Oral anticoagulants and the risk of an osteoporotic fracture among the elderly

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To Pierre and Thomas,

for their love

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1. Abstract

Background: Oral anticoagulants are associated with a decrease in bone mass density. Our study evaluates the association between an osteoporotic fracture and oral anticoagulants.

Methods: We conducted a case-control study on subjects aged 70 years and older enrolled in the Quebec health insurance plan between 1992 and 1994. Incident cases of an osteoporotic fracture (index event) were identified by ICD-9 codes and surgical procedure codes. Exposure defined as one or more prescriptions of oral anticoagulants dispensed before the index event. Ten controls for each case, matched by age and date of index event, were selected.

Results: Among 1,523 cases, 48 (3.2%) were exposed to oral an anticoagulant; among 15,205 controls, 461 (3.0%) were exposed (adjusted odds ratio:1.1, 95% CI: 0.8-1.4). These negative results persisted after stratifying the exposure into the cumulative dose and duration of treatment.

Conclusions: Oral anticoagulants are not significantly associated with an osteoporotic fracture in the elderly.

1. Résumé

Introduction: Les anticoagulants oraux sont associés à une réduction de la densité osseuse. Cette étude évalue le risque d'une fracture ostéoporotique associée aux anticoagulants oraux.

Méthode : Étude cas-témoin chez des patients de plus de 70 ans inscrits à la Régie de l'assurance maladie du Québec entre 1992 et 1994. Les fractures ostéoporotiques incidentes sont identifiées par la CIM-9 et les procédures chirurgicales et l'exposition définie par au moins une prescription dispensée d'un anticoagulant oral avant la fracture. Dix contrôles appariés pour l'âge et date de fracture sont sélectionnés pour chaque cas.

Résultats : 3,2% des 1523 cas ont été exposés à un anticoagulant oral et 3,0% des 15205 contrôles l'ont été (ratio des cotes ajusté : 1,1, IC 95% : 0,8-1,4). Ces résultats demeurent inchangés après stratification selon la dose cumulative ou durée de traitement.

Conclusion : Les anticoagulants oraux ne sont pas significativement associés à un risque accrû de fracture ostéoporotique.

2. Introduction

The antithrombotic effect of oral anticoagulants is produced by interfering with the activation of vitamin K, which is a cofactor necessary for the synthesis of the different proteins involved in the coagulation cascade.[1] The interest of studying the effect of oral anticoagulants on the risk of osteoporotic fractures comes from the results of certain studies revealing that oral anticoagulants have been associated with a decrease in bone mineral density. This evidence comes from small retrospective observational studies and is explained by the fact that one of the proteins of bone matrix, osteocalcin, requires the action of vitamin K in order to be active.[2-5] Only one prospective study did evaluate the impact of oral anticoagulants on the risk of osteoporosis without finding any significant association between the use of oral anticoagulants and osteoporosis. It also did not find any significant association between the use of these drugs and the risk of an osteoporotic fracture. This study was however limited in its exposure characterization mainly because it used a self-administered questionnaire to evaluate the exposure to oral anticoagulants in the previous two years.[6] This method of gathering the data is known to be subjected to recall bias. Also, this study did not have a sample size calculation despite its negative results limiting our interpretation of the data.

Oral anticoagulants are mainly indicated for the prevention and treatment of arterial and venous thromboembolic diseases.[7] The most common manifestation of arterial

embolic disease is a cerebrovascular accident, or stroke, which is often secondary to atrial fibrillation induced cardio embolism. [8]

Chronic atrial fibrillation is a prevalent condition affecting almost 15 % of the elderly population and represents a well-known independent risk factor for embolic stroke with an incidence of 5% per year. [9-10] This incidence increases with age to reach an incidence of 25% for patients older than 80 years affected with chronic atrial fibrillation. [9] As a complication of chronic atrial fibrillation, stroke represents a major health problem with a mortality rate of 50 per 100,000 per year in Canada and substantial costs either in terms of hospitalization days (2,5 million hospitalisation days in 1995 in Canada) or in terms of loss of productivity from the affected individuals. [11] Clinical randomized controlled studies have demonstrated that the use of oral anticoagulants is effective in reducing the risk of embolic stroke by approximately 50 % in patients 65 years and older with chronic atrial fibrillation. [12] In fact, in the elderly, the main indication for prescribing oral anticoagulants remains the prevention of embolic stroke secondary to chronic atrial fibrillation. [13]

Osteoporosis is another major health problem for elderly patients and is defined as a decrease in bone mineral density at specific bone sites (vertebra, hip and wrist). [14] It is associated with the following risk factors: female sex, age over 50 years, menopause, immobility or paralysis, medications, family history of osteoporosis, and hyperthyroidism (excess of thyroid hormones). [14] The main impact of osteoporosis on the health status of a population is the risk of osteoporotic fracture with an incidence rate of 5-6 per 1,000 person-years for vertebral fracture, of 3-4 per 1,000 person-years

for wrist fracture and of 8 per 1,000 person-years for hip fracture in a population aged less than 70 years old.[15-17]

The incidence of hip fracture increases steeply thereafter to reach an incidence rate of 35 per 1,000 person-years in a population of patients 90 years and older. [17] In Canada, the average 50-year old woman has a lifetime osteoporotic hip fracture risk of 17.5 %. [18] Of all the fractures caused by osteoporosis, hip fractures remain the most severe. They are associated with an increased risk of mortality and morbidity as they generally occur in patients older than 70 years who often also have other health problems that decrease their chance of an uneventful recovery. [19] The total cost of treating osteoporosis in Canada was around $ 1.3 billion in 1993.[18]

Osteoporotic fractures are not only related to osteoporosis but also to an increased risk of falling. [20] Amongst other risk factors for such fractures are included: a past history of an osteoporotic fracture, visual disturbance, poor health status, institutionalization, immobility/inactivity, alcohol abuse and psychotropic medications (benzodiazepine, antidepressant, antiparkinsonism drugs). [21-24] Osteoporotic fractures are thus a complex problem with an enormous impact on the health of the elderly population.

The exact role of oral anticoagulants on bone mineral density as well as their potential impact on osteoporotic fractures needs to be clarified because oral anticoagulants are frequently used in the elderly and because osteoporotic fractures represent a major health problem in terms of morbidity for the patients and health care costs.

3. Objectives

General objective

To clarify the association between the exposure to oral anticoagulants and the risk of an osteoporotic fracture by conducting a case-control study on a large administrative population-based database.

Specific objectives

1. Ascertain the effect of both a cumulative dosage and oral anticoagulant duration of treatment on the risk of an osteoporotic fracture.
2. Ascertain the possibility of an acute effect of exposure to oral anticoagulants on the risk of an osteoporotic fracture.

4. Literature review

Osteocalcin is a protein that when activated binds to hydroxyapatite, the core of the bone matrix.[2] In animals, although the levels of inactivated osteocalcin are increased when oral anticoagulants are administered, there has been no report of alteration in bone homeostasis.[25] Several studies have attempted to clarify the role of activated osteocalcin in bone metabolism in humans. Up until recently, the exact role of activated osteocalcin was unclear but Plantalech et al. have demonstrated that the inactivation of osteocalcin is a natural phenomenon increasing with age.[26] In that same study, they

reported that an increase level of inactivated osteocalcin was significantly associated with a decrease in bone mineral density (correlation: -0.26, $p < 0.001$). Szulc et al. found that an increased level of inactivated osteocalcin was associated not only with a decrease in bone mineral density but also with an increased risk of hip fracture in women aged 70 years and older (relative risk: 5.5, 95% CI: 1.5-22.7). They concluded that an increased level of inactivated osteocalcin was an independent predictor of hip fracture in that population.[27] From these studies, an increased level of inactivated osteocalcin seems to be related not only to a decrease in bone mineral density but also to an increased risk of hip fracture in elderly women.

When oral anticoagulants are administered to humans, it has been shown that there is an increase in the level of inactivated osteocalcin because its activation in humans is also vitamin K-dependant.[28-29] Subsequent studies have attempted to demonstrate the impact of this effect on bone mineral density and osteoporotic fractures. Philip et al. have demonstrated a decrease in bone mineral density of the axial and peripheral skeleton in patients on long-term oral anticoagulants (more than three months). In fact, this small cohort study (n = 80) revealed a significant decrease in the bone mineral density of the lumbar spine for patients on long-term oral anticoagulants. There was a tendency to a decrease in bone mineral density for other bone sites but none of these results were statistically significant.[3] Sato et al. reported a decrease in bone mineral density of the second metacarpal bone of the hand in stroke patients taking long term oral anticoagulants compared with stroke patients and normal subjects not taking oral anticoagulants.[5] These two latter studies were in fact prevalence studies measuring the

bone density at the time the patients were recruited, without any follow-up evaluation. They did not adjust their results for some potential confounding variables for osteoporosis like other medications and a past history of osteoporosis. Finally, by their design, they were not able to adjust their results for the baseline bone mineral density before oral anticoagulants were taken. A few other retrospective studies did evaluate the same question but they were either too small or without any control group decreasing the validity of their results. [4, 29]

Recently, Jamal et al. conducted a prospective study evaluating the effect of oral anticoagulants and the risk of osteoporosis. [6] This study took place as a part of a large cohort study, the Study of Osteoporotic Fractures where 6201 postmenopausal ambulatory women were recruited by population-based listings in the U.S. The sub-study addressing the question of the association between oral anticoagulants and osteoporosis, took place over a two year-period. Women were evaluated at the beginning of this study and after two years of follow-up at which visits they had a detailed medical history including a history of medication use. At these two visits, women had osteodensitometries to measure their mineral bone density. In addition, every four months, each woman completed a survey on radiologicaly proven fractures. Of this population, 149 (2.4 %) were taking oral anticoagulants at the first visit and almost half of these women were still on oral anticoagulants at their second visit two years later. For those who were no longer on oral anticoagulants at the second visit, the duration of treatment was not reported. Among those women still on oral anticoagulants after two years of follow-up (1.5 %), there was no significant difference on bone mineral density between the two visits. In this same study, among 576 non-vertebral fractures, 15 women were exposed to oral anticoagulants at the first visit

while 561 were not exposed (adjusted OR: 1.2, 95% CI: 0.7-1.9). This result did not significantly differ when only women still taking oral anticoagulants at the second visit were taken into account in the analysis. The authors did adjust their results for some potential confounding variables but did not take into consideration some of the important variables, namely the medications known to be associated with osteoporosis or those associated with an increase in bone mineral density like biphosphonates, calcitonine and selective oestrogen receptor modulators. Effectively, these latter have been demonstrated to increase bone mineral density and to decrease the risk of osteoporotic fractures.[30-32] One of the other limitations of this study is the potential differential misclassification bias introduced by the fact that the non-users of oral anticoagulants at the second visit were defined as women who had not taken oral anticoagulants since the last visit. This information may be subjected to recall bias since a percentage of these non-users could have been on oral anticoagulants somewhere between the two visits. This bias would direct the results toward the null for the issue of bone mineral density and osteoporotic fractures. Finally the authors were not able to evaluate the effect of cumulative dosage nor the duration of oral anticoagulation on their outcome for those women who were taking oral anticoagulants at the first visit but not at the second visit. Nevertheless, the major strengths of this study were the prospective follow-up and the large sample size.

As pointed out by this latter study and as described earlier, medications need to be considered when dealing with a study in osteoporosis because of their association with either osteoporosis or osteoporotic fractures. One of the main classes of medication associated with osteoporosis are corticosteroids. It has been reported that an oral dose

equivalent to more than 7.5 mg of prednisone per day for a period of three months has been related to a decrease in bone mineral density.[33] This effect may last as long as one year after the corticosteroid is stopped. Even if large doses of inhaled corticosteroids can lead to a systemic absorption of these drugs leading to known systemic secondary effects usually attributed to oral corticosteroids (glaucoma, cataract),[34-35] no study has clearly demonstrated their effect on bone mineral density in adults. Another medication that is associated with a decrease in bone mineral density is unfractioned heparin.[36] A dose of 18,000 units of unfractionned heparin per day for a month has been associated with osteoporosis and this effect seems to be reversible after the cessation of heparin. The association between the fractioned heparin, low molecular weight heparin, is still a matter of debate. Thyroid hormone replacement (L-Thyroxin) has been related to osteoporosis when it is administered in supraphysiologic dosages.[37] In their study, Paul et al. revealed a 13 % decrease in bone mineral density of the femoral trochanter (hip) in prememauposal women who had been taking thyroid hormone replacement therapy for at least five years. An *in vitro* study demonstrated the effect of short term clinically apparent hyperthyroidism on bone remodelling.[38] There still is a debate on the risk of osteoporosis associated with anticonvulsive drugs. It is actually more of a theoretical concern since these drugs have the pharmacodynamic properties of decreasing the intestinal absorption of calcium necessary for bone mineralization. In fact, Cummings et al. have reported a non-significant odds ratio of 2.0 for the risk of hip fracture in association with the use of anticonvulsive drugs.[22] Finally, thiazide diuretics can induce a decrease in urinary excretion of calcium but have not been convincingly related to a decrease in hip fractures.[39-40] Psychotropic drugs are a heterogeneous class of medications that have

been linked to an increase in falls in the elderly. In their study, Cummings et al. have reported an odds ratio of 1.6 (95 % CI: 1.1-2.6) for hip fractures in association with the use of long-acting benzodiazepines.[22] These results were reproduced in the study conducted by Ray et al. They also demonstrated that short half-life benzodiazepines are not significantly associated with hip fracture (OR: 1.1, 95 % CI: 0.9-1.3).[41] Antidepressants have been associated with an increased risk of falls. Thapa et al. showed that tricyclic antidepressants significantly increased the risk of falls in the elderly (OR: 2.0, 95 % CI: 1.8-2.2).[42] Also in that study they revealed a significant association between the risk of falls and the concurrent use of a new class of antidepressants, the selective serotonin-reuptake inhibitors (OR: 1.8, 95 % CI: 1.6-2.0). Finally, Parkinson's disease has been associated with an increased risk of falls (OR: 2.6, 95 % CI: 1.8-3.8).[22] However it should be noted that this disease is usually treated with L-Dopa, a drug that can induce orthostatic hypotension (fall in blood pressure with the standing position). This secondary effect may represent a confounding variable explaining, at least partially, the association between Parkinson's disease and the increased risk of falls.

5. Methods

Data source

This study used data from the administrative database of the province of Quebec's health insurance agency, the ''Régie de l'assurance maladie du Québec'' (RAMQ).

Large databases like the RAMQ's have become an important tool in conducting pharmacoepidemiological research. [43] They allow investigation of rare side effects on a large sample size at limited cost and within a reasonable time frame.

The RAMQ database is a population-based administrative database that contains information on medical and pharmaceutical services for the elderly 65 years and older as well as individuals on social assistance. Up until August 1996, the RAMQ covered all medications for these individuals without any cost sharing plan. [44]

Apart from demographic data, this database includes detailed information on all medical services provided in the provincial health establishments, including diagnostic and therapeutic procedures, diagnosis coded according to the International Classification of Diseases, Ninth Revision (ICD-9), and the types of institutions where the medical procedures were performed. The pharmaceutical data contains information on all dispensed prescriptions, including the prescribing physician and dispensing pharmacist, the drug name, dosage and formulation, the quantity dispensed, the date and duration of the dispensation. The pharmaceutical file has been validated in a recent study and found to be highly reliable.[45] This study compared the prescriptions written by the physicians, in a sample of elderly patients seen in a Montreal teaching hospital, with the prescription claim file of the RAMQ. The results indicate that the RAMQ database is quite complete with respect to drug information (drug name, dosage, date and duration of a dispensed prescription, date of renewal of a dispensed prescription) with less than 1 % of information being out of range or missing. The only problematic variable was the duration of the dispensed prescription with a sensitivity of 70 % compared to the duration of the prescriptions written by the physicians. In fact, the

duration of 30 % of the written prescriptions was not correctly registered in the claim file and this tended to be systematically for a shorter period. The authors explained this observation by the fact that pharmacist are not allowed to dispense more than what is prescribed but they can however dispense less than what is prescribed for numerous reasons: more regular monitoring of patients, reduced available supplies to lessen the possibility of misuse and minimization of financial penalties for dispensing more than 30 days. Even if the information on the dispensed prescription has been validated, there remains the possibility of a discrepancy between the dispensed prescription and the real consumption of the drug. Patient compliance has not been evaluated for the pharmaceutical files of the RAMQ database. Finally, the drugs dispensed during hospitalization or for patients living in public nursing homes are not covered by the RAMQ health insurance drug plan and are thus not included in the pharmaceutical files. Also, the RAMQ database does not contain information on the indication for the dispensed medication and on the over-the-counter drug utilization.

The accuracy of the medical files of the RAMQ database has not been validated. The recording of the medical procedures done by the physicians is likely to be accurate since it is required for payment. However, the medical diagnosis written at each visit is likely to be unreliable since it's recording is not necessary for payment. To encompass this limitation in pharmacoepidemiological research, a disease can be identified by using the combination of a medical diagnosis and the specific medication dispensed for this disease or the medical procedure done for that disease. This is possible when the indication of the drug is specific to a particular disease. For some acute diseases, like stroke or myocardial infarction, we can presume that the diagnosis included in the

medical file will be more reliable but this remains to be ascertained. Finally, in relation to the demographic data contained in the RAMQ database, one cannot obtain information on some relevant data like smoking, alcohol intake and personal / familial history.

In summary the RAMQ database has the advantages of being population-based and being highly reliable for drug exposure. Its main limitation remains the lack of information on potential confounding variables.

Study population

This study was conducted using a random sample of 10% of subjects aged 65 years and older and enrolled in the RAMQ database between January 1987 and December 1994. From this sample, we selected subjects that were aged 70 years and older between January 1992 and December 1994, which corresponds to the study period. This study population was chosen because of the increase risk of hip fracture after 70 years of age. Demographic, medical and pharmaceutical data were thus available on all theses subjects for 5 to7 years prior to the study period.

Definition of cases

Cases were defined as subjects aged 70 years and older who had sustained an incident minor trauma induced osteoporotic fracture in the study period (1992-1994). An osteoporotic fracture was defined as either a hip or wrist fracture and identified using the following codes of the International Classification of Diseases, Ninth edition (ICD-9 codes): 813.4, 813.5, 820.0, 820.1, 820.2, 820.3, 820.8 and 820.9 combined to a

therapeutic procedure code for hip and wrist surgery. The different types of surgery indicated for these fractures were identified with a panel of experts, namely orthopaedic surgeons. The codes of these different surgeries are as follow: 2637, 2638, 2653, 2654, 2675, 2714, 2715, 2716, 2735, 2736, 2739, 2740, 3742, 2768, 2769, and 2770. Vertebral fractures (733.1) were not included in our study since this type of fracture can frequently be asymptomatic and not require any surgical intervention or specific medical treatment.[46] Therefore the information included in the RAMQ database would not be reliable for measuring this outcome. Minor trauma induced osteoporotic fractures were defined as hip or wrist fractures not associated with any other major fractures (cranial or facial fracture, humerus or femoral body fracture) needing a surgical procedure in the same month as the index date. This was intended to exclude traumatic fractures since multiple fractures occurring at the same time is probably not related to osteoporotic fractures. The date of the osteoporotic fracture was termed the index date and an incident osteoporotic fracture was defined by the absence of an osteoporotic fracture in the 5 to 7 years before the index date.

In order to control for some potential confounding variables, we excluded subjects who were hospitalized for more than one month before the index date or had been living in a public nursing home, because the RAMQ database does not include the medication administered during hospitalisation or in public nursing homes. The patients who had been living in a public nursing home could not be identified from this database and were thus not excluded. We excluded hospitalized patients since unfractioned heparin is usually administered in hospital and because its administration for at least one month is associated with an increased risk of osteoporosis. At the time of this study, the low

molecular weight heparin, that can now be administered on an outpatient basis, was not commercialized and thus was not considered in this study. Finally we excluded patients with a diagnosis of stroke (ICD-9 codes: 433, 434 and 435) any time before the index date because these subjects may be paralysed with immobility being a strong risk factor of osteoporosis and because these subjects may be more prone to receive oral anticoagulants since their stroke may have been caused by a cardiac embolus secondary to chronic atrial fibrillation.

Definition of controls

Controls were selected among subjects aged 70 years and older who had not sustained a non traumatic hip or wrist fracture before the index date. Controls were chosen with the density sampling frame, meaning that a subject could be chosen more than once as a control and that a case could be chosen as a control before becoming a case. Controls were submitted to the same exclusion criteria as cases and ten controls for each case were matched for age and index date.

Definition of exposure

Because the effect of oral anticoagulants on bone matrix is presumed to be a cumulative effect, exposure was defined in two ways. The first definition of exposure corresponds to at least one dispensed prescription of at least 30 days of acenocoumarol or warfarin (the two oral anticoagulants available on the provincial formulary of insured drugs during the study period) in the 5 to 7 years preceding the index date. The second definition of exposure to oral anticoagulants was defined by stratification according to the cumulative dose of oral anticoagulant and to treatment duration. The

cumulative dose of oral anticoagulants was stratified as follows: 30 mg to 1000 mg or more than 1000 mg. The cumulative duration of treatment was stratified as follows: 1 to 12 months or more than 12 months. In both definitions, unexposed subjects were either those truly unexposed or exposed to less than 30 days of oral anticoagulation. Accordingly, in our second definition of exposure, because a daily dose of less than 1 mg a day is an unusual dose, unexposed subjects were defined as those who were not dispensed a prescription of oral anticoagulant or those who received less than 30 mg as a cumulative dose before the index date.

We also wanted to evaluate the possibility of an acute effect of oral anticoagulants on the risk of an osteoporotic fracture by measuring the current exposure to these drugs. Current exposure was then defined as a dispensed prescription at or in the 30 days before the index date. Past exposure was defined as a dispensed prescription more than 60 days before the index date. The 30 day-gap between these two definitions of exposure was intended to compensate for the renewals of dispensed prescription at the end of the 60 day-period prior to the index date. Considering the evaluation of a possible acute effect, the unexposed patients where those never exposed to oral anticoagulants in the study period.

Definition of covariates

Gender and several covariates that could represent *a priori* potential confounding variables were captured in our study. The diagnosis of hyperthyroidism was measured in the year before the index date. A diagnosis of hyperthyroidism was suspected to be an *a priori* potential confounding variable because an excess of exogenous thyroid hormones has been reported to be associated with the development of osteoporosis.

Also hyperthyroidism is known to be associated with an increased risk of atrial fibrillation in the elderly thus increasing their risk of being exposed to oral anticoagulants. The diagnosis of hyperthyroidism was defined as the combination of the ICD-9 codes (242.0, 242.9) with a dispensed prescription of an antithyroid drug in the month following the diagnosis by ICD-9 codes.

Many medications were also measured at different times depending on their time risk for osteoporosis or osteoporotic fractures: the current use of benzodiazepines of long and short elimination half-life, current use of a first generation antidepressant and levo-dopa at the index date (current use being defined as a prescription dispensed at or in the 30 days before the index date). Newer antidepressants, the selective serotonine-uptake inhibitors, were not included since they were not available on the provincial formulary of insured drugs of the RAMQ during the period of observation. We also measured the use of at least 100 micrograms per day of L-thyroxin (thyroid hormone replacement) for at least 90 days in the year before the index date, the use of at least 90 days of an oral corticosteroid with an equivalent dosage of 7,5 mg per day of prednisone in the year before the index date and the use of any form of estrogenotherapy (oral or transdermic formulation) before the index date (Table 1). The dose of thyroid hormone was selected based upon discussion with endocrinologists who indicated that any higher dosage is rarely needed in the elderly and would presumably lead to an excess of thyroid hormone. This measure is however a proxy given the fact that an excess of thyroid hormones is usually determined by measuring these hormones in blood samples. Thiazide diuretics were not included as a covariate since their protective effect on bone density remains to be adequately determined. Also, inhaled

corticosteroids were not included in our covariate measurements since their association with osteoporosis has not been clearly established in adults. Finally, some drugs that are actually indicated for the treatment of osteoporosis and prevention of osteoporotic fractures, namely biphosphonates and calcitonine, were not included as covariates because they were either not commercialized or indicated for osteoporosis in the years during which this study was conducted.

Statistical analysis

Considering that 5 % of our study population would be exposed to oral anticoagulants we needed 1300 cases of an incident osteoporotic fracture in order to detect an odds ratio (OR) of 2.0, with a type 1 error of 0.05 and a type 2 error of 0.2. We estimated a crude OR and a 95% CI for an incident osteoporotic fracture in relation to oral anticoagulants and for all the covariates measured in our study. Since we used a matched design, our crude OR were calculated by using the conditional logistic regression model without including any covariates in the model. The crude OR were in fact matched OR.

Cumulative effect : We estimated an adjusted OR and a 95% CI for an incident osteoporotic fracture in relation to oral anticoagulants using the conditional logistic regression model, including all the covariates. In that model, the reference exposure category was the non-users of oral anticoagulants or the users of less than 30 mg of oral anticoagulants as a cumulative dose, before the index date. We then estimated an adjusted OR and a 95 % confidence interval for an incident osteoporotic fracture in relation to a cumulative dosage of oral anticoagulants. In that model, the reference exposure category was the non-users of oral anticoagulants or those who used less than

a total of 30 mg of oral anticoagulants before the index date. Finally, we estimated an adjusted OR and a 95 % confidence interval for an incident osteoporotic fracture in relation to a cumulative duration of oral anticoagulants. In that model, the reference exposure category was the non-users of oral anticoagulants or those who used less than 30 days of oral anticoagulants before the index date. All these models controlled for the different covariates stated above.

Acute effect: We estimated an adjusted OR and a 95% CI for an incident osteoporotic fracture in relation to current use and past use of oral anticoagulants using the conditional logistic regression model, including all the covariates. In that model, the reference exposure category was the non-users of oral anticoagulants. This model also controlled for the different covariates stated above.

6. Results

Demographic characteristics

We identified 1,523 patients with an incident osteoporotic fracture in our study period and 15,205 controls matched by age and index date. The mean age of the cases and controls was 83.2 years (± 6.7 years). Most of the fractures were hip fractures (87.7%) as opposed to distal radius fractures (12.3%). Characteristics of cases and controls are summarized in Table 2. The distribution of variables between cases and controls is in accordance with clinical practice and the risk factors for osteoporotic fracture described

in previous studies. Cases included more women (76.4%) and were more likely to be exposed to medication susceptible of reducing bone density (corticosteroids and L-thyroxin) or increasing the risk of fall (benzodiazepines, antidepressants and L-dopa). Hyperthyroidism was similarly distributed between cases and controls without any significant difference between the two groups. The use of estrogens was higher for cases and can be related to a higher proportion of women in that study group. The duration of treatment of any oestrogen therapy did not extend to more than 2 years for any patient in our study with a median duration of 14 months (standard deviation: 7 – 24 months)

Univariate analysis

The univariate analysis of the association between oral anticoagulants and the risk of osteoporotic fracture is reported in Tables 3 and 4. The use of an oral anticoagulant anytime before the index date did not increase significantly the risk of an osteoporotic fracture (matched OR: 1.1, 95 % CI: 0.8-1.5). The reference category for this analysis was the subjects with no exposure to oral anticoagulants or with an exposure of less than 30 mg of an oral anticoagulant in the five years preceding the index date. The absence of a significant association persisted even when the exposure to oral anticoagulants was stratified into the cumulative dosage or the duration of treatment.

In Table 5 are shown the univariate analysis for the different covariates measured at different points in time in relation to the index date. The female sex was significantly associated with an increased risk of an osteoporotic fracture with an OR of 1.8 and a 95 % CI of 1.4-2.0. The following drugs were significantly associated with an increased

risk of an osteoporotic fracture: the daily use of the equivalent of at least 7.5 mg of prednisone for a period of 90 days or more in the year before the index date (OR: 1.7, 95 % CI: 1.4-2.6), use of L-Dopa in the month before the index date (OR: 2.5, 95 % CI: 1.5-3.9) and the use of any tricyclic antidepressant in the month before the index date (OR: 1.6, 95 % CI: 1.2-1.9). Neither the use of long half-life nor short half-life benzodiazepines in the month before the index date were significantly associated with an osteoporotic fracture (OR: 1.3, 95 % CI 0.6-2.3 and OR: 1.1, 95 % CI: 0.8-1.9). Also the use of L-thyroxin for at least 90 days in the year before the index date was not significantly associated with osteoporotic fractures (OR: 1.2, 95 % CI: 0.9-1.5). Finally, the use of estrogens anytime before the index date was also not significantly associated with an osteoporotic fracture with an OR of 1.1 and a 95 % CI of 0.9-1.4 nor was for hyperthyroidism with an OR of 1.1 with a 95 % CI of 0.6-1.6 respectively.

Multivariate analysis

Table 6 describes the results of our multivariate analysis of the association between the use of any oral anticoagulant in the five years preceding the index date. We used a conditional logistic regression including the covariates listed in the section 5 f) of the methods.

We observed no significant association between an exposure of 30 days or more to an oral anticoagulant and an osteoporotic fracture (adjusted OR of 1.1, 95% CI: 0.8-1.4). Also, as described in Tables 7, there was no significant association with the risk of an osteoporotic fracture when the exposure was stratified into a cumulative dosage of 30 mg or more (adjusted OR of 1.1, 95% CI: 0.8-1.4 for 30 mg to 1000 mg and 1.1, 95%

CI: 0.7-1.8 for more than 1000 mg) or a treatment duration of 30 days or more (adjusted OR of 0.9, 95% CI: 0.6-1.4 for 1 month to 12 months and 1.1, 95% CI: 0.7-1.7 for more than 12 months). Finally, there was no significant association between the current use of oral anticoagulants and an osteoporotic fracture (OR: 1.0, 95 % CI: 0.7-1.7) (Table 8).

The adjusted odds ratio for each of the covariates did not differ from the univariate analysis leaving the use of corticosteroids, L-Dopa , tricyclic antidepressants and the female sex as being significantly associated with an osteoporotic fracture (Table 5). In order to ascertain completely the possible association between oral anticoagulants and an osteoporotic fracture we did an analysis where the days on treatment on oral anticoagulant where included as a continuous variable into the model. This analysis revealed an adjusted OR (1.1, 95 % CI: 0.7-1.4) very similar to the one reported in table 6.

7. Discussion

a) Interpretation of results

i) Main exposure

This study demonstrates a lack of significant association between oral anticoagulants and an osteoporotic fracture even when the exposure to oral anticoagulants is stratified into a cumulative dosage and duration of treatment. It also shows no significant

association with the outcome under study with a current exposure to oral anticoagulants. When a study fails to demonstrate a significant association between two variables, one has to evaluate the random variability of the data, the possibility of any misclassification bias and the possibility of an absence of effect.

1. *Random variability*

When a study demonstrates an absence of effect, the primary consideration is to assess the power of the study. The power is defined as the probability of rejecting the null hypothesis and concluding that there is a statistically significant effect when one truly exists. It is calculated as one minus the beta error. The beta error (type II error) is defined as the probability of not rejecting the null hypothesis when the alternative hypothesis is true. Finally, the alpha error or type I error is the probability of rejecting the null hypothesis when it is true. These probabilities are derived from the statistical hypothesis testing and are usually determined *a priori* with a universal acceptance of an alpha error set at 5 %. Since the trade off between the alpha and the beta error depends on the alpha error, decreasing the alpha error to less than 5 % will necessarily increase the beta error.[47] Given the controversy on the association between oral anticoagulants, we felt that decreasing the alpha error to less than 5 % would lead to an unacceptably high risk of a beta error and thus would not permit us to clarify the association between oral anticoagulant use and the occurrence of osteoporotic fractures. The power of a study is an indirect indicator of the precision and as said before requires an *a priori* estimation of the magnitude of an effect. The confidence limits of the confidence interval give not only the interval of values that are compatible with the data but also an appreciation of the significance of the association. Thus, the confidence interval

depends on the variability of the data under study and is not an *a priori* quantification. [47-48]

Given our results, the absence of an association between oral anticoagulants and an osteoporotic fracture may probably not be explained by random variability since we did have sufficient power to detect an OR of 2.0 with an alpha error of 5 % and a beta error of 20 % and because the width of our confidence intervals demonstrates that there is very low random variability in our data collection.

2. *Misclassification bias*

This type of bias is further subdivided into differential misclassification bias when the classification error depends on other variables and non-differential misclassification bias when the classification error does not depend on other variables. One type of differential misclassification bias is the recall bias that may arise whenever noncomparable information is obtained from the different study groups.[49] Since the pharmaceutical files of the RAMQ database is a valid source of information on drug exposure, conducting this study by using this database reduced the possibility of recall bias that can be introduced when drug exposure is ascertained by a self administered questionnaire like a previous study evaluating the association between the use of oral anticoagulants and osteoporotic fractures.

A non-differential misclassification of exposure may arise by using a database for a drug study since the compliance to drugs is estimated by the dispensed prescription and the renewals but no study has validated such data. [50-51] If for some patients the compliance was less than optimal, this would be distributed in both groups and therefore would be considered a non-differential misclassification bias. The direction

of this type of bias is usually toward the null value. However, even if this bias cannot be excluded completely in our study, we think that it cannot explain by itself the absence of any significant association between oral anticoagulants and osteoporotic fractures. In fact, oral anticoagulants are considered drugs with a narrow therapeutic range and therefore patients taking these drugs need to have their coagulation monitored frequently in order to adjust the dosage. This represents a standard clinical practice protecting for non-compliance in a certain way. Finally our study may have suffered from a non-differential misclassification on the disease. Our definition of an osteoporotic fracture considered hip and wrist fractures but there is a possibility that humerus fracture and even rib fracture may be associated with osteoporosis. Some controls may have had these types of fractures and given a possible positive association with oral anticoagulants, this could have reduced the strength of the association.

3. *Absence of an effect*

As stated before, osteoporosis is defined as a decrease in bone mineral density and is therefore associated with an increase risk of osteoporotic fractures. Also, it has been reported that an increase in bone metabolism (bone turnover) is also and perhaps more strongly associated with an increase in osteoporotic fractures and patients having both a decrease in bone density and an increase in bone remodelling are at the highest risk of osteoporotic fractures. [52-53] Activated osteocalcin constitutes a protein of the bone matrix and no study has related a decrease in its concentration with high bone remodelling. The only evidence relating inactivated osteocalcin to osteoporosis is a decrease in bone mineral density in specific locations.[3,5]

Randomized controlled studies have demonstrated that the magnitude of increase in bone density induced by different drugs is not a good predictor of fracture protection.

[30-32] In the study evaluating the effect of fluoride on osteoporotic fractures, the authors showed that independently of an increase in bone mineral density, fluoride was associated with an increase in osteoporotic fractures. [54] Also, the different studies evaluating the effect of biphosphonates on bone density and fractures, revealed, after two years of treatment, an approximately 2 % increase in bone mineral density associated with these medications while they reported a 50 % decrease in the risk of osteoporotic fractures for the same study period. [30-32] Given the importance of bone remodelling as a predictor of osteoporotic fractures compared to bone mineral density, the absence of a significant association between the use of oral anticoagulants and an osteoporotic fracture may be explained by a lack of effect of inactivated osteocalcin on bone turnover, even if it seems that it can induced a reduction in bone mineral density. However, this remains to be demonstrated.

ii) Covariates exposure

The population under study is representative of the population of patients with osteoporotic fractures (Table 1). In fact, the distribution of variables in the group with an osteoporotic fracture is in accordance with the risk factors proposed in the literature for this condition with more women in the group with an osteoporotic fracture and a greater exposure, in that same group, to drugs related either to osteoporosis and an increase in the risk of falls.[21-24] Finally considering the epidemiology of hip fractures reaching a peak in the seventies, this may explain the higher proportion of hip fractures as opposed to wrist fractures.

The absence of association between a diagnosis of hyperthyroidism and an osteoporotic fracture may be due to an absence of effect or a differential misclassification induced

by the definition used for a diagnosis of hyperthyroidism. In fact, patients with longstanding hyperthyroidism not treated would have been considered unexposed and given the known association between hyperthyroidism and osteoporosis, our results may have underestimated this association.

The risk of osteoporosis associated with thyroid hormone replacement at a supraphysiologic dosage has been demonstrated for different time-risk exposures. In his study, Paul et al. revealed a positive association for women who had been using thyroid hormones replacement for at least 5 years as opposed to another study that revealed an effect after a shorter exposure. [37-38] We decided to measure the effect of at least 90 days of thyroid hormone replacement but we were not able to stratify further the exposure because of the small number of patients on that drug. The absence of a significant association between the use of thyroid hormone replacement therapy (L-Thyroxin) and an osteoporotic fracture in our study may thus be related either to a short exposure period or to our definition of exposure. Effectively, we were not able to precisely determine if thyroid hormones were really administered at supraphysiologic dosages because we did not have access to blood samples, which is the more precise measure of the supraphysiologic dosage.

Interestingly, the use of any estrogens before the index date was not protective against an osteoporotic fracture. Only one randomized controlled trial has evaluated the impact of estrogenotherapy on the risk of osteoporotic fractures, mainly vertebral fractures, after 2 years of treatment. [55] However, numerous observational studies have revealed that a minimum period of probably four years on estrogenotherapy is needed in order to assure a protective effect on the risk of hip fracture. [56-57] Also, when the estrogenotherapy is taken for an effective period and then stopped, it seems that the risk

of osteoporotic hip fracture returns to the risk of the general population 5 years after stopping the medication. [57] We recently conducted a retrospective study evaluating the persistence on estrogenotherapy and found that only 15 % of the women who started on this treatment persisted for more than 5 years. [58] The lack of a protective effect of estrogenotherapy on an osteoporotic fracture in the present study could therefore be explained by a low persistence on treatment, which was *a posteriori* estimated to be a median of 14 months on estrogenotherapy.

Finally, another interesting point of our multivariate analysis was the magnitude of association between the current use of L-Dopa and the risk of an osteoporotic fracture. In a previous study, Parkinson's disease was strongly associated with either an increased risk of falls or hip fractures.[22] Parkinson's disease is divided in at least five stages with the last stages being associated with an important functional limitation. This disease is treated mainly with the use of L-Dopa that can induce orthostatic hypotension (fall in blood pressure when standing). However, even early Parkinson's disease (that is manifested only by tremor without any impact on the functional status) can be treated with L-Dopa mainly in the elderly because the alternative treatments are associated with an increase in the risk of side effects in that particular population. We thus believe that L-Dopa is the variable mainly associated with an increase risk of osteoporotic fractures and that this variable may have play a role of confounding variable in previous studies, which did not control for it.

b) Strengths and limitations

The use of the RAMQ database has permitted us to conduct a study on a large sample size for a disease with a long latency period that would have otherwise needed a long

follow up period. Because this database is population-based, the controls were selected from the same source population that gave rise to the cases, i.e. the general population, therefore limiting the possibility of selection bias.[59] Even this, however, may not protect from selection bias as was demonstrated by Garbe et al. [60] In their study, they showed that a selection bias may be introduced in database case-control study when the disease under investigation has a prolonged asymptomatic clinical course. In that instance, cases represent those who had a chance of being diagnosed. Because our cases included symptomatic hip and wrist fractures for which the diagnosis did not depend on a special physical examination, we think that our method of selecting the controls did not induce a selection bias.

Aside from obtaining a large sample size, our study has the advantage of having obtained a complete characterization of exposure without being submitted to a recall bias. In fact, the use of the RAMQ database allows us to obtain complete information on dispensed prescription of medication to insured patients: this information contains not only the drug name but also the dosage and the duration of the dispensed prescription. This strength applies to the main exposure (oral anticoagulants) but also to other medications that are associated with an increased risk of osteoporotic fractures for which we could obtained complete information on characterization. This complete characterization has thus permitted us to evaluate the effect of a cumulative dose, duration of treatment but also the impact of current versus past exposure on the risk of an osteoporotic fracture.

This database is limited in its ability to permit us to measure some risk factors of osteoporotic fractures. In fact, we are not able to measure immobilization for each patient. Because, immobility was considered a highly plausible confounding variable, we decided to control for it by excluding the patients having a risk of immobility mainly by excluding those hospitalized for more than 30 days and those living in a public nursing home. The latter was possible by excluding every patient that had a physician claim with an establishment code related to this type of establishment. Nevertheless, we are aware that this definition of immobilization is imprecise and that residual confounding may persist.

8. Conclusion

This study does not reveal any significant association between the use of oral anticoagulants and the risk of osteoporotic fractures in the elderly despite the stratification of exposure into cumulative dosage or duration of treatment. The complementary strengths and limitations of our study and the more recent cohort study [6] which have both addressed this important question and revealed the absence of a significant association between oral anticoagulants and osteoporotic fractures provide reassurance for the elderly who represents the population at risk for both osteoporosis and oral anticoagulant use.

9. References

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Table 1. List of the medications included as covariates

A. **Oral corticosteroids**

Cortisone

Dexamethasone

Fludrocortisone

Hydrocortisone

Methylprednisolone

Prednisolone

Prednisone

Benzodiazepines

Short half-life:

Alprazolam

Bromazepam

Lorazepam

Oxazepam

Triazolam

Long half-life:

Chlordiazepoxide

Diazepam

Flurazepam

B. Tricyclic antidepressants

Amitriptyline

Clomipramine

Desipramine

Doxepin

Imipramine

Nortriptyline

Protriptyline

Trimipramine

Table 2. Study population characteristics

	CASES (n = 1,523)	CONTROLS (n =15,205)
	Mean (standard deviation)	
Age	83.2 (6.7)	83.2 (6.7)
	Percentage (n)	
Sex female	76.4 (1,164)	63.7 (9,686)
Hip fracture	87.7 (1,335)	
Hyperthyroidism	1.7 (26)	1.3 (198)
Medications		
Corticosteroids	3.2 (49)	1.6 (243)
L-Thyroxin	10.4 (158)	7.9 (1,201)
Benzodiazepines	36.2 (553)	30.4 (4,615)
short half-life	27.0 (411)	22.8 (3,467)
long half-life	9.3 (142)	7.5 (1,140)
Tricyclic antidepressants	5.6 (85)	3.3 (502)
L-Dopa	1.3 (20)	0.5 (79)
Estrogens	9.4 (143)	7.4 (1,125)

Table 3. Univariate analysis for oral anticoagulants and osteoporotic fracture

	OR* of osteoporotic fracture (95% CI‡)		
Oral anticoagulants	Cases (n)	Controls (n)	Matched OR§
0-30 days of treatment	1,475	14,744	reference
> 30 days or more of treatment	48	461	1.0 (0.7-1.5)

* odds ratio

‡ confidence interval

§ OR obtained from the conditional logistic regression model without any covariables, because of the matched design

Table 4. Univariate analysis for oral anticoagulants and osteoporotic fracture, stratified by cumulative dose and duration of treatment

	OR* of osteoporotic fracture (95% CI‡)		
Oral anticoagulants	Cases (n)	Controls (n)	Matched OR§
Cumulative dose			
Exposed 0-30 mg	1,470	14,728	reference
Exposed 30 mg-1000 mg	30	276	1.1 (0.7-1.5)
Exposed > 1000 mg	23	201	1.2 (0.8-1.6)
Treatment duration			
Duration < 1 month	1,475	14,744	reference
Duration 1-12 months	27	275	1.0 (0.7-1.5)
Duration >12 months	21	186	1.1 (0.6-1.6)

* odds ratio

‡ confidence interval

§ OR obtained from the conditional logistic regression model without any covariables, because of the matched design

Table 5. Univariate analysis for covariates and osteoporotic fracture

	OR* of osteoporotic fracture (95% CI‡)		
Covariates	Cases (n)	Controls (n)	Matched OR§
Female sex	1,164	9,686	1.8 (1.4-2.0)
Hyperthyroidism	26	198	1.1 (0.6-1.6)
Corticosteroids	49	243	1.7 (1.4-2.6)
L-Thyroxin	158	1,201	1.2 (0.9-1.5)
Benzodiazepines (short half-life)	411	3,468	1.1 (0.8-1.9)
Benzodiazepines (long half-life)	141	1,147	1.3 (0.6-2.3)
L-Dopa	20	76	2.5 (1.5-3.9)
Tricyclic antidepressants	85	502	1.6 (1.2-1.9)
Estrogens	143	1,125	1.1 (0.9-1.4)

* odds ratio

‡ confidence interval

§ OR obtained from the conditional logistic regression model without any covariables, because of the matched design

Table 6. Multivariate analysis for oral anticoagulants and osteoporotic fracture

	OR* of osteoporotic fracture (95% CI‡)		
	Cases	Controls	Adjusted§ OR
Oral anticoagulants	(n)	(n)	
0-30 days of treatment	1,475	14,744	reference
> 30 days or more of treatment	48	461	1.1 (0.8-1.4)

* odds ratio

‡ confidence interval

§ adjusted for sex, history of hyperthyroidism, use of corticosteroids, L-thyroxin, benzodiazepines, L-dopa, antidepressants and estrogens.

Table 7. Multivariate analysis for oral anticoagulants and osteoporotic fracture, stratified by cumulative dose and duration of treatment

	OR* of osteoporotic fracture (95% CI‡)		
	Cases	Controls	Adjusted§ OR
Oral anticoagulants	(n)	(n)	
Cumulative dose			
Exposed 0-30 mg	1,470	14,728	reference
Exposed 30 mg-1000 mg	30	276	1.1 (0.8-1.4)
Exposed > 1000 mg	23	201	1.1 (0.7-1.8)
Treatment duration			
Duration < 1 month	1,475	14,744	reference
Duration 1-12 months	27	275	0.9 (0.6-1.4)
Duration >12 months	21	186	1.1 (0.7-1.7)

* odds ratio

‡ confidence interval

§ adjusted for the variables described in table 2.

Table 8. Multivariate analysis for a concurrent exposure to oral anticoagulants and osteoporotic fracture

	OR* of osteoporotic fracture (95% CI‡)		
Oral anticoagulants	Cases (n)	Controls (n)	Adjusted§ OR
No exposure	1,468	14,722	reference
Current exposure£	20	180	1.0 (0.7-1.7)
Past exposure£	35	303	1.1 (0.8 – 1.7)

£current exposure defined as a dispensed prescription in less than a month before the index date and past exposure defined as a dispensed prescription at least 60 days before the index date

* odds ratio

‡ confidence interval

§ adjusted for the variables described in table 2.