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Fall-risk increasing drugs and recurrent injurious falls association in older patients after hip fracture: a cohort study protocol

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***Abstract*:** Polypharmacy and fall-risk increasing drugs (FRIDS) have been associated with injurious falls. However, no information is available about the association between FRIDS and injurious falls after hospital discharge due to hip fracture in a very old population. We aim to assess the association between the use of FRIDS at discharge and injurious falls in patients older than 80 years hospitalized due to a hip fracture. A retrospective cohort study using routinely collected health data will be conducted at the Orthogeriatric Unit of a teaching hospital. Patients will be included at hospital discharge (2014), with a 2-year follow-up. Fall-risk increasing drugs will be recorded at hospital discharge, and exposure to drugs will be estimated from usage records during the 2-year follow-up. Injurious falls are defined as falls that lead to any kind of health care (primary or specialized care, including emergency department visits and hospital admissions). A sample size of 193 participants was calculated, assuming that 40% of patients who receive any FRID at discharge, and 20% who do not, will experience an injurious fall during follow up. This protocol explains the study methods and the planned analysis. We expect to find a relevant association between FRIDS at hospital discharge and the incidence of injurious falls in this very old, high risk population. If confirmed, this would support the need for a careful pharmacotherapeutic review in patients discharged after a hip fracture. However, results should be carefully interpreted due to the risk of bias inherent to the study design.

Keywords: accidental fall, adverse drug event, elderly, fall-risk increasing drugs, hip fractures

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Introduction

Fall-related injuries in older people are relevant outcomes, both for the person who falls and for the health care and social support systems. In older people, falls are a risk factor for hospitalization or institutionalization.[1] Usually, falls are the consequence of the interaction between different risk factors and situations that could be prevented. Age, sex, comorbidities, history of previous falls or polypharmacy are among the risk factors associated with falls in older people.[2] Patients who have suffered a hip fracture due to a fall are at high risk of falling. Between 36% and 56% of these patients will fall again over the following 6–12 months after the fracture,[3–6] and 9% will be hospitalized due to a new fracture or other injury within the 6 months after the hip fracture.[7] Therefore, it is important to identify the risk factors for falling, and to implement strategies to mitigate those risk factors and help prevent additional falls.

The relationship between polypharmacy and different pharmacological groups of drugs with the risk of people falling has been evaluated in several studies.[8–10] These studies have shown that polypharmacy is an independent risk factor for falls, although this could be explained by the fact that

some drugs, such as benzodiazepines or antidepressants, are likely to be present when multiple drugs are prescribed.[11,12] According to previous studies, a list of drugs associated with risk of injurious falls was made by van der Velde in 2007,[8,13,14] using the acronym *FRID* for the first time. The Swedish National Board of Health and Welfare created a list of FRIDS in 2010,[15] clustering the drugs in pharmacological groups following the Anatomical Therapeutic Chemical (ATC) classification system.[16] This list was used by some authors to show that patients admitted to the hospital due to an injurious fall had more FRIDS in their treatment than those who did not fall.[5,12,17] However, after a search in PubMed, Cochrane, and CINAHL using the terms 'fall risk increasing drugs' and 'drug related falls' we found no information about use of FRIDS after hospital discharge in persons hospitalized for the treatment of a hip (proximal femoral) fracture, one of the most serious adverse outcomes after a fall in older persons.

Therefore, we designed a study to assess the use of FRIDS at hospital discharge in this vulnerable, high-risk population (old patients admitted to the hospital due to a hip fracture), and the association between the use of FRIDS and injurious falls (falls that result in the patient receiving any kind of health care). We hypothesized that many patients would be using FRIDS at hospital discharge that would predict a high risk of injurious falls in the 2 years following hospital discharge. We also intend to assess the temporal patterns of falls after discharge, the influence of exposure to FRIDS, severity of injuries, and mortality during follow up.

Methods

Study design

This is a retrospective cohort study using routinely collected health data. The study will comprise a follow-up period of 2 years from hospital discharge (starting on January 2014) to 2 years later.

Study setting and population

The study will be performed at the Orthogeriatric Unit of a large university hospital with a catchment area of around 600,000 people. This Unit, follows the clinical pathway detailed in the Trondheim Hip Fracture Trial,[18] and provides care to all hip-fractured patients over 80 years old.

The study population will be composed of patients over 80 years old, and consecutively discharged from the Orthogeriatric Unit since January 2014, who were hospitalized due to a hip fracture, and who were able to walk before the fracture (Functional Ambulation Categories FAC scale $\geqslant 1$).[19] Patients will be excluded if they were not allowed by the surgeon to walk after surgery, were receiving end-of-life or palliative care, or if there were missing drug information in the discharge letter.

Data collection

Clinical data will be anonymized and collected retrospectively from two different electronic records: CAJAL®, a locally developed software for hospital records, and HORUS®, a regional software used in Madrid region, for primary care records. Both tools are used by physicians in their clinical practice, and both will be used to obtain information related to pharmacological treatment, further falls leading to medical care, and deaths during the follow-up period (2 years after hospital discharge). All prescriptions have recently (2019) been included in a common prescription system used both by primary and specialized care within the public health system (Módulo Único de Prescripción, MUP). This includes all drugs prescribed to all patients (community dwelling or living in nursing homes), who get refills at any community pharmacy using a personal ID card. Refills have been registered for several years in this database, which allows for an indirect measure of compliance.

Inclusion of patients. All patients consecutively discharged from the Orthogeriatric Unit in 2014 will be screened until the estimated sample size is completed.

Characteristics of the population. The variables at hospital admission will be collected from the hospital electronic medical records (CAJAL®). Such records have shown to be reliable and accurate for measures of multimorbidity, and also to assess the drugs recommended in the discharge letter. We will collect anthropometric variables such as age at the time of admission and gender; variables of function and clinical conditions such as type of fracture, history of falls within the previous

Table 1. List of FRIDS by the Swedish National Board of Health and Welfare (2010).

Anatomical therapeutic chemical (ATC) classification system	
Drugs that cause high risk of falling	
N02A	Opioids
N05A excl. Lithium	Antipsychotics
N05B	Anxiolytics
N05C	Hypnotics and sedatives
N06A	Antidepressants
Drugs that cause orthostatism/hypotension	
C01D	Vasodilators used in cardiac diseases (nitrates)
C02	Antihypertensives
C03	Diuretics
C07	Beta-blockers
C08	Calcium channel blockers
C09	Agents acting on the renin-angiotensin system
G04CA	Alpha-adrenoreceptor antagonists (used in benign prostatic hyperplasia)
N04B	Dopaminergic agents (anti-Parkinson drugs)

6 months, ambulation capacity (FAC scale), baseline and instrumental activities of daily living (Barthel index and Lawton index, respectively), cognitive impairment (Reisberg's Global Deterioration Scale, GDS), impairment of hearing and vision, renal failure (estimated Glomerular Filtration Rate, eGFR < 45 ml/min) nutritional status (Mini Nutritional Assessment, MNA); and social features such as place of residence (living at home or at nursing home), living alone or with relatives, and use of home care services.

Exposure to drugs. We will review the pharmacological treatment prescribed at discharge first by counting the total number of drugs (polypharmacy defined by the use of 5 or more drugs and hyperpolypharmacy by the use of 10 or more drugs[20]). Drug counting will be done by generic name. Secondly, we will identify those drugs that are considered FRIDS according to the list made by the Swedish National Board of Health and Welfare and the Anatomical Therapeutic Chemical (ATC) classification system (Table 1). This list was chosen because it has been used in several studies,[5,12,17] and includes the pharmacological groups also recognised as FRIDS in other studies. For example, NSAIDS are not included in the Swedish list of FRIDS, as they are not always recognised as FRIDS.[21] Chronic medications, medications recommended for subacute care (i.e. analgesics, heparins, oral iron supplementation) and medications prescribed on demand, as well as eyedrops, will be recorded as part of the total number of drugs. Topical medications will not be recorded. According to the Scottish Polypharmacy Guide, we will also classify the FRIDS in two groups: those considered to have a low or moderate risk of causing a fall, and those considered as having high risk of causing a fall.[22]

Outcome. We will review the medical records and will collect the number of patients who suffered from at least one injurious fall (defined as a fall that lead to any kind of health care, primary or specialized care, including emergency room visits and hospital admissions) within 2 years after discharge from the hospital. Injurious falls will be classified as either serious or moderate according to the categories and definitions given in the systematic review by Schewnk

on behalf of the Prevention of Falls Network Europe (ProFaNE).[23,24,25] According to this classification, a serious fall-related injury could be a fracture, head or internal injury requiring emergency or inpatient treatment. A moderate fall-related injury will be a wound, bruise, sprain, or cut requiring a physical examination, X-ray or suture. Falls will be searched in both databases, CAJAL® and HORUS®, that collect any primary care or hospital care received under the national health system. There is no a specific code for falls, so we will review the fall-related data from the medical records over the 2 years of follow-up. For time analysis, only the first injurious fall will be used.

Study variables

The variables listed in Table 2 will be collected.

Sample size and statistical analysis

Sample size was calculated according to the best-found evidence at the moment of the study design: a study conducted in a community setting with patients older than 65 years (mean age 73 years) who went to a primary care center due to a fall, and were followed for 2 years.[26] According to this study, the risk of falling was 12.4% and 6.1% for those patients who have been using FRIDS and for those patients who have not been, respectively. Supposing a higher risk of falling for the participants in our study, as they are 80 years old or more and have suffered from a previous hip fracture, we estimate, considering the same proportion of risk as in the aforementioned study, that 40% of patients in treatment with FRIDS and 20% without FRIDS will fall. This is also according to the incidence of falls from other similar studies.[3–6] This calculation estimates that 193 participants are required to conduct the study. The sample size was calculated with a statistical power of 80% after adding 15% of losses during follow up. The sample size was calculated by using free software (Epidat® 4.1).

A descriptive analysis of the patient's characteristics will be performed. Continuous variables will be described by means and standard deviation, and categorical variables will be described as frequencies (percentage). To compare categorical variables, Chi-square test or Fisher's exact test will be used (if the number of observations is less than five). The comparison of parametric variables will be performed using the Student's t test, and, in the case of nonparametric variables, the Mann-Whitney U will be used (the Shapiro-Wilk test will be used to evaluate the parametric nature of the quantitative variables).

The main objective of the study, the relationship between the exposure (FRIDS at hospital discharge) and the outcome (number of fallers) during the 2 years of follow-up or at last evidence of life (censoring), will be evaluated by performing a competing-risks regression (last evidence of life). In addition, a multivariate analysis will be performed to adjust for potential confounding variables (age, gender, gait, and any other variable found in univariate analysis). The measure of association between the risk factor and the event will be calculated using the Standardized Hazard Ratio (SHR). A graphical survival analysis will be performed using Kaplan–Meier curves.

Censoring Patients who have not completed the follow-up period due to death, or loss of clinical information in the consulting software will be considered as non-informative censoring. This will be checked in both databases, CAJAL® and HORUS®. In addition, to obtain the missing dates of death, another electronic system, the hospital admission database (HP-HIS®), where all personal patients' data are registered, will be checked.

The two-tailed level of significance used will be 0.05. For the statistical processing the Stata® program version 13.0 will be used.

Data access and cleaning methods

The authors are familiar with the databases used in this work, as use them on a daily basis. Patients that fulfil the inclusion criteria will be followed for 2 years. Only patients who are not registered in the primary care database (because they are from another region) will be excluded.

Confidentiality and ethics approval

The information handled is confidential, and participants will be identified by a numeric code. Data will be treated according to the Protection of Personal Data Organic Law 15/13 December 1999. Study approval was obtained from the local Ethics Committee on Clinical Research in May 2016.

Table 2. Study variables

Independent variables at hospital discharge	Dependent variables during follow-up
a. Anthropometric variables: - Age (Date of birth) - Gender	**a. Falls:** - Date of first injurious fall - Assistance in a primary care centre due to a fall - Assistance at the emergency department due to a fall - Hospital admission due to a fall - Severity of fall-related injuries: • Fracture • Traumatic brain injury (TBI) • Open wound • Sprain or twist • Contusion and pain • Others
b. Pharmacotherapy: - FRIDS according to the Swedish National Board of Health and Welfare at hospital discharge - Number of drugs at hospital discharge (polypharmacy or hyperpolypharmacy)	**b. Competitive event:** - Deaths (date of death)
c. Clinical/functional status: - Type of fracture (extracapsular or intracapsular fracture) - Six-month History of previous falls - Ambulation ability (FAC scale) - Baseline activities of daily living (Barthel index) - Instrumental activities of daily living (Lawton index) - Cognitive impairment (Reisberg GDS) - Hearing and vision impairment - Stage IIIb Renal failure (TFG $<$ 45 ml/min) - Mini Nutritional Assessment (MNA)	**c. Pharmacotherapy:** - Start and end date of a FRID prescription
d. Social situation: - Place of residence: home, nursing home - Living alone or living with relatives - Needing home help	

Publication

The results of this study will be published independently of their direction, maintaining the confidentiality of the handled information.

Discussion

This protocol explains the methods of this retrospective cohort study using regional health data that aims to quantify the likely relationship between FRIDS use and injurious falls in an older population with a previous hip fracture. High and low risk FRIDS will be analyzed, as well as polypharmacy. This information will allow medications or prescription patterns associated with injurious falls to be identified, and future intervention studies to be designed for fall prevention in this high-risk population. In addition, factors such as polypharmacy, functional status, and social aspects will be used as confounders for adjustment in multivariate analysis, as they might also be related with the risk of falls. We have opted not to use multimorbidity scores, as evidence shows that, after adjusting for drugs and functional and cognitive variables, they are not (or only very modestly) predictive of falls.[27–29]

There are, however, some methodological issues that should be highlighted. As a retrospective cohort study based on routinely collected data, several biases inherent to the study design can be anticipated, since the exposure and the final results have already occurred when participants are selected for the study. These include bias in

selection of participants for the study at the time of patient inclusion. To minimize this, the inclusion and exclusion criteria have been defined as looking for full inclusion, only excluding those that are expected to have different care needs. Bias might also be due to missing data. Data collection will be clearly affected by the accuracy of the information recorded in the medical notes, both at the time of hospitalization and during primary care. For instance, dates of drug prescriptions might be affected by potentially outdated prescription records. Loss to follow up can be also a major limitation. However, the new electronic prescription record, and the fact that most older patients in our country are cared for the national health system, should reduce the risk of this bias.

Regarding the outcome, as we will collect falls that lead to a medical assistance (the most relevant ones), the overall incidence of falls in the study population could be higher as mild injuries that do not lead to medical care will not be identified, and, therefore, not registered. In addition, falls and injuries are not registered with a coding system so this could be a limitation when we will review the medical records searching for an injurious fall.

Bias due to confounding factors is also possible. Confounding factors are those factors that influence the association between an exposure (FRIDS) and an outcome (falls) because they are independently associated with both exposure and outcome. This may be the case for measures of disability and cognition. To minimize this confusion, a multivariate analysis will be performed. In addition, we are aware that some non-recorded variables may act as confounders (i.e. fear of falling, dual tasking, or minor gait disturbances). This study is not a large cohort study involving national databases; however, it is based on regional health data involving 583,397 inhabitants (January 2017) of the hospital's catchment area where 36,400 are older than 80 years. The study population represents those patients usually hospitalized in Spanish Orthogeriatric Units.

This study would highlight the need to focus on this vulnerable population. To avoid further injurious falls and fractures, a close follow up with a discharge medication review focused on FRIDS will be key. Moreover, when a medication review is established, it gives the opportunity to find other potentially inadequate prescriptions, correct them, and eventually optimize health resources.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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