistically significant positive effect of the intervention, with estimated between-group differences ranging from 0.030 to 0.055 (eTable 5).

Deceased patients with the value "0" represented outliers, but the distributional challenges were reduced by square-root transformations. As a general tendency, analyses on transformed data reported lower p values than non-transformed data (data not shown). The per-protocol analysis indicates that the positive result is not due to a higher number of deceased patients in the control group (eTable 5).

13 of the 15D questionnaires were filled in by proxy raters in the intervention group, 6 in the control group.

Secondary outcomes

For Trail Making Test A, we imputed values (because of cognitive difficulties) for seven patients at week 16 and for 13 patients at week 24. Trail Making Test B proved a difficult task, with 78 patients being imputed at week 16 and 79 patients at week 24. This makes the results difficult to interpret, as only about 40 patients were able to complete the test.

For Five Digits Test (FDT) 1, three patients were imputed at week 16 and five patients at week 24. For FDT2, four patients were imputed at week 16 and 16 patients at week 24. For FDT3, 16 patients were imputed at week 16 and 14 patients at week 24. For FDT4, 57 patients were imputed at week 16 and 61 patients at week 24.

All these outcomes suffered from many missing patients, with the main reason being poor vision.

eFigure 1. Patient assessments carried out by the geriatrician

PATIENT ASSESSMENTS

Medical history

Go through medical history obtained from family physician. Is the information accurate? Any indistinctness?

Systematic screening for current problems

Cognition: Known/suspected dementia? (IQCODE, CDR, relatives, impression of patient)? NPS?
Depression/anxiety: Screening by ICD-10 criteria.
Nutrition: Weight loss, reduced appetite, nausea, dyspepsia? BMI, MNA-SF.
Pain: Previous/current problem? Is the cause identified? In need of better analgesia?
Breathing: Dyspnea?
Hydration: Signs of dehydration? Overhydration/edema?
Natural functions: Urinary incontinence? Voiding problems? Diarrhea/constipation?
Mobility: Gait problems? Dizziness? Walking aids? History of falling?
Sleep: Any problems related to sleep?

Sort out current main problem(s) concerning the patient's health.

Medications

Are all drugs used as prescribed? Any problems with administration? Has the patient any suspicions regarding side effects? Is the patient aware of the indication for different drugs? If symptomatic medications – what is the current situation regarding the target symptom? If unclear indication, explore the patient's willingness to reconsider dosages or to discontinue the drug in order to assess effectiveness. For prophylactic medications, identify thoughts on the balance between current drug use and reducing future risks.

Clinical examination

Clinical examination with emphasis on relevant conditions and current symptoms.

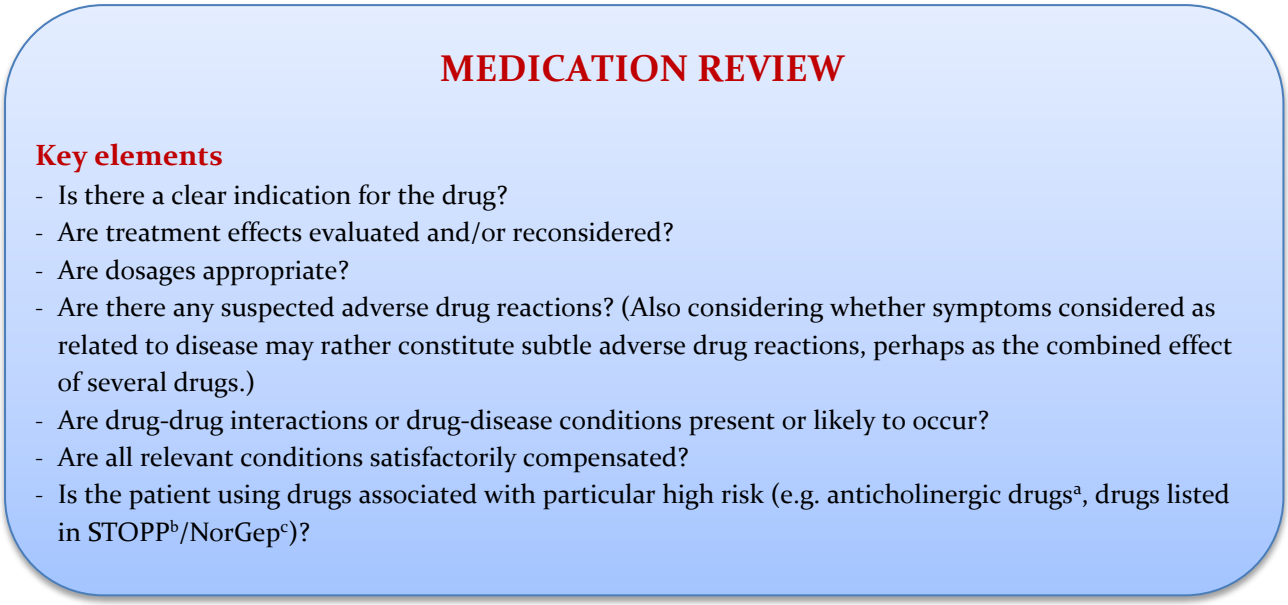
Supplementary tests

Blood pressure (including orthostatic)
Pulse rate, respiratory rate
ECG
Relevant blood analyses
Serum concentration of relevant drugs
Pharmacogenetic tests:

- CYP2C19, CYP2C9, CYP2D6 (all patients)
- CYP3A5 and SLCO1B1 if using statins
- SLC6A4 if using SSRI's
- VKORC1 if using warfarin

Abbreviations: IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly. CDR=Clinical Dementia Rating Scale. NPS=Neuropsychiatric symptoms. BMI=Body Mass Index. MNA-SF=Mini Nutritional Assessment Short Form. ECG=Electrocardiogram.

eFigure 2. Key elements of the medication review carried out by the geriatrician



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[c] Rognstad S, Brekke M, Fetveit A, Spigset O, Wyller TB, Straand J. The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study. Scand J Prim Health Care 2009;27:153-9.

eTable 1. Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Listed with one of the participating FPs Home-dwelling Medications administered by the home nursing service Age 70 years or more Use of at least seven different systemic medications taken regularly (preparations for inhalation, vitamin supplements and laxatives are included, but not topical drugs like eye drops and ointments) Signed informed consent given by the patient or his/her closest proxy	Expected to become permanently institutionalized within six months Life expectancy judged to be six months or less Moderate/severe dementia (i.e., CDR score > 1) and contact with the closest proxy less than once every second week Not speaking or understanding Norwegian The FP does not want the particular patient to participate (in case of important reasons not covered by the other exclusion criteria)

Abbreviations: FP=Family physician. CDR=Clinical Dementia Rating Scale.

eTable 2. Study assessment procedures and timetable

Assessments	Baseline	16 weeks	24 weeks
Assessments directly involving the patient			
Demographics, diagnoses, CIRS, MNA-SF	x		
15D	x	x	x
SPPB	x	x	x
Gait speed	x	x	x
Grip strength	x	x	x
Digit Span	x	x	x
Trail making test A + B	x	x	x
Five Digits Test	x	x	x
Falls		x	x
Orthostatic blood pressure	x	x	x
Weight	x	x	x
Assessments of drug use			
Current drug use and changes in pharmacotherapy	x	x	x
MAI	x	x	x
AOU	x	x	x
Assessments based on observation and/or proxy information			
FIM	x	x	x
CDR	x		
Assessments based on information from a close relative			
15D	x	x	x
RSS	x	x	x
IQCODE	x		
Administrative data			
Hospital admissions		x	x
Number of days in own home		x	x
Admission to permanent institutional care		x	x
Use of home nursing service (hours per week)	x	x	x
Mortality		x	x

Abbreviations: CIRS=Cumulative Illness Rating Scale. MNA-SF=Mini Nutritional Assessment Short Form. SPPB=Short Physical Performance Battery. MAI=Medication Appropriateness Index. AOU=Assessment of Underutilization. FIM=Functional Independence Measure. CDR=Clinical Dementia Rating Scale. RSS= Relative Stress Scale. IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly.

eTable 3. Details on secondary outcomes

Outcome measure	Description
Medication Appropriateness Index (MAI)[19]	Assessed by a clinical pharmacist experienced in geriatric pharmacotherapy. The clinical pharmacist was not involved in the intervention, and was blinded for group allocation. Assessments were based on anonymized patient summaries, including information from the FP's electronic patient record on important events during the follow-up period. Each drug in use was given a score from 0 to 18, then scores of all drugs were summated to obtain the patient's total MAI score, with higher scores representing less appropriate drug use.
Assessment of Underutilization (AOU)[20]	Assessed by a clinical pharmacist, as described for the MAI. The AOU assess the number of omissions of drugs that should have been prescribed.
Short Physical Performance Battery (SPPB)[21]	Assessed by the research assistant. Scores range from 0 to 12, with higher scores representing better physical function.
Gait speed[22]	Assessed by the research assistant, using a 4 meter long track, starting from a still, standing position.
Grip strength	Assessed by the research assistant. We carried out three measurements for each arm, using a Kern MAP 80K1 dynamometer. The highest value was used in the analyses.
Functional Independence Measure (FIM)[23]	Assessed by the research assistant. Scores range from 18 to 126, with higher scores indicating more independence.
Relative Stress Scale (RSS)[18]	Assessed by the research assistant, by interview of the closest relative. Scores range from 0 to 60, with higher scores representing a higher burden of care.
Digit span forwards[24]	Assessed by the research assistant. Reported as the maximum digit span completed by the patient.
Digit span backwards[24]	Assessed by the research assistant. Reported as the maximum digit span completed by the patient.
Trail Making Test A[25]	Assessed by the research assistant. Reported as the time (in seconds) spent on completing the test. For patients cognitively incapable of completing Trail Making Test A, a value of 500 s was imputed (worse than the slowest patient completing the test).
Trail Making Test B[25]	Assessed by the research assistant. Reported as the time (in seconds) spent on completing the test. For patients cognitively incapable of completing Trail Making Test B, a value of 550 s was imputed (worse than the slowest patient completing the test).
Five Digits Test (FDT)[26]	Assessed by the research assistant. FDT consists of four conditions; reading, counting, inhibiting and shifting. For all conditions, the time (in seconds) spent on completing the test and the number of uncorrected mistakes were registered. Because of the large amount of secondary outcomes, we chose to focus on *time* when reporting results on FDT. Patients who failed to complete FDT because of cognitive difficulties were imputed with a value worse than the slowest patient completing the test.
Five Digits Test 1 (reading)	For patients cognitively incapable of completing the test, a value of 300 s was imputed.
Five Digits Test 2 (counting)	For patients cognitively incapable of completing the test, a value of 400 s was imputed.
Five Digits Test 3 (inhibiting)	For patients cognitively incapable of completing the test, a value of 300 s was imputed.
Five Digits Test 4 (shifting)	For patients cognitively incapable of completing the test, a value of 350 s was imputed.

eTable 3. Details on secondary outcomes (continued)

Outcome measure	Description
Orthostatic blood pressure	Assessed by the research assistant, using a validated, automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA, USA). Supine blood pressure and pulse rate were measured twice, after a minimum of five minutes of rest, and the mean value was used for the analyses. The patient then stood up, and measurements were repeated after one minute.
Falls	Falls were registered in calendars handed out to patients or caregivers (in case of dementia), and the number of falls were assessed by the research assistant at each follow-up visit.
Use of home nursing service	Assessed by the research assistant. Information on the current use of home nursing service was given by the home nursing service at each follow-up visit.
Hospital admissions	The research assistant asked the patients, their closest proxy and the home nursing service about admissions to hospital, nursing home or other institutions. The FP's electronic patient record for the follow-up period was also checked for notes on hospital admissions etc. In case of hospital admissions, the discharge summary was obtained.

eTable 4. Estimation of power in different scenarios, provided a total of 200 participants

Δ	SD	r	Power %
0.035	0.08	1	59
0.035	0.08	0	87
0.035	0.07	1	71
0.035	0.07	0	94

Δ = Difference in change in 15D HRQoL single index score
SD = Standard deviation of change over time in 15D score
r = Correlation between patients within each cluster

eTable 5. Estimated effect of intervention by various analyses of the primary outcome at week 16

Analysis	Estimated effect of intervention (95% CI)	P value
Primary analysis, unadjusted[a]	0.045 (0.004 to 0.086)	0.033
Primary analysis, adjusted[b]	0.055 (0.014 to 0.096)	0.010
Linear mixed model, unadjusted[c]	0.048 (0.006 to 0.090)	0.025
Linear mixed model, adjusted[d]	0.048 (0.006 to 0.090)	0.026
Sensitivity analysis 1, unadjusted[e]	0.030 (0.008 to 0.052)	0.009
Sensitivity analysis 1, adjusted[f]	0.036 (0.015 to 0.057)	0.001
Sensitivity analysis 2, unadjusted[g]	0.045 (0.003 to 0.086)	0.036
Sensitivity analysis 2, adjusted[h]	0.055 (0.013 to 0.096)	0.010
Sensitivity analysis 3, unadjusted[i]	0.042 (0.002 to 0.083)	0.040
Sensitivity analysis 3, adjusted[j]	0.053 (0.012 to 0.094)	0.012

[a] Deceased patients were given the value “0” on 15D, and patients missing for other reasons were handled with multiple imputation. Analyzed by analysis of covariance, adjusted for baseline values and stratum. Robust estimation of standard errors with FP as the cluster was applied. N=174.

[b] Deceased patients were given the value “0” on 15D, and patients missing for other reasons were handled with multiple imputation. Analyzed by analysis of covariance, adjusted for baseline values, stratum and CDR-SOB score. Robust estimation of standard errors with FP as the cluster was applied. N=174.

[c] Linear mixed model with FP as a random factor, time point (baseline and 16 weeks), treatment and the interaction between time and treatment as fixed factors, and cluster size as a covariate. N=174.

[d] Linear mixed model with FP as a random factor, time point (baseline and 16 weeks), treatment and the interaction between time and treatment as fixed factors, and cluster size, age, sex, CDR-SOB and use of home nursing service as covariates. N=174.

[e] Patients not handled according to randomization and patients that were missing (all reasons) were excluded (per protocol analysis). Analyzed by analysis of covariance, adjusted for baseline values and stratum. Robust estimation of standard errors with FP as the cluster was applied. N=162.

[f] Patients not handled according to randomization and patients that were missing (all reasons) were excluded (per protocol analysis). Analyzed by analysis of covariance, adjusted for baseline values, stratum and CDR-SOB score. Robust estimation of standard errors with FP as the cluster was applied. N=162.

[g] Patients missing for other reasons than death were excluded, but deceased patients were kept with the value “0” on 15D. Analyzed by analysis of covariance, adjusted for baseline values and stratum. Robust estimation of standard errors with FP as the cluster was applied. N=169.

[h] Patients missing for other reasons than death were excluded, but deceased patients were kept with the value “0” on 15D. Analyzed by analysis of covariance, adjusted for baseline values, stratum and CDR-SOB score. Robust estimation of standard errors with FP as the cluster was applied. N=169.

[i] Patients missing for other reasons than death were handled as “last observation carried forward” (LOCF), but deceased patients were kept with the value “0” on 15D. Analyzed by analysis of covariance, adjusted for baseline values and stratum. Robust estimation of standard errors with FP as the cluster was applied. N=174.

[j] Patients missing for other reasons than death were handled as “last observation carried forward” (LOCF), but deceased patients were kept with the value “0” on 15D. Analyzed by analysis of covariance, adjusted for baseline values, stratum and CDR-SOB score. Robust estimation of standard errors with FP as the cluster was applied. N=174.

eTable 6. Secondary outcomes

Outcome	Time	Estimated effect of intervention (95% CI)	Comment
		OR	
Assessment of Underutilization	Week 16	0.24 (0.09 to 0.61)[a]	OR for having ≥ 1 medication omission
	Week 24	0.33 (0.15 to 0.71)[a]	OR for having ≥ 1 medication omission
Falls	Entire study period	0.75 (0.35 to 1.60)[a]	OR for experiencing ≥ 1 fall
Hospital admissions	Entire study period	2.03 (0.98 to 4.24)[a]	OR for being admitted to hospital at least once
Admission to permanent institutional care	Entire study period	0.49 (0.09 to 2.72)[a]	
Mortality	Week 24	0.36 (0.08 to 1.58)[a]	
		Mean difference	
Weight, kg	Week 16	0.23 (-0.97 to 1.42)[b]	
	Week 24	0.37 (-0.72 to 1.47)[b]	
Use of home nursing service, min/week	Week 16	-2.6 (-37.4 to 32.1)[b]	
	Week 24	-2.2 (-31.7 to 27.3)[b]	
Time spent in own home, days	Entire study period	1.9 (-3.7 to 7.6)[c]	

Abbreviations: CI=Confidence interval. OR=Odds ratio.

[a] Analyzed by logistic regression, adjusted for cluster size, age, sex, severity of dementia and use of home nursing service at baseline, and using a clustered sandwich estimator to estimate standard errors. The control group constitutes the reference.

[b] Analyzed by linear mixed model, adjusted for cluster size, age, sex, severity of dementia and use of home nursing service at baseline, applying an unstructured covariance matrix, and using a clustered sandwich estimator to estimate standard errors.

[c] Analyzed by multiple linear regression, adjusted for cluster size, age, sex, severity of dementia and use of home nursing service at baseline, and using a clustered sandwich estimator to estimate standard errors.

eTable 7. Drugs in use at baseline

ATC group	Intervention group (n=87)		Control group (n=87)	
	Prescriptions	Patients, n (%)	Prescriptions	Patients, n (%)
Alimentary tract and metabolism (ATC group A)	**184**	**75 (86)**	**184**	**77 (89)**
A02 Drugs for acid related disorders	30	28 (32)	29	29 (33)
A03 Drugs for functional gastrointestinal disorders	1	1 (1)	0	0 (0)
A06 Drugs for constipation	22	20 (23)	21	16 (18)
A07 Antidiarrheals, antiinflammatory agents	7	6 (7)	3	3 (3)
A10 Drugs used in diabetes	27	17 (20)	27	18 (21)
A11 Vitamins	69	51 (59)	76	56 (64)
A12 Mineral supplements	28	26 (30)	28	25 (29)
Blood and blood forming organs (ATC group B)	**112**	**76 (87)**	**89**	**72 (84)**
B01 Antithrombotic agents	87	70 (81)	74	68 (78)
B03 Antianemic preparations	25	23 (26)	15	13 (15)
Cardiovascular system (ATC group C)	**243**	**77 (89)**	**246**	**80 (92)**
C01 Cardiac therapy	13	13 (15)	18	17 (20)
C02 Antihypertensives	2	2 (2)	4	4 (5)
C03 Diuretics	48	41 (47)	61	56 (64)
C07 Beta blocking agents	55	55 (63)	52	52 (60)
C08 Calcium channel blockers	27	27 (31)	29	28 (32)
C09 Agents acting on the renin-angiotensin system	46	44 (51)	47	47 (54)
C10 Lipid modifying agents	52	52 (60)	35	35 (40)
Genitourinary system and reproductive hormones (ATC group G)	**31**	**23 (26)**	**17**	**14 (16)**
G03 Sex hormones and modulators of the genital system	4	4 (5)	4	4 (5)
G04 Urological drugs	27	20 (23)	13	11 (13)
Systemic hormonal preparations, excl. reproductive hormones and insulin (ATC group H)	**20**	**18 (21)**	**21**	**20 (23)**
H02 Corticosteroids for systemic use	9	9 (10)	5	5 (6)
H03 Thyroid therapy	11	11 (13)	15	15 (17)
H05 Calcium homeostasis	0	0 (0)	1	1 (1)

eTable 7. Drugs in use at baseline (continued)

ATC group	Intervention group (n=87)		Control group (n=87)	
	Prescriptions	Patients, n (%)	Prescriptions	Patients, n (%)
Antiinfectives for systemic use (ATC group J)	**9**	**9 (10)**	**12**	**12 (14)**
J01 Antibacterials for systemic use	9	9 (10)	12	12 (14)
Antineoplastic and immunomodulating agents (ATC group L)	**3**	**3 (3)**	**4**	**4 (5)**
L01 Antineoplastic agents	2	2 (2)	1	1 (1)
L02 Endocrine therapy	1	1 (1)	2	2 (2)
L04 Immunosuppressants	0	0 (0)	1	1 (1)
Musculoskeletal system (ATC group M)	**23**	**22 (25)**	**21**	**21 (24)**
M01 Antiinflammatory and antirheumatic products	2	2 (2)	2	2 (2)
M04 Antigout preparations	10	10 (12)	11	11 (13)
M05 Drugs for treatment of bone diseases	11	11 (13)	8	8 (9)
Nervous system (ATC group N)	**174**	**68 (78)**	**156**	**69 (79)**
N02A Opioids	15	13 (15)	18	16 (18)
N02B Non-opioids	33	33 (38)	28	27 (31)
N03 Antiepileptics	19	15 (17)	16	15 (17)
N04 Anti-parkinson drugs	6	3 (3)	6	3 (3)
N05A Antipsychotics	11	10 (12)	4	3 (3)
N05B Anxiolytics	9	9 (10)	11	11 (13)
N05C Hypnotics and sedatives	37	31 (36)	34	32 (37)
N06A Antidepressants	31	26 (30)	30	27 (31)
N06D Anti dementia drugs	12	11 (13)	7	6 (7)
Respiratory system (ATC group R)	**75**	**31 (36)**	**72**	**32 (37)**
R03 Drugs for obstructive airway diseases	57	22 (25)	48	18 (21)
R05C B Mucolytics	6	6 (7)	5	5 (6)
R05D A04 Codeine[a]	3	3 (3)	8	8 (9)
R06 Antihistamins for systemic use	9	9 (10)	10	10 (12)
Various (ATC group V)	**0**	**0 (0)**	**1**	**1 (1)**
V03AE Drugs for treatment of hyperkalemia and hyperphosphatemia	0	0 (0)	1	1 (1)

[a] All prescriptions of codeine classified in ATC group R are codeine used as an analgesic (in combination with paracetamol)

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