Results from the Improving Medication Prescribing to reduce Risk Of FALLs (IMPROveFALL) Study

A Randomized Controlled Trial

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ABSTRACT

Importance: Fall incidents represent a public health problem in aging societies worldwide. A major risk factor for falls is the use of fall-risk increasing drugs (FRIDs).
Objectives: To investigate the effect of withdrawal of FRIDs versus 'care as usual' on reducing falls in community-dwelling older men and women.
Design: Randomized multicenter trial.
Setting: Community, Primary care, Geriatric care.
Participants: 612 older adults who visited an Emergency Department due to a fall.
Interventions: A structured medication assessment including withdrawal of FRIDs.
Main Outcomes and Measures: A 3-monthly falls calendar was used for assessing the number of falls and associated injuries during 12 months of follow-up. Primary outcome was incidence of falls. Secondary outcome measures were falls requiring a general practitioner consultation or Emergency Department visit, and possible health effects of medication withdrawal. Data were analyzed using an intention-to-treat (primary) and a per protocol (secondary) analysis. Both overall FRID withdrawal as well as major subgroups (psychotropic and cardiovascular drugs) were assessed. The hazard ratios for time-to-fall were calculated using a Cox-regression model. Differences in cumulative incidence of falls were analysed using Poisson regression.
Results: During the 12 months follow-up, 91 (34%) of the control participants and 115 (37%) of the intervention participants experienced a fall. FRIDs withdrawal did not have a significant effect on the time to the first fall (hazard ratio [HR] 1.17; 95% confidence interval [CI] 0.89-1.54), the time to the second fall (1.19; 0.78-1.82), the time to the first general practitioner consultation due to a fall (0.66; 0.42-1.06), or the time to the first Emergency Department visit due to a fall (0.85; 0.43-1.68). Cardiovascular FRID withdrawal increased the time to the first general practitioner consultation due to a fall (0.57; 0.34-0.93). Per-protocol analyses did not alter the results.
Conclusions and Relevance: The risk of falls did not differ between the usual care and intervention groups. There was a trend towards fewer healthcare visits in the intervention group, and this was significant in the cardiovascular-drugs withdrawal subgroup. Surprisingly, no effect of psychotropic drug withdrawal was seen, possibly due to the group size and low compliance.
Trial Registration: Netherlands Trial Register NTR1593 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1593).

INTRODUCTION

Falls affect a large proportion of persons aged 65 years and older [1], and are associated with negative consequences such as high morbidity and mortality rates [2-4], disability, loss of quality of life, and institutionalization [5-8]. Furthermore, fall-related injuries place a substantial burden on healthcare systems due to the large number of visits to Emergency Departments (ED), hospital admissions, and admissions to long-term care and rehabilitation facilities [6,9-12]. In order to reduce the prevalence of falls, risk factors have been identified and documented [13-15], and a substantial number of falls-prevention trials has been published [1,16,17].

The use of certain drugs, i.e. the so-called fall-risk increasing drugs (FRIDs) [18-21], mainly psychotropic and cardiovascular drugs, has been associated with increased risk of falls and related injuries [18,19,21,22], and withdrawal of FRIDs appears to be feasible and effective [20,23-25]. Although FRIDs withdrawal is frequently incorporated in multifactorial intervention trials, evidence regarding overall FRID withdrawal as a single intervention is scarce [17].

In the present study, we investigated the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' on reducing falls in community-dwelling older men and women, who visited the ED after experiencing a fall [26].

METHODS

Study population

The IMPROveFALL study is a randomized, multicenter trial, assessing the effect of a structured medication assessment including withdrawal of FRIDs versus 'care as usual' as a method for falls reduction [26]. Patients meeting the following inclusion criteria were eligible for enrolment: aged 65 years or older, visited the ED of a participating hospital due to a fall, use of one or more fall-risk increasing drugs [18,19,21,26] (Table 1), Mini-Mental State Examination (MMSE) score of at least 21 out of 30 points [27,28], ability to walk independently, and community dwelling. Participating hospitals included two academic and four regional hospitals in the Netherlands. Enrolment started in October 2008 and was completed in October 2011. The follow-up period was 12 months. The study was performed in accordance with the Declaration of Helsinki and all participants gave written

informed consent. The local Medical Research Ethics Committees in all participating hospitals approved the study protocol.

Covariates

All persons visiting the ED due to a fall received care as usual for their injuries. Following the ED visit, patients were contacted by telephone. Subsequently, eligible and interested potential study participants received an appointment for the research outpatient clinic. The visits to the outpatient clinic took place within two months after the fall-related ED visit. If the patient met all eligibility criteria, the patient was asked to sign the Informed Consent Form. During the visit to the outpatient clinic a fall-related assessment was performed by the clinical investigator. This included a falls history (a single faller was defined as someone who had fallen once in the 12 months preceding inclusion, a recurrent faller was defined as someone who had fallen twice or more in the 12 months preceding inclusion), a fall-risk questionnaire [29], medical history and physical examination, physical performance tests, and a blood sample. The blood sample was used for measuring 25-hydroxyvitamin D levels, and to screen for hematologic, electrolyte, and liver and kidney function abnormalities. During the baseline assessment and at the follow-up clinic visit, participants completed questionnaires on generic Health Related Quality of Life (HRQoL). HRQoL was measured using the Dutch versions of the EuroQol five dimensions [30], and the Short Form-12 version 2 [31], at baseline and at 12 months-follow-up. A detailed description of the study protocol can be found elsewhere [26].

Randomization

Participants were randomized to one of the treatment arms, the intervention group versus 'care as usual' using a web-based variable block randomization program that was available 24 hours a day. Randomization using the trial website was done by the research physician. A block randomization with a block size of 4 was used. Due to the nature of the intervention, participants, research physicians, and care-givers could not be blinded to group assignment.

Intervention

All participants received a structured medication assessment, which included withdrawal of FRIDs in the intervention group only. In the 'care as usual' group, the medication was not changed. The intervention consisted of a systematic FRIDs assessment combined with drug withdrawal or modification, when safely possible.

FRIDs, as defined in the literature [18-21,26], were discontinued, reduced or substituted with potentially safer drugs in the intervention group. A complete list of FRIDs, based on current literature, is shown in Table 1. For each drug, the clinical investigator assessed whether the initial indication still existed. Proposed changes in medication were discussed with a senior geriatrician, the participant's General Practitioner (GP), and with the prescribing physician if other than the GP. For each drug modification, the clinical investigator followed the standardized instructions of the Dutch National Formulary [32], and a clinical pharmacologist was available for advice when needed. A research nurse offered counselling, evaluated possible negative effects via a standardized telephone follow-up, and discussed any problems with the clinical investigator and geriatrician.

All participants with follow-up were included in the intention-to-treat analyses. Regarding the per protocol analyses, the intervention group included both participants in whom FRID withdrawal/substitution was successful and participants in whom FRID withdrawal was not necessary or safely possible. In the event of more than one attempted FRID withdrawal, the successful withdrawal of at least one FRID was considered successful. The control group included participants in whom no FRID withdrawal/substitution was performed during follow-up.

Definition fall incident

A fall was defined as coming to rest unintentionally on the ground or a lower level with or without losing consciousness, but not induced by acute medical conditions, *e.g.*, stroke, or exogenous factors such as a traffic accident [33]. The history of falls was ascertained during a structured interview with the use of a falls questionnaire [29].

All participants received a Falls Calendar for reporting falls during a one-year follow-up period. Falls were recorded weekly on the Fall Calendars and had to be returned every three months. Follow-up started two weeks after completed intervention or two weeks after initial research clinic visit when no intervention was performed.

Laboratory values

Non-fasting blood samples were collected at the baseline assessment. Vitamin D deficiency was defined as serum 25(OH)D < 50 nmol/l [34,35]. Anemia was defined as haemoglobin levels < 8.1 mmol/L for men and < 7.5 mmol/L for women.

Statistical analyses

All analyses were performed using the Statistical Package of the Social Sciences (SPSS version 17.0, Chicago, Ill.). A p-value of < 0.05 was used as threshold for statistical significance.

After sample size calculations, our aim was to include a total number of 620 participants in the study, 310 in the control group and 310 in the intervention group [26]. Calculation of the required sample size was based on the assumption that the annual cumulative incidence of further falling is 50% without intervention [36], a 15% drop-out rate (including death) [1], drug withdrawal being possible in 50% of the participants in the intervention group and a 50% decrease of further falls among participants with successful withdrawal [24]. A single-sided test with an alpha level of 0.05 and a beta of 0.2 indicated that 310 patients in each group would be sufficient in order to detect a 25% decrease of participants reporting further falls in the intervention group [26].

Data were analyzed according to the intention-to-treat principle (primary), and per-protocol (secondary). The per-protocol analysis only included participants without a protocol violation as mentioned above. The hazard ratios for falling were calculated using a Cox-regression model. Herein, the time between the start of follow-up and the first fall served as the primary outcome measure. The time between the start of follow-up and the second fall, first GP consultation and first ED visit due to a fall were also analyzed. Differences in cumulative incidence of falls, GP consultations and ED visit were analyzed using Poisson regression, adjusted for overdispersion because of interdependence among the dependent variable (falls). Subgroup analyses were performed, assessing the separate effect of cardiovascular and psychotropic drug withdrawal.

Predefined models were constructed in order to adjust for age, gender and potential confounders. Potential predefined confounders that were considered for inclusion in the multivariate model were MMSE, BMI, the Charlson Comorbidity index, vitamin D deficiency, anemia HRQoL, physical performance, number of drugs, the number of FRIDs, smoking, alcohol intake, history of recurrent falls, use of walking aid, urinary incontinence, vision problems, fear of falling, and dizziness. Confounders that led to a change in the regression coefficient (B) of 10% or more were retained in the multivariate-adjusted regression model.

RESULTS

In total, 7,081 ED visits were screened for possible trial participants, of which 3,294 were not eligible, and 1,954 refused to participate. Subsequently, 612 participants were randomized in the IMPROveFALL study (Figure 1). Randomization resulted in 293 participants being allocated to the control group and 319 participants to the intervention group (Figure 1).

The mean age was 76 years, and 62% of the study population was female. No obvious differences in baseline characteristics were noted between the intervention and control group (Table 2). The mean number of drugs and FRIDs used at baseline were six ± three and four ± two, respectively. Table 3 specifies the interventions according to FRID categories and specific drug types, and also includes details on compliance to attempted interventions. Notably, in 40% of all FRIDs, 61% of cardiovascular FRIDs, 33% of psychotropic FRIDs, and 79% of other FRIDs, an intervention was not deemed possible or necessary. Of all attempted interventions 36% failed (37% of cardiovascular FRID interventions,47% of psychotropic FRID interventions, and 31% of other FRID interventions), either due to non-compliance or a return of the primary ground for which the drug was prescribed.

The percentage of participants using ≥ 3 FRIDs at baseline was 72% in the control group and 70% in the intervention group, these percentages did not decrease during follow-up, 75% and 70% respectively. Furthermore, in the intervention group 66 participants (22%) used a higher number of FRIDs after 12 months of follow-up than they used at baseline, compared to 68 (25%) in the control group (Supplementary data).

The number of participants in the control group (n=91; 34%) and intervention group (n=115; 37%) experiencing a fall during the one-year follow-up did not differ significantly (p = 0.33). Similarly, the number of participants in the control group (n=38; 14%) and intervention group (n=50; 16%) experiencing a recurrent fall during the one-year follow-up did not differ significantly (p = 0.45). Furthermore, the number of fallers requiring a GP consultation (n=46; 17% vs. 36; 12%, p=0.07) or ED visit (n=21; 8% vs. 16; 5%, p=0.22) did not differ significantly. The mean number of falls during follow-up in the control group was 0.83 and the mean number of falls in the intervention group was 0.80 (p = 0.88). The mean number of GP consultations in the control and intervention group were 0.21 and 0.16 respectively, p=0.25. The mean number of ED visits in the control and intervention group were 0.08 and 0.06 respectively, p=0.51.

In the intention-to-treat analysis, cox-regression analyses adjusted for age and gender showed that FRIDs withdrawal had no significant effect on the time to first fall (hazard ratio [HR] 1.17; 95% confidence interval [CI] 0.89-1.54), or on the time to the second fall (1.19; 0.78-1.82) (Table 4). Similarly, no significant effect on the time to the first GP consultation due to a fall (0.66; 0.42-1.06) or the time to the first ED visit due to a fall (0.85; 0.43-1.68) was found (Table 4). Subgroup analyses of cardiovascular and psychotropic FRIDs withdrawal were similar, except for an increased time until the first GP consultation due to a fall for cardiovascular FRIDs withdrawal(0.57; 0.34-0.93). The per protocol analyses did not alter the results.

Poisson regression analyses showed FRIDs withdrawal did not have a significant effect on the cumulative incidence of falls (β -0.05; 95% confidence interval [CI] -0.52- 0.42), or on the cumulative incidence of GP consultations (-0.28; -0.75- 0.18) or ED visits (-0.22; -0.88- 0.44) due to a fall. Subgroup analyses of cardiovascular and psychotropic FRIDs withdrawal were again similar, and per protocol analyses did not alter these results (Supplementary data).

During the 12-months follow-up, 28 participants in the control group and 27 participants in the intervention group sustained an injurious fall ($p = 0.64$). Seven participants in the control group and six participants in the intervention group sustained a fracture due to a fall ($p = 0.66$). Two participants, both in the control group, sustained a traumatic brain injury due to a fall ($p = 0.14$). Six participants died in the control group, causes were a ruptured coronary artery during a coronary angiography [1], kidney failure [1], esophageal cancer [1], leukemia [1], motor vehicle collision [1], and unknown [1]. Thirteen participants died in the intervention group, causes were sepsis [4], cancer [3], cerebrovascular accident [2], encephalopathy [1], cardiac failure [1], and unknown [2] ($p = 0.15$).

DISCUSSION

Contrary to our hypothesis, the risk of falls did not differ significantly between the usual care and intervention groups. However, there was a tendency towards fewer healthcare visits in the intervention group, which was significant in the cardiovascular-drug withdrawal subgroup.

In previous literature, the withdrawal of FRIDs has been shown to be safely possible and effective [20,23-25]. However, evidence regarding FRIDs withdrawal as single intervention is scarce [17,24,25]. When comparing studies that were successful in

reducing falls to this study, there are a few notable differences. In a study by Pit *et al.* the intervention was carried out by the participants' GP, probably increasing and sustaining the number of successful withdrawals due to the more substantial doctor-patient relationship [25]. Second, Campbell *et al.* performed a psychotropic drug withdrawal intervention that was complete and double-blind, demonstrating the effectiveness of total psychotropic drug withdrawal on preventing falls [24]. Yet this complete withdrawal was difficult to maintain, even during the study. This was also a limitation in our study. Notably, in our study the withdrawal of cardiovascular FRIDs appeared to reduce risk of GP consultations due to a fall, possibly due to fewer injurious falls. Most studies associate greater fall risk with psychotropic drugs [19,21], however, besides our finding, another study has also reported greater risk reduction after withdrawal of cardiovascular drugs [20].

There are several possible explanations for our findings. First, since in the last decade, fall prevention guidelines have been incorporated into usual care, this may well have blunted the effect of the intervention. Second, a large proportion of FRIDs were prescribed adequately and thus withdrawal was not appropriate (Table 3). Third, a large proportion of the participants was not compliant to the intervention, especially concerning psychotropic drugs. Fourth, it might be possible that participants in the intervention group were more diligent when filling out their Falls Calendars than the usual care group. Although not statistically significant, the intervention group displayed a tendency towards a shorter time until the first fall, yet a longer time until the first GP consultation or ED visit due to a fall. Furthermore, when studying the participants in the successful withdrawal group individually, it was apparent that although one or more FRIDs were successfully withdrawn, reduced, or substituted, several participants were prescribed additional FRIDs during the follow-up year. Furthermore, the percentage of participants using ≥ 3 FRIDs in the intervention group (70%) was not decreased at 1 year follow-up.

Notably, during follow-up, six participants in the control group and thirteen participants in the intervention group died, however, this was not a significant difference. Furthermore, looking at the separate causes of death the distribution of these deaths seem coincidental and not due to adverse effects of drug withdrawal. Also, another fall prevention trial including FRID withdrawal observed the opposite distribution [16].

In addition to the potential explanations mentioned above, the following limitations should be taken into account when interpreting our results. First, recruiting participants proved challenging. Possible reasons for refusing to

participate have been reported previously [37]. Most common reasons for refusal were the added burden of additional visits to the hospital; highly independent older adults feeling “too healthy”; and personal opinions regarding the cause of a fall. Second, possibly the method of reporting falls was not as accurate as anticipated; as mentioned above, the intervention group reported as many falls as the control group, but the numbers of healthcare visits due to a fall (which were verified with GP records) were higher in the control group. The newest guidelines state fall incidence is best monitored with weekly phone calls instead of self-report calendars [38]. Third, as mentioned before, in the intervention group compliance with withdrawal was limited, especially in the group with psychotropic drug withdrawal. This might be improved if the prescribing physician performs the withdrawal, as was the case in the study by Pit *et al.* [25]. A major strength of this study is that current recommendations regarding falls prevention studies were followed [39], i.e., addressing a single intervention in a randomized controlled trial. Furthermore, participants included were high-risk fallers, i.e., older men and women who visited the ED due to a fall. In this target group even a small reduction of their fall risk might prevent loss of independence.

Overall, FRIDs withdrawal did not result in fewer falls, however, cardiovascular FRIDs withdrawal did reduce risk of falls requiring a healthcare visit. Surprisingly, no effect of psychotropic drug withdrawal was seen, which might have been caused by low compliance to the intervention. This study increases insight into both the effectiveness of FRIDs withdrawal as a method for falls reduction in older adults, and the complexity of this intervention in an older, multi-morbid population. The current study adds to the understanding of effective falls-prevention interventions. However, further research is warranted focusing on the optimal method for implementation, thus ensuring participation and compliance of sustained FRIDs withdrawal in older fallers.

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Author contributions

NvdV, EvL, KH, TvdC, PP, and EvB designed the study, obtained funding and recruited participating centres. NB, NvdV, KH, OdV, and TvdC, supervised conduct of trial, screening of records, and collected data. NB, NvdV, OdV, EvL, EvB, TvdC, PL, and PP, analyzed and interpreted data. NB, NvdV, and OdV, drafted the manuscript, and all authors contributed substantially to its revision. All authors approved the final version of the manuscript. NB had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of data analysis.

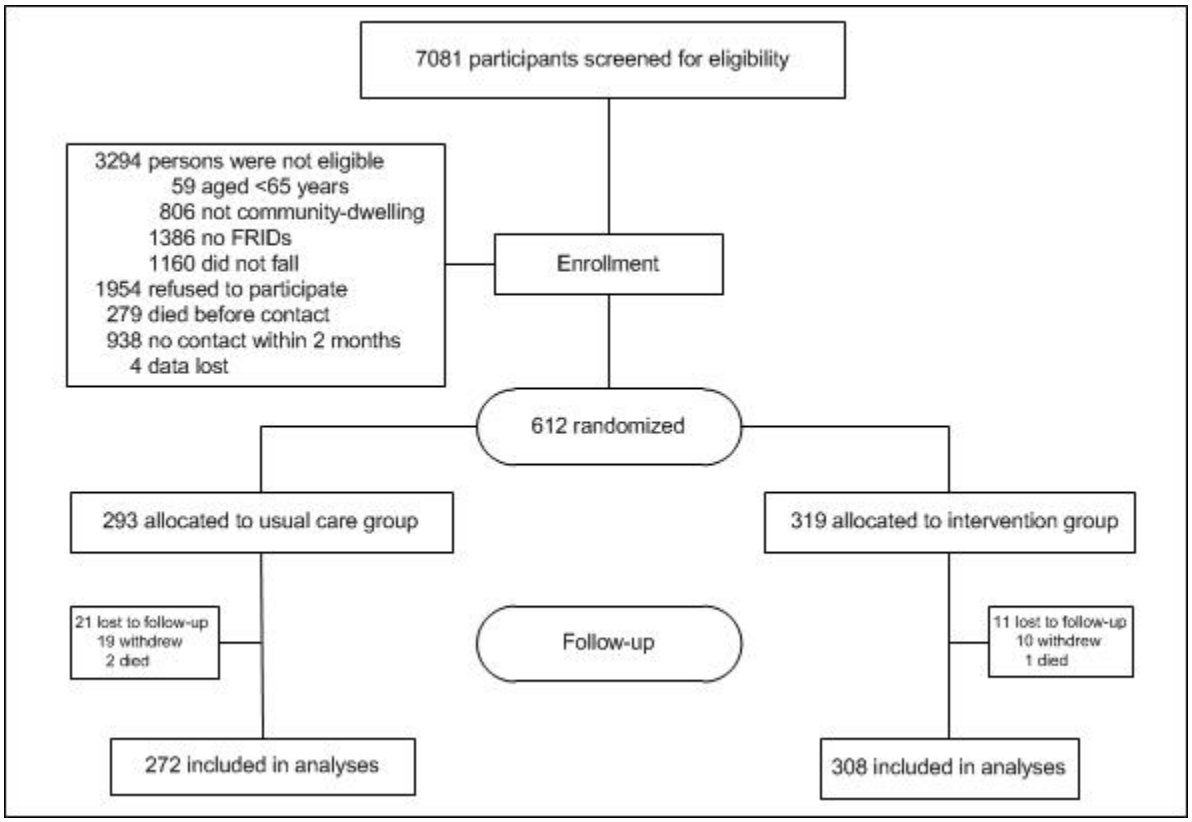
Trial collaborators participated in the screening of potential participants, and collecting trial data.

Conflict of Interest Statement

The authors declare no conflict of interest.

FIGURES & TABLES

Figure 1. Flowchart of study participants



ED, Emergency Department; FRID, Fall-risk increasing drug. *Of the participants that died during follow-up, most were included in the analyses, except for two in the usual care and one in the intervention group.

Table 1. Fall-risk increasing drugs

Drug category	Drug type	Therapeutic subgroups	ATC code
Psychotropic	Analgesics	Opioids	N02A
	Anti-epileptic	Barbiturates, fatty-acid derivatives, carboxamide derivatives, other	N03
	Anti-Parkinson	Dopaminergics, anticholenergics	N04
	Neuroleptics	Dopamine D2-receptor agonists and serotonin dopamine receptor antagonists	N05A
	Anxiolytics & Sedative/Hypnotics	Benzodiazepines and others	N05B N05C
	Antidepressants	Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors	N06
	Other	Anti-vertigo agents	N07CA
Cardiovascular	Cardiac therapy	Digitalis, anti-arrhythmics, nitrates	C01
	Anti-hypertensives	Alpha-adrenoceptor blockers, centrally acting antihypertensives	C02
	Diuretics	Thiazide diuretics, loop diuretics	C03
	Beta-blockers		C07
	Calcium-channel blockers		C08
	ACE/Angiotensin-II inhibitors		C09
	HMG CoA reductase inhibitors		C10AA
Other drugs	Gastro-Intestinal	Anticholenergics Hypoglycemics	A03AA A10
	Urogenital system	α –blockers, spasmolytics	G04BD G04CA
	Anti-inflammatory	Steroids Non-steroidal anti-inflammatory drugs (NSAID) Anti-gout	H02AB, R01AD B01AC06/08, M01A M04
	Muscle relaxant	Hydroquinine	M09AA
	Pulmonary	Sympathomimetics, cough suppressants, anti-histaminics	R03AC, R05DA, R06A

*According to study protocol [26]. ATC, Anatomical Therapeutic Chemical.

Table 2. Baseline characteristics

	Control n = 293	Intervention n = 319
Demographics		
Age (year)	76.4 ± 6.6	76.5 ± 7.2
Gender (female)	182 (62)	198 (62)
MMSE	27.0 ± 2.4	27.0 ± 2.3
BMI (m^2/kg)	27.6 ± 4.7	27.6 ± 4.6
Home care	69 (24)	82 (26)
Fall risk factors		
Charlson Comorbidity Index	1.9 ± 1.6	1.9 ± 1.6
Number of drugs	6.4 ± 3.3	6.3 ± 3.3
Number of FRIDs	3.9 ± 2.0	3.9 ± 2.1
History of recurrent falls	128 (44)	148 (46)
Use of walking aid	72 (27)	78 (27)
Urinary incontinence	37 (13)	52 (16)
Vision problems	85 (30)	98 (32)
Nycturia	177 (60)	181 (57)
Fear of falling	104 (36)	118 (37)
Dizziness	75 (26)	102 (32)
Indoor fall	107 (37)	148 (46)
Smoking	37 (13)	34 (11)
Alcohol intake (≥ 3 units/day)	33 (11)	34 (11)
Functional status		
Activities of Daily Living	0.80 ± 4.5	0.80 ± 3.3
Instrumental Activities of Daily Living	1.39 ± 5.4	1.37 ± 4.0
Biochemical		
Vitamin D deficiency	119 (41)	135 (42)
Anemia	34 (13)	58 (19)

Continuous data are shown as mean values ± standard deviation, categorical data as number with percentage.
MMSE, Mini-Mental State Examination; BMI, Body Mass Index; FRID, Fall-Risk Increasing Drugs.

Table 3. Specification of interventions and compliance in intervention group

	Intervention group	No withdrawal*	Attempted withdrawal	Failed withdrawal	Successful withdrawal
All FRIDs	319	126	193	69	124
Cardiovascular FRIDs	275	168	107	40	67
Digitalis	4	3	1	1	0
Anti-arrhythmics	16	14	2	2	0
Nitrates	29	25	4	1	3
Antihypertensives	9	6	3	1	2
Diuretics	129	85	44	21	23
Beta-blockers	137	103	34	15	19
Calcium channel blockers	66	50	16	7	9
ACE/Angiotensin-II inhibitors	148	123	25	5	20
HMG CoA reductase inhibitors	124	122	2	0	2
Psychotropic FRIDs	118	39	79	37	42
Opioids	21	16	5	1	4
Anti-epileptic	10	8	2	1	1
Anti-Parkinson	9	6	3	0	3
Neuroleptics	3	1	2	2	0
Anxiolytics	28	5	23	10	13
Sedatives/Hypnotics	43	10	33	22	11
Antidepressants	37	21	16	8	8
Anti-vertigo	7	3	4	0	4
Other FRIDs	227	179	48	15	33
Anticholinergics (GI)	4	3	1	1	0
Hypoglycemics	51	49	2	1	1
Anti-spasmodics (GU)	15	6	9	5	4
Alfa-blockers (GU)	24	17	7	2	5
Steroids	16	15	1	0	1
NSAID	149	140	9	2	7
Anti-gout	12	10	2	1	1
Hydroquinine (muscle relaxant)	5	3	2	1	1
Adrenergics (respiratory)	25	23	2	0	2
Cough suppressants (opioids)	19	13	6	2	4
Antihistamines	11	2	9	3	6

*Participants in intervention group where withdrawal, dose reduction and/or substitution of FRID was not necessary or safely possible. FRID, Fall-Risk Increasing Drugs; ACE, Angiotensin-Converting-Enzyme; GI, Gastrointestinal; GU, Genitourinary; NSAID, Non-steroidal anti-inflammatory drug. Data are shown as number of patients.

Table 4. Cox-regression analyses including subgroup analyses

	Intention to treat			Per protocol		
	HR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
All FRIDs						
First fall	1.17	0.89; 1.54	0.27	1.19	0.89; 1.60	0.24
Second fall	1.19	0.78; 1.82	0.41	1.26	0.80; 1.99	0.31
GP consultation due to a fall	0.66	0.42; 1.06	0.09	0.61	0.37; 1.02	0.06
ED visit due to a fall	0.85	0.43; 1.68	0.64	0.78	0.37; 1.63	0.50
Cardiovascular FRIDs						
First fall	1.10	0.82; 1.49	0.51	1.12	0.81; 1.54	0.49
Second fall	1.21	0.78; 1.88	0.41	1.31	0.81; 2.12	0.27
GP consultation due to a fall	0.57	0.34; 0.93	0.03	0.52	0.30; 0.91	0.02
ED visit due to a fall	0.77	0.38; 1.58	0.48	0.68	0.31; 1.50	0.34
Psychotropic FRIDs						
First fall	1.28	0.84; 1.94	0.26	1.44	0.91; 2.29	0.12
Second fall	1.17	0.64; 2.15	0.60	1.37	0.71; 2.67	0.35
GP consultation due to a fall	0.74	0.37; 1.48	0.40	0.88	0.42; 1.85	0.74
ED visit due to a fall	0.78	0.28; 2.16	0.64	0.93	0.32; 2.69	0.89

Adjusted for age and gender. FRID, fall-risk increasing drug.

eTable 1. Amount of FRIDs at baseline and at 12 months follow-up
=> SUPPLEMENTARY DATA

	Control n=272	**Intervention n=308**
Baseline FRIDs		
0 - 1	31 (11)	36 (11)
2	45 (17)	58 (19)
≥ 3	196 (72)	214 (70)
Follow-up FRIDs		
0 - 1	30 (11)	52 (17)
2	37 (14)	41 (13)
≥ 3	205 (75)	215 (70)
Change in amount of FRIDs		
Decrease	53 (20)	115 (38)
No change	151 (56)	127 (41)
Increase	68 (25)	66 (22)

Categorical data are given as number with percentages.

eTable 2. Poisson distribution of fall incidence => SUPPLEMENTARY DATA

	Intention to treat			Per protocol		
	β	95% CI	*p*-value	β	95% CI	*p*-value
All FRIDs						
Falls	-0.05	-0.52; 0.42	0.84	-0.01	-0.53; 0.52	0.98
GP consultations	-0.28	-0.75; 0.18	0.23	-0.28	-0.78; 0.22	0.27
ED visits	-0.22	-0.88; 0.44	0.51	-0.37	-1.08; 0.34	0.30
Cardiovascular FRIDs						
Falls	-0.06	-0.57 5; 0.46	0.83	-0.01	-0.59; 0.57	0.97
GP consultations	-0.34	-0.84; 0.16	0.18	-0.35	-0.88; 0.20	0.21
ED visits	-0.19	-0.90; 0.52	0.59	-0.38	-1.16; 0.39	0.33
Psychotropic FRIDs						
Falls	0.31	-0.22; 0.84	0.25	0.53	-0.05; 1.10	0.07
GP consultations	-0.32	-1.03; 0.40	0.38	-0.15	-0.91; 0.61	0.70
ED visits	-0.25	-1.26; 0.75	0.62	-0.17	-1.22; 0.89	0.76

Adjusted for age and gender. FRID, fall-risk increasing drug.

REFERENCES

1. Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *N Engl J Med.* Sep 29 1994;331(13):821-827.

2. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. *Jama.* Oct 14 2009;302(14):1573-1579.

3. Kochanek KD, Xu JQ, Murphy SL, al. e. Deaths: Preliminary data for 2009. . Vol National vital statistics reports; vol 59 no 4.: Hyattsville, MD: National Center for Health Statistics. ; 2011.

4. Stevens JA, Corso PS, Finkelstein EA, Miller TR. The costs of fatal and non-fatal falls among older adults. *Inj Prev.* Oct 2006;12(5):290-295.

5. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a prospective controlled study. *Osteoporos Int.* Feb 2004;15(2):87-94.

6. Close JC, Lord SR, Antonova EJ, et al. Older people presenting to the emergency department after a fall: a population with substantial recurrent healthcare use. *Emerg Med J.* Sep 2012;29(9):742-747.

7. Hartholt KA, van Beeck EF, Polinder S, et al. Societal consequences of falls in the older population: injuries, healthcare costs, and long-term reduced quality of life. *J Trauma.* Sep 2010;71(3):748-753.

8. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. *Osteoporos Int.* 2000;11(5):460-466.

9. Greenspan AI, Coronado VG, Mackenzie EJ, Schulman J, Pierce B, Provenzano G. Injury hospitalizations: using the nationwide inpatient sample. *J Trauma.* Nov 2006;61(5):1234-1243.

10. Hartholt KA, van der Velde N, Looman CW, et al. Trends in fall-related hospital admissions in older persons in the Netherlands. *Arch Intern Med.* May 24 2010;170(10):905-911.

11. Hartholt KA, Van Lieshout EMM, Polinder S, Panneman MJ, Van der Cammen TJM, Patka P. Rapid increase in hospitalizations resulting from fall-related traumatic head injury in older adults in The Netherlands 1986-2008. *J Neurotrauma.* May 2011;28(5):739-744.

12. Scuffham P, Chaplin S, Legood R. Incidence and costs of unintentional falls in older people in the United Kingdom. *J Epidemiol Community Health.* Sep 2003;57(9):740-744.

13. AGS/BGS. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc.* Jan 2010;59(1):148-157.

14. AGS/BGS/AAOS. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* May 2001;49(5):664-672.

15. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* Dec 29 1988;319(26):1701-1707.

16. de Vries OJ, Peeters GM, Elders PJ, et al. Multifactorial intervention to reduce falls in older people at high risk of recurrent falls: a randomized controlled trial. *Arch Intern Med.* Jul 12 2011;170(13):1110-1117.

17. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* 2012;9:CD007146.

18. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):40-50.

19. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* Jan 1999;47(1):30-39.

20. van der Velde N, Stricker BH, Pols HA, van der Cammen TJ. Risk of falls after withdrawal of fall-risk-increasing drugs: a prospective cohort study. *Br J Clin Pharmacol.* Feb 2007;63(2):232-237.

21. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* Nov 23 2009;169(21):1952-1960.

22. Sterke CS, Ziere G, van Beeck EF, Looman CW, van der Cammen TJ. Dose-response relationship between selective serotonin re-uptake inhibitors and injurious falls: a study in nursing home residents with dementia. *Br J Clin Pharmacol.* May 2012;73(5):812-820.

23. Alsop K, Mac Mahon M. Withdrawing cardiovascular medications at a syncope clinic. *Postgrad Med J.* Jun 2001;77(908):403-405.

24. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc.* Jul 1999;47(7):850-853.

25. Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. *Med J Aust.* Jul 2 2007;187(1):23-30.

26. Hartholt KA, Boyé NDA, Van der Velde N, et al. [Cost]effectiveness of withdrawal of fall-risk increasing drugs versus conservative treatment in older fallers: design of a multicenter randomized controlled trial (IMPROveFALL-study). *BMC Geriatr.* 2011;11:48.

27. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. *J Am Geriatr Soc.* Jul 1988;36(7):613-616.

28. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* Nov 1975;12(3):189-198.

29. Pluijm SM, Smit JH, Tromp EA, et al. A risk profile for identifying community-dwelling elderly with a high risk of recurrent falling: results of a 3-year prospective study. *Osteoporos Int.* 2006;17(3):417-425.

30. Brooks R. EuroQol: the current state of play. *Health Policy.* Jul 1996;37(1):53-72.

31. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol.* Nov 1998;51(11):1171-1178.

32. *Farmacotherapeutisch Kompas.* Diemen, Netherlands: College voor zorgverzekeringen; 2012.

33. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan Med Bull.* Apr 1987;34 Suppl 4:1-24.

34. Holick MF. Vitamin D deficiency. *N Engl J Med.* Jul 19 2007;357(3):266-281.

35. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev.* Aug 2001;22(4):477-501.

36. Close J, Ellis M, Hooper R, Glucksman E, Jackson S, Swift C. Prevention of falls in the elderly trial (PROFET): a randomised controlled trial. *Lancet.* Jan 9 1999;353(9147):93-97.

37. Elskamp AB, Hartholt KA, Patka P, van Beeck EF, van der Cammen TJ. Why older people refuse to participate in falls prevention trials: a qualitative study. *Exp Gerontol.* Apr 2012;47(4):342-345.

38. Reelick MF, Faes MC, Lenferink A, Esselink RA, Olde Rikkert MG. The fall telephone for falls assessment in frail older persons; feasibility, reliability, and validity. *J Am Geriatr Soc.* Feb 2011;59(2):372-373.

39. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc.* Sep 2005;53(9):1618-1622.