FRIDs and fall risk among older adults - protocol

Title:

Potential Fall-Risk-Increasing Drugs and falls in community-dwelling older adults: A prospective cohort study

Registration

Clinicaltrials.gov Identifier: NCT05169476

Document date

12-23-2021

Funding

This research will be funded by The Department of Geriatrics, Aalborg University Hospital, Denmark, The Department of Clinical Medicine, Aalborg University, Denmark, The municipality of Hjørring, Denmark and by external funding. The external funding sources will have no role in the design of this study, during its execution, analyses, interpretation of data or decision to submit results.

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Introduction

Falls in community-dwelling older adults are a major public health issue with an annual incidence of approximately 30% among adults aged ≥65 years increasing to 32-42% among those aged ≥75 years (1). In addition, the number of fallers is expected to increase in the future since the proportion of older people over 60 years is increasing worldwide (2). In Europe, the most frequent reason for older adults to contact an emergency department is due to falls - accounting for 50% of the total contacts (3). Even though most of the falls result in minor injuries, an increasing proportion leads to fractures or hospitalization. Furthermore, consequences of falls include increased morbidity and mortality along with loss of independence, which may lead to early institutionalization (1,4,5). Finally, the increasing number of fallers also leads to increased financial burden on the health care system (6).

Although some falls have a single obvious reason, most falls have a multifactorial aetiology such as previous falls, advanced age, cognitive impairment, environmental risks, hazardous activities, along with presence of chronic disease, muscle weakness, gait and balance disorders, and medication use (1,4,7–13). Recently, The European Geriatric Medicine Society (EuGMS) Task and Finish Group published a consensus paper classifying 14 medication classes as fall-risk-increasing drug (FRID) (14). Most of them were psychotropics, but several new possible FRIDs were identified. However, the group did not reach consensus on 17 medication classes as potential FRIDs (antihypertensives, cardiac glycosides, antiarrhythmics, gastrointestinal agents, central nervous system agents, chemotherapeutics, hypoglycaemics, fluoroquinolones, corticosteroids, and nonsteroidal anti-inflammatory drugs). This was substantiated by the studies presented for the panellists being heterogenous due to various settings, different cohorts of older adults as well as unclear descriptions of the medication and falls ascertainment methods. Hence, the evidence was insufficient to attain consensus.

This is consistent with the current gap in the literature with only a few studies investigating fall risk related to these types of drugs (15–17). Moreover, the group advocated for a higher research quality in primary studies due to issues with precise definitions of target medications and falls as well as lack of controlling for confounders (14,18). Therefore, to achieve a better understanding of these 17 medication classes as potential FRIDs, more studies taking these issues into account are warranted.

Primary objective:

To examine the association between use of the potential FRIDs and falls rate with a 1-year follow-up in a cohort of community-dwelling older adults, aged 75 years or more.

Study methods

Study design and sample size:

This prospective cohort study builds on previous data from the PREFALL study conducted in cooperation with Hjørring Municipality, Denmark (19). A pre-registered protocol on the PREFALL study was accepted at Clinicaltrials.gov (NCT03608709) on 01/08/2018 (20). The study recruited participants from 14/06/2018 to 18/07/2019 and had a 1-year follow-up period. The sample size was derived without a recommended power calculation; hence, the sample size builds on feasible recruitment within the 13 months inclusion period granted by the municipality due to economical and administrative reasons.

Timing of final analysis:

All study data were accessible from the PREFALL study before the completion of this protocol. Therefore, a detailed statistical analysis plan for this study was prepared before any outcome analysis was conducted to provide transparency on the intended and pre-planned analysis. This is pre-specified later in the protocol.

Study population and setting

The participants were community-dwelling aged 75 or more. Participants were excluded if they had 1) a dementia diagnosis; 2) acute illness defined by the presence of a participant-reported experience of illness within 7 days before inclusion affecting their ability to participate in social activities outside their homes; 3) inability to understand Danish; 4) Unable to stand unassisted for one minute. Support was defined by any assistive devices or help from another person. In Denmark, municipalities develop and initiate prophylactic and health-promoting initiatives for senior citizens (22). Thus, the participants were recruited through preventive home visits (PHV), senior activity centres (SAC), along with senior clubs and associations in Hjørring Municipality, Northern Jutland, Denmark. For PHVs, all the community-dwellers aged 75+ years who accepted the invitation to PHV were assessed for eligibility and included consecutively. For SACs, senior clubs, and senior associations, participants were conveniently recruited by oral study presentations since a

consecutive sampling method was not possible due to varying attendees each day. Lastly, recruitment videos were transmitted by the local televisions channel along with ads in newspapers and social media. For a more detailed description of the study setting and recruitment, the investigators refer to the PREFALL study (19).

Follow-up:

Follow-up time will be defined as the time from inclusion until death, withdrawal, or end of the study at the 18/07/2020. A summary of the participants' loss to follow-up will be presented with reasons and baseline characteristics to describe the adequacy of follow-up.

Baseline characteristics:

Data collection was performed at baseline and based on a multifactorial falls risk test battery including various physical tests (static balance under dual-task conditions, grip- and lower limb strength, reaction time of lower limbs and gait speed); self-report questionnaire on sociodemographic characteristics, frailty, nutrition, disability, fear of falling, health-related quality of life, depressive symptoms, several physical symptoms, cognitive tests; and reporting of comorbidities (23). The participants' comorbidities were obtained from the participants' hospital records and the diagnoses were indexed according to the International Classification of Diseases 10th revision (ICD-10). For a more detailed description of physical test and self-report questionnaire and their rationale, the investigators refer to the PREFALL study (19).

Baseline medication:

To determine the participants' medications at inclusion, the investigators consulted the national Shared Medication Record (SMR). The SMR is a national registry of current medication use and pharmacy records of prescriptions to each citizen in Denmark. Any physician involved in the patients' clinical course has access to the SMR data and all details of each prescription and the date of the latest medication reconciliation are provided (24). For each participant all medication registered in SMR at baseline was documented and indexed according to the WHO-recommended anatomical therapeutic chemical (ATC) medication classification system. The potential FRIDs which will be investigated in this study are: Beta-blockers (C07A); angiotensin-converting enzyme (ACE) inhibitors (C09A); calcium channel blockers (C08); cardiac glycosides (C01A); antiarrhythmic drugs (C01B); laxatives (A06A); proton pump inhibitors (A02BC); antiparkinson drugs (N04); acetylcholinesterase inhibitors (N06DA); beta blocker eye drops (S01ED); corticosteroid (H02A); oral

hypoglycaemic drugs (A10B); vitamin D (A11CC05); nonsteroidal anti-inflammatory (NSAID) drugs (M01A); fluoroquinolones (J01MA); and antineoplastic agents (L01).

Confounding covariates:

Many different risk factors and predictors for falls in older adults have been described previously and classified into different domains: sociodemographic, medical conditions, psychological, balance and mobility, and medication use (4,25,26). All these risk factors are possible confounders to the potential FRIDS; hence, the following a priori list specifies the confounding variables to be adjusted for in the multivariate regression model:

- Age (5,8).
- Sex (4).
- History of previous falls (19,27,28).
- The comorbidity related to the potential FRID to adjust for confounding by indication (18).
- Fear of falling using Short Falls Efficacy Scale-International 7-item (4,27–30).
- Gait speed measured with a 4-meter walk test (31–33).
- Cognitive impairment estimated by the Orientation-Memory-Concentration test performed over the telephone (4,27,33,34).
- Frailty using the Tilburg Frailty Indicator (35).
- Physical and instrumental disability in activities of daily living using the Vulnerable Elders Survey 13 (4,32,33,36).
- Depressive symptoms using Geriatric Depression Scale 4 item, a depression diagnosis or prescription of any antidepressants (4,16,27,28).
- Use of benzodiazepines, benzodiazepines derivatives or non-benzodiazepines (Z-drugs) (16,37).
- Use of opioids (15,38).

Statistical analysis

Outcome:

The primary outcome is fall rate per person-year. Fall rate will be calculated as the total number of falls divided by length of follow-up in years. A fall was defined as “an unexpected event in which the participants come to rest on the ground, floor, or lower lever” (39). Falls were recorded

prospectively with daily fall calendars with a monthly reporting and validated by a phone call if a fall was registered. If the calendar was not received within 14 days after deadline, the participant was contacted to retrieve the missing data.

Statistical methods:

A flowchart will be given to illustrate the flow of participants through the study including number of participants with and without falls. The participants' baseline characteristics and follow-up time will be summarised using descriptive statistics. Continuous variables will be summarized using medians with interquartile range, and categorical variables will be presented using counts and percentage proportions. Furthermore, the number of participants with missing data for the outcome, baseline characteristics, and confounding covariates will be presented. Then, missing data will be handled with multiple imputation methods. Finally, a univariate and multivariate Poisson regression model will be used to specify the association (expressed as incidence rate ratio, IRR) between the potential FRID and the rate of falls. For each potential FRID, a multivariate Poisson regression model will be performed adjusting for the medical indication of each drug and all other confounders from the a priori list. However, the Poisson regression model will only be performed for the potential FRID if more than 5 participants have a prescription registered at baseline. P-values lower than 0.05 will be considered as statistically significant. All statistical analyses will be carried out using R, version 4.0.2, (R Foundation).

Dissemination and reporting

The investigators want to publish the study in peer-reviewed journals in English. The reporting of the study will follow the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

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