University of Alberta

Management and Health Care Utilization for Osteoporosis and Osteoporosis-Related Fractures

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Faculty of Nursing

Fall, 2012
Edmonton, Alberta

Dedication

This thesis is dedicated to Simon, Alexander, and Avery. Without your ongoing love, support, and belief in me I would have not realized this goal.

ABSTRACT

BACKGROUND: Osteoporosis is a skeletal disease characterized by low bone mass and deterioration of bone, leading to increased bone fragility and risk of fracture.

PURPOSE: The purpose of this research was to examine clinical utilization patterns and use of osteoporosis medications, and their possible side effects, in relation to patient age and co-morbidity.

METHODS / RESULTS: This dissertation included four interrelated studies; a systematic review and three population-based retrospective cohort studies utilizing administrative healthcare data, leading to four manuscripts for publication. The first paper was a systematic review of the use of salmon calcitonin for treating acute and chronic back pain of vertebral compression fractures. The findings suggested that calcitonin was effective for managing acute pain of recent fractures, but not for chronic back pain associated with more remote fractures. In the second paper, I examined the association between older age, co-morbidity, and treatment status of incident osteoporosis-related fractures. I found that the majority of patients, particularly those who were older, male, and lived in a remote location had not received osteoporosis treatment. In the third paper, I studied a cohort of patients with a diagnosis of osteoporosis and compared treatment rates based on dementia status. The findings of this paper suggested that the majority of older adults with a diagnosis of dementia, and fewer co-morbid conditions, had not received osteoporosis treatment. In the fourth and final paper, I examined a cohort of new users of bisphosphonate drugs (a

common osteoporosis treatment) to determine if older patients were more likely to suffer serious upper gastrointestinal bleeding (UGIB) within 120 days of drug initiation. I found an overall low rate of UGIB, but confirmed that older patients (those > 80 years) were significantly more likely to develop an UGIB when compared to younger patients.

CONCLUSIONS: The combined findings of these papers confirmed that despite the wide availability of osteoporosis medications, the majority of high risk patients (especially those who were older) were not receiving guideline recommended treatment. This information will be useful for clinicians and for policy makers to focus efforts on those most at risk for osteoporosis and related fractures.

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INTRODUCTORY CHAPTER

This thesis represents the output of a comprehensive doctoral program of education and research (thesis). The overall purpose of my thesis was to answer clinical questions related to osteoporosis treatments and their possible side effects. In this introductory chapter, I outline my motivation for choosing this as a focus for my research and provide an overview of the topic, a description of each of the four papers, and implications for knowledge development, clinical practice, and future research.

Motivation for Research Topic

My motivation for this research began over 10 years ago when I started my clinical work as a nurse practitioner in family medicine. Following my master's degree, which prepared me as a nurse practitioner, I began my career in acute care working primarily with older adults. I quickly began to notice trends in the type of patients that were admitted to our service; these patients were typically older, quite frail, and often times had had a fall preceding their admission. As a result of falling, these patients had often sustained a fragility fracture in which surgery was not indicated (hip fracture patients, requiring surgery, were admitted to orthopedic units). The fractures were typically of the humerus, pelvis, and vertebra and were often painful resulting in significant disability. The fracture pain was commonly treated with narcotic analgesics with an attempt to control pain and encourage mobilization. As a result of the narcotic (and other factors related to hospital stays in general), patients often developed a delirium which only added to their length of stay. I began to wonder about alternative analgesics, particularly for vertebral fractures, and noticed that clinicians were using a drug called calcitonin even though there seemed to be no standard dosing regimen. I had attempted a literature review on the topic and found very few, small scale studies supporting the use of the drug. At the same time, I had begun my PhD program and was enrolled in one of my first courses related to systematic reviews. This provided me the avenue that I needed to start my research career. My first systematic

review was therefore, related to the use of calcitonin for the acute pain associated with osteoporosis-related vertebral compression fractures. [1]

While my initial question was answered (the efficacy of using calcitonin for acute pain) I began to notice that clinicians were not only using the drug for acute pain, but also for more chronic type back pain. This led me to the topic for my first paper – an update on my first systematic review and an added dimension on the use of calcitonin for chronic pain associated with more remote vertebral compression fractures.

I also began noticing that patients, who had already sustained a fragility fracture, were not always being treated with osteoporosis medications. This seemed to be even more common for those patients who were the most frail (older, more co-morbid conditions, a diagnosis of dementia, etc). By this time, I had started working with Dr. Voaklander who had done extensive work with large administrative healthcare data bases. After the appropriate approvals were in place, he offered me access to a seniors fracture data set derived from the province of British Columbia, Canada that he had been using for other falls related research. Access to this data, allowed me the ideal platform to assess osteoporosis treatment related questions in an entire population. Thus, I felt that focusing on this "problem" for my doctoral studies would lead to useful answers "evidence" that could be used to inform practice benefiting both patients and clinicians. I will now provide a brief synopsis of the clinical topic and introduce each of the four resulting research papers.

INTRODUCTION TO THE RESEARCH TOPIC

Osteoporosis is a serious public health problem for older women, and to a lesser extent men, with an estimated 1.4 million Canadians affected. [2] The epidemiological and clinical importance of osteoporosis lies in the fractures associated with the disease with over 80% of all fractures in older adults being attributed to osteoporosis. [3, 4] Osteoporosis-related fractures are even more common than heart disease or cancer, affecting 1 in 2 women and 1 in 4 men over the age of 50 years in North America. [5, 6] Not only is this condition common, it is

also costly, and in 2008 in the United States alone there were more than 2 million new fractures costing over $17 billion in direct healthcare costs. [7, 8] With the aging population, the prevalence of osteoporosis is expected to rise sharply and thus is an important population health concern.

Osteoporosis Diagnosis

Osteoporosis is a skeletal disease characterized by low bone mass and micro-architecture deterioration of bone tissue, leading to increased bone fragility and risk of fracture. [5] Bone strength reflects the integration of two main features: bone density and bone quality. [9] The diagnosis of osteoporosis, based on bone mass density alone, can be made using the *T*-score criteria of the World Health Organization (WHO). [10] Unfortunately, bone quality is a vague entity and is difficult to measure clinically; furthermore, many factors that contribute to bone strength are not captured by bone mass density making this only one determinant of fracture risk. [11]

More recently, the WHO and other organizations have recommended calculating an individual's 10-year fracture risk, [12, 13] a concept similar to cardiovascular risk assessment using a tool such as the Framingham. The risk score is based on possibly the strongest clinical predictors of fracture risk, independent of bone mass density, the presence of prior fragility fracture after age 40, [14] and the recent prolonged use of glucocorticoids. [15] Other factors associated with fracture risk include older age, sex, and a lower body mass index, history of parental hip fracture, current smoking status, high alcohol intake, and presence of rheumatoid arthritis. [9, 13] In addition, other recent data suggest that the history of falls may also be a strong predictor of fracture. [16]

Osteoporosis Treatment

Ideally, the routine management of osteoporosis should target all aspects of the disease, including maximizing and preserving bone mass and preventing future fractures through pharmacotherapy and lifestyle modification. Although the choice of pharmacological treatment is contingent on co-morbidities, the presence of prevalent fractures, patient preferences, and bone mass density, [17] first-line

treatment typically includes calcium and vitamin D, along with an antiresorptive agent (usually a bisphosphonate drug). [9] Bisphosphonates have been shown to rapidly reduce bone-remodelling, thus increasing bone mass density, and are associated with the largest reduction in fracture risk compared with other therapies. [18] However, bisphosphonate treatment is not without risk and serious gastrointestinal side effects, although infrequent, have been described. [19, 20]

The Treatment of Osteoporosis Fracture Pain

Osteoporotic fractures may occur at multiple sites; hip and vertebral fractures, two of the most common fractures, are associated with the highest burden of disability. [21] While the primary objective of osteoporosis care is typically the prevention of further fractures, in order to maximize functional capacity, clinicians must also recognize and focus on pain management in the post fracture period. Although hip fractures are almost always treated with surgical repair and then standard analgesics, vertebral compression fractures are usually managed conservatively with supportive analgesics and sometimes bed rest. While most patients recover from the back pain within one to three months, some patients go on to experience significant disability and chronic back pain. A number of studies, including a systematic review by this author, suggest the use of calcitonin as an adjunct treatment for the acute management of vertebral compression fracture pain as it exhibits known analgesic properties. [1, 22] Although, many clinicians have used calcitonin for vertebral compression fracture associated back pain that is more chronic in nature (> 3 months), to date, there is no convincing evidence to support this.

RESEARCH QUESTIONS

My research addressed the management of osteoporotic vertebral compression fracture pain and the clinical utilization of osteoporosis treatments, and their potential side effects, in frail older adults. Osteoporosis and related sequela are serious health issues of importance to patients, clinicians, and health administrators.

Four specific questions guided my research:

1. Do patients with back pain related to an acute or chronic osteoporosis-related vertebral compression fracture, who take calcitonin (any route), have improved pain control compared to patients who are treated with standard analgesics alone?
2. Are patients who are elderly and have multiple chronic conditions less likely to receive osteoporosis treatment following an osteoporosis fracture than younger healthier patients with fewer co-morbid conditions? Do age and co-morbidity influence the treatment of incident osteoporotic fractures?
3. Do patients with a pre-existing diagnosis of dementia (any type) and the concurrent diagnosis of osteoporosis receive the same rate of osteoporosis treatments compared to patients without a diagnosis of dementia?
4. Are older patients (≥ 80 years) more likely to suffer serious gastrointestinal associated side effects following the initiation of an oral bisphosphonate drug in comparison to younger patients (< 80 years)?

THE PAPERS

Overview of Papers

My doctoral research included four interrelated studies; a systematic review and three population-based retrospective cohort studies utilizing administrative healthcare data, leading to four manuscripts for publication. The first paper (paper 1) included a Cochrane style systematic review that examined the use of calcitonin, a drug known for its analgesic qualities, on the analgesic efficacy for acute and chronic pain of vertebral compression fractures.

The next papers (papers 2 to 4) involved the use of administrative healthcare data derived from the British Columbia Linked Health Database (BCLHD). The BCLHD integrates health service records making it possible to link records anonymously at the individual level, allowing longitudinal exposure-outcome research. In 2009, the BCLHD and its data holdings transitioned to Population Data BC. These papers involved multiple research questions all related to the treatment of osteoporosis and related fractures and included the

examination of a common osteoporosis therapy. In the following paragraphs I briefly describe each of the papers.

Paper 1: Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis

Vertebral collapse is a common fracture associated with osteoporosis. The subsequent pain may be severe and often requires medications and bed rest. Several studies, including a systematic review by this author, have suggested the use of calcitonin for the treatment of acute fracture pain. However, only a few studies, all with small sample sizes, have recommended the use of calcitonin for pain of a more chronic nature. Therefore a Cochrane style systematic review was necessary to describe the analgesic efficacy of calcitonin for both acute and chronic pain of vertebral compression fractures.

The specific objectives of the review were:

1. To assess the analgesic effects of calcitonin (any route), as judged by a quantitative pain scale, in older adults with acute or chronic pain of a recent or remote vertebral compression fractures,
2. To assess concomitant consumption of other analgesic drugs, side effects, and withdrawals from studies (based on route of calcitonin administration), and
3. To update the previous systematic review with the latest evidence

This study included randomized, placebo, and controlled trials that used a quantitative pain scale to evaluate the analgesic efficacy of calcitonin for pain attributable to vertebral compression fractures. I performed meta-analyses to calculate standardized mean differences (SMDs), using a fixed or random effects model where appropriate. The review process included examining 308 potentially relevant titles and abstracts; after applying inclusion and exclusion criteria, 13 trials were selected for inclusion in the review.

The combined results from 13 trials (n = 589) determined that calcitonin significantly reduced the severity of acute pain in recent OVCFs. Pain at rest was reduced by week 1 (mean difference [MD] = -3.39; 95% confidence interval [CI],

-4.02 to -2.76), with continued improvement through 4 weeks. At week 4 the difference in pain scores with mobility was even greater (SMD = -5.99; 95% CI, -6.78 to -5.19). For patients with chronic pain, there was no statistical difference between groups while at rest; there was a small, statistically significant difference between groups while mobile at 6 months (SMD = 0.49; 95% CI, -0.85 to -0.13; p = 0.008). Side effects were mild, with enteric disturbances and flushing reported most frequently.

I concluded that although calcitonin has proven efficacy in the management of acute back pain associated with a recent VCF, there was no convincing evidence to support the use of calcitonin for chronic pain associated with older fractures of the same origin.

This paper was published in *Osteoporosis International* in 2012. [23]

Paper 2: The association between older age, co-morbidity, and treatment status of incident osteoporotic fractures: A population-based nested cohort study

Despite strong evidence-based rationale for both the primary and secondary prevention of osteoporosis, there remains an overall low prevalence of osteoporosis treatment in older adults. Furthermore, there is some question whether low treatment rates in older adults are simply age related variations (in treatments) or due to the presence of co-morbid conditions. The purpose of this study was to examine the association between older age, co-morbidity, and the use of osteoporosis medications following an incident osteoporosis-related fracture.

To answer this question, I used a retrospective nested cohort design utilizing administrative healthcare data from British Columbia, Canada. The cohort contained 11,870 individual patients, 65 years and older, with 12,025 incident fractures between April 1, 1999 and March 31, 2002. A multivariate logistic regression model was used to examine the relationship between osteoporosis medication dispensation within six months of index fracture and the variables - age, sex, co-morbidity, fracture site, year of fracture, health region, and osteoporosis treatment prior to fracture.

Overall, there was a low rate of treatment with osteoporosis medications in the six months before the incident fracture (15% treatment); this rate improved after the index fracture, with 19% of the sample receiving treatment within six months. Those receiving treatment after the index fracture were significantly younger, more often female, and had fewer co-morbid conditions ($p < 0.001$). The use of an osteoporosis medication prior to the index fracture was the strongest predictor of post-fracture treatment (adjusted OR = 15.89; 95% CI = 9.69–26.04). Increasing age, more than one co-morbid condition, and male sex were all associated with a significant decrease in the likelihood of dispensing osteoporosis drugs when compared to younger and healthier women.

I concluded that despite the wide availability of osteoporosis medications, the findings suggested that the majority of older patients, particularly those who were male, or lived in a remote location, were not receiving treatment to prevent the progression of the disease and to prevent further fractures.

This paper was presented at the National Osteoporosis Foundation's 9th International Symposium on Osteoporosis (ISO9) - Translating Research into Clinical Practice; May 18-21, 2011; Las Vegas, NV and was published as an abstract in the conference proceedings. [24] Unfortunately, the full paper was submitted to three separate journals but was not accepted for publication. As practice patterns change over time, the results were deemed possibly not relevant as the paper was based on data that were 10 years old. Given the time lag between applications for data from the British Columbia provincial Ministry of Health, it was unlikely that I would receive updated data in time to repeat this study. Once I complete my PhD, as part of my ongoing research program, I plan to request updated data and will formally compare the results with my findings. This will allow a useful longitudinal comparison of osteoporosis treatment patterns.

Paper 3: Dementia diagnosis and osteoporosis treatment propensity: A population-based nested case-control study

Increasing age and a diagnosis of dementia both dramatically increase the risk of serious osteoporosis-related sequela. I sought to examine the association between osteoporosis drug dispensation in relation to a concurrent diagnosis of

osteoporosis, dementia (any type), and other co-morbidities, among community dwelling men and women residing in a Canadian province.

This was a population based retrospective nested case-control study utilizing administrative healthcare data from British Columbia, Canada. Community based individual's 65 years and older with an osteoporosis diagnosis and continuous enrollment in the provinces' drug plan between 1991 and 2007 were eligible for inclusion. A multivariate logistic regression model was assembled to examine the relationship between dementia diagnosis and osteoporosis medication dispensation. Other variables examined included age, sex, co-morbidity, and residence.

Almost half of the total osteoporosis cohort (N = 39,452) were dispensed an osteoporosis medication during the study period. Individuals with no dementia diagnosis were dispensed a medication significantly more often than those with a diagnosis of dementia ($p < 0.001$). Those patients with dementia ($n = 13,315$), who had been dispensed an osteoporosis drug, were more often younger, female, had four or more co-morbid conditions, and lived in the most central health region ($p < 0.001$). A diagnosis of dementia was found to be a significant negative predictor of osteoporosis drug dispensation (adjusted OR = 0.55; 95% CI = 0.44–0.69). Increasing co-morbidity was significantly associated with receiving treatment (adjusted OR = 3.30; 95% CI = 2.88–3.78).

Despite the wide availability of osteoporosis medications, our findings suggest that many older adults with a diagnosis of dementia, but not necessarily fewer co-morbid conditions, were not receiving treatment. Future studies should focus on evaluating prescriber and patient awareness of osteoporosis treatments to identify barriers and other factors associated with under treatment. Interventions aimed at enhancing osteoporosis treatment should be a priority and may include prescriber educational initiatives, the use of point of care management tools such as automated reminders and electronic risk assessment tools, and the use structured case management for post fracture care. Future research should focus on examining the utility of such strategies particularly in older adults with a diagnosis of dementia.

This paper has been submitted for publication.

Paper 4: The association between serious upper gastrointestinal bleeding and incident bisphosphonate use: A population-based nested cohort study

Oral bisphosphonates are commonly used to prevent / treat osteoporosis. However, bisphosphonate treatment is not without risk and serious adverse effects, including upper gastrointestinal bleeding, have been described. The purpose of this paper was to determine if new users of bisphosphonate drugs were more likely to suffer a serious upper gastrointestinal bleed within 120 days of drug initiation.

I utilized a population-based nested cohort design using administrative healthcare data from British Columbia, Canada. Community based individual's 65 years and older with a new prescription for a bisphosphonate drug that had continuous enrollment in the provinces drug plan between 1991 and 2007 were eligible for inclusion in the study. A multivariate logistic regression model was then used to examine the relationship between older age and the development of a serious upper gastrointestinal bleed within 120 days of new exposure to oral bisphosphonate drugs. Other variables of interest included sex, co-morbidity, past history of gastric ulcer disease, past history of serious upper gastrointestinal bleeding, concurrent use non-steroidal anti-inflammatory drugs, antiplatelet / anticoagulants, and proton pump inhibitors.

Within the exposure cohort (n = 26 223), there were 117 individuals who suffered a serious upper gastrointestinal bleed within 120 days of incident bisphosphonate use. Cases tended to be 81 years and older (60%), and when compared to those who did not suffer a upper gastrointestinal bleed, they were significantly more likely to have had a past history of gastric ulcer disease (21 % vs. 11%), a remote history of serious upper gastrointestinal bleeding (12% vs. 5%), and had been dispensed proton pump inhibitor medications (29% vs. 17%) ($p < 0.001$ for chi square differences). After adjustment for confounding covariates, those 81 years and older were more than twice as likely to suffer an upper gastrointestinal bleed when compared to those 80 years and younger (adjusted OR = 2.03; 95% CI = 1.40–2.94). A past history of serious upper

gastrointestinal bleeding was the strongest predictor of new upper gastrointestinal bleeding within 120 days of incident bisphosphonate use (adjusted OR = 2.28; 95% CI = 1.29–4.03).

In conclusion, upper gastrointestinal bleeding is a rare, but serious, side effect of bisphosphonate therapy with older patients being affected more often than younger ones. At the same time, concern about potential rare adverse events should not discourage clinicians from prescribing bisphosphonate drugs, particularly in older patients many of who have already sustained a fragility fracture. Clinician must remain cognizant of potential adverse events associated with bisphosphonate use and should routinely ask patients about pre-existing gastro intestinal disorders and concurrent medication history prior to prescribing these drugs.

This paper has been submitted for publication.

SIGNIFICANCE OF FINDINGS

The Osteoporosis Care Gap

The combined findings of this research confirm that despite the fact that older adults are at a considerably higher risk of developing fractures, they are generally not receiving evidence-based treatments. Much of this care gap has been summarized in a number of well-designed systematic reviews.

Two separate systematic reviews described the rates of investigation and diagnosis of fragility fractures as well as the types of post fracture treatment. In the first review, the authors included 37 articles of varying methodology, finding that patients received either none, or a very low rate of investigation and treatment following fracture. [25] Only two of the studies included were large, population-based studies. [26, 27] A second similar review concluded that the majority of individuals, who sustained fragility fractures, were not receiving adequate osteoporosis management. [28]

Also of note is a more recent population-based administrative healthcare data analysis, conducted by a prominent Canadian-based osteoporosis researcher, assessing temporal changes in post-fracture care. Lesley and colleagues looked at

bone mass density testing and osteoporosis treatment initiation rates comparing trends from 1996/1997 to 2007/2008. They found an initial improvement in osteoporosis interventions but in later years discovered the treatment rates had actually declined. [29]

Barriers to Optimal Osteoporosis-Related Care

Even with the relatively recent evidence-based advances in osteoporosis detection and treatment, barriers to optimal osteoporosis-related management exist at the patient, clinical provider (typically a physician), and the healthcare system levels. Much has been published around management barriers; one could argue that these sorts of barriers are not exclusive to osteoporosis, and have been noted in the management of chronic disease in general.

Barriers at the healthcare system level: [30-33]

- Lack of notification and reminder systems – to queue providers
- Lack of system wide resources – including human resources
- Lack of access to investigations, including bone mineral density testing and serum markers for osteoporosis
- Fragmented system financing for preventative care
- Disconnection and insufficient coordination of care between acute care (specialists) and primary care providers
- Static nature of traditional healthcare processes

Barriers at the clinical provider level: [25, 30, 33-36]

- Lack of knowledge, including a bias against men
- Clinical inertia
- Lack of time to provide preventative care, including a lower prioritization of osteoporosis among multiple co-morbidities
- Resistance to change
- Lack of recognition of fragility fracture as osteoporosis-defining events with increased morbidity, mortality, and healthcare costs

- Reluctance (from specialists, including orthopedic surgeons) to take "out-of-scope" responsibilities in prescribing treatments
- Lack of an inter-disciplinary team to collaborate on care

Barriers at the patient level: [30, 33, 36-40]

- Lack of knowledge
- Non-adherence with investigation and persistence with treatment recommendations
- Cost of treatments
- Lack of recognition of fragility fracture as osteoporosis-defining events with increased morbidity and mortality
- Denial of osteoporosis risks factors and diagnosis
- Bias toward acute fracture symptom relief versus prevention of future events
- A lower prioritization of osteoporosis among multiple co-morbidities
- Worry about potential adverse drug events associated with treatments

Barriers to preventative care have been described for other chronic conditions, such as coronary artery disease and diabetes; at the same time, other areas of acute post-event care, such myocardial infarction care, have been excellent. [41] If exceptional disease management is found in some areas of patient care, one then wonders what it is about osteoporosis post-fracture care that keeps clinical providers from implementing evidence-based care. I speculate that there are several reasons for this, most notably is the "silent" nature of osteoporosis; once the acute pain of an osteoporosis-related fracture passes, the patient no longer experiences any symptoms of osteoporosis. Alternatively, if a post-myocardial infarction patient does not take their beta-blocker medication, they are more likely to experience symptoms such as angina. Another reason is likely related to the unappreciated mortality associated with fractures versus cardiac disease. [42] Thus, a coordinated approach to post-fracture care is warranted.

Knowledge Translation Strategies Used in Osteoporosis Care

Regardless of the wide availability of evidence, including evidence-based clinical practice guidelines focused on osteoporosis management strategies, there remains relatively little research describing the *successful* implementation and efficacy of osteoporosis-related knowledge translation activities. In general terms, the goal of translating knowledge into practice is to ensure that (new) evidence or knowledge actually reaches patients and populations (for whom they were intended) in order to improve health outcomes. [30, 39, 43] Unfortunately, despite the considerable resources devoted to controlled trials and the generation of new knowledge, the transfer of evidence to practice is often an unpredictable and a "slow and haphazard" process. [44] There is agreement that methods to improve quality of care ought to be multifaceted and designed to involve strategies at all levels of care: individual patients, clinical providers, and at the healthcare systems level. [39] A recent systematic review, by Laliberte and colleagues, evaluated the effectiveness of primary care interventions to improve the detection and treatment of osteoporosis. [45] They included 13 controlled trials and found that multifaceted interventions targeting high-risk patients and their primary care providers may improve the management of osteoporosis, but improvements were often only clinically modest. Interventions typically included patient educational materials, physician notification, and/or physician education. One of the main limitations of this study was the relatively short follow up period; the included studies typically had a follow-up duration of less than one year. The authors identify this period as clearly insufficient for assessing the impact of any interventions on fracture rates. Post fracture knowledge translation / intervention strategies that have been effective, although modestly effective when examined on a relatively short term basis, are described at the patient, provider, and healthcare systems levels. [30, 36, 45-47]

Post-fracture *patient level* strategies typically focus on the education using printed materials. Other specific strategies that have been described include: (1) individual letters to patients indicating their risk of osteoporosis and advisement to discuss this with their family physician; and (2) and the use of osteoporosis

case managers who manage a group of specific patients relative to their complete osteoporosis-related care, including lifestyle counselling, ordering investigations, and drug therapy.

Interventions aimed at the *clinical provider level* include: (1) the use of written education materials mailed to physicians regarding general recommendations for osteoporosis assessment and treatment; (2) letters to primary care physicians notifying them of a specific patients recent fracture and providing treatment recommendations; (3) acute care (in-patient) standing orders for post fracture care, these typically include the ordering of a bone mass density test and drug therapy; (4) reminders and opinion-leader-generated treatment guidelines provided to family physicians; (5) risk assessment tools for physicians; and (6) physician education by academic detailing.

Healthcare system level intervention strategies, examined less often, include: (1) the utilization of interdisciplinary teams of healthcare professionals (physicians, nurses, pharmacists, etc) in delivering comprehensive osteoporosis care for groups of at risk patients; and (2) electronic medical record prompts for physicians to identify patients eligible for osteoporosis treatments / investigations.

GENERAL DISCUSSION

The Generation of New Knowledge

Findings presented in this dissertation not only support what has generally been found by others, but also report on newer dimensions of care gaps that to date have been poorly captured. Furthermore, existing literature does not adequately delineate whether the low treatment rates in the older population are simply age related variations (in treatments), or due to the presence of co-morbid conditions including the diagnosis of dementia. New knowledge generated from these studies identifies older age (those > 80 years) and a pre-existing diagnosis of dementia as strong, independent negative predictors of osteoporosis treatment.

As dementia typically affects older patients perhaps ageism, at both the clinical provider and healthcare systems level, is in some measure responsible for the barriers to osteoporosis care. Ageism refers to a profound prejudice against

older adults; an ageist bias leads to ignoring the concerns of older adults which in turn results in the failure to prevent and treat medical conditions which comes at a cost to individuals and society. [48] Ageism in osteoporosis management, although not named as such nor well described in the literature, is generally reflected in the underuse of investigations and essential treatments to prevent and manage the disease. Underuse of essential care, is one of the main problems for knowledge translation in the field of osteoporosis care; one estimate has suggested that it takes on average 17 years for definitive evidence to reach most patients potentially eligible to benefit from it. [30] Therefore, it can be said that knowledge translation is fundamentally about accelerating processes that are known to work and that may be already in place. [43, 49, 50]

I have hypothesized several approaches that may be useful in contending with ageism in osteoporosis management and further investigation into the efficacy of the approaches will be required. As the problem of ageism is not unique to osteoporosis, strategies or approaches to combat the problem may generally be applicable to ageism in general. Strategies should focus on the selection of investigations and treatments based on an individual's functional status versus age alone. Regardless of age, a strong focus is needed in all levels of the prevention of disease; in osteoporosis care, secondary prevention (the treatment of established disease to prevent adverse outcomes) is of utmost importance. In addition, as caring for older adults in a clinical setting is complex; there should be a heightened emphasis on the training and education of healthcare providers, including more research into aging. Lastly, as we have a rapidly aging population and the notion of ageism is largely a societal concern, the use of mass-media type public service announcements / education focused on the prejudices and solutions to overcome them may be useful.

NEXT STEPS

This paper-based dissertation constitutes the end product of a doctoral research program focused on the management of osteoporosis and related fractures. The

papers have all provided me with a number of directions for further exploration which I will briefly describe.

Osteoporosis Fracture Pain

To further explore osteoporosis vertebral fractures and related disability, I would like to examine the effectiveness of vertebroplasty as a treatment for acute vertebral fracture pain. Vertebroplasty, a percutaneous interventional radiological procedure, involves the injection of bone cement into the fractured vertebral body to reinforce the structure and relieve pain. [51] This procedure is typically done using conscious sedation by highly specialized and trained radiologists and orthopedic surgeons. [52] Although the procedure is considered minimally invasive, it does not go without risk. Adverse events during and after the procedure include increased back pain, leakage of cement into adjacent structures, and an increased risk of new vertebral fractures adjacent to the previously cemented one.[53] While there have been many smaller scale randomized controlled trials showing favorable clinical responses to the procedure, there are also two more recent trials that show no difference between treatment and control groups. [54, 55] As a result, there is now some question about the utility of the procedure; conducting a Cochrane style systematic review on the topic may provide clinically important answers.

Osteoporosis Treatment Rates

Further to papers 2 and 3, where I explored osteoporosis treatment rates in relation to patient age, co-morbidity, and a diagnosis of dementia, I would now like to differentiate possible reasons for the low osteoporosis treatment rates. In managed care populations, the literature supports the notion that low osteoporosis treatment rates are often as a result of inadequate clinician (physician and / or nurse practitioners) prescribing versus patients receiving a prescription and then choosing not to fill it. In order to design an effective interventional study to improve investigation and prescriptive rates, I will utilize a health behavior theoretical framework, the Theory of Planned Behaviour model, to examine a clinician's knowledge, attitudes, and behaviours related to osteoporosis

management. [56] Experts in the field of knowledge translation stress the use of theory in order to develop testable and useful knowledge-translation interventions. [44, 57] Briefly, Theory of Planned Behaviour is a social cognition model that has been used to predict individual behaviours, and has been used to explore the determinants of (health) professional behaviour. [58] The theory assumes that the intention to perform a behavior is determined by an individual's attitudes (a person's overall evaluation of the behaviour), subjective norms (a person's own estimate of the social pressure to perform or not perform the target behaviour), and perceived behavioral control (the extent to which a person feels able to enact the behaviour). [59] From this, clear predictions could be made about the factors that would likely increase motivation to improve osteoporosis management. This is also an ideal mechanism to explore the concept of ageism (as a reason for low rates of investigation and prescribing) among clinical providers.

Although several studies have suggested that Theory of Planned Behaviour may be useful in explaining the attitudes and intentions of clinical providers, studies assessing the actual utility of the model in explaining real behaviours are limited. [58, 60] This would be one of the first studies attempting to explain prescribing behaviours, in relation to osteoporosis clinical practice guidelines, based on the Theory of Planned Behaviour model. This is potentially significant as ideally an effective intervention could then be tailored to the clinician's intention to initiate / prescribe treatment.

Additional next steps would include an interventional study aimed at addressing clinical provider barriers in osteoporosis management of older adults. As osteoporosis-related vertebral fractures are extremely common, and often disabling, I will plan a controlled trial aimed at identifying and treating osteoporosis post-vertebral fracture. The specific intervention chosen will be based on the findings from the observational study using the Theory of Planned Behaviour. I envision a controlled trial comparing "usual care" to the structured care provided by an interdisciplinary group of clinical providers led by an osteoporosis case manager. Previous research identifies improvements to patient and service delivery from the shared decision making and coordinated activities

of a multi-disciplinary group. [61] The primary aim of this type of project would be to develop and implement a model of care for the most at-risk patients; this project would need to be longitudinal, over the course of several years, in order to identify more long-term benefits (i.e. fracture reduction) to osteoporosis case management.

Future Program of Research

My desired professional path ultimately leads me to a career as clinician scientist. This includes a strong desire to maintain a balance between teaching and clinical research, as well as continuing my current clinical practice as a nurse practitioner in family medicine. I see this as an ideal combination of academia and practice with a goal of contributing to evidence-based practice within the field of older adult care.

Overall, the values guiding my future program of research are related to translational and hypothesis-driven research with a focus on real clinical problems facing nurse practitioners and other direct care providers with the ultimate goal of improving clinical outcomes for patients. Objectives of my future program of research include: (1) becoming an independent investigator utilizing epidemiological research methods to explore chronic disease management in older adults with an emphasis on health services utilization, and (2) to promote a positive view on aging and to describe the effect of ageism on chronic disease management at the patient, provider, and healthcare system levels.

CONCLUSIONS

Knowledge generated from this study, has not only identified areas of concern related to osteoporosis care and treatments but can also be used to stimulate further discussion, and provide feedback for policy and practice. This type of information is critical for the planning and organization of healthcare services for both patients and populations in the prevention and management of osteoporosis and related fractures and subsequent sequela. [62] More specifically, the knowledge may now be translated to facilitate disease prevention program planning, the development of evidence-based clinical practice guidelines and educational

materials for both patients and clinicians, and may be useful in evaluating the cost-effectiveness of community-based intervention efforts. Finally, as research and science in the discipline of nursing are all about the health of humans, [63] projects such as this (concerned with various approaches for measuring health status with the hope of improving the health of a population) will thus advance the knowledge of nurses and nursing as a discipline.

The unique contribution of my work through this dissertation is to confirm the high incidence inadequate post fracture care, particularly among patients who would be considered at the highest risk of developing subsequent fractures. I have highlighted gaps in the Canadian literature (related to osteoporosis treatment patterns in community-based older adults) and have done one of the first population based studies assessing a rare adverse drug event in new users of a common osteoporosis treatment. The challenge and next steps will include insuring that this knowledge can be integrated into the clinical care of older adults.

My main concluding remarks can be summarized into a seemingly simple message related to the need for translating knowledge into clinical practice. That is, future research should focus on: (1) identifying and addressing barriers to appropriate osteoporosis management, and (2) the efficacy of various management implementation strategies designed to close the osteoporosis care gap.

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PAPER 1:

Calcitonin for Treating Acute and Chronic Pain of Recent and Remote Osteoporotic Vertebral Compression Fractures: A Systematic Review and Meta-Analysis

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A version of this paper has been published:

Knopp-Sihota, J.A., Newburn-Cook, C.V., Homik, J., Cummings, G.G., & Voaklander, D., Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis. *Osteoporos Int.* 2012; 23(1): 17-38.

PAPER 1:

Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: A systematic review and meta-analysis

INTRODUCTION

Background

Osteoporosis is a serious public health problem for older adults, with an estimated 1.4 million Canadians and 10 million Americans affected. [1, 2] The epidemiological and clinical importance of osteoporosis lies in the fractures that are associated with the disease, with over 70% of all fractures in older adults being attributed to osteoporosis. [3] Although osteoporotic fractures may occur at multiple sites, vertebral collapse is one of the most common; in developed countries like Canada, the lifetime risk of an osteoporotic vertebral compression fracture (OVCF) is one in four among women and one in eight among men, and increases in prevalence with age in both sexes. [2] Not only is the condition common, it is costly; in 2005, in the US alone, patients sustained more than 2 million fractures, costing the health care system nearly $17 billion. [4]

Description of the condition

An OVCF can be diagnosed radiographically or as a symptomatic clinical event whereby patients present with back pain typically of sudden onset associated with a relatively atraumatic event such as bending or coughing. [5] When an acute OVCF occurs, the pain may be so devastating and disabling that hospital admission is required; length of stay for such fractures may be as long as 10 to 14 days. [6-8] On the other hand, OVCFs may be associated with mild back pain and stiffness, and the diagnosis of a fracture often goes unnoticed. [9] Although many patients with OVCF experience a predictable improvement in pain over 6 to 8 weeks, [7] some patients experience persistent pain and disability. Multiple OVCFs can lead to a gradual but noticeable loss of vertebral height, leading to progressive dorsal

kyphosis. Chronic back pain may result from the associated deformity, joint incongruity, and tension on muscles and tendons; consequently, a significant impairment in spinal range of motion and physical function, including mobility, and lower overall quality of life may be reported.[10, 11]

Description of the intervention

The pain of an OVCF is often treated with standard analgesics, although these commonly used analgesics (e.g., acetaminophen with codeine) and non-steroidal anti-inflammatory drugs (NSAIDs) are not always helpful or appropriate in the older adult population. Sedative-hypnotic medications and narcotics are frequently prescribed for patients with fractures; however, these agents are often associated with important and dangerous side effects. [12]

A number of studies have suggested the use of calcitonin as an initial and adjunctive treatment for acute, severe, unrelenting back pain secondary to fracture, as calcitonin exhibits known analgesic properties. [13-15] Some studies have suggested that calcitonin may also be useful in the treatment of chronic back pain related to a more remote OVCF. [16, 17] Calcitonin is a 32-amino acid polypeptide produced and secreted by the thyroid gland of mammals and is available as a nasal spray (intra nasal [IN]), an injection (intra muscular [IM] or subcutaneous [SQ]), and as a rectal suppository. [18] Although a number of mechanisms have been suggested, there are two most likely hypotheses explaining the analgesic mechanism of calcitonin: a direct central nervous system action involving calcitonin-binding receptors, and an increase in plasma β-endorphin levels. [19, 20]

Relevance of Systematic Review and Meta-Analysis

The original Cochrane style systematic review on this topic [21] was published in 2005 and focused solely on the acute pain of recent OVCFs. This review not only provides an update to the previous results, but also adds an additional dimension related to the use of calcitonin for chronic pain of more remote OVCFs. Given the morbidity associated with these types of fractures, and the frequent necessity of providing analgesia for patients with acute and chronic fracture pain, it is important to determine the effectiveness of calcitonin for both indications.

Therefore, we conducted a formal Cochrane style systematic review and meta-analysis of controlled trials to examine the analgesic efficacy of participants receiving calcitonin (any route) compared with a control group receiving either a placebo, no intervention, or "usual care" in older adults with acute (onset < 10 days) or chronic pain (> 3 months) attributed to a recent or remote OVCF.

Objectives

The objectives of this systematic review were:

1. To assess the analgesic effects of calcitonin (any route), as judged by a quantitative pain scale, in older adults with acute or chronic pain of a recent or remote OVCF,
2. To assess concomitant consumption of other analgesic drugs, side effects, and withdrawals from studies (based on route of calcitonin administration), and
3. To update the previous systematic review with the latest evidence.

METHODS

We followed the procedures for conducting systematic reviews and meta-analysis as outlined by the Cochrane Collaboration [22] and the reporting guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. [23]

Criteria for Considering Studies for This Review

Types of studies

We planned to include a broad range of controlled comparison studies: randomized controlled trials (RCTs), controlled trials, and controlled before and after studies. As there were few such experimental studies, we planned to include observational studies if they included a control group, to compare outcomes. The studies needed to compare the analgesic effect of calcitonin to either placebo, to no intervention, or to "usual care", in any setting (including acute care hospital, rehabilitation facility, nursing homes, and the community), published in any language, and for which adequate information was provided or could be obtained

from the primary researchers. Retrospective studies and studies in which there was no comparison group were excluded from the review.

Types of participants

To be eligible for inclusion, studies needed to involve older adults (aged 60 years and older) of either sex who suffered from acute (onset < 10 days) or chronic back pain (> 3 months) associated with a clinician diagnosis of an OVCF (by radiograph or clinical presentation) who received calcitonin (any route and any dose) or placebo or "usual care". Patients may have resided in any health care facility (acute or rehabilitation care), a community care setting (nursing home or assisted living), or in their own homes.

Types of interventions

Studies were included if they evaluated the effectiveness of calcitonin given by any route to achieve analgesia. Comparative treatments included placebo, usual treatment, or other known analgesics. Trials that compared different doses or routes of calcitonin, with no inactive comparator group, were excluded.

Types of outcome measures

All clinical outcomes were considered; however, the primary outcome of interest was the analgesic efficacy of calcitonin as judged by a quantitative pain scale (e.g. visual analogue scale [VAS]). Pain scores ideally were assessed with patients at rest, sitting, standing, and walking in order not only to describe pain relief, but also to describe the length of time to mobilization. The concomitant consumption of other analgesic drugs, side effects, and withdrawals from studies (based on route of calcitonin administration) were also examined. *A priori*, we planned subgroup analyses based on: the sex and age of participants, route of calcitonin administration, and acute versus chronic pain.

Search Methods for Identification of Studies

Studies were identified by several methods. First, we searched for randomized trials in the Cochrane Musculoskeletal Group (CMSG) specialized trial register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966-present), EMBASE (1988-present) and the LILACS (Latin American and

Caribbean Computer Library Center) databases. Grey literature was searched using 'Dissertation Abstracts and Index to Theses'. All databases were last accessed in October 2010. We used the following text words and Medical Subject Headings: *calcitonin; osteoporosis; vertebral compression fracture; analgesia; pain control; aging; elderly; placebo;* and *clinical trial*. In addition, reference lists of all relevant articles were examined for further pertinent studies; and conference proceedings were sought from various web sites and organizations. Forward citation searches of included studies and relevant literature reviews were also done. Primary authors, experts in the field, and the manufacturer of calcitonin (Novartis) were contacted to identify additional published, unpublished, or 'in-progress' studies. The search was not limited by language or publication status. See **Appendix 2-1** for details of the MEDLINE search; this search strategy was adapted for all electronic search engines.

Data Collection and Analysis

Selection of studies

One of the study investigators (JKS) performed the initial search of all databases to identify potentially relevant citations. Where it was not possible to accept or reject the study, the full text of the citation was obtained for further evaluation. Following the screening of titles and abstracts, the full texts of potential articles were retrieved (and translated into English where required) and assessed independently by two of the study investigators (JKS, CNC). If any differences in opinion occurred, they were resolved by consensus with a third reviewer.

Data extraction and management

Data were independently extracted by one unmasked reviewer (JKS) using a standardized electronic data collection form (based on the Cochrane Collaboration checklist of items to consider in data collection). [24] When raw data were not provided, the data were extracted from figures; where necessary, we attempted to seek additional information from the first or corresponding authors of the included studies via electronic mail. The following information was obtained for each study (where possible): source, eligibility, methods, participants,

interventions, outcomes, results, and funding sources. When possible, data from intention to treat (ITT) analysis were extracted; otherwise, we used the data presented on available cases.

Assessment of risk of bias in included studies

After identification of articles meeting the inclusion criteria, two review authors (CNC, JH) independently assessed the methodological quality of studies according to the 'risk of bias approach' of the Cochrane Collaboration. [25] Specifically, we used the following six separate criteria:

- Adequate sequence generation (method of randomization);
- Allocation concealment;
- Blinding of participants, personnel, and outcome assessors;
- Incomplete outcome data addressed;
- Free of selective reporting;
- Free of other potential threats to bias / validity.

These criteria, which reflect the internal validity of the trials, were assessed for each of the included studies, and were presented in a two-part "risk of bias" table. Within each entry, the first part of the tool involves describing what was reported in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry with each criterion scored as "yes", "no", or "unclear". This was achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgment of 'yes' indicates low risk of bias, 'no' indicates high risk of bias, and 'unclear' indicates unclear or unknown risk of bias (see **Appendix 2-1:** The Cochrane Collaborations Risk of Bias Tool). Studies that met all criteria, or all but one criteria, were considered to be of high quality. [25] In the case of disagreement between reviewers, differences were to be resolved by discussion until consensus was achieved.

Measurement of treatment effect

A priori we planned that for continuous data reported as means with standard deviations (SD), the effect measures would be generated as a mean difference (MD) or as a standardized mean difference (SMD) with 95% confidence intervals

(CI). Specifically, for data measured on the same scale (i.e. a 10 cm or 100 mm VAS), a MD and the 95% CIs were calculated. When different methods of pain measures were used (i.e. a 10 cm VAS and a 5-point pain scale), we calculated the SMD and 95% CIs to pool the results across trials. The SMD is used as a summary statistic in meta-analyses when the studies all assess the same outcome but measure it in a variety of ways (for example, all studies measure pain but they use different scales). In this circumstance, it is necessary to standardize the results of the studies to a uniform scale before they can be combined. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. [26]

Where appropriate, data for dichotomous outcomes were pooled using the Mantel-Haenszel (MH) approach to calculate a risk ratio (RR) with 95% CIs. Numbers needed to treat for an additional harmful outcome (NNTH) were calculated for the reported side effects using the pooled RR and the assumed control risk (ACR) using the method described in Chapter 12.5.4.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*. [27]

Dealing with missing data

As missing data (statistics) were evident in many of the included trials, we attempted to contact the trial investigators at least twice. In all but three cases, there were no responses; therefore, the available data were extracted from the published report, and missing data were imputed. When only *p* values or the standard error of the mean (SEM) were reported, SDs were calculated according to the approach described in Chapter 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* for handling missing data. [24] Sensitivity analyses were performed to check the effect of imputation.

Assessment of heterogeneity and reporting bias

Heterogeneity between studies was described non-statistically and statistical heterogeneity between studies was examined visually using an I^2 statistic and a chi-squared test (a chi-squared *P* value of less than 0.1 or an I^2 value equal to or greater than 50% was considered indicative of possible heterogeneity). Deeks and

colleagues (for the Cochrane Collaboration) [27] suggest the following as a rough guide for interpreting the I^2 statistic:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Possible sources of heterogeneity were assessed by sensitivity analyses. Heterogeneity was also examined qualitatively and described in **Table 1-1** (Characteristics of included studies) and **Table 1-2** (Risk of bias in included studies). We planned to explore publication bias and other potential reporting biases using funnel plots. [28]

Data synthesis

Meta-analyses were performed using the Cochrane Collaboration software program Review Manager (Rev Man) Version 5. [29] Meta-analyses methods were selected based on study heterogeneity and the number of trials included in the analyses. When the I^2 statistic was greater than 75%, we considered it substantial heterogeneity and pooled the study results using a random effects (RE) model. If no significant statistical heterogeneity was detected, or there were a small number of trials included in the analysis (three or fewer), we used a fixed-effect (FE) model. [27]

Continuous data were entered into Rev Man in such a way that, when analyzing the forest plot graphs, the area to the left of midline (less than zero) indicated a positive effect of the treatment drug calcitonin. When interpreting results of the forest plots for dichotomous data, the area to the right side of the forest plot graph (greater than 1) favoured the control group.

Subgroup analysis and investigation of heterogeneity

A priori, we planned to explore and address possible clinical heterogeneity as well as to investigate the effect modification of participants and treatments, by performing sub-group analyses on the route of calcitonin administration (IN, IM/SQ, or rectal), the synthetic derivative of calcitonin (salmon *vs*. eel. *vs*. human), and the efficacy of calcitonin for both acute (< 10 days) and chronic pain

(> 3 months). For studies examining acute fracture pain, we defined five periods for which we tried to extract data and analyze study findings: baseline, week 1, week 2, week 3, and week 4. For studies examining chronic pain of remote fractures, we aimed to extract data and analyze study findings: at baseline, and then again at 1, 3, 6, 9, and 12 months.

Sensitivity analysis

We performed sensitivity analyses by examining the results of the meta-analysis under different assumptions and checked for the robustness of the observed findings. *A priori*, the following sensitivity analyses were planned:

1. For trials in which the SD was not reported and therefore had to be imputed, do the results of the pooled analysis change if these are excluded from the results?
2. By limiting included studies in the analyses to those with the highest methodological quality, do the results change?

RESULTS

Figure 1-1 outlines the study selection process. We initially identified 308 citations, of which 55 were potentially relevant studies. Of the 55 full text articles retrieved for closer examination, 42 were excluded for the following reasons: eleven included patients with no vertebral fracture; [20, 30-39] nine had insufficient data, and we were unable to locate study authors; [40-48] six had a diagnosis other than osteoporosis; [49-54] six lacked an inactive (or no drug) comparison group; [55-60] the library was unable to locate three full text articles and we were unable to locate the study authors; [61-63] three were review articles; [64-66] two were duplicate publications from a single study reporting the same results; [67, 68] one was a case report; [69] and one included participants with multiple fracture sites. [70] Thirteen trials were identified which met the inclusion criteria for the systematic review; six were studies focused on the acute pain of recent fractures, [71-76] and seven were chronic pain studies. [16, 17, 77-81] We were unable to include three of the studies in the meta-analysis due to insufficient data (means and SD of pain score not

provided). [17, 76, 78] Therefore, 10 studies were included in the quantitative synthesis.

Characteristics of Included Studies

Participants

The 13 included studies involved 589 participants, all of whom contributed data to the withdrawal and side effect analyses; 10 studies with 467 participants provided data in the analgesic efficacy (pain scale) meta-analyses. Recruitment procedures were predominantly not defined or were poorly reported, with little detail provided; however, it appeared that convenience samples predominated. See characteristics of included studies in **Table 1-1**.

Design

All studies included were randomized, prospective, controlled trials; most of the trials described withdrawals and side effects. Three of the trials were randomized and double blinded [73-75] with the use of sealed, serially numbered opaque envelopes. As patients met the appropriate criteria and became eligible for entry into trial, the next in a pile of sealed envelopes was opened. Inside was a card that indicated whether the patient was assigned to the treatment or control group. The ordering of the cards within the envelopes was determined from a table of random numbers. An additional three of the studies utilized "block randomization"; [16, 17, 78] one of the trials was randomized according to a "randomization list"; [71] one randomized participants according to a table of randomized numbers; [76] and the remaining five studies simply stated that they randomized participants but did not describe their methods. [17, 72, 77, 79, 80]

Setting

A single research group in Greece conducted three of the studies, [73-75] and three of the studies were conducted in Italy; [16, 77, 80] the remaining studies were conducted in Austria, [79] Brazil, [81] Chile, [71] France, [72] Greece, [78] Hong Kong, [76] and Sweden. [17] Four of the studies were conducted using hospitalized patients; [73-76] the remaining nine studies included participants from the community. Only one of the studies was a multicentre trial. [16]

Interventions

The intervention groups received calcitonin by various routes: either nasal spray (seven studies), [16, 74, 76-80] injection (six studies), [17, 71, 72, 75, 80, 81] or by rectal suppository (one study). [73] Ten studies included an identical placebo group, [17, 71-77, 80, 81] and three studies included a comparison group, where the participants received various doses of calcium and vitamin D, but did not receive a placebo. [16, 78, 79]

Outcomes

Of the 13 studies included, six involved patients with acute back pain (< 10 days) attributed to a recent OVCF; [71-76] and seven included patients with chronic back pain (> 3 months) attributed to a remote OVCF. [16, 17, 77-81] Although all studies analyzed pain scores, three studies presented their data in such a way that the results could not be included in the meta-analysis. [17, 76, 78] The timing of outcome measures was variable, ranging from 14 to 28 days for measures of acute pain and from one week to one year for measures of chronic pain. Various pain scales were used in the trials; a 10 cm or 100 mm VAS predominated (0 = no pain to 10 = intolerable pain), [17, 72-76, 78-81] followed by studies utilizing a descriptive 4-point scale (0/1 = normal to 4 = movement impossible / very severe), [16, 77] and a 5-point scale (0 = none to 5 = pain in bed without moving). [71] All studies provided information on withdrawals and side effects experienced by both treatment and comparison groups. With the exception of the participants in one of the studies, [80] all participants were allowed concomitant analgesics but only a few of the studies provided data on their usage.

Quality Assessment – Risk of Bias in Included Studies

The methodological quality of trials varied significantly (see summary results presented in **Table 1-2)**. The initial agreement of the reviewers on the total assessment of risk of bias was 97% (74 of 76 items). Any initial disagreements were solved by consensus. An adequate method of sequence generation was reported in five trials, [73-76, 78] and an adequate method for allocation concealment in three trials. [73-75] Patients were blinded in all but three studies; [16, 78, 79] and

attrition was low or adequately accounted for in all but one study. [72] Three studies met all formal quality criteria, [73-75] one study met four criteria, [80] and four studies met three of the quality requirements. [17, 71, 76, 77] *A priori*, publication bias was to be tested using the funnel plot visually and quantitatively, that is, the rank correlation test [82] and the graphical test with or without heterogeneity. [28] However, given the small number of trials included in the review, the interpretation of these plots must be undertaken with caution and are not included here.

Effects of Interventions: Analgesic Efficacy of Calcitonin

The statistical analysis (related to the analgesic efficacy of calcitonin) included data from 10 trials with 467 participants (420 women [90.0%], and 47 men [10.0%]). The mean ages of participants (at entry) in the treatment and control groups were 67.4 years and 66.9 years respectively. The studies were analyzed and results pooled for two separate groups, those including participants with 1) acute back pain (< 10 days duration) [71-75] attributed to a recent OVCF and, 2) chronic back pain (> 3 months duration) [16, 77, 79-81] attributed to a remote OVCF.

Acute back pain

Five studies included participants with acute back pain of a recent OVCF (260 participants; 213 females [82%] and 47 males [18%]). The mean age of participants was 70.8 years in the calcitonin group and 71.2 years in the control group. Of the five studies, three used a 10 cm VAS, [73-75] one used a 100 mm VAS, [72] and the final used a descriptive 5-point scale as a subjective measure of participant self-reported pain. [71] In three of the trials, VAS measures were initiated on day 0 (baseline), and then again at least weekly for up to four weeks during bed rest, sitting, standing, and walking. [73-75] Another study measured pain scores with patients only at rest and assessed pain on a 100 mm VAS at baseline, week 2, and again at week 4. [72] The final study measured pain by assessing patients' activity/mobility using a 5–point scale; the measurements were assessed at day 0 (baseline), day 3, 7, 14, 21, and 28. [71]

As determined *a priori*, two sub groups were created: 1) pain assessed at rest, and 2) pain assessed with mobility. Because there were too few trials and insufficient data, we were unable to carry out subgroup analysis based on sex and age of participants or the route of calcitonin administration. Within the subgroups, analyses were done at baseline, and then weeks 1 to 4. All five of the studies employed the use of salmon calcitonin; therefore, sensitivity analysis related to calcitonin derivative was not necessary. Overall, a small number of trials were included and the pooled analyses displayed statistical heterogeneity; therefore, the estimates were based on the RE model. [27]

Acute pain at rest

Four trials studied participants while at rest or stationary; [72-75] baseline results of the population revealed a relatively homogeneous sample with moderate to severe pain (VAS ranged from a mean score of 6.1 to 10 out of 10) with no statistical difference between the groups ($p = 0.56$). Following one week of treatment, there was a statistically significant improvement in the resting pain score for patients receiving calcitonin (MD = -3.39; 95% CI, -4.02 to -2.76) compared to the control group. The chi-square test of heterogeneity was not significant for the RE pooled result ($I^2 = 24\%$, $p = 0.27$). This result was not significantly different from the results seen at 2, 3, and 4 weeks with the subjects at rest (forest plot of the results presented in **Figure 1-2**).

Significant heterogeneity ($I^2 > 90\%$) of the RE pooled results (with participants at rest), was demonstrated in weeks 2 and 4. Sensitivity analyses, based on the imputing of SDs where means were provided (but no SD), [72, 73] were non-significant as the direction and magnitude of treatment effect did not change. For example, the VAS (pain scores) measured at rest on week 2, excluding the studies with no SD provided, showed a homogeneous sample ($I^2 = 0\%$) with a MD of -4.65 (95% CI, -5.18 to -4.12), as compared with a MD of -3.75 (95% CI, -5.52 to -1.98) when including all four studies.

Acute pain with mobility

Four trials studied participants while mobile; [71, 73-75] baseline results of the population revealed a homogeneous sample ($I^2 = 18\%$; $p = 0.30$) with no

statistical difference between the groups ($p = 0.46$). By week 1, there was a significant improvement in the RE pooled score, (SMD = -2.60; 95% CI, -4.07 to -1.13) compared to the control group. This result was not significantly different from results seen at weeks 2, 3, and 4 (forest plot of the results presented in **Figure 1-3**).

The only comparisons demonstrating significant heterogeneity in their RE pooled results were at weeks 1 and 2 ($I^2 > 90\%$). Sensitivity analyses, based on the imputing of SDs into the studies where means were provided (but no SD),[71, 73] were non-significant as the magnitude of the treatment effect did not change. For example, the pain scores with mobility at week 2, excluding the studies where the SD was imputed, showed a SMD of -4.35 (95% CI, -6.23 to -2.47), as compared with a SMD of -3.75 (95% CI, -5.52 to - 1.98).

Chronic back pain

The five studies including participants with chronic back pain of a remote OVCF included 207 participants (100% women). The mean age of participants was 64 years in the calcitonin group and 63.1 years in the control group. Of the five studies, two used a 10 cm VAS, [79, 81] one used a 100 mm VAS, [80] and two used descriptive 4–point scales as a subjective measure of participant self-reported pain. [16, 77] All of the trials initiated pain score measurements at baseline (day 0), one of the trials followed patients closely for six months, [81] and two of the trials followed patients for up to one year. [16, 79] The remaining two trials employed short term measures; one assessed pain scores weekly for up to four weeks, [80] and the other assessed patients at two weeks and then monthly for three months. [77]

As determined *a priori*, two sub groups were created: 1) pain assessed at rest, and 2) pain assessed with mobility. Because there were too few trials and insufficient data, we were unable to carry out subgroup analysis based on sex and age of participants or the route of calcitonin administration. For pain assessed at rest, pooled analyses were only possible at baseline, and then at 3 months. For the group assessed while mobile, pooled analyses were possible at baseline, weekly until week 4 and then again at 3 and 6 months. Overall there were a small number

of trials included and the pooled analyses displayed statistical heterogeneity; therefore, the estimates were based on the RE model. [27]

Chronic pain at rest

Two of the five studies included assessments while patients were at rest. [16, 77] The baseline result of this chronic back pain population, revealed a homogeneous sample ($I^2 = 0\%$, $p = 0.36$) with slight statistical difference between the groups ($p = 0.01$). After 3 months of treatment, there were no statistically significant improvements in the resting pain scores for patients receiving calcitonin (SMD = 0.17; 95% CI, -1.46 to 1.12) compared to the control group. The chi-square test for heterogeneity was relatively significant for the RE pooled result ($I^2 = 84\%$, $p = 0.01$). One study reported results for up to 1 year, [16] with no statistically significant difference in pain scores between the calcitonin group and the control group (SMD = -0.42; 95% CI, -0.84 to 0.00; $p = 0.05$).

Sensitivity analysis, based on the imputing of SDs into the studies where means were provided (but no SD), was not done as the SD had to be imputed for both of the included trials. Of the two included studies, one used synthetic eel calcitonin [77] and the other synthetic salmon calcitonin; [16] with limited data provided, sensitivity analyses related to calcitonin derivative could not be done.

Chronic pain with mobility

Four of the five studies measured chronic back pain with activity; [16, 79-81] RE pooled results of the population at baseline, revealed a homogeneous sample ($I^2 = 0\%$; $p = 0.44$) with no statistical difference between groups ($p = 0.29$). With the exception of the pooled results at 6 months, there were no significant improvements in pain scores. At 6 months, there appeared to be a significant difference in pain scores for the calcitonin group (SMD = -0.49; 95% CI, -0.85 to -0.13; $p = 0.008$; $I^2 = 0\%$) compared to the control group (forest plot of the results presented in **Figure 1-4**).

The only comparisons demonstrating heterogeneity ($I^2 = 86\%$, $p < 0.0009$) in their RE pooled results was at 3 months. As SD for both of the studies reporting results at 3 months were not provided (and were therefore imputed), [16, 81] sensitivity analysis was not done.

Effects of Interventions: Withdrawals and Side Effects

Of the 13 studies included in the review, all provided information on withdrawals and side effects (n = 589 participants); data were stratified by route of calcitonin administration (IN, injection [IM or SQ], and rectal).

Withdrawals

Of the 13 included studies, six reported 16 patient withdrawals; nine (7.2%) withdrawals were from the calcitonin group (eight due to side effects, and one with no reason provided) and seven (5.3%) from the control group (one related to side effects, five due to lack of efficacy, and one with no reason provided). The pooled RE model provided a RR of 1.26 (95% CI, 0.46 to 3.43) and the calculated number needed to treat to prevent one additional withdrawal (NNTH) for all cause withdrawal was 73. Specifically, two studies, both examining chronic pain, reported two withdrawals from the IN calcitonin group (3.9%) and none from the control group, giving a RR of 3.07 (95% CI, 0.34 to 27.79; p = 0.32). Four studies using injectable calcitonin (IM or SQ), two of which reported on acute pain and two on chronic pain, reported six (11.1%) withdrawals from the calcitonin group and four (6.8%) from the control group; the RE pooled analysis showed a RR of 1.49 (95% CI, 0.40 to 5.61; p = 0.55) and a calculated NNTH of 30. One study utilizing rectal suppository calcitonin, reported one withdrawal (5%) from the treatment group and three (15%) withdrawals from the control group; this was not statistically significant (p = 0.32). See **Table 1-3** Withdrawals from included studies.

Side effects

The 13 included studies reported 104 separate side effects; 85 were reported in the calcitonin group (the majority due to enteric disturbances [47%] and flushing [32%]), and 19 in the control group (mainly due to enteric disturbances [68%]). The pooled RE model showed a RR of 3.09 (95% CI, 1.80 to 5.32; $p < 0.0001$) and a calculated NNTH of 12 (the number of patients who receive calcitonin that will lead to one additional patient experiencing a side effect, in comparison to the control group). Side effects were generally reported as mild, with the majority

being either enteric disturbances (RR = 2.58; 95% CI, 1.10 to 6.04) or flushing (RR = 6.91; 95% CI, 2.47 to 19.36) both of which were statistically significant. See **Table 1-4** Side effects reported in included studies.

Concomitant Analgesic Use

We were not able to utilize statistical methods to assess concomitant analgesic use, as there were not only substantial gaps in the data reported but also important differences in the reporting of results between studies. Seven studies reported analgesic use as an outcome of the study; this varied significantly from reporting the daily or weekly mean consumption of acetaminophen, [16, 71, 73, 74, 77, 81] to converting the analgesic administered to equivalent mg of morphine ingested daily. [76] In five of the studies, concomitant analgesic use was not an outcome of interest and was therefore not reported on; [17, 72, 75, 78, 79] in one of the studies, concomitant analgesia was not permitted. [80]

DISCUSSION

Overall, the evidence presented in this review supports the use of calcitonin as an effective analgesic for the acute pain of recent OVCF in older adults. The included studies demonstrated a clear benefit with respect to pain relief. Pain was rated as severe by patients in both groups at baseline, suggesting this diagnosis is important not only to health care providers, but also to individual patients. By one-week post treatment, there were clinically (≥20/100 mm on the VAS), and statistically significantly differences in the pain scores of the calcitonin group compared to those in the control group. Various studies have investigated the minimum clinically significant change in patients' pain severity measured with a 10 cm VAS and found that 1.3 cm as the cutoff. [83, 84] This along with the finding that all studies of acute pain of OVCF reported statistically significant results for the analgesic efficacy of calcitonin, suggest that these results are not due to chance. Although not specifically evaluated in this review, earlier mobilization would be expected to reduce the incidence of other problems associated with immobility such as muscle atrophy and venous thromboembolism.

Although used in clinical practice, the findings of this review do not support the use of calcitonin for chronic pain of more remote OVCFs. The subgroup analysis of analgesic efficacy with patients at rest did not demonstrate any clinical or statistical difference in pooled results from baseline through year 1. For the pooled analyses of patients while mobile, there was statistical significance only at 6 months in pain scores for the calcitonin group compared to the control group; regardless, we did not determine this to be of clinical importance.

We postulated that the route of administration may have in part explained the heterogeneity of the results. Unfortunately, due to so few studies included in the individual analyses, it was not possible to do sub group analysis based on route of calcitonin administration. For example, either there was only one study included per route of administration, or the calcitonin was given in different doses (IM 50IU vs. 100IU), making it impossible to compare the results. The included studies used different routes of administration and various doses of calcitonin; therefore, insufficient data were available to evaluate a dose-response effect of calcitonin. However, it appeared that the trials employing IM or SQ injections showed the greatest difference in pain scores between calcitonin and control groups. This may be in part due to the greater bioavailability of the drug when administered via the IM route. The bioavailability of IN calcitonin is only about 25% of the administered dose as compared with the injectable preparation, which is 70% bioavailable. [85] Clinically, given the age and co-morbidities of the affected patients, it is clearly easier to administer the agent via the IN route than the IM route, adjusting the dose accordingly to reflect bioavailability of the drug.

The withdrawal rate for any cause was low and was seen in slightly more patients in the treatment group than placebo; this was not a statistically significant finding. The NNT to prevent one additional withdrawal (for all cause withdrawal) with calcitonin was high at 73. There were more withdrawals in the acute pain group than in the chronic pain group; this is not surprising as, presumably, the patients in these trials would have been suffering from acute, extreme pain and almost all of the withdrawals were due to lack of perceived efficacy (not side effects).

Overall, this treatment approach seems to be safe. There were side effects reported in these trials; however, they were generally described as mild and self-limiting. There were statistically significant increases in gastrointestinal / enteric disturbances and flushing compared to placebo. These side effects may in part be related to the route of administration, as both were noticed predominantly in the studies where injectable calcitonin was utilized. There were also more side effects in the chronic pain group; given the much longer duration of these studies (1 year vs. 4 weeks), this was expected.

Overall Completeness and Applicability of Evidence

There are several methodological issues that would limit the generalizability (external validity) of these results, although the overall findings seem to apply to all patients. Due to the small number of trials included in this meta-analysis, and the overall small number of patients upon which these results are based, no firm conclusions regarding the subgroups (other than the acute pain group) can be made.

Four of the five studies included in the acute pain analysis were conducted in a hospital setting where patient presentations may be more severe than in an ambulatory office, or clinic setting. Consequently, the results pertaining to the use of calcitonin for acute OVCF need confirmation in the community setting. In addition, the overall findings may only be generalized to people who have OVCF and limited co-morbid disease as described in the exclusion criteria of the studies. People with secondary osteoporosis or those receiving concomitant osteoporosis treatments were not studied. Moreover, analyses adjusting for confounding factors or population stratification were not performed due to insufficient data.

Quality of the Evidence

The methodological quality of the individual included studies was assessed according to the 'risk of bias approach' of the Cochrane Collaboration. [25] Information related to acceptable randomization, allocation concealment, and blinded outcome assessments varied significantly and were not adequately reported in most of the studies. In fact, only three studies addressed all six of the

formal quality criteria. Although the authors of the 13 included studies all claimed that their study design was a randomized controlled trial, an appropriate method of randomization and concealment of treatment allocation was determined in only three of the studies after contact with the study author (all three studies were by the same author). Perhaps, if all study authors had been successfully contacted, this would have been clarified for all of the studies.

None of the studies followed the CONSORT reporting guidelines. [86] Consequently, there were no reports on numbers of patients excluded from the studies prior to randomization and there was no information on how those included differed from those who were excluded. We do not know how this would influence the estimate of effect; however, since the effect in the acute pain subgroup is very robust (note the narrow confidence intervals), we are reasonably confident of the results.

Although all studies reported data on side effects and withdrawals, none reported on compliance with the chosen treatment. Compliance can be a confounding factor when studying the effectiveness of any treatment; when the compliance is generally low (usually a matter of self-selection), it is difficult to be certain of the real effectiveness of the treatment.

Potential Biases in the Review Process

The two review authors who assessed the methodological quality were not blinded for authors, journal, or institution. The potential bias caused by the non-blinded quality assessment was expected to be low as neither review author had a conflict of interest. Specifically, the review authors did not have any (financial or other) interest in positive or negative results. Furthermore, we searched the grey literature extensively for eligible trials, presented the search strategy and the inclusion criteria list, and all of the final results of the assessment, so that readers can make their own determinations of the results and our conclusions.

There is a possibility of publication bias or study selection bias in this meta-analysis. For example, by missing unpublished negative trials we may be over-estimating the treatment effect of calcitonin. However, a comprehensive

search of the published literature for potentially relevant studies was conducted, using a systematic strategy to avoid bias. This was followed by attempts to contact corresponding and first authors, as we recognize that unpublished or negative trials may exist. We did identify three relevant trials that were not included in the meta-analysis; however, despite concerted efforts to communicate with the authors to clarify methodological issues and obtain additional data, we were unable to locate primary study authors and therefore could not include them in the analysis.

Authors' Conclusions

Implications for practice

OVCFs are a significant problem for which many older adults seek medical attention, some of whom are subsequently admitted to hospital. The evidence from this meta-analysis suggests that calcitonin should be considered as an adjunctive analgesic for acute pain associated with recent OVCF. When comparing the route of calcitonin administration, injections may provide more rapid analgesic effect, reducing the time to return to mobilization; however, this observation requires confirmation. Despite a small statistically significant improvement in pain scores at six months, there is insufficient evidence to support the use of calcitonin for chronic back pain attributed to remote OVCFs.

Implications for research

Further RCTs, with adequate sample sizes, are necessary to elucidate the analgesic properties of calcitonin and the significance of side effects. Future research should focus on effective dose ranges and their duration of response, and the long-term efficacy of calcitonin, particularly in post-menopausal women, in whom the majority of OVCF fractures are seen. A cost analysis of calcitonin therapy versus conventional therapy (e.g., narcotics, newer COX-2-inhibitors, etc) taking into account health related quality of life issues, length of time to mobilization, length of hospital stay, and patient preference all need careful consideration when choosing one treatment over another. Finally, trials

comparing calcitonin to other analgesics or in combination with other analgesics are needed. Considering the complexity of pain control, it may not be reasonable to look for a single drug to control the severe pain of vertebral compression fractures.

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Appendix 1-1. MEDLINE search strategy

1. control group/
2. meta analysis/
3. random$.mp.
4. ((singl$ or doubl$ or tripl$ or trebl$) adj10 (blind$ or mask$)).mp.
5. (cross?over or placebo$ or control$ or factorial or sham$).mp.
6. (meta?analy$ or systematic review$).mp.
7. (therapy or treat$).mp.
8. ((clin$ or intervention$ or compar$ or experiment$ or preventive or therap$) adj10 (trial$ or study or studies)).mp.
9. exp Experimentation/ or clinical research.mp. or exp Treatment Effectiveness Evaluation/
10. (longitudinal study or meta analysis or program evaluation or prospective study or retrospective study or treatment outcome study or empirical study or experimental replication or followup study).fc.
11. ((prospective or retrospective or longitudinal or followup or evaluation or outcome$) adj10 (trial$ or study or studies)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. (follow adj2 study).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
13. (follow adj2 studies).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
14. or/1-13
15. exp clinical trial/
16. randomi?ed.ti,ab.
17. placebo.ti,ab.
18. dt.fs.
19. randomly.ti,ab.
20. trial.ti,ab.
21. groups.ti,ab.
22. or/15-21
23. animal/
24. human/
25. 23 not (23 and 24)
26. 22 not 25
27. exp osteoporosis/
28. exp bone demineralization, pathologic/
29. osteoporosis.tw.
30. or/27-29
31. calcitonin/
32. calcitonin.tw.
33. calcitonin.rn.
34. or/31-33
35. 30 and 34
36. fracture.tw.
37. 35 and 36
38. 37 and 26
39. 37 and 14
40. 38 and 39

Appendix 1-2. The Cochrane Collaboration's tool for assessing risk of bias

Domain	Description	Review authors' judgment
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias?

Table 1-1. Characteristics of included studies

Acute Pain							
Author (year) and Country	Design*	Study population			Intervention		Outcomes (pain assessment, analgesic consumption, and withdrawals)
		N	Setting	Mean age; Sex	Treatment group	Control group	
Arinoviche (1986) Chile	RCT, DB, PC Duration 14 days	32	Community	70 years; 29 females 3 males	*n* = 15 Synthetic salmon calcitonin 100 IU SQ injection daily	*n* = 17 Identical SQ placebo injection	Outcomes assessed at baseline, day 3, 7, and 14. • Pain with mobility (0 = none to 5 = pain in bed without moving), • Functional capacity (0 = no problem with everyday activities to 3 = maximum) • Global effectiveness (0 = no problems with everyday activity to 3=impossible due to pain) • Number of paracetamol tabs and side effects were reported in each group daily
Levernieux (1986) (includes Attali 1986 and Bordier 1986)	RCT, DB, PC Duration 28 days	34	Community	71 years All female	*n* = 15 Salmon calcitonin 50 IU IM or SQ injection daily	*n* = 17 Placebo injection of identical form daily	Outcomes assessed at baseline, day 14, and 28. • Pain assessed by a 10 cm VAS (0 = no pain to 10 = intolerable pain) • Biochemical markers for bone turn over and BMD
Lyritis (1999) Greece	RCT, DB, PC Duration 28 days	40	Hospital	Ages 63 to 91 years 28 female 12 male	*n* = 20 Synthetic salmon calcitonin 200 IU rectal suppository daily	*n* = 20 Placebo rectal suppository daily	Outcomes assessed at baseline and then daily (reported weekly). • Pain assessed by a 10 cm VAS (0 = no pain to 10 = agonizing pain) during bed rest, sitting, standing, and walking, at the same time by the same observers • Pain assessed by a pain meter device (direct pressure on the fractured vertebra) in the same 4 positions (range 0 to 6) • Numbers of paracetamol tabs were reported in each group daily • Side effects recorded daily • Tolerability of calcitonin or placebo

Acute Pain							
Author (year) and Country	Design*	Study population			Intervention		Outcomes (pain assessment, analgesic consumption, and withdrawals)
		N	Setting	Mean age; Sex	Treatment group	Control group	
							evaluated (3 = very good, 2 = good, 1 = poor, 0 = not tolerated) • Biochemical measurements done at baseline, day 14, and day 28
Lyritis (1997) Greece	RCT, DB, PC Duration 28 days	100	Hospital	Female 71 years; males 76 years 68 female 32 male	*n* = 50 Synthetic salmon calcitonin 200 IU IN daily	*n* = 50 IN placebo daily	Outcomes assesses at baseline and daily. • Pain assessment by VAS (0 = no pain to 10 = agonizing pain) every day during bed rest, sitting, standing, and walking • Side effects recorded daily • Tolerance of intervention reported (3 = very good, 2 = good, and 1 = poor)
Lyritis (1991) Greece	RCT, DB, PC Duration 14 days	56	Hospital	68 years All female	*n* = 28 Synthetic salmon calcitonin 100 IU of IM injection daily	*n* = 28 Placebo IM injection daily	Outcomes assesses at baseline and daily. • Pain assessment by VAS (0 = no pain to 10 = agonizing pain) every day during bed rest, sitting, standing, and walking • Number of paracetamol tablets consumed reported in each group daily • Side effects recorded daily • Tolerance of intervention reported (3 = very good, 2 = good, and 1 = poor)
Pun (1989) Hong Kong	RCT, DB, PC Duration 28 days	18	Hospital	Age range 67-81 years 13 female 5 male	*n* = 9 Synthetic salmon calcitonin 100 IU IN BID	*n* = 9 Placebo IN	Outcomes assessed at rest and were initiated at baseline (on day 0), and then analyzed weekly on day 7, 14, 21, and 28 days. • Pain assessed with a VAS (0 = no pain and 10 = pain as bad as it could be) • Concurrent analgesics evaluated daily

Chronic Pain (> 3 months duration)							
Author (year) and Country	Design *	Study population			Intervention		Outcome (pain assessment, analgesic consumption, and withdrawals)
		N	Setting	Mean age (years) & Sex	Treatment group	Control group	
Abellan Perez (1995) Italy	RCT, no blinding, no placebo Duration 12 months	88	Community Multi centre	63 years All female	*n* = 43 Synthetic salmon calcitonin 100 IU IN for 14 days then 14 days off and then repeat pattern for 1 year and calcium 500 mg daily for 1 year	*n* = 45 Calcium 1 gram daily for 1 year, no placebo	Outcomes reported at baseline, 3, 6, 9, and 12 months. • Pain scale with mobilization (1= normal to 4 = movement impossible due to pain) • Analgesic consumption weekly (1= null to 5 = more than 1 a day) • Self reported pain scale (1= absent to 4= intense) • Drug tolerance and side effects reported daily
Consoli (1991) Italy	RCT, DB, PC Duration 6 months	20	Community	Treatment group 70 years, control group 61 years All female	*n* = 10 Synthetic eel calcitonin IN 80 MRCU daily	*n* = 10 Placebo nasal spray	Outcomes assessed at baseline and after 15, 30, 60, 90, and 180 days of treatment. • Pain intensity at rest (0 = absent to 3 = very severe) • Daily analgesic consumption • Possibility of ADLs (0 = bed-bound to 3 = normal) • Compliance to treatment
Ljunghall (1991) Sweden	RCT, PC, DB Duration 4 months	60	Community	Aged 58 to 82 years All female	Group 1: *n* = 20 Synthetic human calcitonin 0.25 mg SQ injection 3 times a week Group 2: *n* = 20 Synthetic human calcitonin 0.125 mg SQ injection 3 times a week	*n* = 20 Placebo injection 3 times a week	Outcomes assessed at baseline and after 1 and 4 months. • Self-reported pain intensity measured on a 100 mm VAS (reported only at 1 and 4 months – baseline results were not provided) • Side effects were assessed monthly
Papado-kostakis	Open clinical	40	Community	Treatment group 65	*n* = 20	*n* = 20	Outcomes assessed at baseline and at 3 months (the end of the trial).

Chronic Pain (> 3 months duration)							
Author (year) and Country	Design *	Study population			Intervention		Outcome (pain assessment, analgesic consumption, and withdrawals)
		N	Setting	Mean age (years) & Sex	Treatment group	Control group	
(2006)	trial. Random-ized, no blinding, no placebo Duration 3 months			years; control group 66 years All female	Synthetic salmon calcitonin 200 IU IN daily and 1000 mg of calcium daily	Calcium 1000 mg daily (no IN placebo)	• Pain intensity using an 11 point numerical rating scale (NRS) (0 = no pain and 10 = the most severe pain) • Functional status measures using the Oswestry disability questionnaire • Compliance evaluated by a telephone call monthly
Peichl (1999) Austria	Open, RCT, no placebo Duration 12 months	42	Community	63 years All female	*n* = 24 Synthetic salmon calcitonin 200 IU IN daily for 2 months, then a 2 month pause over a total of 12 months (3 cycles) AND calcium 500 mg daily	*n* = 18 Calcium 500 mg and vitamin D 400 IU daily for 12 months, no placebo	Outcomes measured at baseline and at the end of the trial (12 months). • Pain assessed on a 10 cm VAS (0 = no pain and 10 = unbearable pain) • Side effects recorded
Pontiroli (1994) Italy	RCT, DB, DP. Duration 4 weeks	28	Community	Age range 49-65	**Group 1**: Synthetic salmon calcitonin 200 IU IN daily AND IM placebo, *n* = 9, (analyzed 8) **Group 2**: Synthetic salmon calcitonin 100IU IM injection daily AND IN placebo, *n* = 10, (analyzed 8)	**Placebo** IN AND placebo IM injection, *n* = 9, (analyzed 8)	Outcomes assessed by the same physician at baseline and again on day 7, 14, 21, and 28 days (weekly). • Pain score was measured by a VAS (0 to 100 mm - scores not defined) • VAS results presented as means with SEM
Szejnfeld	RCT, DB	33	Community	65 years	*n* = 16	*n* = 17	Outcomes assessed at baseline and every

Chronic Pain (> 3 months duration)							
Author (year) and Country	Design *	Study population			Intervention		Outcome (pain assessment, analgesic consumption, and withdrawals)
		N	Setting	Mean age (years) & Sex	Treatment group	Control group	
(1991) Brazil	Duration 6 months			All female	Synthetic salmon calcitonin 100 IU IM during 5 days of the first 2 weeks of each month AND 1 gram of calcium and 400 IU vitamin D daily	Placebo IM injection for the first 5 days of 2 weeks of each month AND 1 gram of calcium and 400 IU vitamin D daily	2 weeks until 24 week (6 months). • Pain intensity using a 10 point numerical scale (0 = no pain and 10 = maximum pain) • Functional capacity: ability to dress, walking capacity, and ability to climb or descend stairs (0 = no difficulty and 3 = maximum difficulty). The final value is in the sum of the values obtained in each of the items surveyed, with a maximum possible value of 9 • Side effects • Amount of analgesics used

DB double blind, *DP* double placebo, *ITT* intention to treat, *IM* intramuscular, *OP* osteoporosis, *PC* placebo controlled, *RCT* randomized controlled trial, *SD* standard deviation, *SQ* subcutaneous, *VAS* visual analogue scale

Table 1-2. Risk of bias in included studies (methodological quality summary)

Acute pain (onset < 10 days post fracture)						
Study	**Adequate sequence generation**	**Allocation concealment**	**Blinding**	**Incomplete outcome data addressed**	**Free of selective reporting**	**Free of other bias**
Arinoviche (1986)	Unclear	Unclear	Yes	Yes	Yes	Unclear
	Quote… "randomized according to a randomization list".	No information; comment: may have not been done.	Described as DB, PC study. Placebo IN administered in the exact method as the TG.	3 patients in the CG and 5 patients in the TG noted SE, 3 patients from the TG discontinued the study due to reported SE – not included in the sample sizes reported.	All of the studies specified patient outcomes have been reported on.	Insufficient information to assess whether an important risk of bias exists.
Levernieux (1986)	Unclear	Unclear	Yes	No	Yes	Unclear
	Described as "randomized" but not defined.	No information. Comment: may have not been done.	Described as DB, PC study. Placebo IM injection administered in the exact method as the treatment group.	Two patients from the TG did not complete the study and were excluded from the results.	All of the studies specified patient outcomes have been reported on.	Insufficient information to assess whether an important risk of bias exists. This study was described in 3 separate publications.
Lyritis (1999)	Yes	Yes	Yes	Yes	Yes	Yes
	Quote "prospective, DB, randomized, PC clinical trial". Method of randomization not described in the publication	The ordering of the cards within the envelopes was determined from a table of random numbers.	Quote "DB". Suppositories administered by a nurse at the same time every day.	4 withdrawals: 1 from the TG because of enteric disturbances, and 3 from the CG: 2 because more potent analgesics needed, 1 at his	All of the studies specified patient outcomes have been reported on.	The study appeared to be free of other sources of bias.

Acute pain (onset < 10 days post fracture)						
Study	**Adequate sequence generation**	**Allocation concealment**	**Blinding**	**Incomplete outcome data addressed**	**Free of selective reporting**	**Free of other bias**
	but author reports adequate sequence generation procedures.			own request.		
Lyritis (1997)	Yes	Yes	Yes	Yes	Yes	Yes
	Quote "prospective, DB, randomized, PC clinical trial". Method of randomization not described in the publication but author reports adequate sequence generation procedures.	The ordering of the cards within the envelopes was determined from a table of random numbers.	Quote "…assigned to receive either salmon calcitonin IN 200 IU or a matching placebo IN". Patients in hospital and received IN spray from a nurse.	No withdrawals or dropouts.	All of the studies specified patient outcomes have been reported on.	The study appeared to be free of other sources of bias.
Lyritis (1991)	Yes	Yes	Yes	Yes	Yes	Yes
	Quote "prospective, DB, randomized, PC clinical trial". Method of randomization not described in the publication but author reports adequate sequence generation procedures.	The ordering of the cards within the envelopes was determined from a table of random numbers.	Quote "…salmon calcitonin or placebo injections..." Patients in hospital and received injections from a nurse.	No withdrawals or drop outs.	All of the studies specified patient outcomes have been reported on.	The study appeared to be free of other sources of bias.
Pun (1989)	Yes	Unclear	Yes	Unclear	Yes	Unclear
	Quote	No information;	Quote "...received	Withdrawals and	All of the studies	Insufficient

Acute pain (onset < 10 days post fracture)						
Study	**Adequate sequence generation**	**Allocation concealment**	**Blinding**	**Incomplete outcome data addressed**	**Free of selective reporting**	**Free of other bias**
	"randomized according to a table of randomized numbers".	comment: may have not been done.	salmon calcitonin IN twice a day…or placebo containing only carrier".	dropouts not described. Side effects not mentioned.	specified patient outcomes have been reported on.	information to assess whether an important risk of bias exists.

Chronic Pain (> 3 months duration)						
Study	**Adequate sequence generation**	**Allocation concealment**	**Blinding**	**Incomplete outcome data addressed**	**Free of selective reporting**	**Free of other bias**
Abellan Perez (1995)	Unclear	Unclear	No	Yes	Yes	Unclear
	Quote "numerous randomized blocks of two". Comment: probably done.	No information; Comment: may have not been done.	Comment: CG administered only calcium; no placebo IN preparation. Assume that blinding was not done as it was not directly mentioned.	1 patient discontinued in the TG due to side effects of the drug. No missing outcome data.	All of the studies specified patient outcomes have been reported on.	Insufficient information to assess whether an important risk of bias exists.
Consoli (1991)	Unclear	Unclear	Yes	Yes	Yes	Yes
	Quote "randomized, DB clinical trial"; randomization not described.	No information. Comment: may have not been done.	Quote "...DB clinical trial".	All patients completed the trial and all reported on.	All of the studies specified patient outcomes have been reported on.	The study appeared to be free of other sources of bias.
Ljunghall (1991)	No	Unclear	Yes	Yes	Unclear	Yes
	Quote "randomly allocated in equal numbers to each of the three	No information. Comment: may have not been done.	Quote "PC". Three groups self administered the drug / placebo in	All patients completed the trial and all reported on.	Self reported pain intensity measured on a 100 mm VAS (reported only at 1	The study appeared to be free of other sources of bias.

Chronic Pain (> 3 months duration)						
Study	**Adequate sequence generation**	**Allocation concealment**	**Blinding**	**Incomplete outcome data addressed**	**Free of selective reporting**	**Free of other bias**
	groups" Randomized in blocks of 3.		the same method with identical syringe.		and 4 months – baseline results were not provided).	
Papado-kostakis (2006)	Yes	Unclear	No	Yes	No	Unclear
	Quote "block (or restricted) randomization was used." Quote "randomly assigned in 1:1 ratio."	No information. Comment: may have not been done.	No placebo, patients received either calcitonin by injection and calcium or just calcium.	Two patients discontinued the calcium treatment but ITT analysis done.	Incomplete description of outcomes for one of the groups.	Insufficient information to assess whether an important risk of bias exists.
Peichl (1999)	Yes	Unclear	No	Yes	Yes	Unclear
	Quote "…open randomized study". Methods of randomization not described.	No information. Comment: may have not been done.	Open study with no placebo, patients received either IN calcitonin and calcium or just calcium and vitamin D.	No description or mention of withdrawals or dropouts.	All of the studies specified patient outcomes have been reported on.	Insufficient information to assess whether an important risk of bias exists.
Pontiroli (1994)	Unclear	Unclear	Yes	Yes	Yes	Yes
	Quote"...randomly allocated to one of 3 groups". Methods of randomization not described.	No information. Comment: may have not been done.	Described as DB with double placebo and a PC group.	Dropouts were described and were equal in all 3 groups.	All of the studies specified patient outcomes have been reported on.	The study appeared to be free of other sources of bias.
Szejnfeld (1991)	Unclear	Unclear	Yes	Yes	No	Unclear
	Quote "…randomized, DB study".	No information. Comment: may have not been done.	Quote "DB". Patients received an injection (calcitonin or placebo) and calcium and	4 dropouts in PG due to SE - ITT analysis done.	Did not report VAS scores for weeks 6, 10, 14, 18, or 22.	Insufficient information to assess whether an important risk of bias exists.

Chronic Pain (> 3 months duration)						
Study	**Adequate sequence generation**	**Allocation concealment**	**Blinding**	**Incomplete outcome data addressed**	**Free of selective reporting**	**Free of other bias**
			vitamin D.			

CG control group, *DB* double blind, *DP* double placebo, *IN* inter nasal, *ITT* intention to treat, *IM* intramuscular, *OP* osteoporosis, *PC* placebo controlled, *RCT* randomized controlled trial, *SD* standard deviation, *SE* side effects, *SQ* subcutaneous, *TG* treatment group, *VAS* visual analogue scale

Table 1-3. Withdrawals from included studies

Route of administration	No. of studies	No. of patients		Illustrative comparative risks [a] (95% CI)		Relative effect (95% CI)	p [b] value	NNTH [c]
				Assumed risk	Corresponding risk			
		Control group	Calcitonin group	Control group	Calcitonin group			
Intranasal	2 (*n*=104)	0/53 (0%)	2/51 (3.9%)	**Study population**		**RR 3.07** (0.34 to 27.79)	0.32	0 [d]
				0 per 1000	0 per 1000			
Injection	4 (*n*=113)	4/59 (6.8%)	6/54 (11.1%)	**Study population**		**RR 1.49** (0.4 to 5.61)	0.55	30
				68 per 1000	103 per 1000 (34 to 306)			
Per rectum - suppository	1 (*n*=40)	3/20 (15%)	1/20 (5%)	**Study population**		**RR 0.33** (0.04 to 2.94)	0.32	10
				150 per 1000	50 per 1000 (6 to 441)			
Total withdrawals	7 (*n*=257)	7/132 (5.3%)	9/125 (7.2%)	**Study population**		**RR 1.26** (0.46 to 3.43)	0.65	72
				53 per 1000	68 per 1000 (29 to 158)			

[a] The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

[b] p value is for the Z statistic

[c] NNTH = $\left|\frac{1}{ACR \times (1-RR)}\right|$

[d] Unable to estimate, no withdrawals in the control group

ACR Assumed control risk, *CI* Confidence interval, *NNTH* Number needed to treat to prevent one withdrawal, *RR* Risk ratio

Table 1-4. Side effects reported in included studies

Side effects	No. of studies	No. of patients		Illustrative comparative risks [a] (95% CI)		Relative effect (95% CI)	p [b] value	NNTH [c]
				Assumed risk	Corresponding risk			
		Control group	Calcitonin group	Control group	Calcitonin group			
GI / enteric	**10** (*n*=381)	13/193 (6.7%)	40/188 (21.3%)	**Study population** 67 per 1000	182 per 1000 (109 to 304)	RR 2.52 (1.10, 6.04)	0.03	9
Flushing	**7** (*n*=305)	1/155 (0.6%)	27/150 (18%)	**Study population** 6 per 1000	46 per 1000 (17 to 128)	RR 6.91 (2.47, 19.36)	0.0002	28
Dizziness / headache	**2** (*n*=56)	2/28 (7.1%)	7/28 (25%)	**Study population** 71 per 1000	213 per 1000 (54 to 836)	RR 1.92 (0.10, 36.81)	0.66	15
Ears, nose, throat	**3** (*n*=74)	0/34 (0%)	5/40 (12.5%)	**Study population** 0 per 1000	0 per 1000 [d]	RR 3.89 (0.70, 21.66)	0.12	0 [d]
Other, not specified	**2** (*n*=132)	3/67 (4.5%)	6/65 (9.2%)	**Study population** 45 per 1000	83 per 1000 (24 to 288)	RR 1.45 (0.02, 110.08)	0.87	49
Total side effects	**12** (*n*=948)	19/477 (4.0%)	85/471 (18.1%)	**Study population** 40 per 1000	136 per 1000 (92 to 202)	RR 3.09 (1.80, 5.32)	<0.0001	12

[a] The **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Corresponding intervention risk, per 1000 = 1000 * ACR * RR

[b] NNTH = $\left|\frac{1}{ACR \times (1-RR)}\right|$

[c] p value is for the Z statistic.

[d] Unable to estimate, no adverse reaction in the control group

ACR Assumed control risk, *CI* Confidence interval, *NNTH* Numbers needed to treat for an additional harmful outcome, *RR* Risk ratio

Figure 1-1. Flow diagram of study selection

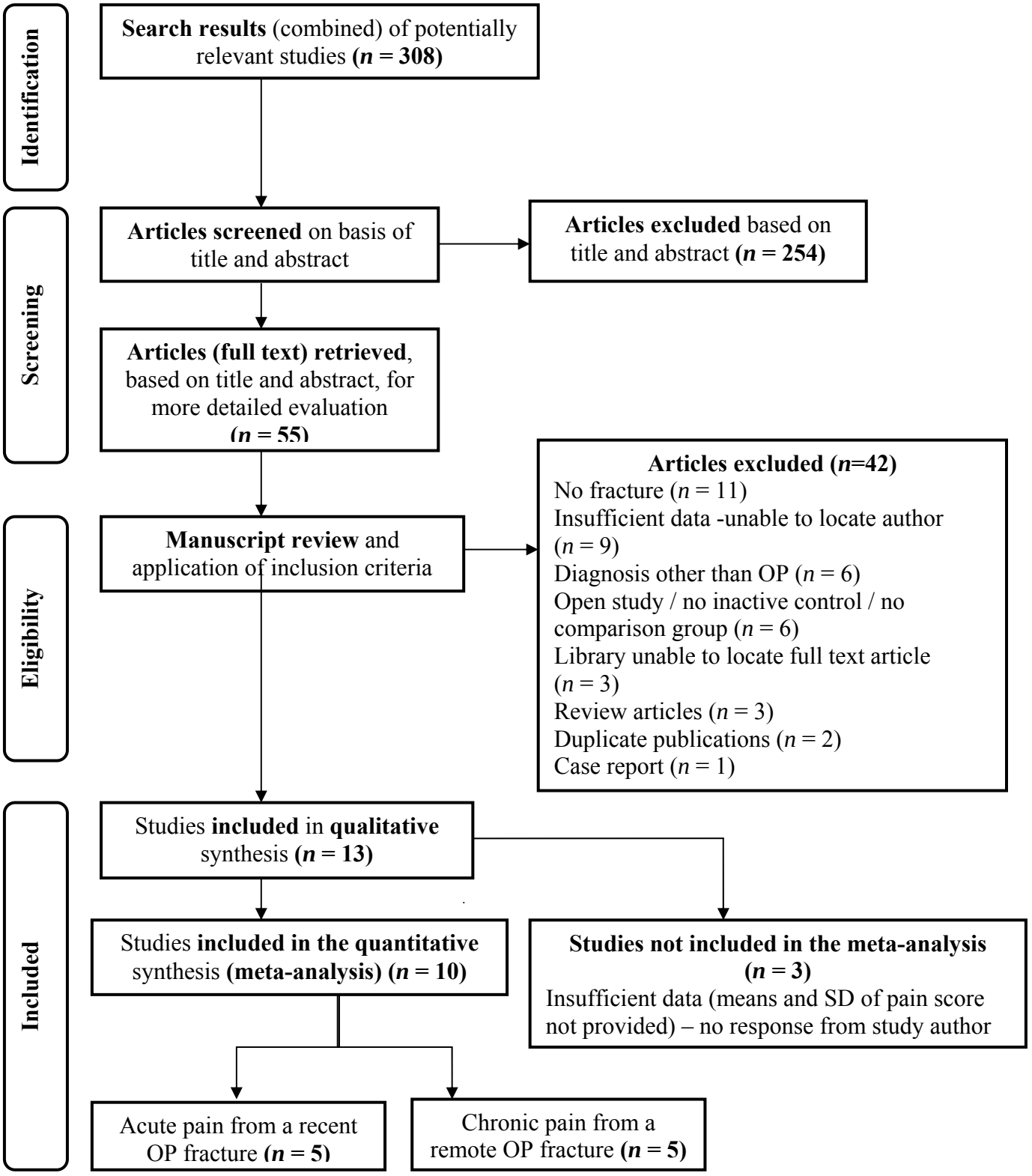

Figure 1-2. Acute pain measured at rest

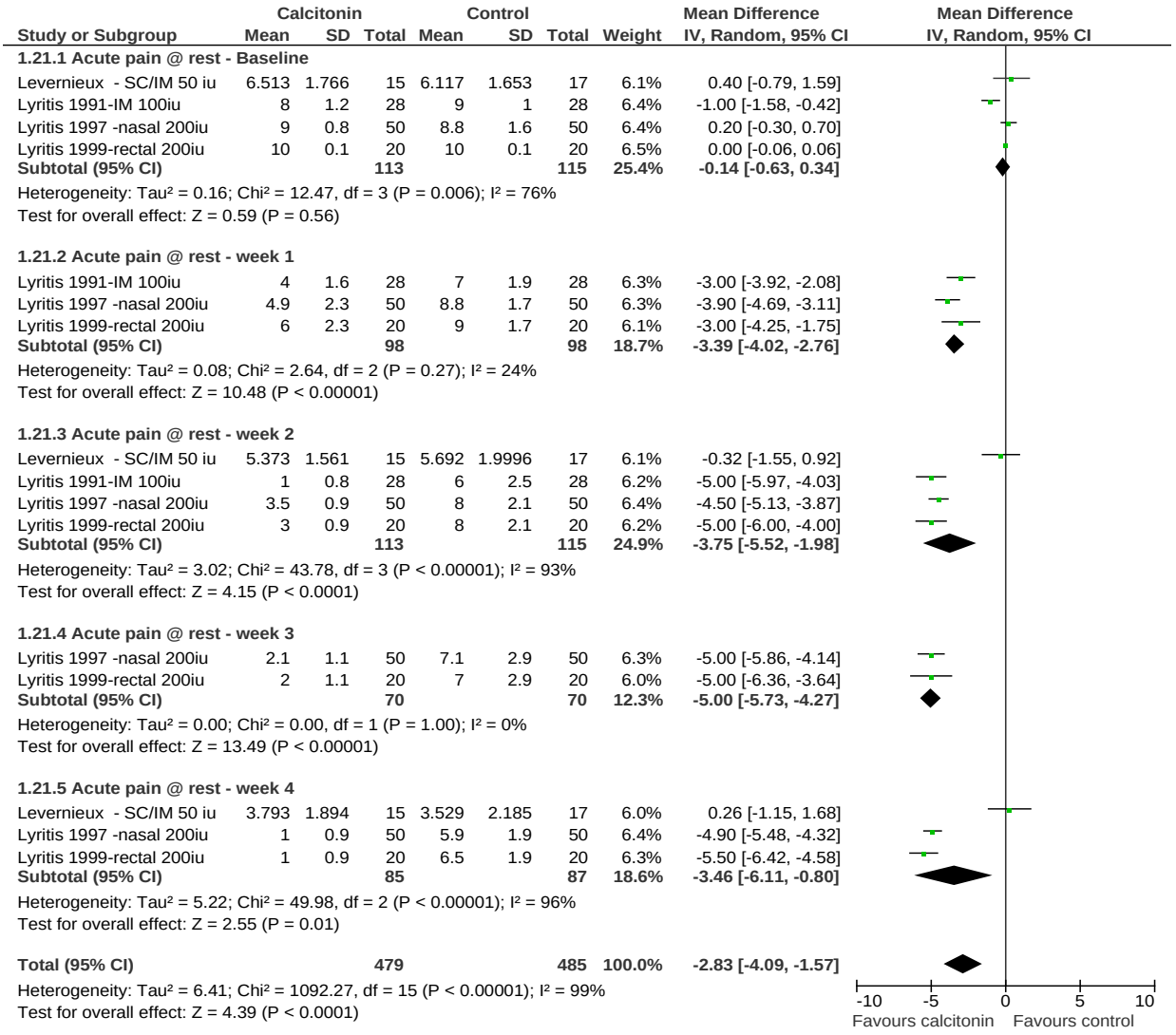

Fig 2 Forest plot of all included studies reporting the acute pain of a recent OVCF, measured at rest on day 0 (baseline) and weeks 1 to 4. *Horizontal lines*, 95% CIs of each study; *green squares*, MDs of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond*, the summary estimate; solid vertical line, null value. MDs less than zero indicate a treatment benefit.

Figure 1-3. Acute pain measured with activity / walking

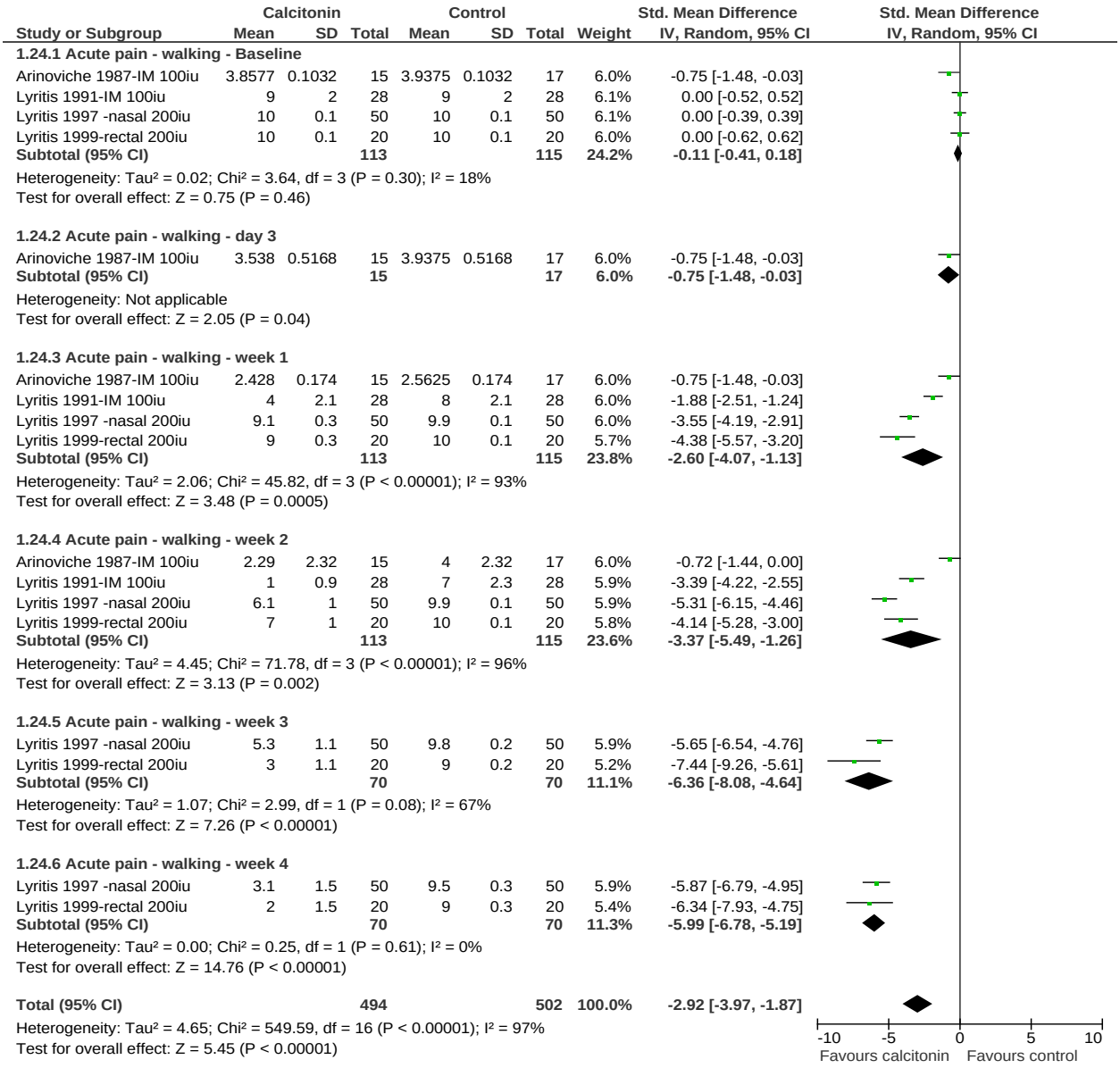

Fig 3 Forest plot of all included studies reporting the acute pain of a recent OVCF, measured at while mobile on day 0 (baseline) and weeks 1 to 4. *Horizontal lines*, 95% CIs of each study; *green squares*, SMDs of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond*, the summary estimate; solid vertical line, null value. SMDs less than zero indicate a treatment benefit.

Figure 1-4. Chronic pain measured with activity

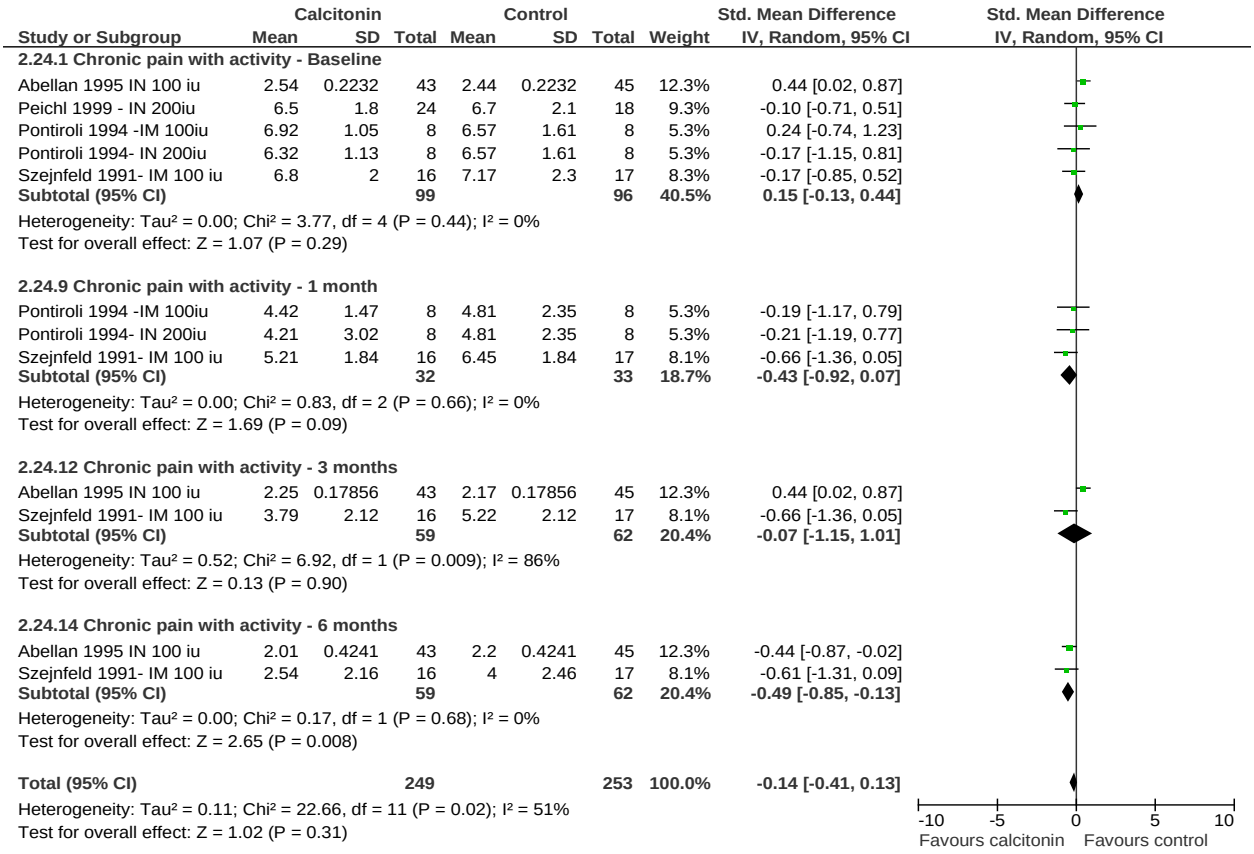

Fig 4 Forest plot of all included studies reporting chronic pain of a remote OVCF, measured while mobile on day 0 (baseline), week 1 to 3, and months 1, 2, 3, 6, 9, and 12. *Horizontal lines*, 95% CIs of each study; *green squares*, SMDs of each individual study (the size represents the weight that the study was given in the meta-analysis); *diamond*, the summary estimate; solid vertical line, null value. SMDs less than zero indicate a treatment benefit.

PAPER 2:

The Association between Older Age, Co-Morbidity, and Treatment Status of Incident Osteoporotic Fractures: A Population-Based Nested Cohort Study

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Citation.

Knopp-Sihota, J.A., Newburn-Cook, C.V., Cummings, G.G., Homik, J., & Voaklander, D., The association between older age, co-morbidity, and treatment status of incident osteoporotic fractures: A population-based nested cohort study. *Osteoporos Int.* 2011; 22(Suppl 2): S424.

PAPER 2:

The association between older age, co-morbidity, and treatment status of incident osteoporotic fractures: A population-based nested cohort study

INTRODUCTION

Osteoporosis is a skeletal disease characterized by low bone mass and micro-architecture deterioration of bone, leading to increased bone fragility and risk of fracture. [1] The epidemiological and clinical importance of osteoporosis lies in the fractures that are associated with the disease, with over 70% of all fractures in older adults being attributed to osteoporosis. [2]

Ideally, the routine management of osteoporosis should target all aspects of the disease, including maximizing and preserving bone mass and preventing future fractures through pharmacotherapy and lifestyle modification. [1] Therefore, an important management strategy is to identify those who have already sustained a typical osteoporosis fracture (low energy or fragility fracture), and initiate treatment aimed at secondary prevention, as these types of patients derive the greatest absolute benefit from treatment. [3, 4] This sort of case finding approach is an important complementary strategy (to traditional care); it should not only entail immediate initiation of pharmacologic treatment aimed at secondary prevention of re-fracture but also active rehabilitation, in addition to bone mass density (BMD) measures to monitor disease progression. [5, 6]

Although the choice of treatment is contingent on patient age, co-morbidities, the presence or absence of prevalent fractures, patient preferences, and BMD, [7] first-line treatment typically includes calcium and vitamin D, along with an antiresorptive agent (usually a bisphosphonate drug). [1, 8] Bisphosphonates have been shown to rapidly reduce bone-remodelling, thus increasing BMD, and are associated with the largest reduction in fracture risk compared with other therapies. [9]

However, despite strong evidence-based rationale for both the primary and secondary prevention of osteoporosis, there remains an overall low prevalence of osteoporosis treatment in older adults. [10, 11] Furthermore, existing literature does not adequately delineate whether the low treatment rates in the older adult population are simply age related variations (in treatments) or due to the presence of co-morbid conditions. Co-morbidity is defined as the co-existence of two or more chronic conditions or impairments that have an impact upon patient independence and survival. [12]

Purpose and objectives

We sought to examine the incidence of osteoporotic fractures and the use of antifracture therapy, in relation to patients' age and co-morbidity, among men and women residing in British Columbia (BC), Canada. Given the suggestion that older adults receive less than optimal care for other conditions such as diabetes, we hypothesized that secondary prevention of osteoporosis (i.e., the prescribing of osteoporosis medications following an incident fracture) would be inversely related to age and severe patient co-morbidity. Specifically, we sought to determine if older adults with multiple co-morbid conditions were less likely to receive osteoporosis treatment following an osteoporosis fracture than younger healthier patients with fewer co-morbid conditions.

MATERIALS AND METHODS

Data sources

We performed a retrospective nested cohort analysis utilizing de-identified administrative healthcare data derived from the British Columbia Linked Health Database (BCLHD). This database contained comprehensive healthcare utilization data for nearly all residents of British Columbia (BC), Canada (population 4.1 million, 2006 Statistics Canada census data). The BCLHD, which integrates health service records, population health data, and census statistics, makes it possible to link administrative records anonymously at the individual level by using a unique personal health number (PHN). The BCLHD has been used in numerous healthcare and health services research projects since 1996;

thus, this database is well suited to explore clinical questions. Prior to accessing data, ethics approval was received from the Health Research Ethics Board at the University of Alberta.

Study population and patient selection

All residents in the province of BC, Canada aged 65 years and older who had continuous enrolment in the PharmaCare prescription benefits plan (Fair PharmaCare or Plan B) were eligible for inclusion in the study. Between 1999 and 2002 the population aged 65 years and older in the province of BC grew from 681,700 to 728,200. [13]

Using the Discharge Abstract Database (DAD), we identified all patients aged 65 years and older with index fractures (defined as the first documentation of a study-defined osteoporosis-related fracture (ICD-9 classification of a non-traumatic fracture of the neck of femur [hip], vertebra, distal radius [wrist], proximal humerus [arm], rib, or pelvis) during the study period of April 1, 1999 to March 31, 2002. The DAD contains demographic, administrative, and clinical data for hospital discharges (inpatient acute, chronic, rehabilitation) and day surgeries. [14] The data were collected per patient admission, contained up to 16 diagnosis codes, and identified the primary and secondary responsible diagnoses for the admission, and co-morbid conditions present at the time of admission.

To ensure the identification of only new fractures (incident cases), subjects with the same fracture within 1 year prior to the index fracture were excluded (i.e. fracture wash-out period). To avoid identifying fractures that may not have been attributed to osteoporosis, we then excluded patients with any one of the following: (1) fractures associated with a high-energy injury or multiple fractures; (2) fractures combined with a primary or secondary cancer diagnosis; (3) previous diagnosis of a medical condition that may increase the risk of osteoporosis (i.e., hyperthyroidism, hyperparathyroidism, and Paget's disease). We also excluded those patients who died in hospital, as our main outcome of interest was osteoporosis medication prescription, which obviously did not apply. See **Figure 2-1** for the study subject (cohort) selection procedures.

After exclusion criteria were applied, the initial fracture cohort was linked to the PharmaCare data to identify those patients who were dispensed an osteoporosis medication within 6 months of the index fracture. A 6 month follow up period was chosen, as this is sufficient for both acute fracture healing and chronic disease management. PharmaCare is BC's public drug insurance program that assists BC residents in paying for eligible prescription drugs and certain medical supplies. [15] The PharmaCare dataset includes patient level prescription drug expenditures for community and permanent residents of licensed residential care facilities.

The prevalence of co-morbidity, using the Charlson –Deyo Index (CDI), was calculated for each subject using the diagnostic codes available in the DAD. The CDI includes 19 diseases weighted (1 to 6) based on their association with mortality; the CDI score is the sum of the weights for all conditions with a maximum score of 37. [12] The CDI has been previously documented for use in patients with chronic disease [16] and has been validated for use with the BCHLD. [17]

Outcome measures and analysis

All analyses were stratified by fracture location, and descriptive statistics were used to summarize the characteristics of the population. The determination of statistical differences between groups was made using Pearson's chi square (χ^2) statistics for categorical variables, with alpha (p) set at 0.05 to determine the statistical significance of the estimate. As this was a population-based study, including all BC residents who met the study inclusion criteria, a sample size calculation was not warranted.

We initially assessed the unadjusted odds ratio (OR) and 95% confidence interval (CI) of the association between osteoporosis medication dispensation (dependent variable) and age and co-morbidity (the main independent variables) using simple univariate logistic regression. We then assessed the relationship and strength of association among all predictor variables and the outcome (osteoporosis medication dispensation), using multivariate logistic regression techniques, controlling for age, sex, CDI, fracture site, year of fracture, health

region, and osteoporosis treatment prior to the index fracture. We used the *Enter* procedure in which all independent variables are entered in a single step and then tested for the possibility of statistical interaction between the main independent variables (age and CDI score) and all other covariates. We pre- specified that we would consider only interaction terms that achieved a level of statistical significance of $p < 0.10$. The calculated ORs were considered statistically significant if the 95% CI did not include 1.

Specifically, the outcome of interest (dependent variable) was the dispensation of osteoporosis medication within six months following an index fracture. We chose a six-month period after the fracture because we wanted to assess patient management in response to the fracture, rather than patient compliance with ongoing therapy; [4] therefore, compliance beyond a single filled prescription was not considered important (for this research question). We believe that six months after a fracture allows for sufficient healing time and adequate time for a patient to access treatment for secondary prevention. All analyses were conducted using SPSS version 18.0 (SPSS, Inc., Chicago, IL).

RESULTS

Study population

After exclusion criteria were applied, we identified 11,870 consecutive patients who had been hospitalized with 12,025 incident fractures between April 1, 1999 and March 31, 2002. The mean age of the sample was 81.1 years (SD 7.7; range 65–104 years), and 74% of the subjects were women. The majority of patients (99%) sustained one fracture (range 1 to 4) during the study period, and the fractures were predominately of the hip (63%) followed by fractures of the arm / wrist (17%), pelvis (9%), vertebra (7%), and ribs (4%). The majority of subjects had no co-morbid conditions or only one (63%); 31% had two to three co-morbidities, and 6% had four or more co-morbid conditions (as measured by the CDI).

During the 3-year study period, there was an even distribution of fractures per year (approximately 33% of the fractures each year). With the exception of

fewer patients receiving care in the Northern region of the province (4% of patients), there was a similar patient distribution in each of the other four health regions in the province (approximately 24% in each health region). There were significant differences (between fracture location groups) in age categories, sex, CDI scores, and health region when stratified by fracture location ($p < 0.001$ for chi square differences between categories within each group). See **Table 2-1** for a description of patient characteristics stratified by fracture site.

Osteoporosis treatment

Overall, there was a low rate of treatment with osteoporosis medications in patients in the six months before the incident fracture (15% of the sample); this rate improved after the index fracture, with 19% of the sample receiving treatment within six months. Those receiving treatment after the index fracture were significantly younger, more often female, and had fewer co-morbid conditions ($p < 0.001$). The prescription rates significantly increased during the study period, from 17% receiving treatment in 1999 / 2000 compared to 21% receiving treatment in 2001 / 2002 ($p < 0.001$). Those receiving care in the Fraser (22%) or Vancouver Coastal (22%) health regions were significantly more likely to have filled a prescription than those receiving care in the Vancouver Island (17%), Interior (16%), or Northern (12%) health regions ($p < 0.001$). The percentage of subjects receiving treatment was significantly higher among those who sustained a vertebral fracture (29%) compared to those sustaining a hip (17%), arm / wrist (22%), pelvis (25%), or rib fracture (15%). See **Table 2-2** for the characteristics of patients who received an osteoporosis drug within six months of the index fracture.

Among the 10,199 patients (85% of the sample) who had not received a medication prior to the index fracture, 1,062 patients (10%) filled a prescription for an osteoporosis drug within six months following the index fracture. The majority of the 1,826 subjects who had received a medication prior to the fracture also filled at least one prescription following the index fracture (69%). Similar to the overall analysis, age, sex, co-morbidity, fracture site, and health region were

all significantly associated with the dispensation of an osteoporosis medication within six months following the index fracture. There was no difference in treatment based on the year the fracture was sustained in those who had been dispensed a drug before the index fracture ($p = 0.496$).

Factors predicting osteoporosis treatment (logistic regression analysis)

The initial multivariate logistic regression model for the dependent outcome (osteoporosis medication dispensation) included the categorical variables age, CDI, sex, fracture year, fracture site, prior treatment, and health authority. Fracture year was later dropped from the model as it was not statistically significant. There were statistically significant interactions between the following factors: (1) prior treatment and sex ($p = 0.000$), (2) prior treatment and fracture category ($p = 0.001$), and (3) prior treatment and age ($p = 0.010$); therefore, these interaction terms were retained in the final model.

The use of an osteoporosis medication prior to the index fracture was the strongest predictor of post-fracture treatment (adjusted OR = 15.89; 95% CI = 9.69–26.04). Increasing age, more than one co-morbid condition, and male sex were all associated with a significant decrease in the likelihood of dispensing osteoporosis drugs when compared to younger and healthier women. Subjects 85 years and older were significantly less likely to receive treatment compared to younger subjects (adjusted OR = 0.64; 95% CI = 0.49–0.83); this was even more pronounced for subjects 90 years and older, who were dispensed medication less than 50% of the time compared to subjects 69 years and younger (adjusted OR = 0.47; 95% CI = 0.35–0.63).

Those patients with more than one co-morbid condition were significantly less likely to have been dispensed treatment compared to those with one or fewer co-morbid conditions. Those with 2 to 3 conditions were 1.2 times less likely, and those with 4 or more co-morbid conditions were 1.6 times less likely, to have been dispensed treatment. Men were 4.3 times less likely to have been dispensed treatment than women (adjusted OR = 0.23; 95% CI = 0.19–0.29).

Patients with a vertebral fracture were more than two and a half times more likely to be dispensed treatment compared to those sustaining a hip fracture (adjusted OR = 2.64; 95% CI = 2.12–3.29); subjects with a pelvic fracture were also more likely to receive treatment when compared to hip fracture subjects (adjusted OR = 1.27; 95% CI = 1.01–1.60). Those subjects sustaining an arm / wrist fracture (adjusted OR = 1.10; 95% CI = 0.93–1.32) or a rib fracture (adjusted OR = 1.01; 95% CI = 0.69–1.46) were no more nor less likely to have been dispensed osteoporosis treatment compared to those sustaining a hip fracture.

When comparing treatment based on residence (Health Region) at the time of the fracture, there were significant differences in treatment status. Those residing in any location other than the reference category (Vancouver Coastal) were 1.4 to 2 times less likely to have been dispensed treatment: of significance were the Interior region (adjusted OR = 0.68; 95% CI = 0.58–0.80) , the Vancouver Island region (adjusted OR = 0.69; 95% CI = 0.59–0.81), and the Northern region (adjusted OR = 0.48; 95% CI = 0.35–0.67). See **Table 2-3** for factors predicting osteoporosis medication dispensation following an incident fracture.

DISCUSSION

As with many disease and risk states, patients with the highest baseline risk should be treated the most aggressively. Yet, for many older adults with an established diagnosis of osteoporosis with or without fracture, this is not always the case. In this retrospective population-based nested cohort study, we identified subjects with an incident osteoporotic fracture and followed them for six months to determine osteoporosis treatment status. We found an overall low rate of treatment in the fracture cohort, with only 19% of subjects dispensed a medication during the study period. Using multivariate logistic regression techniques, we found that post-fracture treatment was primarily predicted by pre-fracture treatment status, with those who had received treatment prior to their fracture having the greatest probability of also receiving treatment following the incident

fracture. Patients who were older, less healthy, and male were less likely to be dispensed osteoporosis medications. These relationships remained after controlling for other potential confounding variables including fracture site, health region, and the year the fracture was sustained.

Patients' residence also predicted fracture treatment; patients residing in the Northern region of the province were two times less likely to receive fracture treatment compared to those residing in a more central location. This may in part be explained by the central location of the reference category in the analysis (Vancouver Coastal), which includes the provinces' tertiary care university teaching hospitals. These findings are similar to other studies reporting the under-treatment of chronic conditions, such as cardiovascular disease, in patients residing in more remote locations. [18]

Another important finding of this study was the low rate of treatment for hip fractures; hip fractures are associated with the highest mortality of all fragility fractures. [19] The under- treatment of hip fractures has been demonstrated in other studies and has been the recent focus of intervention studies, whereby orthopaedic teams are aiming to both identify and diagnose patients with osteoporosis and initiate treatment prior to hospital discharge. [20]

The degree of co-morbidity is often a powerful negative factor in predicting patient outcomes such as life expectancy and is correlated with worse health outcomes, increased healthcare utilization, and costs; therefore, it is important to identify and treat high risk patients in order to avoid further undesirable outcomes, including the need for long term institutionalization. [21, 22] Similar to our findings, other studies have consistently demonstrated similar inverse relationships between osteoporosis treatment propensity, older age, and co-morbidity. Three recently published systematic reviews described the rates of investigation and diagnosis of fragility fractures as well as the types of post-fracture treatment. [10, 11, 23] The authors included articles of varying methods, finding that patients were dispensed either none, or a very low rate of treatment following fragility fracture. Also consistent with our findings, post-fracture treatment was substantially less frequent in men than women.

Several reasons, other than a simple lack of physician recognition that osteoporosis and related fractures are important and possibly preventable with treatment, may exist for this gap in care. Older age is often associated with higher rates of co-morbidities as well as increased medication use; both of which have been shown to be deterrents in osteoporosis treatment. This is perhaps in part because of presumed patient adherence problems, polypharmacy concerns, and the idea that treatment would be futile. [20]

This study, as with other studies based solely on administrative data, has some limitations that must be recognized. First, as fractures are not only related to skeletal load, but also bone strength and quality, it is not possible to use secondary data to determine in exact terms whether a reported fracture is related to fragility (osteoporosis) or to high impact/trauma. [24] Furthermore, the operational definition of osteoporosis developed by the WHO is based on BMD, which is not easily captured in administrative databases for population-wide comparisons. [25] Second, the evaluation of drug prescription was based on dispensation rates instead of the actual number of written prescriptions; therefore, we have likely underestimated intended physician endorsed treatments. Lastly, due to the claims-based nature of the dataset, information related to other potentially confounding variables could not be assessed or controlled for. These include BMD results, smoking status, history of falls, over the counter medication use such as vitamin D and calcium supplementation, and more remote fracture history. Although the inclusion of these variables may have provided a more inclusive description of osteoporosis and related fractures, we do not believe that controlling for these variables would have altered the results of this study.

The strengths of this study include its population-based design, a large sample size, and its use of detailed data made possible by the use of a comprehensive linkable dataset including clinical and prescription drug information of most residents in the province. Compared to other studies (evaluating osteoporosis management) which have relied on chart audits, patient or physician surveys and questionnaires, or involved highly selective patient recruitment, our study had a larger sample size and was based on a population

dataset, which allowed for patient level analysis of a complete geographic population of community dwelling Canadian residents. In addition, our study used a co-morbidity index that had been previously validated with the population and used sophisticated statistical analysis to control for potentially confounding variables.

Conclusion

In conclusion, individuals who have already sustained a fragility fracture are at a considerably higher risk of developing future fractures; therefore, occurrence of a fracture should result in timely initiation of effective treatment. Despite availability of several therapeutic options in the province of BC, our findings suggest that the majority of patients are not receiving treatment to prevent the progression of the disease and to prevent further fractures.

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Table 2-1. Patient characteristics by fracture site*

Variable	Hip n = 7,531 (62.6)	Arm / wrist n = 2,012 (16.7)	Pelvis n = 1,108 (9.2)	Vertebra n = 872 (7.3)	Ribs n = 502 (4.2)	Total n = 12,025
Age (years) †						
65–69	418 (5.6)	355 (17.6)	84 (7.6)	102 (11.7)	82 (16.3)	1,041 (8.7)
70–74	790 (10.5)	419 (20.8)	118 (10.6)	152 (17.4)	83 (16.5)	1,562 (13.0)
75–79	1,376 (18.3)	474 (23.6)	198 (17.9)	199 (22.8)	106 (21.1)	2,353 (19.6)
80–84	1,832 (24.3)	361 (17.9)	249 (22.5)	192 (22.0)	96 (19.1)	2,730 (22.7)
85–89	1,902 (25.3)	267 (13.3)	273 (24.6)	151 (17.3)	72 (14.3)	2,665 (22.2)
≥ 90	1,213 (16.1)	136 (6.8)	186 (16.8)	76 (8.7)	63 (12.5)	1,674 (13.9)
Sex †						
Female	5,600 (74.4)	1,649 (82.0)	887 (80.1)	529 (60.7)	269 (53.6)	8,934 (74.3)
Male	1,885 (25.0)	350 (17.4)	216 (19.5)	337 (38.6)	229 (45.6)	3,017 (25.1)
Unknown	46 (0.6)	13 (0.6)	5 (0.5)	6 (0.7)	4 (0.8)	74 (0.6)
Year of fracture						
1999/2000	2,541 (33.7)	651 (32.4)	375 (33.8)	284 (32.6)	186 (37.1)	4,037 (33.6)
2000/2001	2,321 (30.8)	678 (33.7)	339 (30.6)	271 (31.1)	161 (32.1)	3,770 (31.4)
2001/2002	2,669 (35.4)	683 (33.9)	394 (35.6)	317 (36.4)	155 (30.9)	4,218 (35.1)
Charlson-Deyo Index (CDI) †						
≤ 1	4,419 (58.7)	1,645 (81.8)	612 (55.2)	572 (65.6)	351 (69.9)	7,599 (63.2)
2–3	2,602 (34.6)	321 (16.0)	420 (37.9)	258 (29.6)	123 (24.5)	3,724 (31)
≥ 4	510 (6.8)	46 (2.3)	76 (6.9)	42 (4.8)	28 (5.6)	702 (5.8)
Health Authority †						
Vancouver Coastal	2,097 (27.8)	490 (24.4)	290 (26.2)	217 (24.9)	108 (21.5)	3,202 (26.6)
Interior	1,557 (20.7)	472 (23.5)	202 (18.2)	232 (26.6)	148 (29.5)	2,611 (21.7)
Fraser	1,971 (26.2)	425 (21.1)	312 (28.2)	233 (26.7)	106 (21.1)	3,047 (25.3)
Vancouver Island	1,551 (20.6)	478 (23.8)	255 (23.0)	143 (16.4)	104 (20.7)	2,531 (21.0)
Northern	288 (3.8)	123 (6.1)	42 (3.8)	39 (4.5)	33 (6.6)	525 (4.4)
Unknown	67 (0.9)	24 (1.2)	7 (0.6)	8 (0.9)	3 (0.6)	109 (0.9)

* All data are shown as number (percentage)

† $p < 0.001$ for chi square differences between categories within the group

Table 2-2. Characteristics of patients who received an osteoporosis drug within 6 months after an incident osteoporosis fracture*

Variable	Total fracture cohort N = 12,025	*No* treatment within 6 months *before* fracture n = 10,199 (84.8)
Total receiving treatment within 6 months after fracture	2,318 (19.3)	1,062 (10.4)
Age category (years)		
65–69	199 (19.1) †	103 (11.2) †
70–74	356 (22.8)	173 (12.9)
75–79	509 (21.6)	232 (11.9)
80–84	569 (20.8)	260 (11.5)
85–89	470 (17.6)	196 (8.7)
≥ 90	215 (12.8)	98 (6.6)
Sex		
Female	2,118 (23.7) †	947 (13.1) †
Male	189 (6.3)	111 (3.8)
Unknown	11 (14.9)	4 (6.3)
Charlson-Deyo Index (CDI)		
≤ 1	1,560 (20.5) †	717 (11.2) ‡
2–3	664 (17.8)	298 (9.4)
≥ 4	94 (13.4)	47 (7.7)
Year of fracture		
1999 / 2000	698 (17.3) †	350 (9.9) †
2000 / 2001	750 (19.9)	341 (10.7)
2001 / 2002	870 (20.6)	371 (10.7)
Fracture site		
Hip	1,270 (16.9) †	589 (9.1) †
Arm / Wrist	445 (22.1)	211 (12.3)
Pelvis	277 (25.0)	100 (11.4)
Vertebrae	251 (28.8)	129 (18.3)
Ribs	75 (14.9)	33 (7.5)
Health Authority		
Vancouver Coastal	707 (22.1) †	343 (12.8) †
Interior	429 (16.4)	205 (9.0)
Fraser	664 (21.8)	287 (11.4)
Vancouver Island	436 (17.2)	190 (8.8)
Northern	64 (12.2)	30 (6.3)
Missing	18 (16.5)	7 (7.2)

* All data are shown as number (percentage)

† $p < 0.001$ for chi square differences between categories within the group

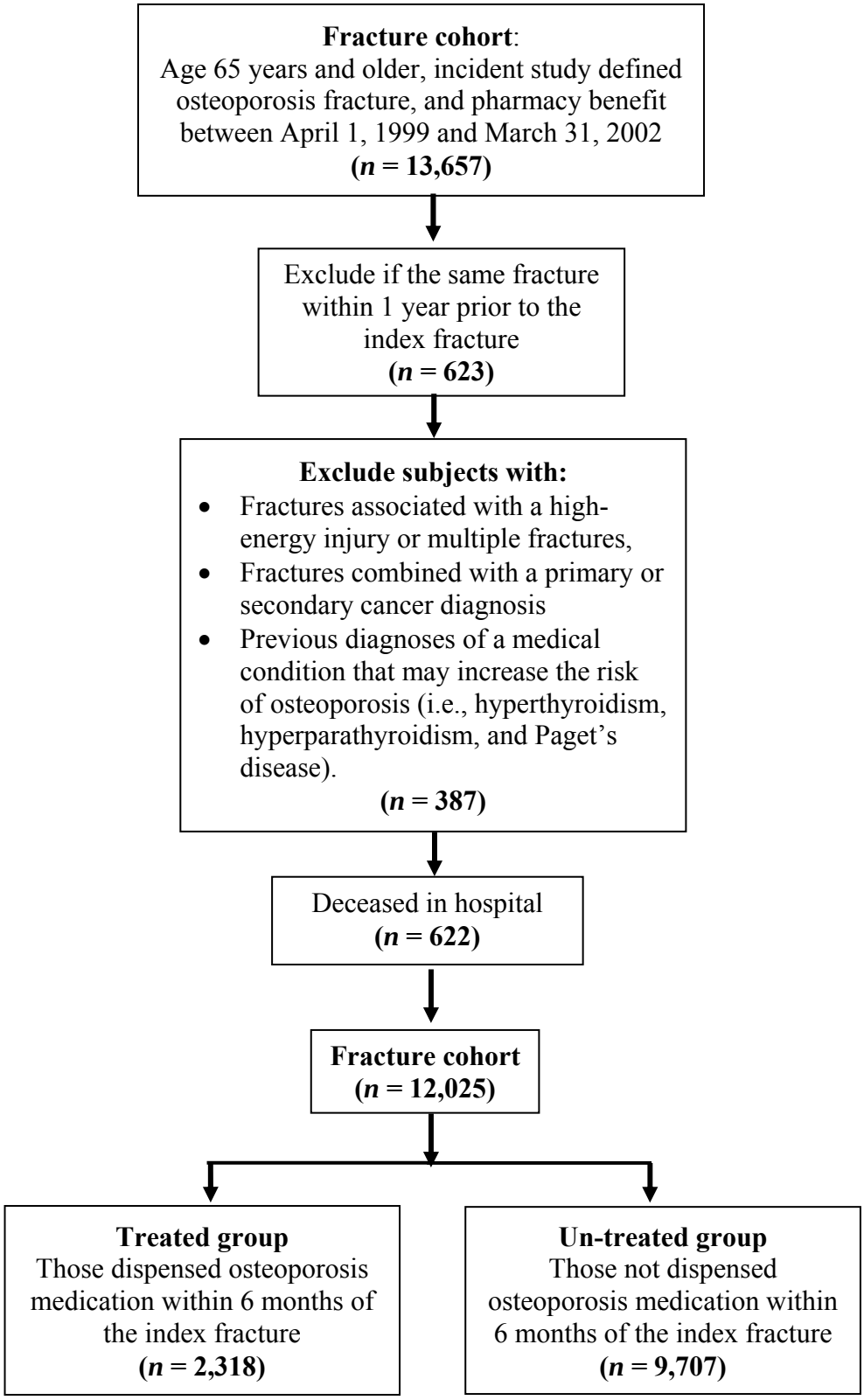
‡ $p < 0.002$ for chi square differences between categories within the group

Table 2-3 Logistic regression: Factors predicting drug treatment post-fracture

Variable	Adjusted odds ratio (95% Confidence Interval)	*p*-value
Constant	0.220	0.000
Age category (years)		
65–69	1 (reference)	
70–74	1.12 (0.86 – 1.47)	0.389
75–79	0.96 (0.75 – 1.24)	0.777
80–84	0.90 (0.70 - 1.16)	0.414
85–89	0.64 (0.49 - 0.83)	0.001
≥ 90	0.47 (0.35 - 0.63)	0.000
Sex		
Female	1 (reference)	
Male	0.23 (0.19–0.29)	0.000
Charlson-Deyo Index (CDI)		
≤ 1	1 (reference)	
2–3	0.83 (0.73–0.94)	0.003
≥ 4	0.63 (0.48–0.83)	0.001
Fracture site		
Hip	1 (reference)	
Arm / Wrist	1.10 (0.93 – 1.32)	0.273
Pelvis	1.27 (1.01 – 1.60)	0.039
Vertebrae	2.64 (2.12 – 3.29)	0.000
Ribs	1.01 (0.69 – 1.46)	0.976
Health Authority		
Vancouver Coastal	1 (reference)	
Interior	0.68 (0.58 – 0.80)	0.000
Fraser	0.92 (0.80- 1.07)	0.287
Vancouver Island	0.69 (0.59 – 0.81)	0.000
Northern	0.48 (0.35 – 0.67)	0.000
Missing	0.71 (0.39 – 1.32)	0.282
Prior treatment		
No treatment	1 (reference)	
Prior treatment	15.89 (9.69 – 26.04)	0.000
Prior treatment × sex		
Prior treatment (1) × Female	1 (reference)	
Prior treatment (1) × Male	3.03 (1.96–4.68)	0.000
Prior treatment (1) × fracture site		
Prior treatment (1) × Hip	1 (reference)	
Prior treatment (1) × Arm / wrist	1.60 (1.13 – 2.28)	0.009
Prior treatment (1) × Pelvis	1.43 (0.95 – 2.13)	0.084
Prior treatment (1) × Vertebrae	0.53 (0.35 – 0.82)	0.004
Prior treatment (1) × Ribs	1.21 (0.62 – 2.38)	0.579

Variable	Adjusted odds ratio (95% Confidence Interval)	*p*-value
Prior treatment (1) × age category (y)		
Prior treatment (1) × Age (65 – 69)	1 (reference)	
Prior treatment (1) × Age (70 – 74)	1.18 (0.65 – 2.15)	0.597
Prior treatment (1) × Age (75 – 79)	0.73 (0.43 – 1.25)	0.250
Prior treatment (1) × Age (80 – 84)	0.68 (0.40 – 1.16)	0.154
Prior treatment (1) × Age (85 – 89)	0.98 (0.57 – 1.67)	0.928
Prior treatment (1) × Age (≥ 90)	1.21 (0.66 – 2.20)	0.542

Figure 2-1. Selection of study cohort



PAPER 3:

Dementia Diagnosis and Osteoporosis Treatment Propensity: A Population-Based Nested Case-Control Study

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A version of this chapter has been submitted for publication.

Knopp-Sihota, J.A., Cummings, G.G., Newburn-Cook, C.V., Homik, J., & Voaklander, D., Dementia diagnosis and osteoporosis treatment propensity: A population-based nested case-control study. 2012. Osteoporosis International.

PAPER 3:

Dementia diagnosis and osteoporosis treatment propensity: A population-based nested case-control study

INTRODUCTION

Aging of the population has led to a shift in disease profiles with age related chronic conditions, such as osteoporosis, becoming important public health concerns. [1, 2] Osteoporosis is a skeletal disease characterized by low bone mass and micro-architecture deterioration of bone, leading to increased bone fragility and risk of fracture. [2] Fragility fractures, the most serious osteoporosis-related disease burden, are associated with not only high healthcare-related expenditures but also increased mortality and significant post fracture disability. [3-5] Increasing age, a prior history of fragility fracture, and a diagnosis of dementia all dramatically increase the risk of subsequent fracture. [6] Dementia is an umbrella term for a variety of disorders defined by impaired or loss of cognitive function. The incidence of dementia increases exponentially with age; by age 85 years, 33% (men) to 46% (women) of the Canadian population will have been diagnosed with dementia. [7] Dementia has been associated with an increased risk for falls of which hip and other fragility fractures are a common sequela. [8-12] Other common risk factors found in both diseases include nutritional deficiencies, lower sunlight exposure resulting in vitamin D deficiencies, less physical activity, and lower body mass indexes. [13]

Despite the availability of effective treatments (usually a bisphosphonate drug) [1] there remains an overall low rate of osteoporosis treatment particularly in older, frailer adults. [14-16] In addition, the frequency with which community dwelling older adults with dementia are treated with osteoporosis medications has not been well described. Furthermore, existing literature does not adequately delineate whether the low treatment rates in the older adult population are simply age related variations (in treatments) or due to the presence of co-morbid conditions, principally dementia. Co-morbidity is defined as the co-existence of

two or more chronic conditions or impairments that have an impact upon patient independence and survival. [17]

Purpose and Objectives

We sought to examine the use of osteoporosis drug dispensation in relation to a concurrent diagnosis of osteoporosis, dementia (any type), and other co-morbidities, among community dwelling men and women residing in British Columbia (BC), Canada. Given the suggestion that older adults receive less than optimal care for other conditions such as diabetes and heart disease, [18] we hypothesized that the secondary prevention of osteoporosis (i.e., the prescribing of osteoporosis medications) would be inversely related to dementia diagnosis, age, and severe patient co-morbidity. Specifically, we sought to determine if older adults with a diagnosis of dementia were less likely to receive osteoporosis treatment than younger healthier patients with no dementia diagnosis.

METHODS

Data Sources

We performed a retrospective nested cohort analysis utilizing de-identified administrative healthcare data derived from the British Columbia Linked Health Database (BCLHD). This database contained comprehensive healthcare utilization data for nearly all residents of British Columbia (BC), Canada (population 4.1 million, 2006 Statistics Canada census data). The BCLHD, which integrates health service records, population health data, and census statistics, makes it possible to link administrative records anonymously at the individual level by using a unique personal health number. The BCLHD has been used in numerous healthcare and health services research projects since 1996; thus, this database is well suited to explore clinical questions. Prior to accessing data, ethics approval was received from the Health Research Ethics Board at the University of Alberta.

Study Population and Patient Selection

Our study population consisted of all persons aged ≥ 65 years who had suffered a fracture between April 1, 1991 and March 31, 2002 (n = 81,870). In addition a comparison group, consisting of a random sample (n = 142,077) of non-fracture sufferers registered in the BCLHD over the same time period, was included. Follow-up of these populations continued an additional 5 years until March 31, 2007. All persons in the cohort had continuous enrolment in the PharmaCare prescription benefits plan (Fair PharmaCare or Plan B) during the study period. Between 1991 and 2007 the population ≥ 65 years in the province grew from approximately 428,088 to 616,804. [19]

To assemble the osteoporosis cohort, we initially used the Discharge Abstract Database (DAD) to identify patients with at least one hospital diagnosis of osteoporosis (ICD-9 classification of 733.0, 733.1, 733.01, 733.02, or 733.09) during the study period. The DAD contains demographic, administrative, and clinical data for hospital discharges (inpatient acute, chronic, and rehabilitation) and day surgeries. [20] The data are collected per patient admission, and contain up to 16 diagnosis codes. To identify additional cases, we then linked to the Medical Services Plan (MSP) payment file and included patients with at least two MSP claims. The MSP is the province's universal health insurance program, and contains data on outpatient services provided by fee for service practitioners. One diagnosis code is reported per patient encounter; this code is assumed to be the primary diagnosis or reason for the visit or service. [21]

After identifying the initial cohort, we again linked to the DAD and MSP files to construct the nested dementia case group. We included patients with at least one dementia diagnosis (ICD-9 codes 290, 291, 294, or 331) within the DAD and at least two MSP claims. As this was a prevalent controls design, those with no dementia diagnosis by the end of the study period acted as the internal control group.

After the case and control groups were constructed, we lastly linked to the PharmaCare data file to identify those patients who had been dispensed an osteoporosis medication at any time during the study period. PharmaCare is BC's

public drug insurance program that assists residents in paying for eligible prescription drugs and certain medical supplies. [22] The PharmaCare dataset includes patient level prescription drug expenditures for community and residents of licensed residential care facilities. Osteoporosis medications that are available and covered by PharmaCare include bisphosphonates (alendronate, risedronate, and etidronate), hormone (estrogen) replacement therapy, and selective estrogen receptor modulators (raloxifene). See **Figure 3-1** for study selection procedures.

To assess the prevalence of co-morbidity, *a priori* we assembled a constellation of 13 chronic disease diagnoses, which are often symptomatic and are thus important in predicting morbidity and mortality. Specifically, the co-morbidities included in the analysis were: cancer, cerebrovascular disease, diabetes, cardiovascular disease, hypertension, osteoarthritis, rheumatoid arthritis, neurotic disorders, depression / psychosis, incontinence, Parkinson's disease, chronic obstructive pulmonary disease (COPD), and asthma. The diagnoses chosen were largely based on those identified in other co-morbidity indices (i.e. The Charlson Index [23] and Elixhauser's method [24]) and have been used in previous studies. [25] Co-morbidity was identified by searching the MSP file to identify those patients with at least two primary care visits for the same diagnosis within the last two years of the study period. To avoid potential confounding, we excluded the diseases of interest - dementia and osteoporosis. In order to compare co-morbidity between subjects, we simply added the number of diagnoses. This "disease counting" approach is less complex and studies have shown them to be as effective (if not more effective) as other more complex measurements in predicting and controlling for co-morbidity such as the Charlson Index. [26-29]

Outcome Measures and Analysis

All analyses were stratified by dementia status, and descriptive statistics were used to summarize the characteristics of the population. The determination of statistical differences between groups was made using Pearson's chi square (χ^2) statistics for categorical variables, with alpha (p) set at 0.05 to determine the statistical significance of the estimate. As this was a population-based study,

including all BC residents who met the study inclusion criteria, a sample size calculation was not warranted.

We initially assessed the unadjusted odds ratio (OR) and 95% confidence interval (CI) of the association between osteoporosis drug dispensation (dependent variable) and dementia diagnosis (the main independent variable) using simple logistic regression. We then assessed the relationship and strength of association among all predictor variables and the outcome (osteoporosis drug dispensation), using multivariate logistic regression techniques, controlling for age, sex, co-morbidity, and residence (health region). We used the *Enter* procedure in which all independent variables are entered in a single step and then tested for the possibility of statistical interaction between the main independent variable (dementia diagnosis) and all other covariates. We pre-specified that we would consider only interaction terms that achieved a level of statistical significance of $p < 0.10$. The calculated ORs were considered statistically significant if the 95% CI did not include 1.

Specifically, the outcome of interest was the dispensation of osteoporosis medication, thus recognizing and treating the underlying osteoporosis. We were primarily interested in assessing patient management in response to an osteoporosis diagnosis, rather than patient compliance with ongoing therapy; therefore, compliance beyond a single filled prescription was not considered important (for this research question). All analyses were conducted using SPSS version 19.0 (IBM SPSS Statistics).

RESULTS

Study Population

We identified 39,452 community dwelling patients who had been diagnosed with osteoporosis and had continuous drug coverage between April 1, 1991 and March 31, 2007. The mean age of the sample was 80.1 years (SD 7.5; range 65–104 years), and 79% of the subjects were female. Most of the sample had no dementia diagnosis (66%). Approximately 5% of the sample had no co-morbid conditions; the majority of patients (52%) had one to three co-morbid conditions (SD 2.0;

range 0–12 conditions) and 42% of the sample had more than four co-morbidities. See **Figure 3-2** for the frequency of co-morbid conditions in the osteoporosis cohort. With the exception of fewer patients living in the Northern region of the province (4% of patients), there were similar patient distributions in each of the other four health regions (approximately 24% in each health region). There were significant differences in age categories, frequency of co-morbidity, and health region when stratified by dementia status ($p < 0.001$ for chi square differences between categories within each group) and sex ($p < 0.05$ for chi square differences between categories within each group). Basic characteristics of the sample, stratified by dementia status, are presented in **Table 3-1**.

Osteoporosis Drug Dispensation

Almost half of the total osteoporosis cohort were dispensed an osteoporosis medication at least once during the study period (43%; $p < 0.001$ for chi square differences between categories within each group). Those who had been dispensed drug treatment were more often younger (approximately 50% of those < 80 years received medications versus 27% for those ≥ 90 years) and female (50% of females received medications versus 15% of men) ($p < 0.001$ for chi square differences between categories within each group). Drug dispensation was directly correlated with the frequency of co-morbid conditions; those with four or more co-morbid conditions were dispensed treatment significantly more often (54%) when compared to those with fewer co-morbid conditions ($p < 0.001$ for chi square differences between categories within each group). Furthermore, those residing in the northern region of the province were dispensed drug treatment significantly less often than those residing in any of the other four regions of the province ($p < 0.001$ for chi square differences between categories within each group).

When further stratified by dementia status, the 26,137 patients with no dementia diagnosis were dispensed an osteoporosis medication significantly more often (45%) than those with a diagnosis of dementia (40%) ($p < 0.001$ for chi square differences between categories within each group). Those patients with a

diagnosis of dementia (n = 13,315), who had been dispensed an osteoporosis drug, were more often younger, female, had four or more co-morbid conditions, and lived in the Vancouver Coastal health region ($p < 0.001$ for chi square differences between categories within each group). Similar trends were found in the subgroup with no dementia diagnosis. See **Table 3-2** for characteristics of patients, by dementia status, dispensed an osteoporosis medication.

Factors Predicting Osteoporosis Drug Dispensation (Logistic Regression Analysis)

The initial multivariate logistic regression model included the variables dementia status, age, co-morbidity, sex, and residence (health region); all variables were statistically significant therefore, all were retained in the final model. There were statistically significant interactions between the following factors: (1) dementia status and sex ($p = 0.026$), (2) dementia status and co-morbidity ($p = 0.000$), and (3) dementia status and residence (health region) ($p = 0.004$); therefore, these interaction terms were retained in the final model.

After controlling for age, sex, co-morbidity, and residence, a diagnosis of dementia was found to be a significant negative predictor of osteoporosis drug dispensation (adjusted OR = 0.55; 95% CI = 0.44–0.69). Male sex was the strongest negative predictor of osteoporosis drug dispensation; males were seven times less likely to have been dispensed treatment than females (adjusted OR = 0.14; 95% CI = 0.13–0.15). Increasing age was associated with a significant decrease in the likelihood of being dispensing an osteoporosis drug when compared to younger patients. Subjects aged ≥ 85 years were significantly less likely to receive treatment compared to younger subjects (adjusted OR = 0.72; 95% CI = 0.66–0.79); this was even more pronounced for subjects 90 years and older, who were dispensed medications less than 50% of the time compared to subjects 69 years and younger (adjusted OR = 0.47; 95% CI = 0.42–0.52).

Those patients with one to three co-morbid conditions were significantly more likely to have been dispensed treatment compared to those with no co-morbid conditions (adjusted OR = 1.79; 95% CI = 1.57–2.05). Those with four or

more conditions were even more likely to have been dispensed treatment and received care more than three times as often than those with no co-morbid conditions (adjusted OR = 3.30; 95% CI = 2.88–3.78).

When comparing treatment based on residence (health region), there were significant differences in osteoporosis drug dispensation. Those residing in any health region other than the reference category (Vancouver Coastal) were less likely to have been dispensed treatment: of significance was the Interior region (adjusted OR = 0.73; 95% CI = 0.68–0.79), the Fraser region (adjusted OR = 0.85; 95% CI = 0.79–0.91), the Vancouver Island region (adjusted OR = 0.83; 95% CI = 0.77–0.89), and the Northern region (adjusted OR = 0.52; 95% CI = 0.45–0.60). See **Table 3-3** for factors predicting osteoporosis drug dispensation.

DISCUSSION

In this retrospective population-based nested case-control study, we identified community dwelling individuals with a diagnosis of osteoporosis and ongoing prescription drug coverage in a Canadian province with universal health care coverage. We linked multiple data sets to determine osteoporosis drug dispensation (a proxy for treatment status) to investigate the relationship between dementia status and treatment. We found that having a diagnosis of dementia was an independent risk factor for predicting osteoporosis drug dispensation. After controlling for age, sex, co-morbidity, and residence this relationship was even stronger with those with dementia being dispensed an osteoporosis drug almost half as often than those with no dementia diagnosis. Regardless of dementia diagnosis, patients who were older and male were the least likely to have been dispensed osteoporosis medications; these relationships remained after controlling for other potential confounding variables.

Residence also predicted osteoporosis medication dispensation; patients residing in the Northern region of the province were almost two times less likely to have been dispensed treatment compared to those residing in a more central location. This may in part be explained by the central location of the reference category in the analysis (Vancouver Coastal), which includes the provinces'

tertiary care university teaching hospitals where possibly more emphasis is placed on prescribing guideline recommended treatment. These findings are similar to other studies reporting the under-treatment of chronic conditions, such as cardiovascular disease, in patients residing in more remote locations. [18]

Dementia Status and Osteoporosis Treatment

Few other studies have investigated the use of osteoporosis drugs in community dwelling seniors with dementia; to our knowledge, this is the first population based Canadian study finding a negative association between osteoporosis drug dispensation and dementia diagnosis in community dwelling seniors. Similar to our results, a recent study by Haasum et al. in a population based longitudinal study including both community and institutionalized older adults in Sweden, found that persons with dementia were almost three times less likely to use osteoporosis drugs than persons without dementia. [30] Other studies utilized mixed populations (community and institutionalized patients) and also found dementia status to be a significant negative predictor of treatment for older adults. [31, 32] However, as we included only community dwelling subjects, the study populations of these other studies are not entirely comparable.

Other researchers have utilized more highly selected samples of either institutionalized patients or home care recipients to investigate the prescription of osteoporosis drugs primarily in relation to patient age; dementia status, among other variables, were examined in separate sub-group analyses. The majority found no significant association between dementia status and osteoporosis medication use in older adults. [33-35] In contrast, one study found a positive association between dementia diagnosis and osteoporosis treatment among older adults receiving home care services in a Canadian province. [36] These researchers also found osteoporosis treatment rates of 59% among those with a documented osteoporosis diagnosis but no related fracture; this rate is much higher than reported in other similar studies.

Co-morbidity and Osteoporosis Treatment

Many studies have shown a negative relationship between co-morbidity and osteoporosis treatment propensity; in other words, those with more co-morbid conditions were less likely to receive treatment. [14, 15, 31, 36, 37] Other studies have found no significant association between increasing patient co-morbidity and osteoporosis treatment. [33] In contrast, we found a strong positive relationship suggesting that the more co-morbid conditions present, the greater the likelihood of receiving treatment. In fact, regardless of dementia diagnosis, patients with four or more co-morbid conditions were more than three times as likely to have been dispensed medications compared to patients with no reported co-morbidity. This may suggest that practitioners are aware that the degree of co-morbidity is often a powerful negative factor in predicting outcomes and is correlated with increased healthcare utilization, and costs. [38, 39] The difference in our results and other studies may be due to the different methods used to define co-morbidity; moreover, our analysis was population based whereas others reported on more selected populations (i.e. nursing home residents) which may not be representative of the care provided to the general population.

Several reasons, other than a simple lack of physician recognition that a diagnosis of osteoporosis is significant, may exist for this gap in guideline recommended care: presumed medication adherence and / or polypharmacy concerns, a perceived risk of complications with some medications, inadequate caregiver support and few resources available for the coordination of care, and a shorter life expectancy among dementia patients meaning that treatment may be futile. [16, 40]

Limitations

This study, as with other studies based solely on administrative data, has limitations that must be addressed. Firstly, we have potentially underestimated the rates of osteoporosis and dementia as we are assuming that these conditions have been detected, diagnosed, and/or treated. Secondly, evaluation of osteoporosis treatment was based exclusively on dispensation rates instead of the actual

number of written prescriptions; therefore, we have likely underestimated intended physician endorsed treatments. Lastly, due to the claims-based nature of the dataset, information related to other potentially confounding variables could not be assessed or controlled for. These include the use of over the counter osteoporosis treatments such as vitamin D and calcium supplementation as well as other information related to potential contraindications to bisphosphonates. We also had no information on other, non-pharmacological based therapies for osteoporosis such as exercise therapy, fall prevention programs, or other lifestyle based interventions that may be suggested for the treatment of osteoporosis. [1] Although the inclusion of these variables may have provided a more inclusive description of osteoporosis treatment, we do not believe that controlling for these variables would have altered the results of this study.

The strengths of this study include its population-based design, a large geographically diverse sample size, and its use of a comprehensive linkable dataset including information for most residents in the province. Compared to other studies which have relied on chart audits, patient or physician surveys and questionnaires, or involved highly selective patient recruitment, our study had a larger sample size and was based on a population dataset, which allowed for patient level analysis of a complete geographic population of community dwelling Canadian residents.

Conclusion

As with many disease and risk states, patients with the highest baseline risk should be treated the most aggressively. Yet, for many older adults with an established diagnosis of osteoporosis with or without fracture, this is not always the case. Our data confirm low treatment rates among patients with a documented osteoporosis diagnosis and even lower treatment rates for those patients with a concurrent dementia diagnosis. The results of this study highlight the need for further research to provide a greater understanding in the prescribing of osteoporosis medications in older adults with a diagnosis of dementia. Future studies should focus on evaluating prescriber and patient awareness of

osteoporosis treatments to identify barriers and other factors associated with under treatment. Interventions aimed at enhancing osteoporosis treatment should be a priority and may include prescriber educational initiatives, the use of point of care management tools such as automated reminders and electronic risk assessment tools, and the use structured case management for post fracture care. Future research should focus on examining the utility of such strategies particularly in older adults with a diagnosis of dementia.

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Table 3-1. Patient characteristics by dementia status *

	***No* dementia Diagnosis n = 26,137 (66.3)**	**Dementia diagnosis n = 13,315 (33.7)**	**Total osteoporosis cohort N = 39,452**
Age (years) †			
65–69	3,299 (12.6)	639 (4.8)	3,938 (10.0)
70–74	5,312 (20.3)	1,539 (11.6)	6,851 (17.4)
75–79	6,338 (24.2)	2,713 (20.4)	9,051 (22.9)
80–84	5,335 (20.4)	3,487 (26.2)	8,822 (22.4)
85–89	3,680 (14.1)	3,126 (23.5)	6,806 (17.3)
≥ 90	2,173 (8.3)	1,811 (13.6)	3,984 (10.1)
Sex ‡			
Female	20,555 (78.6)	10,616 (79.7)	31,171 (79.0)
Male	5,329 (20.4)	2,606 (19.6)	7,935 (20.1)
Unknown	253 (1.0)	93 (0.7)	346 (0.9)
Co-morbidity †			
No co-morbidity	1,277 (4.9)	927 (7.0)	2,204 (5.6)
1–3 co-morbid diagnoses	13,873 (53.1)	6,693 (50.3)	20,566 (52.1)
4–13 co-morbid diagnoses	10,987 (42.0)	5,695 (42.8)	16,682 (42.3)
Health region †			
Vancouver Coastal	6,918 (26.5)	4,351 (32.7)	11,269 (28.6)
Interior	4,962 (19.0)	2,140 (16.1)	7,102 (18.0)
Fraser	7,235 (27.7)	3,373 (25.3)	10,608 (26.9)
Vancouver Island	5,652 (21.6)	2,934 (22.0)	8,586 (21.8)
Northern	1,170 (4.5)	419 (3.1)	1,589 (4.0)
Missing	200 (0.8)	98 (0.7)	298 (0.8)

* All data are shown as number (percentage)

† $p < 0.001$ for chi square differences between categories within the group

‡ $p < 0.05$ for chi square differences between categories within the group

Table 3-2. Characteristics of patients by dementia status dispensed an osteoporosis drug *

	***No* dementia diagnosis n = 26,137 (66.3)**	**Dementia diagnosis n = 13,315 (33.7)**	**Total osteoporosis cohort N = 39,452**
Total who received treatment †	11,778 (45.1)	5,262 (39.5)	17,040 (43.2)
Age (years) †			
65–69	1,530 (46.4)	286 (44.8)	1,816 (46.1)
70–74	2,692 (50.7)	714 (46.4)	3,406 (49.7)
75–79	3,125 (49.3)	1,244 (45.9)	4,369 (48.3)
80–84	2,384 (44.7)	1,454 (41.7)	3,838 (43.5)
85–89	1,426 (38.8)	1,115 (35.7)	2,541 (37.3)
≥ 90	621 (28.6)	449 (24.8)	1,070 (26.9)
Sex †			
Female	10,928 (53.2)	4,876 (45.9)	15,804 (50.7)
Male	781 (14.7)	367 (14.1)	1,148 (14.5)
Unknown	69 (27.3)	19 (20.4)	88 (25.4)
Co-morbidity †			
No co-morbidity	338 (26.5)	154 (16.6)	492 (22.3)
1–3 co-morbid diagnoses	5,433 (39.2)	2,146 (32.1)	7,579 (36.9)
4–13 co-morbid diagnoses	6,007 (54.7)	2,962 (52.0)	8,969 (53.8)
Health region †			
Vancouver Coastal	3,390 (49.0)	1,826 (42.0)	5,216 (46.3)
Interior	2,049 (41.3)	815 (38.1)	2,864 (40.3)
Fraser	3,309 (45.7)	1,349 (40.0)	4,658 (43.9)
Vancouver Island	2,558 (45.3)	1,108 (37.8)	3,666 (42.7)
Northern	392 (33.5)	138 (32.9)	530 (33.4)
Missing	80 (40.0)	26 (26.5)	106 (35.6)

* All data are shown as number (percentage)

† $p < 0.001$ for chi square differences between categories within the group

Table 3-3. Logistic regression: Factors predicting osteoporosis drug dispensation

Variable	Adjusted Odds Ratio (95% Confidence Interval)	*p*-value
Constant	0.67	0.000
Dementia status		
No diagnosis of dementia	1 (reference)	
Diagnosis of dementia	0.55 (0.44 – 0.69)	0.000
Age category (years)		
65–69	1 (reference)	
70–74	1.11 (1.02 – 1.21)	0.014
75–79	1.06 (0.98 – 1.15)	0.170
80–84	0.88 (0.81 – 0.95)	0.002
85–89	0.72 (0.66 – 0.79)	0.000
≥ 90	0.47 (0.42 – 0.52)	0.000
Sex		
Female	1 (reference)	
Male	0.14 (0.13 – 0.15)	0.000
Co-morbidity		
No co-morbidity	1 (reference)	
1–3 co-morbid diagnoses	1.79 (1.57 – 2.05)	0.000
4–13 co-morbid diagnoses	3.30 (2.88 – 3.78)	0.000
Health region		
Vancouver Coastal	1 (reference)	
Interior	0.73 (0.68 – 0.79)	0.000
Fraser	0.85 (0.79 – 0.91)	0.000
Vancouver Island	0.83 (0.77 – 0.89)	0.000
Northern	0.52 (0.45 – 0.60)	0.000
Missing	0.79 (0.57 – 1.08)	0.136
Dementia diagnosis × sex		
Dementia diagnosis (1) × Female	1 (reference)	
Dementia diagnosis (1) × Male	1.20 (1.04 – 1.39)	0.013
Dementia diagnosis × co-morbidity		
Dementia diagnosis (1) × No co-morbidity	1 (reference)	
Dementia diagnosis (1) × 1–3 co-morbid diagnoses	1.31 (1.05 – 1.65)	0.019
Dementia diagnosis (1) × 4–13 co-morbid diagnoses	1.52 (1.21 – 1.91)	0.000
Dementia diagnosis × health region		

Variable	Adjusted Odds Ratio (95% Confidence Interval)	*p*-value
Dementia diagnosis (1) × Vancouver Coastal	1 (reference)	
Dementia diagnosis (1) × Interior	1.21 (1.05 – 1.39)	0.008
Dementia diagnosis (1) × Fraser	1.06 (0.94 – 1.20)	0.358
Dementia diagnosis (1) × Vancouver Island	1.02 (0.89 – 1.15)	0.820
Dementia diagnosis (1) × Northern	1.41 (1.08 – 1.84)	0.013
Dementia diagnosis (1) × Missing	0.59 (0.33 – 1.04)	0.069

Figure 3-1. Selection of study groups

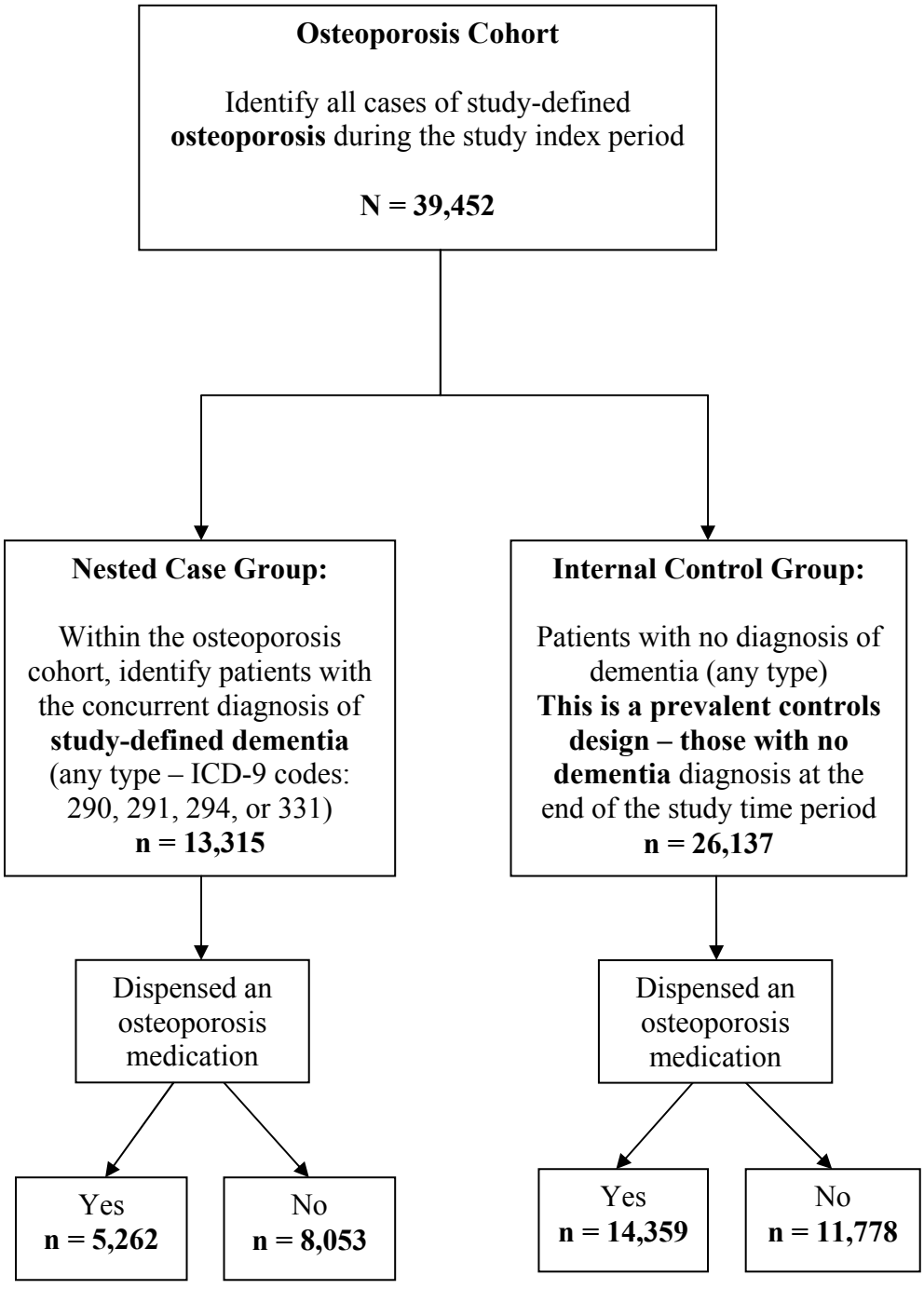
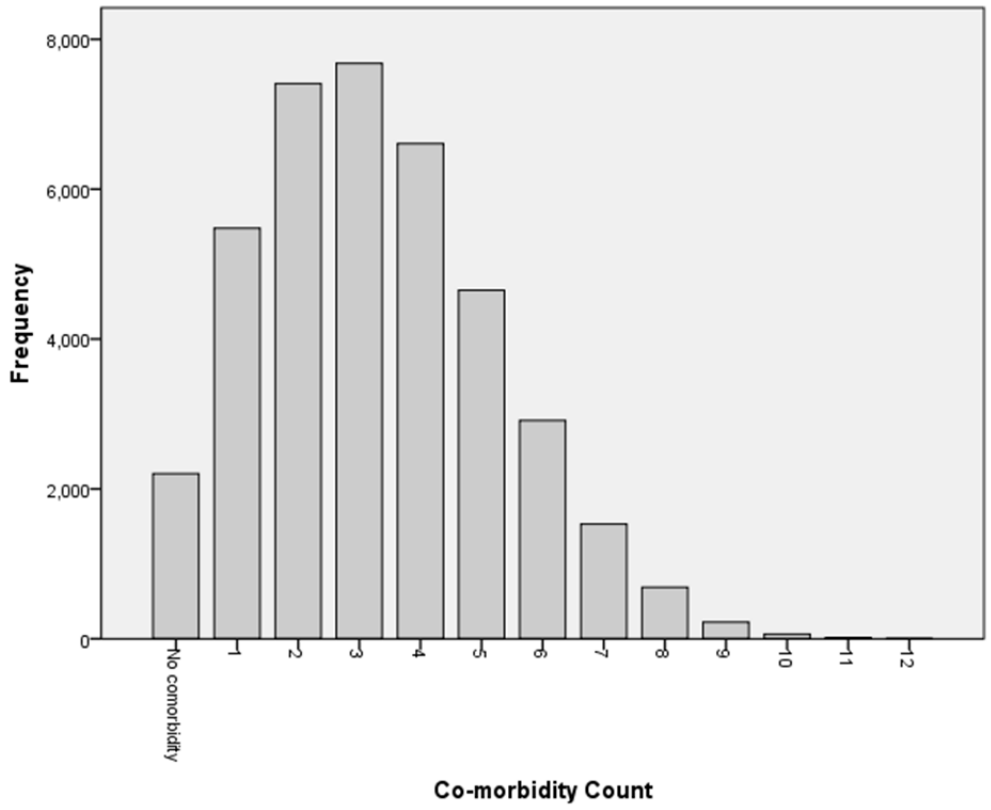


Figure 3-2. Frequency of co-morbid conditions in the osteoporosis cohort



PAPER 4:

The Association between Serious Upper Gastrointestinal Bleeding and Incident Bisphosphonate Use: A Population-Based Nested Cohort Study

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A version of this chapter has been submitted for publication.

Knopp-Sihota, J.A., Cummings, G.G., Homik, J., & Voaklander, D., The association between serious upper gastrointestinal bleeding and incident bisphosphonate use: A population-based nested cohort study**.** *2012. Drugs & Aging.*

PAPER 4:

The association between serious upper gastrointestinal bleeding and incident bisphosphonate use: A population-based nested cohort study

INTRODUCTION

Background

The routine management of osteoporosis should target all aspects of the disease, including maximizing and preserving bone mass and preventing future fractures through pharmacotherapy and lifestyle modification. [1] The mainstay of osteoporosis treatment includes calcium and vitamin D, along with an antiresorptive agent (usually a bisphosphonate drug). [1, 2] Bisphosphonates have been shown to rapidly reduce bone-remodeling, thus increasing bone mass density, and are associated with the largest reduction in fracture risk when compared to other therapies. [3] However, bisphosphonate treatment is not without risk and serious adverse drug reactions (ADRs), including osteonecrosis of the jaw, oral and gastric carcinomas, atypical femur fractures, and upper gastrointestinal bleeding (UGIB), although infrequent, have been described. [4-8] Drug induced esophagitis, the most common gastro intestinal (GI) ADR associated with oral bisphosphonate therapy, has largely been related to improper drug administration regimes (i.e. insufficient water intake and failing to sit upright following medication ingestion). [8] Although several observational studies have reported on minor GI adverse effects such as nausea, dyspepsia, and epigastric pain, few large population based studies have assessed the more serious adverse events of drug-induced acute UGIB. [9] Upper GI tract bleeding is a relatively common GI emergency with an incidence rate (IR) of approximately 1 per 1 000 person years and a mortality rate of 5%-14%. [10, 11] Furthermore, definitive evidence of a causal relationship between bisphosphonate therapy and serious reactions is lacking; there remain concerns about the risks of long term treatment particularly among older patients with increased co-morbidity. Adverse drug

reactions, that are non-preventable, are defined as any injuries resulting from medication use that occur due to pharmacologic properties of the drug. [12]

Objectives

Using a population based design we sought to examine the risk of serious UGIB among incident oral bisphosphonate users in British Columbia (BC), Canada. Specifically, we sought to determine if community dwelling older adults (> 80 years), who were new users of bisphosphonate drugs, were more likely to suffer a serious UGIB within 120 days of drug initiation in comparison to younger (≤ 80 years) incident users of the same therapy.

METHODS

Study Design and Data Source

We performed a retrospective nested cohort analysis utilizing de-identified administrative healthcare data derived from the British Columbia Linked Health Database (BCLHD). This database contained comprehensive healthcare utilization data for nearly all residents of BC, Canada (population 4.1 million, 2006 Statistics Canada census data). The BCLHD, which integrates health service records, population health data, and census statistics, makes it possible to link administrative records anonymously at the individual level by using a unique personal health number (PHN). The BCLHD has been used in numerous healthcare and health services research projects since 1996; thus, this database is well suited to explore clinical questions. Prior to accessing data, ethics approval was received from the Health Research Ethics Board at the University of Alberta.

Identification of the Cohort

We used a previously assembled cohort of all persons aged ≥ 65 years who had suffered a fracture between April 1, 1991 and March 31, 2002 (n = 81 870). In addition, a comparison group consisting of a random sample (n = 142 077) of non-fracture subjects registered in the BCLHD over the same time period were added to the cohort. Follow-up of these populations continued an additional 5

years until March 31, 2007. The study group all had continuous enrolment in the PharmaCare prescription benefits plan (Fair PharmaCare or Plan B) during the study index period. PharmaCare is BC's public drug insurance program that assists residents in paying for eligible prescription drugs and certain medical supplies. [13] The PharmaCare dataset includes patient level prescription drug expenditures for community dwelling individuals and residents of licensed residential care facilities. Between 1991 and 2007 the population aged ≥ 65 years in the province grew from approximately 428 088 to 616 804. [14]

From this initial cohort, we constructed a bisphosphonate "exposure" cohort using PharmaCare data to identify all incident users of bisphosphonate drugs; incident users were defined as patient's ≥ 65 years who had been dispensed an oral bisphosphonate drug during the study index period (April 1, 1991 to March 31, 2007). Oral bisphosphonate drugs available during the index period and covered by the PharmaCare plan included alendronate (Fosamax), etidronate (Didrocal), and risedronate (Actonel). The index date was defined as the date of first claim for an oral bisphosphonate prescription during the index period. Gastrointestinal symptoms appear in similar rates, regardless of the specific oral bisphosphonate or dosing regimen; therefore, we included all available bisphosphonate formulations regardless of whether the dosing was daily or weekly. [15, 16] As we were primarily interested in ADRs associated with new users of the drug, we excluded any person who had received an oral bisphosphonate within the previous 365 days of the index date.

Identification of Cases

To identify nested cases within the bisphosphonate exposure cohort, we then linked to the Discharge Abstract Database (DAD) to identify patients with a diagnosis of UGIB. The DAD contains demographic, administrative, and clinical data for hospital discharges (inpatient acute, chronic, and rehabilitation) and day surgeries. [17] The data are collected per patient admission and contain up to 16 diagnosis codes. We included patients ≥ 65 years with a hospital admission (primary, secondary, or other) for an acute UGIB (ICD-9 codes 530-535 or 578)

occurring within 120 days from the dispensation of an oral bisphosphonate prescription. Rates of GI related adverse events tend to be the highest in the first few months following the initiation of the therapy; thus, a 120 day time period was deemed sufficient to capture the majority of adverse events. [18-21] Oral bisphosphonates are dispensed in 100-day quantities under the PharmaCare plan; therefore, patients will be considered at risk for 120 days after a dispensed prescription. This time period allows for the consumption of the prescription, subsequent early refills (i.e. not beginning the prescription immediately upon filling because the previous prescription of a medication other than a bisphosphonate was not complete), and possible non-adherence (i.e. prescription lasting longer than intended). Other researchers have used this approach to analyze rare events associated with prescription drug use with administrative data. [15, 22]

To identify additional cases of UGIB, and related deaths (without hospitalization), we then linked to the BC Vital Statistics death events registry (for cause of death). This registry includes all deaths that occur within the province. [23] Patients with a previous diagnosis of UGIB, requiring hospitalization or related death, within 365 days prior to the index date of drug dispensation were excluded. See **Figure 4-1** for the study cohort selection procedures. As this was a prevalent controls design, those who had been dispensed oral bisphosphonate therapy, but did not suffer a UGIB or related death by the end of the study period, acted as the internal control group.

Explanatory Variables

Based on clinical relevance and previous research, we planned to control for the following potential confounders: age (grouped as ≤ 80 years and > 80 years), sex (female, male), remote past history (> 1 year prior) of serious UGIB requiring hospital stay (ICD-9 codes 530-535 or 578 in the DAD file), past history of gastric ulcer disease (ICD-9 code of 530-534 in the Medical Services Plan [MSP] or DAD file), concurrent use of prescription oral nonsteroidal anti-inflammatory drugs (NSAIDs), and oral antiplatelet / anticoagulation medications. Concurrent

use of a proton pump inhibitors (PPI) was also examined as other researchers have used the use of PPI's as a marker or proxy for the presence of preexisting GI disease. See **Appendix 4-1** for the specific medications we included in the analysis.

To assess the prevalence of co-morbidity, *a priori* we assembled a constellation of 15 chronic disease diagnoses, which are often symptomatic and are thus important in predicting morbidity and mortality. Co-morbidity is defined as the co-existence of two or more chronic conditions or impairments that have an impact upon patient independence and survival. [24] Specifically, the co-morbidities included in the analysis were: cancer, cerebrovascular disease (CVD), diabetes, cardiovascular disease (CVD), hypertension, osteoporosis, osteoarthritis, rheumatoid arthritis, neurotic disorders, depression / psychosis, incontinence, Parkinson's disease, chronic obstructive pulmonary disease (COPD), and asthma. The diagnoses chosen were largely based on those identified in other co-morbidity indices (i.e. The Charlson Index [25] and Elixhauser's method [26]) and have been used in previous studies. [27] Co-morbidity was identified by searching the MSP payment file to identify those patients with at least two primary care visits for the same diagnosis within the last two years of the study period. The MSP is the province's universal health insurance program, and contains data on outpatient services provided by fee for service practitioners. One diagnosis code is reported per patient encounter; this code is assumed to be the primary diagnosis or reason for the visit or service. [28] In order to compare co-morbidity between subjects, we simply added the number of diagnoses. This "disease counting" approach is less complex and studies have shown them to be as effective (if not more effective) as other more complex measurements in predicting and controlling for co-morbidity such as the Charlson Index. [29-32]

Outcome Measures and Analysis

All analyses were stratified by UGIB status and age and descriptive statistics were used to summarize the characteristics of the population. We planned to explore relationships and determine differences between groups using Pearson's chi

square (χ^2) statistics, with alpha (p) set at 0.05 to determine the statistical significance of the estimate. Where there were unexpected findings, we planned to conduct a post hoc analysis to further explore the relationships between variables. As this was a population-based study, a sample size calculation was not warranted.

To compare the incidence rates (IR) for UGIB between age groups we calculated the person-time of exposure based on the assumption that the exposure cohort were all at risk (exposed) for 120 days post incident bisphosphonate use. To compare the IR for UGIB among incident bisphosphonate users (in the immediate 120 day time period) with the general population, we used a population rate for UGIB as 1 per 1 000 person-years. [11]

Using univariate logistic regression techniques, we initially assessed the unadjusted odds ratios (OR) and 95% confidence intervals (CI) between the dependent variable (UGIB within 120 days of incident oral bisphosphonate use), age group (the main independent variable), sex, co-morbidity, any past history of gastric ulcer disease, past history of serious UGIB requiring hospitalization, and concurrent use of prescription NSAIDs, antiplatelet / anticoagulation medications, and the use of PPIs. We planned to include only those variables that were statistically significant ($p < 0.20$) in the multivariate analysis. The co-morbidity ($p = 0.57$ to 0.49) and anticoagulation ($p = 0.85$) variables were not statistically significant; however, we considered both of these variables to be clinically important so we included them in the initial multivariate model (both were later removed from the model as they continued to show no statistical significance). For the multivariate analysis, we used the *Enter* procedure in which all independent variables are entered in a single step and then tested for the possibility of statistical interaction between the main independent variables (age group) and all other covariates. We pre-specified that we would consider only interaction terms that achieved a level of statistical significance of $p < 0.10$.

We then checked for confounding of the variables that were removed from the model; as none of the beta coefficients changed by more than 15% we were satisfied that neither of the variables were statistically significant predictors of the

dependent outcome nor confounders. There were no statistically significant interactions between the main independent variable (age group) and the remaining variables; therefore, none of the interaction terms were retained in the final model. The final multivariate model included the variables: age, sex, past history of gastric ulcer disease, past history of serious UGIB, concurrent use of prescription NSAIDs and the use of PPIs. The adjusted ORs were considered statistically significant if the 95% CI did not include 1. All analyses were conducted using SPSS version 19.0 (IBM SPSS Statistics).

RESULTS

Study Population

From the initial source cohort (n = 223 947), we identified 26 518 (11.8%) individual patients who had been newly dispensed an oral bisphosphonate drug during the index period (the exposure cohort). We then excluded an additional 295 patients who had a previous UGIB diagnosis within 365 days of the index date leaving a sample of 26 223 individual patients in the exposure cohort. The mean age of the sample was 78.8 years (SD 6.9; range 65–104 years), and 88% of the subjects were female. The majority of the cohort had between 4 and 6 co-morbid conditions (51%), 10% had a past medical history of gastric ulcer disease, 5% had a remote history of serious UGIB, 18% used NSAIDs, 13% used antiplatelet / anticoagulant prescriptions drugs, and 17% used PPIs.

Within the exposure cohort, 117 (0.4%) individual patients had suffered a serious UGIB (116 requiring hospitalization and one death) within 120 days of incident bisphosphonate use; the remaining 26 106, acted as the internal control group. Those who developed an UGIB (the 117 cases) tended to be > 80 years old (60%), and when compared to those who did not suffer a UGIB, they were significantly more likely to have had a past history of gastric ulcer disease (21% vs. 11%), a remote history of serious UGIB (12% vs. 5%), and had been dispensed PPI medications (29% vs. 17%) ($p < 0.001$ for chi square differences between groups). Cases were less likely to have been dispensed NSAIDs compared to controls (9% vs. 18%; $p < 0.05$ for chi square differences between

groups). There were no statistical differences in sex, level of co-morbidity, or use of antiplatelet / anticoagulant prescriptions drugs between groups. See **Table 4-1** for characteristics of the exposure cohort stratified by UGIB status.

We explored a number of post hoc relationships between variables of interest. Those with greater co-morbidity were significantly more likely to have been dispensed a NSAID (20% of those with more than 4 co-morbid conditions were dispensed a NSAID vs. 17% of those with 3 or fewer conditions; $p < 0.001$ for chi square differences between groups). There was an inverse relationship between NSAID use and the past history of gastric ulcer disease; those with a history of gastric ulcer disease were less likely to have been dispensed a NSAID (16%) as compared to those with no history of gastric ulcer disease (18% had been dispensed a NSAID; $p < 0.01$ for chi square differences between groups). There was a significant positive relationship between PPI use and a past history of gastric ulcer disease (25% of those with a past history of gastric ulcer disease had been dispensed a PPI versus 16% of those with no past history of gastric ulcer disease ($p < 0.001$ for chi square differences between groups). There was also a significant positive relationship between PPI use and a past history of a serious UGIB; 34% of those who had suffered a past UGIB had been dispensed a PPI versus 16% of those who had no history of a serious UGIB ($p < 0.001$ for chi square differences between groups).

Incidence of UGIB

Assuming those in the bisphosphonate exposure cohort were at risk for 120 days, we calculated an overall incidence rate (IR) of approximately 14 per 1 000 person-years for UGIB within 120 days of incident bisphosphonate prescription. When stratified by age, those patients > 80 years (IR = 19) had more than two times the incidence of UGIB compared to those ≤ 80 years (IR = 9). See **Table 4-2** for crude incidence rates.

Factors Predicting UGIB: Logistic Regression Analysis

A past history of serious UGIB was the strongest predictor of UGIB within 120 days of incident bisphosphonate use (adjusted OR = 2.28; 95% CI = 1.29–4.03); other predictors of UGIB included a concurrent use of PPI medications (adjusted OR = 2.04; 95% CI = 1.35–3.07), age > 80 years (adjusted OR = 2.03; 95% CI = 1.40–2.94), past history of gastric ulcer disease (adjusted OR = 1.90; 95% CI = 1.21–3.01), and male sex (adjusted OR = 1.69; 95% CI = 1.05–2.72). The use of prescription NSAIDs was found to be a significant negative predictor of UGIB (adjusted OR = 0.41; 95% CI = 0.21–0.80). See **Table 4-3** for the unadjusted ORs and **Table 4-4** for factors (the adjusted ORs) predicting UGIB within 120 days of incident bisphosphonate use.

DISCUSSION

For many older adults with a diagnosis of osteoporosis, oral bisphosphonate drugs are the first line of treatment. While these drugs are typically safe, there have been reports of serious adverse events. In this population-based nested cohort study, we identified subjects in a Canadian province with universal health care coverage, who were newly dispensed a bisphosphonate drug. After linking multiple data sets, we were able to follow these subjects forward to determine the risk of developing a serious UGIB within 120 days of incident bisphosphonate use. We found an overall relatively low rate of UGIBs, with only 0.4% of the exposure cohort developing this rare event. Although the overall cohort rate was low, the incidence of UGIB (within 120 days of incident bisphosphonate use) was much higher for older subjects; in fact, patients > 80 years of age developed a UGIB twice as often than those ≤ 80 years (19 vs. 9 per 1 000 person-years). In addition, regardless of age, the incidence among male patients was approximately double than those among females. Both of these results are consistent with rates for older patients in the general population. [11]

Using logistic regression techniques, we found that older age was an independent risk factor for developing an UGIB within 120 days post bisphosphonate treatment; this relationship remained after controlling for sex,

history of gastric ulcer disease, history of serious UGIB, NSAID, and PPI use. Regardless of age, patients who were male, had a past history of gastric ulcer, a more remote UGIB history, and used a PPI, were more likely to suffer a UGIB post bisphosphonate use. Interestingly, patients who had been dispensed NSAIDs concurrently were less likely to develop a UGIB within 120 days of bisphosphonate use.

NSAIDs, PPIs, and UGIB

Many studies, of various designs, have focused on NSAID use in relation to UGIBs; for the most part, findings over the last 15 years suggest that current users of NSAIDS have at least a 3 to 5 fold increased risk of UGIB. [33] Contrary to these results, in our study we found that a prescription for a NSAID was the strongest negative predictor of UGIB; those who had been dispensed NSAIDs were two and a half times less likely to suffer a UGIB within 120 days of incident bisphosphonate use. Because of the known GI side effects associated with NSAID use, we initially speculated that perhaps patients, who were prescribed a NSAID, were healthier patients with fewer co-morbid conditions, thus less likely to develop a UGIB. We found that those with greater co-morbidities were significantly more likely to be dispensed a NSAID drug; therefore, the notion that those prescribed a NSAID were healthier did not stand. We did find an inverse relationship between NSAID use and past history of gastric ulcer disease; those with a gastric ulcer were less likely to have been dispensed a NSAID. For that reason, we postulated that the "protective" effect of NSAIDs may stem from their use in patients who do not have a history of gastric ulcer thus making users of NSAIDs perhaps less likely to develop a UGIB. The clinical significance of this finding, however, is unclear and caution in the interpretation of this finding is thus warranted.

We also found that those patients who had been dispensed a PPI medication were two times as likely to develop a UGIB post incident bisphosphonate use. As we used the prescription of a PPI as a proxy for the presence of GI disease, this finding was expected. Those who were at an

increased risk, or who have already developed GI disease, are often prescribed drug therapy with either a histamine-2 (H2)–receptor antagonist (typically available as over the counter medications) or a PPI in order to provide mucosal protection. [34] In other words, those patients using a bisphosphonate and a PPI likely had a greater underlying risk of an adverse GI event compared to those persons using a bisphosphonate alone; this would account for the observed increase in UGIB risk for concurrent users of the drugs. [35] This was confirmed during post hoc analysis where we found significant positive relationship between PPI use and both a past history of gastric ulcer disease and past serious UGIB.

Comparison to Previous Research

Although a number of randomized controlled trials (RCTs) have reported higher rates of upper GI tract minor irritations in treatment groups (although not reaching statistical significance), there have been no reports of more serious upper GI tract adverse events such as UGIB. [36-38] RCTs typically follow a smaller group of highly selected individuals for a relatively short period of time and are designed primarily to investigate the fracture prevention efficacy of bisphosphonates. Unfortunately, there are few previous population based studies investigating the risk of UGIB associated with bisphosphonate drugs to compare our study results to.

One large population based case-control study utilized a Canadian population to compare the risk of UGIB between users of bisphosphonates alone and users of bisphosphonates and NSAIDS concurrently.[9] This study by Etminan et al. utilized a previously established community-based cohort of individuals who had undergone a prior coronary revascularization procedure; of note, this population was highly selected, and therefore may not necessarily be representative of the general population. They found no evidence of an increase in the risk of UGIB among current users of bisphosphonate, but did find a two fold increase in risk for concurrent users of bisphosphonates and NSAIDs. Another population based study investigated the excess risk of hospitalizations for UGIB associated with alendronate use. These authors conducted a matched case control

study and found a higher unadjusted rate of UGIB for bisphosphonate users; after controlling for confounding variables such as prior osteoporosis fractures, they found no significant differences in risk between cases and controls. [35]

A different study, based on a Danish population, investigated the risk of esophageal and gastric events in a group of older adults. [39] For their endpoint, these authors did not distinguish between those developing minor GI conditions such as esophagitis with those suffering the more serious event of a UGIB. They measured the rates of adverse GI events both before and after the initiation of various osteoporosis medications. The authors found no difference as they discovered that GI event rates were increased both before and after initiation of the drugs. Other studies have been conducted that have focused on adverse GI events in relation to daily versus weekly dosing of a bisphosphonate or have compared two different specific bisphosphonate medications. For example, one such study by Cadarette et al. compared the GI safety between weekly doses alendronate and risedronate. These authors found no important differences between the two weekly preparations. [15]

Limitations

This study, as with other studies based solely on administrative data, has some limitations that must be recognized. First, bisphosphonates are not only prescribed for the prevention and treatment of osteoporosis, but also for the treatment of certain malignancies and related malignancy complications as well as other serious conditions such as Paget's disease of the bone. As we exclusively examined oral bisphosphonate preparations, we can be fairly certain that these drugs were not used to treat a malignancy or related complication such as hypercalcemia as these conditions are primarily treated with intravenous bisphosphonate infusions. Furthermore, a diagnosis of Paget's disease is relatively rare (in comparison to a diagnosis of osteoporosis); moreover, we were interested in adverse events associated with new bisphosphonate use and as we controlled for co-morbidity, we did not think the primary therapeutic use of the drug would have changed the results of our study.

Second, the exposure cohort was compiled based on dispensation of bisphosphonate drugs and may not be an accurate reflection of actual drug consumption rates; therefore, we may have overestimated the use of bisphosphonates and perhaps have then underestimated UGIBs related to the new use of the drug (non-differential misclassification). This type of misclassification of exposure would bias the effect measure toward an apparent null effect. Third, due to the claims-based nature of the dataset, information related to other potentially confounding variables could not be assessed or controlled for. For example, we lacked data on other factors known to be related to UGIBs such as smoking and alcohol consumption, the use of over the counter medications such as NSAIDs (i.e. ibuprofen) and ASA, and the presence of un-diagnosed helicobacter pylori infections. [11, 40] Although the inclusion of these variables may have provided a more inclusive description of potential UGIB predictors, we do not believe that controlling for these variables would have altered the results of this study.

Lastly, we would be remiss if we did not acknowledge that the relationship between bisphosphonates and UGIBs may also be complicated by the known fact of an already increased prevalence of GI tract symptoms among older adults. [41] In our study, we did not find differences in co-morbidity between those who developed a UGIB and those who did not. We did find that those who developed a UGIB were more likely to both have a concurrent past diagnosis of gastric ulcer disease as well as a remote history of UGIB. Taken together, this may have accounted for some of the decrease in observed risk in the group who did not develop a UGIB - even after controlling for these variables as confounders.

The strengths of this study include its population-based design, a large sample size, and its use of detailed data made possible by the use of a comprehensive linkable dataset including clinical and prescription drug information of most residents in the province. To our knowledge, this is one of the first comprehensive, population based studies of UGIB incidence associated with new oral bisphosphonate use. We used a strict case definition of UGIB, which has

been previously validated; this strategy for identifying cases of UGIB (a rare event) was broad, reducing the likelihood that cases were missed. [42] In addition, our study used a co-morbidity index that had been previously validated with the population and used sophisticated statistical analysis to control for potentially confounding variables. Given the longitudinal nature of the data, it was also possible to examine drug use as both an exposure (bisphosphonate) and an end-point (UGIB) thereby having the advantage of enough accumulated person-time of bisphosphonate exposure for detection of more rare GI associated adverse events. Taken together, these factors ought to contribute to a reliable estimate of the ORs for UGIBs within 120 days of incident bisphosphonate use.

Conclusion

Upper GIB is a rare, but serious, side effect of bisphosphonate therapy with older patients being affected more often than younger ones. In our study, those incident users of oral bisphosphonate drugs aged > 80 years had a two-fold increase in serious UGIB within 120 days of new drug use. Unfortunately, osteoporosis related fracture risk also increases substantially with age and those older adults are at a much higher risk of morbidity and mortality related to fractures. Concern about potential rare adverse events should not discourage clinicians from prescribing bisphosphonate drugs when there is a high risk of fracture, particularly in older patients many of who have already sustained a fragility fracture. Although evidence of a definitive causal relationship between bisphosphonate therapy and serious adverse events such as UGIB is lacking, clinicians need to remain cognizant of potential adverse events associated with bisphosphonate use and should routinely ask patients about pre-existing GI disorders and concurrent medication history prior to prescribing these drugs.

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Appendix 4-1. Oral prescription medications included in the analysis

NSAIDs
ketorolac (Toradol)
indomethacin (Indocid)
naproxen (Naprosyn)
celecoxib (Celebrex)
diclofenac (Voltaren)
rofecoxib (Vioxx)
Antiplatelet / anticoagulant drugs
ASA
warfarin (Coumadin)
clopidogrel (Plavix)
dipyridamole (Aggrenox)
ticlopidine
Proton pump inhibitors
omeprazole (Losec)
esomeprazole (Nexium)
lansoprazole (Prevacid)
pantoprazole (Pantoloc)
rabeprazole (Pariet)

NSAID = Non-steroidal anti-inflammatory drug

Table 4-1. Characteristics of the bisphosphonate exposure cohort stratified by upper gastrointestinal bleeding status [a]

	UGIB n = 117 (0.4)	***No* UGIB n = 26 106 (99.6)**	**Total N = 26 223**
Age (y) [b]			
≤ 80	47 (40.2)	15 213 (58.3)	15 260 (58.2)
> 80	70 (59.8)	10 893 (41.7)	10 963 (41.8)
mean ± SD	81.8 ± 6.9	78.8 ± 6.9	78.8 ± 6.9
Sex [c]			
Female	96 (82.1)	23 030 (88.2)	23 126 (88.2)
Male	21 (17.9)	2 934 (11.2)	2 955 (11.3)
Unknown	0	142 (0.5)	142 (0.5)
Comorbid conditions [c]			
None	6 (5.1)	1 936 (7.4)	1 942 (7.4)
1 – 3	26 (22.2)	6 490 (24.9)	6 516 (24.8)
4 - 6	66 (56.4)	13 256 (50.8)	13 322 (50.8)
7 - 15	19 (16.2)	4 424 (16.9)	4 443 (16.9)
mean ± SD	4.77 ± 2.1	4.41 ± 2.2	4.41 ± 2.2
Comorbid conditions (by diagnosis)			
Cancer [c]	44 (37.6)	9 056 (34.7)	9 100 (34.7)
Cerebrovascular disease [c]	30 (25.6)	5 324 (20.4)	5 354 (20.4)
Diabetes [c]	16 (13.7)	4 269 (16.4)	4 285 (16.3)
Cardiovascular disease [b]	91 (77.8)	16 542 (63.4)	16 633 (63.4)
Hypertension [c]	84 (71.8)	17 437 (66.8)	17521 (66.8)
Osteoporosis [c]	27 (23.1)	7 354 (28.2)	7 381 (28.1)
Osteoarthritis [c]	66 (56.4)	14 954 (57.3)	15 020 (57.3)
Rheumatoid arthritis [c]	11 (9.4)	3 481 (13.3)	3 492 (13.3)
Neurotic disorder [c]	52 (44.4)	9 941 (38.1)	9 993 (38.1)
Depression / psychosis [c]	60 (51.3)	12 403 (47.5)	12 463 (47.5)
Dementia [c]	27 (23.1)	5 050 (19.3)	5 077 (19.4)
Incontinence [c]	48 (41.0)	9 473 (36.3)	9 521 (36.3)
Parkinson's [c]	2 (1.7)	835 (3.2)	837 (3.2)
COPD [c]	38 (32.5)	7 910 (30.3)	7 948 (30.3)
Asthma [c]	16 (13.7)	3 533 (13.5)	3 549 (13.5)
Past history of gastric ulcer disease [b]			

	UGIB n = 117 (0.4)	***No* UGIB n = 26 106 (99.6)**	**Total N = 26 223**
No	93 (79.5)	23 374 (89.5)	23 467 (89.5)
Yes	24 (20.5)	2 732 (10.5)	2 756 (10.5)
Past history of serious GI bleeding (requiring hospital stay) [b]			
No	103 (88.0)	24 895 (95.4)	24 998 (95.3)
Yes	14 (12.0)	1 211 (4.6)	1 225 (4.7)
NSAIDs (oral) [d]			
No concurrent use	107 (91.5)	21 342 (81.8)	21 449 (81.8)
Concurrent use	10 (8.5)	4 764 (18.2)	4 774 (18.2)
Anti-platelet / anti-coagulant prescription drugs (oral) [c]			
No concurrent use	104 (88.9)	22 751 (87.1)	22 855 (87.2)
Concurrent use	13 (11.1)	3 355 (12.9)	3 368 (12.8)
Proton pump inhibitors [b]			
No concurrent use	83 (70.9)	21 725 (83.2)	21 808 (83.2)
Concurrent use	34 (29.1)	4 381 (16.8)	4 415 (16.8)

[a] Data are shown as number (percentage) unless otherwise indicated.

[b] $p < 0.001$ for chi square differences between categories within the group.

[c] Not significant.

[d] $p < 0.05$ for chi square differences between categories within the group.

CI = confidence interval; **GI** = gastrointestinal; **NSAID** = Non-steroidal anti-inflammatory drug; **UGIB** = upper gastrointestinal bleed.

Table 4-2. Crude incidence rates of upper gastrointestinal bleeding within 120 days of incident bisphosphonate drug prescription

	≤ 80 years	**> 80 years**	**Total**
Number of UGIB events	47	70	117
Person-time at risk (y)	5 017	3 604	8 621
Incidence rate [a]	9.4	19.4	13.6

[a] Incidence rate (per 1 000 person-years)

UGIB = upper gastrointestinal bleed

Table 4-3. Characteristics of the bisphosphonate exposure cohort stratified by upper gastrointestinal bleeding status [a]

	UGIB n = 117 (0.4)		Unadjusted odds ratio (95% CI)	p - Value
	≤ 80 years n = 47 (40.2)	> 80 years n = 70 (59.8)		
Age (y)				
≤ 80	47	-	(reference)	
> 80	-	70	2.08 (1.44, 3.01)	0.000
Sex [c]				
Female	39 (83.0)	57 (81.4)	(reference)	
Male	8 (17.0)	13 (18.6)	1.72 (1.07, 2.76)	0.025
Comorbid conditions [c]				
None	2 (4.3)	4 (5.7)	(reference)	
1 – 3	9 (19.1)	17 (24.3)	1.29 (0.51, 3.15)	0.571
4 - 6	28 (59.6)	38 (54.3)	1.61 (0.70, 3.71)	0.267
7 - 15	8 (17.0)	11 (15.7)	1.69 (0.55, 3.48)	0.487
Past history of gastric ulcer disease [b]				
No	35 (74.5)	58 (82.9)	(reference)	
Yes	12 (25.5)	12 (17.1)	2.21 (1.41, 3.46)	0.001
Past history of serious GI bleeding [b]				
No	41 (87.2)	62 (88.6)	(reference)	
Yes	6 (12.8)	8 (11.4)	2.79 (1.59, 4.90)	0.000
NSAIDs (oral) [d]				
No concurrent use	42 (89.4)	65 (92.9)	(reference)	
Concurrent use	5 (10.6)	5 (7.1)	0.42 (0.22, 0.80)	0.009
Anti-platelet / anti- coagulant drugs (oral) [c]				
No concurrent use	40 (85.1)	64 (91.4)	(reference)	
Concurrent use	7 (14.9)	6 (8.6)	0.85 (0.48, 1.51)	0.848
Proton pump inhibitor drugs (oral) [b]				
No concurrent use	33 (70.2)	50 (71.4)	(reference)	
Concurrent use	14 (29.8)	20 (28.6)	2.03 (1.36, 3.03)	0.001

[a] Data are shown as number (percentage) unless otherwise indicated.

[b] $p < 0.001$ for chi square differences between categories within the group.

[c] Not significant.

[d] $p < 0.05$ for chi square differences between categories within the group.

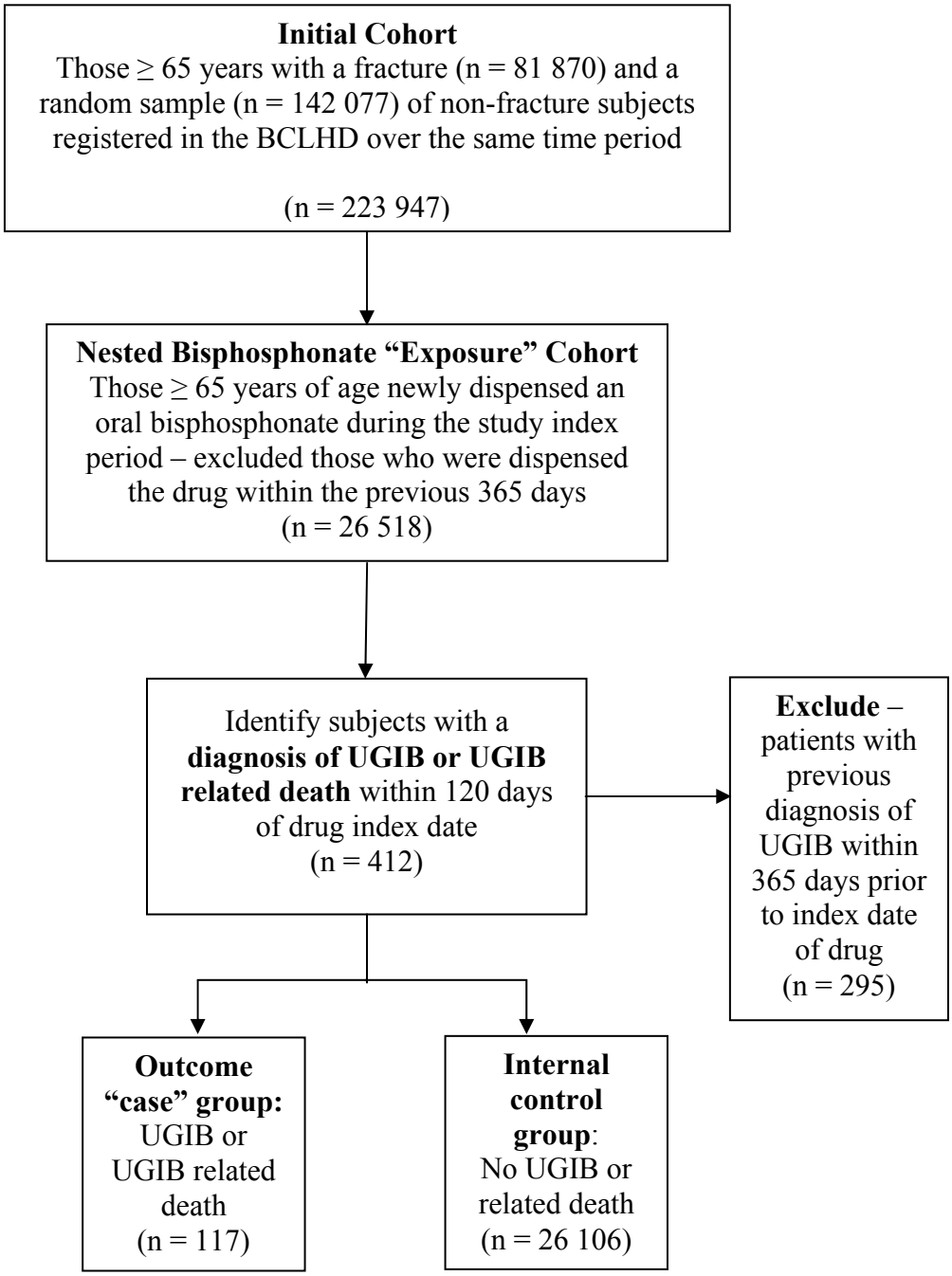
CI = confidence interval; **GI** = gastrointestinal; NSAID = **UGIB** = upper gastrointestinal bleed.

Table 4-4. Final logistic regression model: Factors predicting gastrointestinal bleeding within 120 days of incident bisphosphonate use

Variable	Adjusted odds ratio (95% CI)	p -Value
Constant	0.002	0.000
Age (y)		
≤ 80	1 (reference)	
> 80	2.03 (1.40, 2.94)	0.000
Sex		
Female	1 (reference)	
Male	1.69 (1.05, 2.72)	0.030
Past history of gastric ulcer disease		
No	1 (reference)	
Yes	1.90 (1.21, 3.01)	0.006
Past history of serious GI bleeding		
No	1 (reference)	
Yes	2.28 (1.29, 4.03)	0.005
NSAIDs (oral)		
No concurrent use	1 (reference)	
Concurrent use	0.41 (0.21, 0.80)	0.008
Proton pump inhibitor drugs (oral)		
No concurrent use	1 (reference)	
Concurrent use	2.04 (1.35, 3.07)	0.001

CI = confidence interval; **GI** = gastrointestinal; **NSAID** = Non-steroidal anti-inflammatory drug; **UGIB** = upper gastrointestinal bleed.

Figure 4-1. Selection of study cohort



UGIB = upper gastrointestinal bleed