STUDY PROPOSAL

THE RISK OF FALL AND HIP FRACTURE AMONG USERS OF PROTON PUMP INHIBITORS

Background

Falls and osteoporosis-related fracture are major health concerns in particular for women (1). Each year one in three people aged 65 years or older experiences at least one fall (2) with about 5% resulting in a fracture (3). Of these fractures, hip is the most serious with significant morbidity and mortality. It has been estimated that over 20% of patients die in the first year after a hip fracture (4).

Five recent publications of observational studies have reported an association between acid-suppressive drugs and an increased risk of hip fracture (5-9). All used as primary source of information automated clinical databases. All but one of the studies found a relative risk of hip fracture around 1.5 among users of acid-suppressive drugs but there was substantial heterogeneity in the specific dose and duration response. There is no study addressing the association between acid-suppressive drugs and the occurrence of falls. The mechanisms linking medications to falls have a great variation (eg. orthostatic hypotension, CNS alterations) and are different from the ones linking medications to fractures (eg. mineralization, bone turn-over). Given that not all falls result in fracture (10), the study of an association between acid-suppressive drugs and falls and hip fractures, separately, will help us disentangle where it is present with none, only one or both of these two outcomes. Dizziness and confusion are listed as uncommon or rare adverse drug reactions (ADRs) for most proton pump inhibitors (PPIs) and H2 receptor antagonists (H2Ras). In addition, vision disturbances like blurred vision are listed as rare ADRs for PPIs.

We aim to study the relationship between use of acid-suppressive drugs and falls and hip fractures using data from The Health Improvement Network database (THIN).

Study objectives

1- To estimate the incidence of fall and hip fracture in the general population.

2- To estimate the risk of fall associated with use of proton pump inhibitors and H2 receptor antagonists as well as the effect of individual agents.

3- To estimate the dose and duration-response of PPI and H_2RA on the risk of fall

4- To estimate the risk of hip fracture associated with use of proton pump inhibitors (PPI) and H2 receptor antagonists (H_2RA) as well as the effect of individual agents.

5- To estimate the dose and duration-response of PPI and H_2RA on the risk of hip fracture

Population and methods

- **Design**

A retrospective cohort study with nested case-control analyses will be performed using data from The Health Improvement Network database (THIN) in the UK.

- **Source population**

THIN contains computerized information entered by primary care physicians (PCPs) in the UK (11). Data on over 5 million patients are systematically recorded and sent anonymously to THIN. THIN collects and organizes this information in order to be used for research projects. The computerized information includes demographics, details from general practitioner's visits, diagnoses from specialist's referrals and hospital admissions, results of laboratory tests and a free text section. Prescriptions issued by the general practitioner are directly generated from the computer. An additional requirement for participating practices is recording of the indication for new courses of therapy. The READ classification is used to code specific diagnoses, and a drug dictionary based on data from the MULTILEX classification is used to code drugs.

- **Study population**

We will identify all individuals 40-89 years old between

with a current registration status of permanent or died. Patients will become members of the study cohort on the first day of the study period when they meet the criteria of at least two years enrollment with the general practitioner, one year since the first computerized prescription and at least one encounter recorded in the last two years. That date will be their study start date. We will exclude individuals with antecedents of cancer. Patients with a history of fall or hip fracture before start date will

however not be excluded. Finally, we will exclude persons 70 years and older at start date with a follow-up greater than one year and no recording of any data during their follow-up time (this is done to exclude people whose data completeness is most likely seriously deficient). All remaining patients will constitute the final study population. Two independent follow-up will be performed.

- **Follow-up to ascertain fall**

All study population members will be followed until the earliest occurrence of one of the following endpoints:

1- Fall
2- Age = 90 years
3- Cancer
4- Death
5- End of study period

- **Follow-up to ascertain hip fracture**

All study population members will be followed until the earliest occurrence of one of the following endpoints:

1- Hip fracture
2- Age = 90 years
3- Cancer
4- Death
5- End of study period

- **Case ascertainment: fall**

We will request free text comments for a random sample of 400 patients identified with a code of fall and will manually review their computerized patient profiles. Information will include demographic data and all clinical information. The patient profile will not have any personal identifiers.

Non-case: the information recorded on the computer will be sufficient to exclude a diagnosis of incident fall (eg. prevalent case).

Potential case: the information recorded on the computer will be compatible with an incident case of fall.

If the information based on patient profiles including free text comments confirms a diagnosis of incident fall in 90% of instances or greater, we will not request additional free text comments for the remaining patients identified with the initial computer search.

Incident cases of fall will be assigned into two categories:
- Case of fall with ensuing fracture: a time window of one month after the episode of fall will be searched to ascertain a fracture.
- Case of fall not resulting in fracture.

- **Case ascertainment: hip fracture**

We will request free text comments for a random sample of 400 patients identified with a code of hip fracture and will manually review their computerized patient profiles. Information will include demographic data and all clinical information. The patient profile will not have any personal identifiers.

Non-case: the information recorded on the computer will be sufficient to exclude a diagnosis of incident hip fracture (eg. prevalent case, diagnosis not confirmed).

Potential case: the information recorded on the computer will be compatible with an incident hospitalized case of hip fracture.

If the information based on patient profiles including free text comments confirms a diagnosis of incident hip fracture in 90% of instances or greater, we will not request additional free text comments for the remaining patients identified with the initial computer search.

- **Case Validation with PCPs**

For a random sample of potential cases (N=100 for fall; N=100 for hip fracture), we will send a questionnaire to the PCPs in order to confirm the diagnosis of fall/hip fracture. Also, we will request the PCP to send a copy of all available medical records related to the study episode including hospital discharge letters and reports of diagnostic procedures, whenever available. If the information from the questionnaire and medical records confirms a diagnosis of incident fall/hip fracture in 90% of instances or greater, we will not request additional records for the remaining potential cases (12).

- **Cohort analysis**

Rates of fall and hip fracture will be calculated using the corresponding person-time contribution of all study cohort members as denominator. We will estimate incidence rates per 1,000 person-years both overall, sex and age-specific. Estimates of relative risk and its 95% CIs associated with age and sex will be computed using a Poisson regression model with sex, age and calendar year included in the model.

- **Control selection**

A date encompassed within the study period will be generated at random for each of the study population members. If the random date is included in her/his eligible person-time (corresponding to the follow-up contribution of a study member), we will use this random date as the index date and mark that individual as an eligible control. The same eligibility criteria will be applied to controls as to cases. Ten thousand controls will be randomly selected from the pool of eligible controls frequency matched to the cases on sex, age (within one year) and same calendar year. A series of controls will be sampled for fall cases and another for cases of hip fracture.

- **Nested case-control analysis**

We will compute estimates of relative risk and 95% confidence intervals for fall and hip fracture, separately, associated with use of acid-suppressing dugs compared to non-use by means of unconditional logistic regression models. Frequency-matched factors and other potential risk factors will be introduced in the model. Information on potential risk factors related to fall/hip fracture will be obtained from computerized files, and include among others age, prior fracture, body mass index (BMI), immobility, osteoporosis, chronic renal disease, parathyroidea disease, thyroid disease, Cushing syndrome, inflammatory bowel disease, chronic hepatic disorder, chronic obstructive pulmonary disease, multiple sclerosis, Parkinson, dementia, epilepsy, rheumatoid arthritis, any autoimmune disease, ischaemic heart disease, heart failure, cerebrovascular disease, socioeconomic status-townsend deprivation index (13), smoking, alcohol consumption, use of antipsychotics, antidepressants, hypnotics, sedatives, antihypertensives any drug influencing bone density such as calcium, D vitamin or biphosphonate ,systemic corticosteroid use and use of low dose metothrexate. We will categorize patients as abstainers or occasional drinkers, when

they take less than 2 units per week, light drinkers from 2 to 15 units, moderate from 16 to 24 units and heavy drinkers when they take more than 24 units per week (14).

- **Exposure definition**

We will define three time windows of exposure to acid-suppressing drugs (PPI and H2-antagonists): current use, recent use, past use and non-use. Current use will refer to use that lasts until the index date based on the length of drug therapy as prescribed by the general practitioner or ended in the month prior to the index date. Recent use will be use ending between 1 month and 1 year before the index date. Finally, the time window of non-use will be defined as no recorded use of acid-suppressive drugs in the year before the index date

Among current users, we will evaluate the dose and duration-response as well as the role of treatment indication. Duration of use will correspond to the number of days included in the time period of "consecutive" prescriptions: two prescriptions are considered "consecutive" when the time interval between the end of supply of the first one and the beginning of supply of the second one is less than two months. We will categorize treatment duration into four categories: less than 1 month, between 1 month and 1 year, between 1 year and 3 years and more than 3 years of use. For the dose–response analysis, medium doses of PPIs will be defined as follows: esomeprazole 40 mg, omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and rabeprazole 20 mg; lower doses will be grouped as low dose and higher doses as high doses. The risk associated with the most widely used acid-suppressing drugs will also be examined.

- **Power calculation**

After applying the inclusion criteria, the source cohort will include over 2 million patients. A study in the UK reported an overall incidence rate of hip fracture close to 5 per 1,000 person-years in the nineties (15). Thus, we expect to identify more than 30,000 patients with incident hip fracture during our follow-up. The incidence of fall is expected to be clearly higher than the one of hip fracture (16). The expected prevalence of PPI and H2RAs current use should be close to 8% and 3% among the controls, respectively.

The table below shows different power estimations for a 5% two-sided alpha error and with a sample size of 30,000 cases and 2 controls per case according to variations on the prevalence of exposure and the estimated relative risk. In summary, we will have statistical power greater than 90% to find a relative risk (RR) of 1.25 or higher associated with exposures as low as 1% among controls.

The table presents the statistical power we will have to detect various measures of relative risk (RR) based on two-tailed significance tests at the 0.05 alpha level assuming 30,000 cases and 2 controls per case and a prevalence of use in controls from 3 to 8%.

Prevalence of exposure	RR = 1.1	RR = 1.2	RR = 1.3
3%	0.66	0.99	1.00
5%	0.86	1.00	1.00
8%	0.96	1.00	1.00

- **Limitations of the proposed study**

There will be misclassification of the diagnosis of fall, in particular non severe, as some patients might not seek care from their GP. Also, most patients with hip fracture will go directly to hospital as a first option. As a result, the diagnosis of these episodes could not come to the attention of the GP and would therefore be unrecorded. This scenario is very unlikely to be present for hip fracture as the GP will be responsible for the follow-up of these patients after discharge. The exceptions will be when the patient dies in the hospital due to a complication (eg. pneumonia) after suffering a fall/hip fracture.

Over-the-counter drug use is not recorded in the database and has to be taken into account. A small proportion of PPI or H2-antagonist use is taken without prescription, though OTC use in elderly (above 60 years) and chronic use will be rare.

Secondary care treatment is not included in THIN data and is only covered as recorded by the GP, so any drug prescriptions issued only by secondary care are likely to be omitted. Having said that, hospitals are unlikely to issue prescriptions lasting longer than 1-2 weeks as the budget for these treatments lies within primary care.

- **Strengths of the proposed study**

The mechanisms linking medications to falls (eg. orthostatic hypotension, CNS alterations) are not shared with the ones linking medications to fractures (eg. mineralization, bone turn-over). Therefore, our proposal to study the association between PPIs and these two outcomes will help us to draw causal inference based on whether no association is found with any of the two outcomes, only one or both outcomes. For instance, the finding of an association with both outcomes would a priori question the validity of a causal association given the marked heterogenity between mechanisms leading to falls (not resulting in fracture) and fracture (falls resulting in fracture).

- **Scientific/ethical approval**

This study protocol using THIN Data has to receive ethical approval from a recognised ethical board such as the NHS Multicentre Research Ethics Committee (MREC).

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