



UMEÅ UNIVERSITY

# Benefits and Harms of Bisphosphonates - An Observational Study

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Dissertation for PhD

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# Abstract

**Background:** Bisphosphonates are first-line treatment for osteoporosis, but osteoporosis is considered an undertreated disease. The general aim of this dissertation was to further study the benefits and harms of bisphosphonates. There were four specific research questions: (1) Do bisphosphonates reduce the risk of new fractures in older adults who have a history of fracture? (2) Do bisphosphonates reduce the risk of fracture in people taking glucocorticoids? (3) Does confounding explain why bisphosphonates are associated with lower mortality in observational studies? (4) Do bisphosphonates increase the risk of non-jaw osteonecrosis?

**Methods:** To answer these questions, we used Swedish register data on deaths, diagnoses, and prescription medications to conduct four matched cohort studies of bisphosphonate users and nonusers. The cohorts were selected from patients registered in the Hip Fracture Register and from all residents of Sweden who were aged 50 years or older on December 31, 2005.

**Results:** (1) Bisphosphonate users had an initially increased risk of sustaining new fractures, which appeared to be due to an underlying high risk of fracture. This increased risk diminished over time, which is consistent with a gradual treatment effect, but it is also consistent with a bias known as depletion of susceptibles. (2) Bisphosphonate users had a lower risk of fracture during glucocorticoid therapy. (3) Bisphosphonate users had a lower mortality rate from day 2 of treatment. Although such an early treatment effect cannot be ruled out, this finding is consistent with confounding. (4) Bisphosphonate users had an increased risk of developing non-jaw osteonecrosis.

**Conclusion:** Most of the results were difficult to interpret as true benefits or harms of bisphosphonates because alternative explanations, arising from bias or confounding, were likely. The exception was the results of Study 2, where alternative explanations are more difficult to find. Therefore, Study 2 suggests that bisphosphonates reduce the risk of fractures in glucocorticoid-treated patients. Further research is needed to clarify the potential effects of bisphosphonates on mortality, non-jaw osteonecrosis, and new fractures after a previous fracture.

# Enkel sammanfattning på svenska

## Bakgrund

Bisfosfonater är en grupp läkemedel som stärker skelettet. De används främst för att behandla benskörhet. Syftet med behandlingen är att öka benmassan, för att på så sätt minska risken för frakturer. Trots att det finns vetenskapligt belägg för att bisfosfonater minskar risken för frakturer anses benskörhet vara en underbehandlad sjukdom. Två bidragande orsaker till detta verkar vara att både patienter och vårdpersonal är oroliga för biverkningar och osäkra kring huruvida bisfosfonater verkligen är effektiva, och i sådant fall vem som har nytta av dem.

## Syfte

Syftet med det här forskningsprojektet var att vidare studera effekterna och biverkningarna av bisfosfonater. Det gjorde vi genom att använda register, främst från Socialstyrelsen, för att följa upp och jämföra personer över 50 år som fått bisfosfonater med personer som inte fått bisfosfonater.

Den här typen av studier brukar kallas observationsstudier, eftersom forskarna bara "observerar" det som händer med patienterna, utan att bestämma vilka som ska få behandling (det beslutar vården i vanlig ordning). Det här kan jämföras med hur det går till i så kallade kliniska prövningar, där det är forskarna som avgör vilka som får behandling, oftast genom lottning (även kallat randomisering).

Fördelen med observationsstudier är att de ofta är enklare och billigare att genomföra än kliniska prövningar. Nackdelen med dem är att resultaten är mindre tillförlitliga när man studerar effekter av behandlingar, eftersom de grupper som jämförs (t.ex. behandlade och obehandlade patienter) kan vara ojämförbara. När grupperna är ojämförbara uppstår ett problem som kallas confounding, vilket betyder att eventuella skillnader mellan grupperna kan bero på annat än behandlingen.

För att vidare studera effekterna av bisfosfonater genomförde vi fyra studier. I varje studie hade vi en specifik frågeställning:

1. Minskar bisfosfonater risken för nya frakturer hos äldre personer som tidigare har drabbats av en fraktur?
2. Minskar bisfosfonater risken för frakturer hos personer som samtidigt behandlas med kortison, vilket är dåligt för skelettet?
3. Är confounding förklaringen till att observationsstudier har visat att personer som använder bisfosfonater lever längre än andra?

4. Ökar bisfosfonater risken för osteonekros (benvävnadsdöd) i andra delar av skelettet än i känen, där det sedan tidigare är känt att bisfosfonater kan orsaka osteonekros i sällsynta fall?

## **Resultat**

Så här blev resultaten:

1. Frakturpatienter som fick bisfosfonat hade först en högre risk att drabbas av nya frakturer än övriga patienter, något som verkade bero på en hög underliggande frakturrisik (det vill säga confounding). Skillnaden i risk försvann över tid, vilket kan bero på att bisfosfonaterna gradvis började få effekt, men kan också bero på en felaktighet i den här typen av analys.
2. Patienter som fick bisfosfonat under sin kortisonbehandling hade en lägre frakturrisik än övriga patienter.
3. Patienter som fick bisfosfonat hade en lägre dödlighet än övriga patienter från och med dag två. En så tidig skillnad kan bero på att bisfosfonater ges till personer som har en god förväntad livslängd (det vill säga confounding). Däremot går det inte att utesluta att bisfosfonater har en tidig effekt på livslängden.
4. Patienter som fick bisfosfonat hade en ökad risk för att utveckla osteonekros i andra delar av skelettet än i käkbenet.

## **Slutsatser**

De flesta av resultaten går inte att tolka som effekter eller biverkningar av bisfosfonater, eftersom de behandlade och obehandlade patienterna mycket väl kan vara jämförbara. Undantaget till detta är studie 2, där det är svårt att förklara resultaten på annat sätt än att bisfosfonater minskade risken för fraktur vid kortisonbehandling. Fler studier behövs för att ta reda på om bisfosfonater förlänger livslängden, ökar risken för osteonekros annat än i känen och minskar risken för nya frakturer efter en tidigare fraktur. Man kan diskutera ifall observationsstudier är lämpliga för att besvara de här frågorna, men om sådana studier genomförs i framtiden bör deras kvalitet höjas, så att resultaten blir mera tillförlitliga.

# Original Publications

1. Bergman J, Nordström A, Nordström P. Bisphosphonate use after clinical fracture and risk of new fracture. *Osteoporos Int* 2018;29:937-945.
2. Bergman J, Nordström A, Nordström P. Alendronate use and the risk of nonvertebral fracture during glucocorticoid therapy: a retrospective cohort study. *J Clin Endocrinol Metab* 2018;103:306–313.
3. Bergman J, Nordström A, Hommel A, Kivipelto M, Nordström P. Bisphosphonates and mortality: confounding in observational studies? *Osteoporos Int*;30:1973-1982.

*Correction in:* Bergman J, Nordström A, Hommel A, Kivipelto M, Nordström P. Correction to: Bisphosphonates and mortality: confounding in observational studies. *Osteoporos Int* 2021;32:797-800.

4. Nordström P, Bergman J, Ballin M, Björk S, Nordström A. Bone-specific drugs and osteonecrosis of sites other than the jaw: a nationwide cohort study. *J Bone Miner Res* 2020;35:1703-1710.

# Abbreviations

BMD	Bone mineral density
BMI	Body mass index
ICD-10	International Classification of Diseases, 10 <sup>th</sup> Revision
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market Studies



# Introduction

## The occurrence of fractures

### *Fractures in the general population*

It is difficult to say exactly how common fractures are in the general population, because few studies provide up-to-date information on all fractures that occur. However, a global estimate for the year 2019 showed that 2 fractures occurred per 100 people worldwide.<sup>1</sup> The same rate was reported in a regional study from Australia during 2006-2007.<sup>2</sup> These two studies showed that the most common fractures are fractures of the hand, forearm, lower leg, and upper arm/shoulder.<sup>1,2</sup>

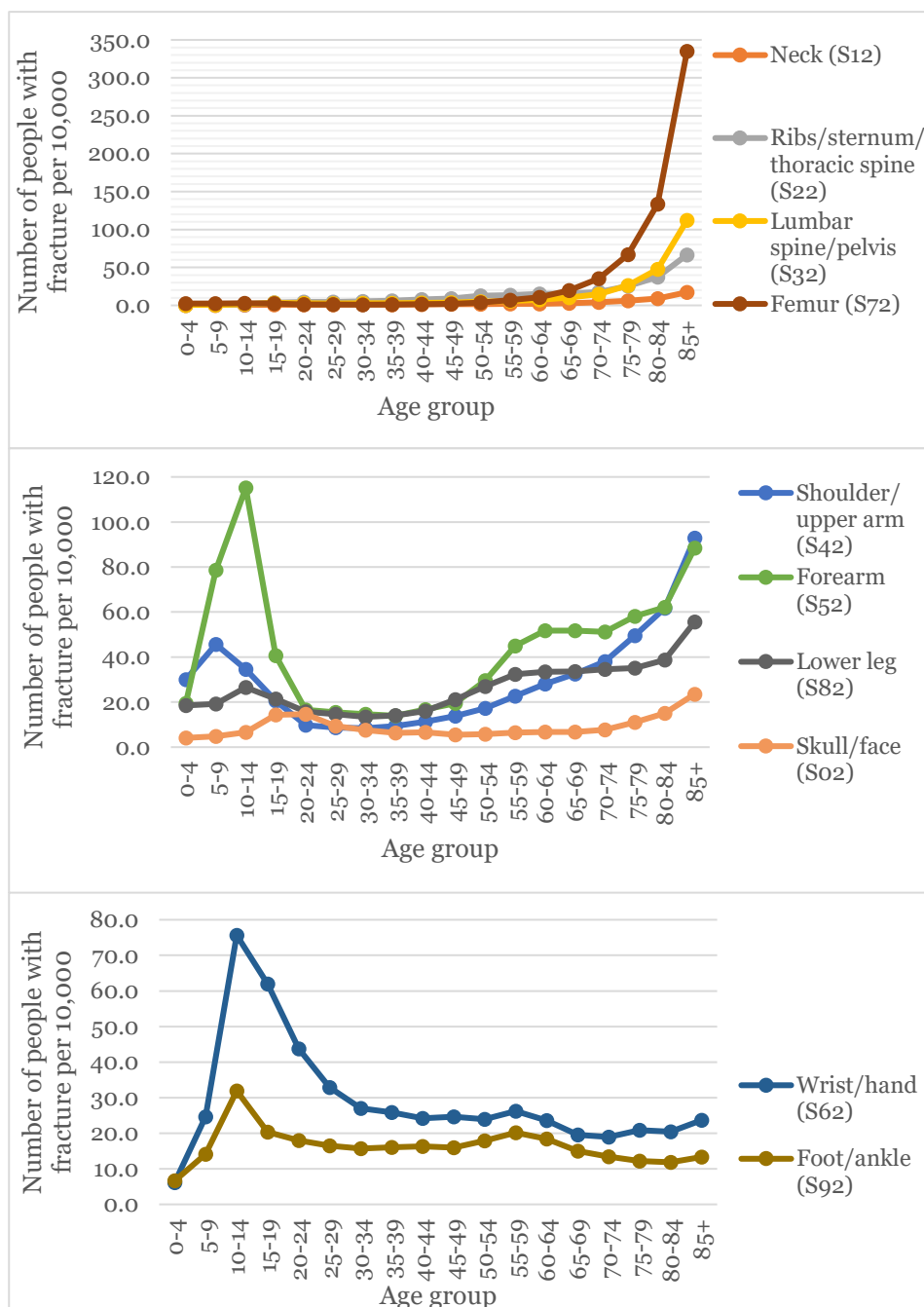
Despite the similarity in fracture rates in these two studies, fracture rates appear to vary considerably among countries. International comparisons are easiest to make for hip fractures because, in contrast to other fractures, hip fractures almost always lead to hospitalization, which means that data on hip fractures are most widely available. In a review of hip fractures in 63 countries,<sup>3</sup> a more than 10-fold variation in rates was observed, even after controlling for differences in population age structure. In the previously mentioned global study of all types of fractures,<sup>1</sup> the estimated fracture rates ranged from a low of 1-1.6 fractures per 100 people in sub-Saharan Africa, Oceania, East Asia, and Southeast Asia to a high of 5 to 9 fractures per 100 people in eastern and central Europe and Australasia (Australia and New Zealand). In between these two extremes, the estimated fracture rate for Sweden was 2.8 fractures per 100 people.

The reasons for these international variations are unclear, but they may be due to environmental factors, genetic factors, and biases (that is, differences in data collection). In the international comparison of hip fracture rates,<sup>3</sup> the authors argued that most of the variation in is probably due to environmental factors, such as affluence. Indeed, affluence explains more than half of the international variation in hip fracture rates, maybe because it leads to reduced physical activity (resulting in lower bone strength) and an increased number of hard surfaces.<sup>4</sup> However, environmental factors do not easily explain why Finland had a much lower hip fracture rate than Sweden, Norway, and Denmark (approximately half of Denmark's rate), despite Finland's geographical proximity and economic similarity. Therefore, bias also seems to be a likely explanation for at least some of the differences.

## *Fractures and aging*

Fractures occur in all age groups, but they are most common in the oldest age groups.<sup>1,2</sup> For example, a study of Skåne County, Sweden, showed that the fracture rate was four times higher in the age group 80-84 than in the age group 20-24 (5.5 versus 1.4 fractures per 100 people per year).<sup>5</sup> However, not all types of fractures increase consistently with age. As shown in Figure 1, three different patterns can be seen:<sup>6</sup>

1. Fractures that increase consistently with age, especially from 70-79 years of age. These include fractures of the femur, spine, pelvis, and thoracic cage (top panel of Figure 1).
2. Fractures that increase during childhood but decrease during the teenage years, before increasing again around age 50. These include fractures of the arm, shoulder, lower leg, and skull/face (middle panel of Figure 1).
3. Fractures that decrease or remain constant with age. These include fractures of the foot and hand (bottom panel of Figure 1).



**Figure 1.** Fractures in Sweden by age group and type of fracture (ICD-10 code) in 2019. The data include both hospitalized care and secondary care.<sup>6</sup>

The increase in overall fracture risk with older age is not due to an increase in high-energy fractures, such as those caused by motor vehicle accidents or falls from one level to another.<sup>7,8</sup> Instead, the increase is due to an increase in low-energy fractures, which might occur spontaneously or after a fall from standing height or less, and which constitute the majority of fractures in adults over 50.<sup>7,8</sup> This increase has been explained by an age-related loss of bone strength, an increased risk of falling, a greater severity of falls, and perhaps a loss soft tissue to cushion falls.<sup>9,10</sup> These explanations will be further discussed below.

### *Fractures over time*

For decades, studies have projected that fractures will become more common in the future due to population growth and aging.<sup>11–13</sup> However, the actual trends that have been seen have been less clear. For example, despite population growth and aging, both the number and rate of hip fractures declined in Sweden between 1998 and 2017 and in the United States between 2002 and 2015.<sup>14,15</sup> Other countries have seen increases in the number of hip fractures due to population growth, but despite population aging, the fracture rates have decreased (that is, the number of fracture relative to population size). Such a trend has been observed in France (2002-2013),<sup>16</sup> Finland (1997-2016),<sup>17</sup> Catalonia, Spain (2003-2014),<sup>18</sup> and Denmark (1995-2010).<sup>19</sup> In Lebanon, a study showed no clear trend in hip fracture incidence from 2006 to 2017.<sup>20</sup>

These remarkable trends - and lack of trends - run counter to projections and have not been clearly explained. Reasons that have been suggested include an improved treatment of osteoporosis, a greater attention to fall prevention, an increased prevalence of overweight (which is associated with lower fracture risk), improvements in nutrition (e.g., calcium and vitamin D status), and improvements in the overall health of older people.<sup>5,14,15</sup>

On the downside of this happy note, the overall fracture rate in Sweden appears to have increased in both younger adults (20-49 years) and older adults (50 years or older), in tandem with the decline in hip fractures.<sup>5</sup> In the UK however, no trend in the overall age- and sex- adjusted fracture rate was observed among adults aged 50 or older between 1990 to 2012.<sup>21</sup> Although an American study did show an increase in fracture rate among people aged 50 or older from 1989-1991 to 2009-2011, this trend was entirely explained by an increase in spine fractures, perhaps because of more frequent diagnosing.<sup>22</sup> In the previously-mentioned global study of fracture rates,<sup>1</sup> the estimated number of fractures increased by 33% worldwide from 1990 to 2019, but the age-standardized incidence rate decreased by 10%. In summary, the most consistent result appears to be a

decrease in the age-standardized fracture rates, with trends in crude incidence rate and absolute numbers varying geographically.

## **The consequences of fractures**

### *Complications*

Some types of fractures are more serious than others are. The most serious are hip fractures, which occur primarily in the oldest age groups (mean age around 80 years<sup>17,18,23</sup>) and often result in permanent disability and loss of independence. For example, an American study showed that the percentage of hip fracture patients who had become dependent, defined as being unable to perform a certain task or needing assistive equipment, one year after their fracture was 20% for putting on pants, 83% for getting in or out of the shower or bathtub, and 90% for climbing 5 stairs.<sup>24</sup> In a UK study, only 40% of hip fracture patients who had been able to walk without an aid before their fracture were able to do so one year later.<sup>25</sup> Furthermore, 73% had lived in their own home before the fracture, but only 44% did so one year later, while 33% had died and 20% had move to a residential care facility. The rest were hospitalized.<sup>25</sup>

Other types of fractures are less serious than hip fractures. For example, while an Australian study showed that only 10% of female hip fracture patients had regained their pre-fracture mobility after 12 months,<sup>26</sup> recovery rates were approximately 90% for wrist and forearm fractures.<sup>26</sup> In between these two extremes, other types of fractures showed 12-month mobility recovery rates of 65 to 75%.<sup>26</sup>

Although mobility recovery rates were better for vertebral fractures than for hip fractures (66% versus 10%),<sup>26</sup> vertebral fractures are also serious. Occurring primarily in older adults,<sup>2,5,27,28</sup> vertebral fractures can lead to kyphosis,<sup>29</sup> height loss,<sup>30</sup> and back pain.<sup>27,28,30</sup> Most vertebral fractures do not come to medical attention, but they are still associated with back pain, disability, and best rest due to back pain.<sup>30</sup> As regards hospitalized cases, a Swedish study of 107 patients with an acute vertebral fracture showed that pain decreased during the first 3 months, but 76% were still in severe pain 1 year later.<sup>27</sup> Similarly, in a Dutch study, 11 out of 36 patients (31%) did not have significant pain relief after nearly 2 years.<sup>28</sup> The authors interpreted this finding as evidence that vertebral fractures can cause chronic pain, contrary to common belief.<sup>28</sup>

However, an American study showed that previous vertebral fractures were not associated with back pain, unless new fractures had occurred.<sup>30</sup> The authors interpreted this as evidence that pain due to vertebral fractures is transient. Two

possible reasons for the discrepancy with the Dutch study could be that the investigators examined morphometric vertebral fractures (meaning fractures that are radiologically detected but do not come to medical attention). In addition, the Dutch study did not examine whether the occurrence new vertebral fractures could have explained why many patients did not experienced significant pain relief within two years.

A limitation of these studies is that they lacked control groups, which means that it is difficult to determine whether the complications are due to the fractures themselves or to an underlying trajectory of deteriorating health. However, a study of lower forearm fractures reported that women with such a fracture experienced a greater functional decline than controls did.<sup>31</sup> There was no indication that the fractured women were in poorer health; indeed, apart from having lower bone mass and more falls, they were of a similar age, were more physically active, and had a better self-rated health and a higher gait speed. This finding suggests that the fractures did cause functional declines.

## *Mortality*

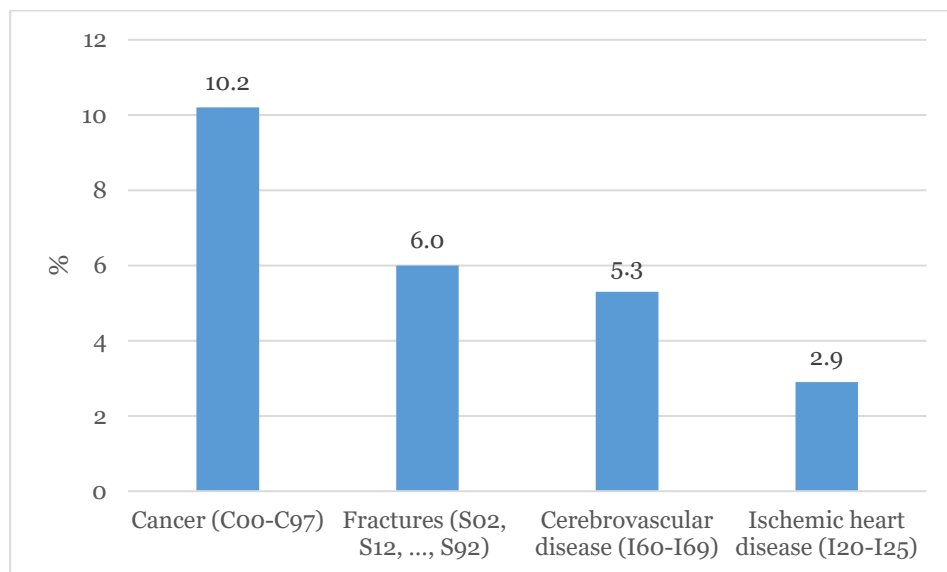
Another potential consequence of fractures, which has been discussed a lot over the years, is premature death. Evidence of such an association is abundant for hip fractures and vertebral fractures,<sup>32–36</sup> but many other types of fractures are also associated with premature death.<sup>37</sup> An exception to this is forearm fractures, which are not associated with premature death.<sup>35,38–40</sup> The highest death rates are seen after a hip fracture.<sup>32</sup> In Sweden, 25% of hip fracture patients die within a year.<sup>14</sup>

Although fractures are clearly associated with premature death, the most important question is whether fractures actually cause premature death or whether they are simply a reflection of poor underlying health. This question is difficult to answer, but two studies estimated that 24% of deaths in hip fracture patients and 28% of deaths in hospitalized vertebral fracture patients are caused by the fracture.<sup>41,42</sup> These estimates were derived by subtracting the mortality rate seen 1 or more years after the fracture from the mortality rate seen during the first year - the assumption was that any excess mortality beyond the first year would be due to poor underlying health. This difference was then compared to the mortality rate in the general population, as an estimate of the excess mortality in fracture patients adjusted for poor underlying health. This method is interesting and creative, but it relies on an untested assumption, which makes it uncertain. Furthermore, a study of vertebral fractures found that poor underlying health explained the excess mortality.<sup>36</sup> In any case, the most widely accepted

view appears to be that at least hip fractures cause premature mortality, one reason for which could be complications such as infections.<sup>43,44</sup>

## *Public health*

The public-health burden of fractures is high in both monetary and human terms. As shown in Figure 2, fractures accounted for 6.0% of hospitalization days in Sweden among people aged 50 or older in 2019.<sup>45</sup> This percentage was less than that for cancer but more than that for ischemic heart disease (e.g., heart attack) and cerebrovascular disease (e.g., stroke). Similarly, a study of American women aged 55 years or older showed that fractures were more common and resulted in larger hospitalization costs than stroke, heart attack, and breast cancer during 2000-2011.<sup>46</sup> In a recent study of six European countries, fractures were ranked as the fourth most burdensome of 17 conditions, after ischemic heart disease, dementia, and lung cancer.<sup>47</sup> The reason for this high burden was primarily fracture-related disability.<sup>47</sup>



**Figure 2.** Percent of all hospitalization days in Sweden by diagnosis (ICD-10) among people aged 50 years or older in 2019.<sup>45</sup>

## **The causes of fractures**

Although older age is an important risk factor for fracture, there are many other risk factors for fractures, as well. These include both skeletal and non-skeletal risk factors, which will be discussed in the next two subsections.

### *Low bone strength and osteoporosis*

Bone strength is typically assessed through bone density, also known as bone mineral density (BMD).<sup>11</sup> BMD explains 70-80% of bone strength in laboratory tests of extracted bones,<sup>10</sup> and it is usually measured at the hip or lumbar spine using dual-energy x-ray absorptiometry, which expresses BMD in bone mass per square centimeter of bone ( $\text{g}/\text{cm}^2$ ).<sup>11</sup>

The lower a person's BMD is, the higher his or her fracture risk is.<sup>48</sup> The increase in risk is gradual, which means that there is no threshold beyond which fracture risks increase sharply.<sup>48</sup> A one standard deviation decrease in BMD is associated with an estimated 50% increase in overall fracture risk and at least a doubled risk of hip and vertebral fractures.<sup>49,50</sup>

BMD can be difficult to interpret when expressed as  $\text{g}/\text{cm}^2$ , so it is often converted to a T-score. A T-score compares a person's BMD to the mean in young adults, and any deviation from the mean is expressed as the number of standard deviations from the young adult mean.<sup>51</sup> The conventional reference group of young adults is, for everyone, White American women in their twenties.<sup>52</sup> The argument for this convention is that White women have a lower BMD and a higher fracture risk than men and non-White women, so using White women as a reference group means that the prevalence of osteoporosis will be highest in White women, which is consistent with their higher fracture risk.<sup>51</sup> For men, another argument is that men and women with the same BMD have a similar fracture risk.<sup>51</sup>

If a person's BMD is sufficiently low, he or she is considered to have osteoporosis. In general terms, osteoporosis is defined as, "a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk."<sup>53</sup> In 1994, this definition was specified by a study group under the World Health Organization as a T-score of -2.5 or less.<sup>10</sup> A T-score greater than -1 was defined as normal, and anything between -2.5 and -1 was defined as osteopenia, also called low bone mass.<sup>10</sup> It should be noted that these definitions focus on bone mass rather than bone microarchitecture, which is part of the general definition of osteoporosis. The reason for this is that bone microarchitecture, which is a parameter of bone quality,<sup>54</sup> is difficult to measure.<sup>11</sup>

The World Health Organization study group acknowledged that the BMD cutoff for osteoporosis is arbitrary.<sup>10</sup> However, the group justified it on the grounds that, according to this definition, 30% of White post-menopausal women in the United States would have osteoporosis, half of whom would have previously sustained a fracture.<sup>10</sup> Men and non-White women were excluded from the analysis because of a lack of data.<sup>55</sup> Another way to think about the T-score cutoff of -2.5 is that a person diagnosed with osteoporosis according to this definition has a BMD lower than at least 99.4% of young adults (BMD follows a Normal statistical distribution<sup>10</sup>).

The prevalence of osteoporosis in the general population is difficult to determine because it varies between studies. For example, the prevalence osteoporosis at the total hip or femoral neck was 4% in a Korean study (age range, 50-79),<sup>56</sup> 9% in a Dutch study (mean age, 66),<sup>57</sup> 7-10% in a Norwegian study (mean age, 65),<sup>58</sup> 16% in two American studies (mean age, 74),<sup>8</sup> and 17% in an Australian study (mean age, 69).<sup>59</sup> Although this variability might reflect true geographic differences, it probably also reflects differences in participant recruitment.<sup>11</sup>

Although fracture risks are highest in people with osteoporosis (because they have the lowest BMD), most people who sustain a fracture do not have osteoporosis. For example, four studies of male and female fracture patients (mean age, 68-77 years) showed that 30-46% had osteoporosis.<sup>8,60,61</sup> These percentages can be compared to 10% of fracture-free patients in the one study that included a control group.<sup>8</sup> This finding indicates a substantial overlap in BMD between people who do and do not sustain a fracture, which means that BMD cannot be used to predict fractures with certainty.<sup>49</sup>

Similarly, osteoporosis can explain only a minority of the fractures that occur.<sup>59,62</sup> In women aged 65 or older, one study estimated that osteoporosis can explain only 39% of vertebral fractures, 28% of hip fractures, and 15% of all non-vertebral fractures.<sup>62</sup> This finding is interesting because it contradicts the previous belief that osteoporosis causes at least 90% of hip fractures,<sup>63</sup> as well as most other fractures that occur in adults aged 50 years or older.<sup>64</sup>

The BMD definition of osteoporosis is well-established, but there is a competing view of how osteoporosis should be defined, which focuses on the occurrence of fractures - the main consequence of osteoporosis.<sup>34</sup> An example of this is that the American College of Physicians states that osteoporosis can be diagnosed by either BMD or the occurrence of a fracture.<sup>65</sup> The relevance of considering fractures can also be seen in the BMD definition of osteoporosis, where severe or established osteoporosis is defined as having both osteoporotic BMD and a history of fragility fracture.<sup>10</sup>

The concept of fragility fracture is central to any discussion of osteoporosis and fractures; two synonyms for fragility fracture are osteoporotic fracture and osteoporosis-related fracture.<sup>7</sup> It is often said that osteoporosis-related fractures affect 1 in 2 women and 1 in 5 men during their lifetime.<sup>66,67</sup> Variants of this statement can also be found; for example, the website of the International Osteoporosis Foundation states that 1 in 3 women and 1 in 5 men worldwide experience a fracture caused by osteoporosis after the age of 50.<sup>68</sup> However, these statements can be misleading because the terms “osteoporotic fracture” and “osteoporosis-related fracture” do not mean that a fracture is necessarily caused by osteoporosis. Instead, it simply means that such a fracture is common in people who have osteoporosis. This difference in meaning can be seen in the original research articles upon which the statements are based, which simply estimated the remaining lifetime risk of sustaining a fracture of the hip, vertebra, forearm, or (in one study) the upper arm after age 50.<sup>40,69,70</sup> Of note, it is not possible to say whether a particular fracture is caused by osteoporosis because, as previously mentioned, all types of fractures occur in people without osteoporosis too.

Hip, vertebral, and (distal) forearm fractures are the classic osteoporotic fractures, known for being common in osteoporosis patients.<sup>71</sup> A limitation of defining osteoporotic fractures in this way is that it excludes the majority of the fractures that occur. For example, three studies of adults aged 50 or older showed that 50-60% of fractures were not of the hip, vertebra, or forearm.<sup>5,22,72</sup> Many other definitions of osteoporotic fracture exist.

Another way to define osteoporotic fracture is a fracture that is associated with low BMD and increases with age after 50 (if it does not increase after 50, then it is probably not related to osteoporosis).<sup>73</sup> Based on this definition, Kanis and colleagues considered fractures of the vertebra, rib, pelvis, upper arm, forearm, femur, lower leg, clavicle, shoulder blade, and sternum to be osteoporotic.<sup>73</sup> They excluded fractures of the face, skull, hands, feet, ankle, kneecap, and (in men) lower leg. Some years later, this definition was simplified to include all fractures except for those of the ankle, hands, feet, skull, and face.<sup>11</sup>

These two definitions are simple because they are based solely on the affected skeletal site. It is interesting to note that these definitions imply that almost all types of fractures are osteoporotic. This is a big shift away from the traditional concept, which focuses mainly on hip, vertebral, and distal forearm fractures.

A third way to define osteoporotic fracture is any fracture occurring after a low-energy event. A low-energy event is typically defined as equivalent to a fall from standing height or less.<sup>11</sup> The idea behind this definition is that such a fall is not expected to result in a fracture in a healthy young person.<sup>74</sup> The limitation of this

definition is that, interestingly enough, high-energy fractures are also associated with low BMD, and the association appears to be as strong as for low-energy fractures.<sup>7,8</sup> Another limitation is that this definition is unfeasible when the cause of a fracture is unknown, which can be the case in research settings. In these situations, a definition based on skeletal site is preferable.

A fourth way to define osteoporotic fracture is a fracture that increases in incidence with age, is more common in women than in men, occurs after a low-energy event, and affects a skeletal site rich in trabecular bone.<sup>75</sup> This definition includes not only the three classic osteoporotic fractures (hip, vertebral, and forearm fractures), but also fractures of the upper arm, pelvis, and some other types of limb fractures (the author does not specify which). However, this definition does not capture all fracture associated with osteoporosis,<sup>75</sup> so it is probably not useful.

### *Non-skeletal risk factors*

There are many non-skeletal risk factors for fractures,<sup>66</sup> some of which are also risk factors for osteoporosis. A good example of such a risk factor is older age, which leads to declines in BMD that explain only part of the higher fracture risk seen in older people.<sup>76–78</sup> Another contributing factor is that older people fall more often,<sup>79,80</sup> as falls cause the majority of fractures.<sup>7,8,22</sup> However, only a small minority of falls lead to a fracture (3–11%),<sup>79,81–83</sup> so neither BMD nor falls explain the entire increase in fractures with aging.<sup>9,10</sup>

One clinical guideline lists no fewer than 95 risk factors for fractures and osteoporosis.<sup>66</sup> These risk factors include genetics, demographics (e.g., age, sex, and race/ethnicity), lifestyle (e.g., poor nutrition, inadequate exercise, high alcohol consumption, and smoking), some medications (e.g., glucocorticoids), some medical conditions (e.g., diabetes and stroke), and having a history of fracture. The guideline also lists 24 risk factors for falls, which are related to environment (e.g., poor lighting and slippery surfaces), nutrition (e.g., vitamin D deficiency and malnutrition), low physical function (e.g., poor balance and muscle weakness), some medications (e.g., sedatives), some medical conditions (e.g., poor vision), low cognitive function, and having a history of falling or a fear of falling. Due to this large number of risk factors, I will limit the rest of this discussion to four of them: female sex, low body mass index (BMI), history of fracture, and glucocorticoid use.

After the age of 50, women sustain fractures about twice as often as men do.<sup>2,5,40,72</sup> Before that age, men sustain more fractures.<sup>2,5,40,72</sup> This change is due to a decline in high-energy fractures in men and a greater rise in low-energy fractures in

women.<sup>84</sup> The greater rise in low-energy fractures in women has often been explained by the fact that BMD is lower in women and declines rapidly after menopause, due to a reduction in estrogen production.<sup>11,85</sup> However, it unclear whether lower BMD entirely explains the higher fracture risk seen in women, as the studies that are often cited show only that men and women have a similar relative risk of fracture with decreasing BMD.<sup>50,86</sup> Studies of the absolute risk of fracture show different results: similar fracture risk at the same BMD,<sup>76,87,88</sup> higher risks in women even after controlling for BMD,<sup>89</sup> or inconclusive results (that is, non-significantly higher risks in women).<sup>77,78,90</sup> The results have even varied in different analyses of the same cohort.<sup>76,88,89</sup> Another explanation for the higher risk seen in women could be that women fall more often than men do.<sup>91,92</sup>

Low BMI is associated with an increased risk of fracture.<sup>93</sup> This association is explained by that fact that people who have a low BMI also tend to have a low BMD.<sup>93</sup> However, low BMI still appears to be associated with hip fractures after controlling for BMD.<sup>93</sup> The reason for this is unclear, but it could be due to low BMI leading to muscle weakness, falls, and a smaller amount of protective padding around the hip.<sup>93</sup>

A strong risk factor for fracture is having a history of fracture at any skeletal site.<sup>94</sup> In general, people who sustain a fracture are at twice the risk of sustaining a new fracture as are others of the same age and sex.<sup>94,95</sup> The mechanism behind this association is unknown, and it cannot be explained by low BMD in fracture patients.<sup>61,95,96</sup> One explanation that has been suggested is that after the fracture, BMD could decrease due to immobilization.<sup>95</sup> Alternatively, having a history of fracture might simply be a marker of increased fracture risk, rather than a cause.<sup>95</sup>

Glucocorticoids are considered to be the leading cause of secondary osteoporosis, secondary meaning that it is caused by an underlying disease or medication.<sup>97</sup> Glucocorticoids have anti-inflammatory and immunosuppressant effects, which means that they are used to treat a variety of conditions, such as rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, and inflammatory bowel disease.<sup>98,99</sup> Although highly effective, glucocorticoids are also harmful to BMD, primarily because they reduce bone formation.<sup>97,100</sup> Other adverse effects of glucocorticoids that might increase the risk of fractures include a reduced calcium uptake, which can negatively affect bone, and muscle weakness, which can negatively affect bone and increase the risk of falling.<sup>97</sup>

In clinical trials of glucocorticoids, vertebral fractures have been detected as an adverse effect.<sup>101,102</sup> These trials have been too small or too short to examine effects on non-vertebral fractures. Therefore, the evidence that glucocorticoids increase the risk of non-vertebral fractures comes from observational studies, which have reported an increased risk within 3 months of glucocorticoid therapy,

a risk that increases with both the dose and duration.<sup>103–105</sup> These increases have mainly been seen in people taking oral glucocorticoids.<sup>103–105</sup> The evidence that non-systemic (e.g., nasal, topical, or inhaled) glucocorticoids increase the risk of fracture is less compelling.<sup>106–109</sup> It should be noted the increased risk of non-vertebral fractures seen in patients taking oral glucocorticoids is difficult to interpret because many of the underlying conditions are also associated with increased fracture risks.<sup>97</sup> Therefore, the effect of glucocorticoids is difficult to separate out.

## **The prevention of fractures**

There is broad agreement in the field of osteoporosis that many fractures are preventable.<sup>44,66,110</sup> Part of this is related to lifestyle changes. Healthy lifestyle habits recommended for everyone include maintaining a healthy diet, exercising, not smoking, and limiting alcohol consumption.<sup>44,66,110</sup> Some people may also benefit from bone-strengthening medications.<sup>44,66,110</sup> Of all these preventive measures, bone-strengthening medications have been the most successful because evidence of that they are effective are most abundant.<sup>111</sup> Even so, treatment rates for osteoporosis remain low. Let us take a look at this issue more closely.

### *Undertreatment of osteoporosis*

Osteoporosis has long been recognized as an undertreated disease. Although some researchers disagree that osteoporosis is undertreated,<sup>112</sup> a 2007 editorial in the *Internal Medicine Journal* drew readers' attention to the issue, sometimes called a "treatment gap", with the following title: *Osteoporosis: it's time to 'mind the gap'*.<sup>113</sup> An even stronger title was published by the American Society for Bone and Mineral Research in 2016: *Call to action to address the crisis in the treatment of osteoporosis* (the document was signed by 33 organizations).<sup>114</sup>

A common way to show that osteoporosis is undertreated is by examining treatment rates after a hip fracture, as treatment can be prescribed after a hip fracture without further evaluation of osteoporosis. During the 10-year period from 2002 to 2011, an American study reported that only 24% of hip fracture patients collected a prescription for an osteoporosis medication in the following year.<sup>115</sup> What is more, the percentage declined over time, from 40% in 2002 to 21% in 2011.<sup>115</sup> Similarly, A UK study from 1990 to 2012 found that prescription rates of oral anti-osteoporosis drugs increased until 2006, after which they plateaued in men and declined in women.<sup>116</sup> A recent study from Singapore found that 40% of hip fracture patients were treated within one year,<sup>117</sup> and in Italy, a recent study found that 23% received treatment.<sup>118</sup> Treatment rates are lower in

Sweden, where an estimated 6-14% of hip fracture patients receive treatment.<sup>119-121</sup>

It should be noted that these studies might have underestimated the use of intravenous and subcutaneous medications administered by health care professionals, as the studies mainly used data on prescribed medications. Even so, a Swedish survey showed that only 8% of patients treated for osteoporosis had received zoledronic acid,<sup>122</sup> which suggests that the underestimation of treatment rates should be modest. In Sweden, the low treatment rate has gained the attention of authorities, which advocate increased treatment of patients with hip and other fractures.<sup>121,123</sup> According to authorities, the treatment rates should perhaps be 60-70%.<sup>121</sup>

The undertreatment of osteoporosis is particularly pronounced in certain groups, such as men and the oldest people. For example, the Swedish National Board of Health and Welfare has concluded that women aged 70 or older are less frequently treated after a fracture than women aged 50-69 years are, which it points out goes against treatment guidelines.<sup>121</sup> Furthermore, the Board states that there is an unjustifiably large difference in prescription rates between men and women after a fracture (17% in women and 4% in men).<sup>121</sup> A recent analysis of Swedish hip fracture patients also concluded that men, persons aged 75 years or older, and people in poor health are less often treated.<sup>119</sup> Lower prescriptions rates have also been seen in male and older hip fracture patients in the United States,<sup>115</sup> although another American study showed little difference in the age of treated and untreated osteoporosis patients.<sup>124</sup>

### *Reasons for the undertreatment*

Surveys of physicians and osteoporosis patients reveal several possible explanations for the low treatment rates.<sup>125-127</sup> One explanation could be that osteoporosis is not prioritized. For example, physicians have reported that they prioritize other conditions and that they do not consider osteoporosis urgent to treat.<sup>125,126</sup> Similarly, an interview of 13 general practitioners showed that patients often do not consider osteoporosis to be very serious, especially because it is asymptomatic.<sup>125</sup> This view has been confirmed by an online survey of 503 self-reported, untreated osteoporosis patients, of whom 24% did not consider osteoporosis serious enough to require medication.<sup>127</sup> Fifty-eight percent of the patients reported that they used dietary supplements instead, and 38% had tried lifestyle changes.<sup>127</sup> Another online survey also showed that there was a preference for supplements and lifestyle changes among untreated osteoporosis patients.<sup>126</sup> The prioritization of other conditions can also be seen in that both

physicians and patients report that the using other medications can be a reason for not starting osteoporosis treatment.<sup>125–127</sup>

A second and similar explanation, which was not mentioned in the surveys, could be that osteoporosis passes by undetected, as it is asymptomatic. For example, a recent Swedish population-based study showed that only 20% of those meeting treatment criteria had received treatment.<sup>122</sup> However, low detection rates do not seem to be the only explanation, as an American study showed that more than half of patients diagnosed with osteoporosis had not been treated 12 months later.<sup>124</sup> A lower but still high percentage of non-treatment was found in a recent Australian study, in which 24% of 25,188 osteoporosis patients in primary care were not treated.<sup>125</sup>

A third explanation could be that patients often do adhere to treatment and feel that taking bone-strengthening medications in pill form is a burden.<sup>125</sup> This explanation has a weakness, however, in that both intravenous and subcutaneous options are available, although these options can be more expensive.

A fourth explanation could be a general reluctance to take medicines among patients.<sup>125,126</sup> However, this does not explain why treatment rates are much higher with, say, statins after heart attack.<sup>128,129</sup>

A fifth explanation could be the cost of treatment.<sup>125–127</sup> However, cheap generic variants have been available since the mid-2000s.<sup>11</sup>

A sixth and well-known explanation, which was not described in the mentioned surveys, is a weakness in the structure of health care.<sup>130</sup> This weakness is the fragmented nature of post-fracture care, which often involves several different physicians.<sup>130</sup> First, there are orthopedic surgeons, who fix the fracture but often leave osteoporosis screening and treatment decisions to primary care. Primary care physicians, in turn, often screen for osteoporosis only if this is recommended by an orthopedic surgeon. All the while, specialists in osteoporosis, often rheumatologists or endocrinologists, do not routinely encounter fracture patients. A response to this problem has been the creation of fracture liaison services, where post-fracture care is coordinated by a dedicated staff member, typically a nurse.<sup>130</sup> However, a recent Swedish study found that only 6% of hip fracture patients received treatment despite the existence of a fracture liaison service.<sup>119</sup>

A seventh explanation may be contraindications, such as hypocalcemia, or comorbidities such as gastrointestinal problems, poor renal function, and poor dental health.<sup>125</sup> Although contraindications by definition make treatment inappropriate, these comorbidities do not preclude treatment because non-oral

medications are available and because not all osteoporosis medications require a good renal function (denosumab).

An eighth explanation, which is reflected in surveys of both physicians and patients, may be concerns about adverse effects.<sup>125–127</sup> In support of this explanation, an American study showed that medication use have declined in the United States, which coincided with Google searches about their adverse effects.<sup>131</sup>

A ninth explanation, also reflected in surveys, could be that there are doubts about the effectiveness of available treatments, including doubts about what patients benefit from treatment.<sup>125,126</sup> This possibility is interesting because it contradicts systematic reviews and clinical guidelines, which clearly state that available medications are effective.<sup>65,132–134</sup> Nevertheless, a study of general practices in Sydney, Australia, failed to find medical reasons for BMD tests to be run on some patients but not others.<sup>135</sup> Furthermore, the treatment decisions seemed to be based solely on the BMD T-score cutoff of -2.5, while other risk factors for fractures were not associated with treatment. These finding led the authors to conclude that physicians seem to be unsure of who they should treat.<sup>135</sup>

In sum, the undertreatment of osteoporosis appears to be related to the perceived seriousness of disease, an unclear clinical responsibility to diagnose and treat it, and the perceived safety and effectiveness of available medications.

### *Who should be treated?*

Although there is broad agreement that osteoporosis is undertreated, determining who should be treated is not a straightforward task. Some clinical guidelines state that osteoporosis, as defined by a BMD T-score of -2.5 or less, is a sufficient condition for treatment.<sup>65,66,136–139</sup> Other guidelines, such as Swedish guidelines, recommend treatment only if additional risk factors for fracture are present, which are determined by a risk calculator (such as FRAX) or a history of fracture.<sup>133,134,140–144</sup> Furthermore, all of these guidelines recommend treatment in patients without osteoporosis who still have a high fracture risk.<sup>65,66,133,134,136–144</sup> Some of the guidelines even state that treatment can be considered in patients with a fragility fracture without further assessment of BMD or future fracture risk.<sup>65,133,137,139,144</sup>

The source of the difficulty probably lies in the definition of osteoporosis, which in turn is difficult - should the diagnosis be based on BMD or fractures? In the year 2000, a well-known osteoporosis researcher argued that the question of “Who has osteoporosis?” is not clinically important.<sup>55</sup> Instead, he argued, the

clinically important question is “Who should be treated?”, and the answer is patients who have a high fracture risk.<sup>55</sup> Recently, another well-known osteoporosis researcher went even further by arguing that osteoporosis, as defined by low BMD, should no longer be classified as a disease.<sup>145</sup> The reason for this, he argued, is that the definition of osteoporosis is both arbitrary and unhelpful; it is unhelpful because both patients and physicians expect people who have a diagnosis to be treated but no one else.<sup>145</sup> Instead, the researcher argued, clinical practice should shift and is shifting toward treating high fracture risks, where BMD is one of many risk factors. Let us take a closer look at the most commonly used medications, which are known as bisphosphonates.

### *Bisphosphonates as first-line treatment*

Bisphosphonates are the most commonly used bone-strengthening medications,<sup>11</sup> and they have the status of first-line treatment for osteoporosis in many clinical guidelines.<sup>65,133,139,146</sup> Bisphosphonates act by reducing the breakdown of bone tissue, a process known as bone resorption.<sup>147</sup> This reduction in resorption leads to an increase in BMD,<sup>147</sup> or to a slowed or stopped decline in BMD.<sup>148</sup>

The increase in BMD is often presumed to be the mechanism through which bisphosphonates reduce the fracture risks. However, meta-analyses and post-hoc analyses of clinical trials have shown that the increase in BMD cannot explain the entire reduction in fracture risk.<sup>149–152</sup> In these analyses, the degree to which the reduction can be explained by BMD varied considerably, from none or little (less than 20%) to most but not all (up to 70%). If additional mechanisms are indeed involved, these are unknown but may be related to improvements in bone quality, which are not captured by BMD, or to a reduction in falls.<sup>150,151,153</sup>

At least 11 different types of bisphosphonates have been developed over the years.<sup>154</sup> Not all of these in use everywhere in the world,<sup>154</sup> but in Sweden, the most common are alendronate, risedronate, and zoledronic acid.<sup>122</sup> Alendronate and risedronate are taken orally as pills, and zoledronic acid is administered intravenously by infusion. In the following two subsections, I will examine what is known about these three types of bisphosphonates, in terms of both their beneficial effects and harmful effects.

### *Benefits of bisphosphonates*

Supplemental Tables 1-3 describe the design and results of the 10 largest placebo-controlled trials of alendronate, risedronate, and zoledronic acid. These trials, which recruited a total of 33,166 participants, reported the following reductions

in fracture risk, although not all of the trials examined all types of fracture or showed statistically significant reductions:<sup>153,155–163</sup>

- 46-77% for clinical vertebral fractures
- 41-70% for morphometric vertebral fractures (morphometric meaning that they were detected by radiograph but did not come to medical attention, as clinical vertebral fractures were)
- 21-51% for hip fractures
- 12-47% for non-vertebral fractures
- 14-40% for any clinical fracture

This simple summary suggests that bisphosphonates have the greatest effect on vertebral fractures, a smaller effect on hip fractures, and the smallest effect on other non-vertebral fractures. Indeed, this pattern is confirmed by multiple meta-analyses of the trials,<sup>164–166</sup> although one found a similar effect on hip fractures and non-vertebral fractures.<sup>167</sup> An explanation for this pattern is that the greatest increases in BMD are seen at the hip and spine because these sites are rich in trabecular bone, which is most affected by bisphosphonates.<sup>11,168</sup> The effect might be greatest for vertebral fractures because these are more directly linked to skeletal fragility than other fracture are, since vertebral fractures are typically not caused by falls.<sup>11</sup>

As can be seen in the list of effects above, the estimated effects varied among trials. Two reasons for this variation could be differences in study design or differences in the effects of bisphosphonates. Although the effects of bisphosphonates on fractures have not been directly compared in head-to-head trials, any differences that may exist are believed to be small.<sup>132</sup> Another explanation could be random fluctuation, as the confidence intervals in the trials were wide. Confidence intervals were also wide in the meta-analyses,<sup>164–167</sup> so the exact magnitude of fracture reductions is unknown.

One of the 10 largest trials showed an unexpected beneficial effect of zoledronic acid: reduced mortality.<sup>153</sup> Although such an effect was not detected in the other trials, and although meta-analyses showed conflicting results,<sup>169–171</sup> many observational studies have shown that bisphosphonates are associated with lower mortality.<sup>172–184</sup> These associations are uncertain, however, because they could arise even if bisphosphonates have no effect on mortality; this would be the case if physicians tend to prescribe bisphosphonates to patients who have a decent life expectancy. This explanation, which is known as confounding, is plausible because older and sicker patients are less likely to receive treatment.<sup>119,122</sup>

The 10 largest trials primarily recruited women in their 60s or 70s who had osteoporosis, osteopenia, and/or a history of vertebral fracture (Supplemental Table 1). Although men sustain one third of all fractures that occur in people aged 50 or older,<sup>2,5,72</sup> men were included in only 2 of the trials (one of these included men only; the other included both men and women).<sup>153,162</sup> People aged 80 or older were also few, as the mean age ranged from 63 to 74 years, despite the fact that the highest fracture risks are seen in the oldest age groups.<sup>2,5,185</sup> Furthermore, more than half of hip fractures in Sweden and the United States occur in people aged 80 years or older.<sup>15,23</sup>

The underrepresentation of men and the oldest adults means that it is unclear whether bisphosphonates have the same effects in these patient groups. The possibility that bisphosphonates are less effective in patients aged 80 or older was raised after a clinical trial of risedronate failed to show a statistically significant reduction in hip fractures in this age group.<sup>160,186</sup> Similarly, a pooled analysis of zoledronic acid trials showed a statistically significant reduction in hip fractures only in participants under 75 (other fractures were, however, significantly reduced in older participants).<sup>187</sup> One proposed explanation for these findings was that the oldest adults fall often, which might offset the beneficial skeletal effects of bisphosphonates.<sup>186,187</sup> Two other possibilities that were given were low statistical power and, in the risedronate trial, the fact that the participants had not primarily been selected for low BMD.<sup>186,187</sup>

Another example that raised the possibility that bisphosphonates are less effective in the oldest age groups is a small trial of zoledronic acid conducted in nursing home residents.<sup>188</sup> When this trial did not detect an effect on fractures, the authors reasoned that treatment might be less effective in the oldest age groups because of their frailty and poor bone quality (separate from their low BMD).<sup>188</sup> Another explanation was that the trial was not powered to examine effects on fractures.<sup>188</sup> In contrast to these studies, a pooled analysis of alendronate trials showed no decline in anti-fracture effects from age 55 to 80.<sup>189</sup> It should also be mentioned that none of the studies showed that adverse effects were more common in the oldest age groups.<sup>186,187,189</sup> Overall, there is not a strong indication that bisphosphonates are less effective in the oldest age groups, although data are indeed scarcer in patients aged 80 or older.

As previously mentioned, data are also scarcer in men. Four trials of alendronate, risedronate, and zoledronic acid have been conducted in men specifically, and these were smaller than those conducted in women.<sup>162,190–192</sup> The four trials in men all showed that bisphosphonates increased BMD, and three of them detected significant reductions in morphometric vertebral fractures,<sup>162,190,191</sup> although one of these trials showed different results depending on the method that was used to determine vertebral fractures.<sup>190</sup> One of the trials also detected a reduction in

non-vertebral fractures.<sup>191</sup> In three of the trials, the investigators concluded that the effects are similar to those seen in women.<sup>162,190,192</sup> This conclusion is also supported by a subgroup analysis in a trial of zoledronic acid in male and female hip fracture patients,<sup>193</sup> which showed a similar increase in BMD among men and women. Although this trial detected a significant reduction in clinical fractures in women but not in men, the difference in effect was not statistically significant.<sup>193</sup>

Another underrepresented group is patients taking glucocorticoids. These patients were excluded from the 10 largest trials of bisphosphonates, which focused on primary osteoporosis (primary meaning that osteoporosis was not caused by a medication or an underlying disease). Separate trials were therefore conducted specifically in glucocorticoid-treated patients,<sup>194–204</sup> which led to the approval of bisphosphonates for the treatment of glucocorticoid-induced osteoporosis.<sup>205</sup> However, these trials primarily confirmed that bisphosphonates increase BMD, as only one showed a significant reduction in morphometric vertebral fractures.<sup>195</sup> None of the trials showed a reduction in clinical vertebral fractures or non-vertebral fractures. The reason for this could be that the trials were underpowered, as they were generally smaller and shorter than trials of primary osteoporosis, with less than 500 participants followed-up over 1 to 2 years instead of thousands of participants followed-up over 2-3 years.

In glucocorticoid-treated patients, greater statistical power has been achieved in meta-analyses. These analyses have shown significant reductions in vertebral fractures with risedronate, although with for other bisphosphonates and no significant reductions in non-vertebral fractures.<sup>205,206</sup> One of these meta-analyses showed that the pooled estimates for vertebral and non-vertebral fractures were similar to those obtained when pooling trials of primary osteoporosis and osteopenia, leading the authors to conclude that there is no signal of different effects.<sup>205</sup> However, there is still no statistically significant evidence from pooled analyses of clinical trials to show that bisphosphonates prevent non-vertebral fractures in glucocorticoid-treated patients.

As mentioned above, several of the 10 largest trials of bisphosphonates required a history of vertebral fracture, with or without low BMD (Supplemental Table 1). One trial required a history of hip fracture, regardless of BMD.<sup>153</sup> These trials were justified on the grounds that hip and vertebral fractures are associated with low BMD and an increased risk of sustaining new fractures.<sup>153,155</sup> However, this is true of most other types of fractures,<sup>94,95</sup> and no clinical trial has examined whether bisphosphonates reduce the risk of new fractures in patients with other types of fractures, unless these have been selected for low BMD. A post-hoc analysis of one clinical trial did examine such an effect, but this analysis failed to detect a reduction in new fractures, perhaps because of low statistical power.<sup>207</sup> Since non-hip, non-vertebral fractures constitute the majority of fractures that

occur,<sup>5,72</sup> the absence of trials demonstrating that bone-strengthening medications are effective for preventing new fractures may mean that an opportunity for secondary fracture prevention has been missed. This is especially the case because BMD might not be assessed in the majority of fracture patients.<sup>119,135</sup>

In summary, clinical trials provide substantial evidence that bisphosphonates reduce the risk of vertebral and non-vertebral fractures. However, these trials have been conducted in specific patient groups, which might limit their generalizability to the diverse groups of patients seen in clinical practice, including men, people aged 80 or older, people taking glucocorticoids, and older adults with a history of any fracture, who are not selected based on low BMD.

### *Harms of bisphosphonates*

As summarized in Supplemental Table 4, the 10 largest trials of bisphosphonates reported only one clear adverse effect: post-infusion, influenza-like symptoms after treatment with zoledronic acid.<sup>153,161,162</sup> One trial also noted that zoledronic acid might have increased the risk of atrial fibrillation, arrhythmia, and inflammatory ocular conditions and caused transient reductions in renal function and calcium levels.<sup>161</sup> However, these results were not confirmed in the three other large trials of zoledronic acid.<sup>153,162,163</sup> One of these three trials suggested that zoledronic acid increases the risk of myocardial infarction,<sup>162</sup> but a another trial found a lower risk of both coronary heart disease and cancer with zoledronic acid.<sup>163</sup> These conflicting results suggest that the higher risks seen in the zoledronic acid groups may well have been coincidences. Nevertheless, severely impaired renal function is still a contraindication for bisphosphonate treatment.

Despite these positive results from large clinical trials of bisphosphonates, two rare but serious adverse effects were detected after marketing: osteonecrosis of the jaw and atypical femur fractures. Osteonecrosis (literally “bone death”) of the jaw is defined as exposed and often painful bone in the mouth that does not heal within 8 weeks.<sup>208</sup> Osteonecrosis of the jaw was first reported to be associated with bisphosphonate treatment in 2003,<sup>209</sup> when an oral and maxillofacial surgeon described 36 cases who were all treated with intravenous bisphosphonates (pamidronate or zoledronic acid). Only one of these patients was treated for osteoporosis, whereas the others were treated for cancer-related hypercalcemia. This 2003 report was followed by additional reports.<sup>210–212</sup> Although no increased risk was observed in the original trials, in extension trials, or in meta-analyses,<sup>213–216</sup> osteonecrosis of the jaw is now a widely accepted adverse effect of bisphosphonate treatment,<sup>208</sup> which is listed in medication package inserts.<sup>217–219</sup> Even so, osteonecrosis it is rare in osteoporosis patients,

occurring primarily in cancer patients, who receive much higher cumulative doses of bisphosphonates (for example, monthly rather than yearly infusions of zoledronic acid).<sup>208</sup> One review estimated that the incidence of osteonecrosis of the jaw is between 1 per 100,000 and 1 per 10,000 per year in osteoporosis patients and 1 per 100 to 15 per 100 per year in cancer patients.<sup>208</sup>

A question that has been raised is why the jaw, of all sites, is affected.<sup>220</sup> This is a particularly relevant question because osteonecrosis is otherwise a condition that typically occurs in the hip, knee, or shoulder.<sup>221,222</sup> Although the reason for this has not been established, one explanation could be that the jaw bones are exposed to the outer environment, which makes them susceptible to bacterial infection, a common finding in cases of osteonecrosis of the jaw.<sup>220</sup> In contrast, bacterial infection is not a feature of non-jaw osteonecrosis, so although the two conditions may sound the same, they may in fact be two different conditions.<sup>220</sup> Another, simpler reason could be that there are few reports of bisphosphonate-related osteonecrosis in other skeletal sites.<sup>223</sup> A few large observational studies have examined whether bisphosphonates are associated with non-jaw osteonecrosis, and these have shown conflicting results.<sup>224,225</sup>

In 2005, two years after the first report on osteonecrosis of the jaw, the other serious adverse effect of bisphosphonates was discovered, atypical femoral fractures. This time, the report was of non-vertebral fractures occurring spontaneously in bisphosphonate-treated patients.<sup>226</sup> Atypical femoral fractures are now defined as fractures of the femoral shaft or subtrochanteric region that typically occur spontaneously or after a low-energy event and meet a few radiographic criteria.<sup>227</sup> As with osteonecrosis of the jaw, similar reports followed the initial one.<sup>228–230</sup> Although the clinical trials showed no increased risk,<sup>214,215,231</sup> atypical femoral fractures are now widely accepted as an adverse effect of bisphosphonate treatment and mentioned in medication package inserts.<sup>217–219,227</sup>

In contrast to osteonecrosis of the jaw, which mainly occurs in patients taking intravenous bisphosphonates for cancer, atypical femoral fractures primarily occur in people taking oral bisphosphonates for osteoporosis.<sup>227</sup> Another difference is that the risk of atypical femoral fracture clearly increases with the duration of bisphosphonate treatment,<sup>232–235</sup> which is not well-established for osteonecrosis of the jaw.<sup>208</sup> A similarity between the two adverse effects is that the associations are strong but the risks are low. For example, three studies estimated that the rate of atypical femoral fracture was 0.2, 1.7, and 5.5 cases per 10,000 treated patients per year, as compared with 0.1 in controls.<sup>232–235</sup>

## **Summary, general aim, and specific research questions**

The above discussion showed that (1) fractures are common; (2) fractures increase with age; (3) fractures can have serious consequences; (4) fractures can be prevented by bone-strengthening medications; (5) these medications are considered underused; (6) this underuse appears to be explained in part by concerns about the safety and effectiveness of available medications, as well as uncertainties about who should be treated; (7) the most commonly used bone-strengthening medications are bisphosphonates; and (9) there are still knowledge gaps in the beneficial and harmful effects of bisphosphonates. Therefore, the general aim of this dissertation was to further study the benefits and harms of bisphosphonates in older adults.

Four specific research questions were addressed:

- 1) Do bisphosphonates reduce the risk of new fractures in older adults who have a history of fracture?
- 2) Do bisphosphonates reduce the risk of fracture in people taking glucocorticoids?
- 3) Does confounding explain why bisphosphonates are associated with lower mortality in observational studies?
- 4) Do bisphosphonates increase the risk of non-jaw osteonecrosis?

It is beyond scope of this thesis to examine whether the undertreatment of osteoporosis is due to factors other than a lack of evidence of the benefits and harms of bisphosphonates. Examples of such factors are a low awareness of the effectiveness and safety of bisphosphonates, an underestimation of the problem of osteoporosis, or deficiencies in the structure of health care. These factors would have different implications for research.

My colleagues and I addressed these four questions in four separate research articles. The results of these articles are summarized in the Results chapter below. First, however, I will explain how the results were obtained.

# Methods

The four studies included in this dissertation were based on similar data and methods. This chapter discusses the data and methods that these studies had in common. Study-specific methods are presented in the Results chapter below and in the original publications.

## Study design

The four studies were all designed as retrospective cohort studies, in which bisphosphonate users and non-users were followed-up for fractures, osteonecrosis, or death. The data were obtained from Swedish registers, which are described in the next subsection.

A retrospective cohort design was chosen because it has several strengths in terms of time, cost, ethics, analysis, and generalizability. Since this type of study is based on pre-existing data, it can be conducted in large groups of people at little cost. The use of pre-existing data also means studies can be conducted quickly, as there is no need spend years enrolling and following-up participants. Furthermore, since Swedish registers cover all residents of the country, it is possible to study groups of people that are representative of the average patient seen in clinical practice. In terms of analysis, cohort studies have an advantage over case-control studies in that disease occurrence can be calculated. An ethical advantage of cohort studies compared to clinical trials is that the researchers do not decide which patients do and do not receive treatment (this is the decision of the health care professionals).

The retrospective cohort design also has several limitations. First, as in any observational study, the possibility of confounding is always a source of uncertainty. Second, retrospective cohort studies can be particularly prone to confounding because the use of pre-existing data means that the researchers cannot ensure that important variables are included and measured accurately. Third, since the researchers do not have contact with the people included in the study, there is no way to encourage good adherence to treatments. Fourth, many medical conditions are underreported in registers, which limits confounding control and outcome tracing. Despite these limitations, my coauthors and I decided to proceed with the retrospective cohort design because of its strengths.

## Data sources

The data came from six Swedish registers. Four of these registers are managed by the National Board of Health and Welfare, which is a government agency under the Ministry of Health and Social Affairs:

1. The National Patient Register
2. The Prescribed Drug Register
3. The Cause of Death Register
4. The Cancer Register

One register is managed by Statistics Sweden, which is the agency of government statistics:

5. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA)

The final register is managed by the regional government in Skåne County:

6. The Hip Fracture Register

These six registers are presented in detail in the next subsection, which is followed by a discussion of their linkage and quality.

### *The registers*

The National Patient Register is a database of hospitalizations and physician visits in secondary care.<sup>236</sup> Although it was created in the 1960s, it was initially a regional register of hospitalizations for somatic conditions around Uppsala. In the 1970s, it was extended to cover hospitalizations for psychiatric conditions, but it did not become national until 1987, when all hospitals in Sweden were required to report somatic and psychiatric hospitalizations to the register. In 2001, it was further extended to include physician visits in secondary care, to which both public and private health-care providers must report visits.<sup>236</sup> Primary care is not included in the register, although this addition has been discussed.<sup>237</sup>

In the National Patient Register, each hospitalization or physician visit is assigned a primary diagnosis, indicating the main reason for the hospitalization or visit<sup>236,238</sup> The primary diagnosis is typically a medical condition, but it can also be a provided treatment or a performed examination (e.g., follow-up care).<sup>238</sup> Secondary diagnoses can be added to indicate additional conditions, treatments,

or examinations.<sup>238</sup> Since 1997, diagnoses have been classified according to the International Classification of Diseases, 10<sup>th</sup> Revision (ICD-10). Other data available in the register include the date of the visit or admission and, for hospitalizations, the discharge date.<sup>236</sup>

The Prescribed Drug register is a database to which all pharmacies in Sweden are required to report sold prescription medications.<sup>239</sup> The term “prescribed” is somewhat confusing, because the register records only prescribed medications that are later collected. The register does not contain information on over-the-counter drugs or drugs given in health care.<sup>239</sup> For each prescription, the available information includes the collection date, prescribing date, Anatomical Therapeutic Chemical code, strength, pack size, and quantity purchased.<sup>239</sup>

The Cause of Death Register contains data on all deaths that occur in Sweden and among residents of Sweden abroad.<sup>240</sup> It was created in 1961, but data from 1952-1960 were added retrospectively.<sup>240</sup>

The Cancer Register was created in 1958. It is a database to which all health care providers in Sweden are required to report newly diagnosed cases of cancer.<sup>241</sup> Although cancer diagnoses are available from the National Patient Register, the Cancer Register is older and more detailed.

The LISA register contains socioeconomic data (e.g., income, education, and early retirement) on the Swedish population since 1990.<sup>242</sup> Only people aged 15 or older are included (until 2009, the lower age limit was 16 years).

The Hip Fracture Register is a database of hip fracture patients that was created in 1988 to monitor and improve the quality of hip fracture care in Sweden.<sup>243</sup> It differs from the other registers in that patients can choose not to participate. The advantage of the Hip Fracture Register over the National Patient Register is that it contains detailed patient information, including type of surgery, physical status, and mental status.

### *Linking the registers*

The different registers could be linked because they all store data along with Personal Identity Numbers. A Personal Identity Number is a 10-digit number consisting of a person’s date of birth and four extra digits. It is assigned by the Swedish Tax Agency to every resident of Sweden upon birth or immigration.<sup>244</sup> To protect the integrity of the registered persons, we received data files in which Personal Identity Numbers had been replaced by arbitrary identifiers. These arbitrary numbers were generated by Statistics Sweden, which sent the list of

generated numbers and the corresponding Personal Identity Numbers to the other agencies that provided us with data. The list is deleted by Statistics Sweden after 3 months.<sup>245</sup> This deletion does not mean that the data are anonymous, because it might still be possible to identify individuals using the large number of variables.<sup>246</sup>

### *The quality of the registers*

The quality of a register is determined by the accuracy of its data and the completeness of its coverage. In a widely cited review of the National Patient Register, most of the reviewed diagnoses were 85-95% accurate.<sup>236</sup> Coverage was lower, especially for conditions that are not always hospitalized (e.g., angina pectoris or hypertension). The review estimated an accuracy and coverage of at least 95% for hip fractures. Other types of fractures were not included, but additional studies have estimated that more than 90% of fracture diagnoses are accurate, although only 84-87% may be accurate to the fourth ICD-10 character (that is, for specific fracture sites).<sup>247,248</sup> One of the studies estimated that the coverage of humeral fractures was 98%.<sup>248</sup>

Only one of the three mentioned validation studies included outpatient care,<sup>248</sup> so the quality of outpatient diagnoses are less certain. According to the National Board of Health and Welfare, 6% of private secondary-care providers fail to report to the National Patient Register.<sup>249</sup> Another limitation is that the occurrence of vertebral fractures is probably underestimated because these are often managed in primary care, which is not included in the register.<sup>250</sup>

To my knowledge, only one previous validation study of the National Patient Register has been conducted for osteonecrosis diagnoses, and that study was published by my research team.<sup>251</sup> In that study, one of my colleagues reviewed 30 osteonecrosis diagnoses at Umeå University Hospital, Sweden. Of these diagnoses, 27 (90%) were determined to be correct, 2 (7%) probably correct, and 1 (3%) incorrect. A limitation of this analysis was that it was a small convenience sample from one university hospital.

In sum, the accuracy and completeness National Patient Register has not been comprehensively reviewed for fracture and osteonecrosis. For osteonecrosis, there is very little data. However, the available data suggest a high but not perfect accuracy and coverage for fractures and a high but not perfect accuracy for osteonecrosis.

To my knowledge, there is no published study of the accuracy and completeness of the Prescribed Drug Register. However, a report from the National Board of

Health and Welfare states that the data quality should be high, as pharmacies are legally required to report sales data, which are submitted automatically and checked by the Board.<sup>252</sup>

Similarly, the Cause of Death Register has not to my knowledge been validated in a published study, but the National Board of Health and Welfare states that it is complete because all deaths reported to authorities are included.<sup>253</sup> Causes of death are less accurate because determining causes of death is notoriously difficult.<sup>240</sup>

The Cancer Register was validated in 1998 (although the study was published in 2009).<sup>241</sup> This study estimated a 96% coverage of cancer diagnoses, which was assessed by comparison with the National Patient Register.

According to Statistics Sweden, the quality of the LISA register is good.<sup>254</sup>

The quality of the Hip Fracture Register has been examined in a comparison with the National Patient Register.<sup>255</sup> This comparison showed that the coverage of the Hip Fracture Register increased from 63% in 2008 to 90% in 2014. By 2017, its coverage had declined to 81%, primarily because five hospitals had withdrawn. Patients included in the Hip Fracture Register were slightly younger and healthier than excluded patients were. Admission dates agreed perfectly in 89% of cases, and 99% were at most a week apart. The authors concluded that the quality of the register is high.

In sum, the registers have a high quality in general. An important limitation is that several conditions are underreported in the National Patient Register, which reduces the ability to control for confounding diseases and to study vertebral fractures.

## **Study cohorts**

Studies 1, 2, and 4 were based on the cohort of all older adults aged 50 years or older who were living in Sweden on December 31, 2005. Study 3 was instead based on the cohort of patients aged 50 years or older who were registered in the Hip Fracture Register from July 2006 through December 2015. We chose the age limit of 50 years because this is common in osteoporosis research.<sup>69,73</sup> The reason for this is that many women go through menopause around this age,<sup>69</sup> which leads to sharp decline in bone mass, particularly trabecular bone mass, due to a reduction in estrogen production.<sup>85</sup>

## Variables

### *Exposure*

The exposure was bisphosphonate use, which was compared to nonuse. Bisphosphonate use was defined as having a record of alendronate, risedronate, or zoledronic acid in the Prescribed Drug Register. The date of treatment initiation was defined as the date of the earliest record (the earliest collected prescription).

Previously treated persons were excluded from the studies, which is called a new-user design.<sup>256</sup> This design avoids the selection bias that can occur when current and adherent users are included, as these are typically healthier than non-adherent patients are. It also avoids adjustment for mediators, that is, variables affected by the treatment.

It has been recommended that observational studies use a grace period equivalent to the run-in period in randomized trials.<sup>257</sup> In such a design, baseline is set as a date after treatment initiation, such as 3 months later, to exclude those who are not adherent. Those who die during the first 3 months can be randomly assigned to the study groups (adherent or non-adherent).<sup>257</sup> We did not use grace periods because we saw no good reason for including only adherent bisphosphonate users.

### *Outcomes*

The study outcomes were fracture (in Studies 1 and 2), death (in Study 3), and non-jaw osteonecrosis (in Study 4). Fractures and osteonecrosis were traced through the National Patient Register. Deaths were traced through the Cause of Death Register.

A caveat in tracing fractures and osteonecrosis through the National Patient Register is that it does not distinguish between new diagnoses and readmissions or follow-up visits for previous diagnoses. Ignoring this limitation can lead to a large overestimate in fracture occurrence. For example, Bergdahl and colleagues showed that it would create a 40% overestimate in inpatient humeral fractures.<sup>248</sup>

In Study 4, we solved this problem by simply excluding people with a history of osteonecrosis before baseline. This solution was not appropriate in Studies 1 and 2, where we wanted to include people with a history of fracture. In Study 1, we therefore required that the fracture was the primary diagnosis, and we ignored

identical primary diagnoses occurring within 3 months. In Study 2, we included both primary and secondary diagnoses, to reduce the risk of underestimating fracture occurrence. However, the use of secondary diagnoses increases the risk of counting readmissions and follow-up visits.<sup>258</sup> Therefore, we used a diagnosis-free period of 6 rather than 3 months, as this seemed to be the most common in previous studies.<sup>259–261</sup> In Study 2, we also incorporated the fact that small changes in the diagnosis are not necessarily new events by applying the 6-month rule to groups of fractures (clavicle, hip, humerus, wrist, pelvis, leg, or vertebrae), rather than exact diagnoses.<sup>258</sup>

Although this approach of defining new events by using a fracture-free time window is common,<sup>259–261</sup> it has been shown to be inadequate for fracture admissions in the National Patient Register. According to one study,<sup>258</sup> 19% of hip fracture readmissions occurred 1 year or more after the initial admission. Many readmissions also had a different diagnosis (35% to the fourth ICD-10 character and 26% to the third character). As an alternative method, the authors derived a prediction model consisting of such variables as patient age, diagnosis (to the fourth ICD-10 character), time between admissions, and type of clinic. The authors reported that the model had a sensitivity and specificity of 97%. In hindsight, we should have used this model or a similar one, but we were not aware of it at the time.

It has been recommended that the outcomes in observational studies be defined similar to outcomes in a clinical trial, so that results are comparable and of a high quality.<sup>257,262</sup> To ensure a high quality, the study staff should preferably collect data systematically and without knowledge of the participants' treatment status, so that the outcomes are measured the same way in all participants.<sup>257</sup> This was not possible in our register-based studies. This limitation probably made little or no difference for fractures and deaths, which are generally straightforward, but it could have made a difference for osteonecrosis.

## *Confounders*

A confounder is a variable that produces confounding. Confounding means that a difference in disease risk between two groups, say, bisphosphonate users and nonusers, is not an effect of the medication. Instead, the difference is due to an underlying difference in risk between treated and untreated people. A confounder can also produce a similar disease risk in the groups even though the medication does have an effect.

As potential confounders, we primarily considered age, sex, diagnoses, medications, and socioeconomic factors (Supplemental Table 5). In Studies 1 and

2, we selected potential confounders based on common risk factors for fracture. In Study 3, we selected confounders that were used in previous studies of bisphosphonates and mortality. In addition, we selected risk factors included in the popular fracture risk assessment tool FRAX. In Study 4, we included primarily risk factors for osteonecrosis among those we had identified in a previous study of ours.<sup>251</sup>

### *Effect modifiers*

Effect modifiers are variables that change the effect of a treatment. This concept should not be confused with a confounder, which masks the treatment effect but does not change it. In the four studies here, we considered different possible effect modifiers, including age, sex, glucocorticoid use, previous fracture, previous fracture site, and type of bisphosphonate.

### **Matching**

All four studies in this dissertation were matched. This means that, for each bisphosphonate user, we selected one or more nonusers with similar characteristics in terms of age, sex, diagnoses, medications, and socioeconomics.

The purpose of matching was twofold. First, by selecting similar bisphosphonate users and nonusers, matching controlled for confounding. The advantage of using matching to control for confounding over analytic techniques such as regression is that it is easy to understand, requiring no particular skills in statistics or mathematics, only the ability to read a comparative table of the study groups' characteristics.<sup>263</sup> Some researchers have suggested that the use of propensity scores and other sophisticated analyses are important for eliminating confounding.<sup>264</sup> However, others have pointed out that these methods do not seem to perform better than ordinary regression analysis.<sup>265</sup>

Second, matching is a way to create clearly distinguishable treatment and control groups with comparable baseline dates when, as in this case, no person is treated when entering the study cohort and those who later receive treatment do so at different times. Therefore, matching can also properly handle pre-treatment follow-up time in the treatment group. Bias can arise if this time is excluded, without an equivalent exclusion in the control group, or if it is misclassified as treated time.<sup>266–269</sup>

We used two different types of matching. These will be explained next.

## *Exact matching*

In studies 1 and 4, we used exact matching (a term I have borrowed from Rosenbaum<sup>263</sup>). By exact matching, I mean that bisphosphonate users were matched to 1-3 controls who had identical values on the matching variables. This approach ensures complete comparability on the matching variables. However, it also means that it can be impossible to find matches on more than a few variables (we used three matching variables in Study 1 and five variables in Study 4). This limitation means that it may be necessary to control for additional confounders in the analysis, as we did in Studies 1 and 4. The second matching method does not have this limitation.

## *Time-dependent, propensity-score matching*

In Studies 2 and 3, we used time-dependent propensity score matching.<sup>269,270</sup> This method has two advantages over exact matching. First, this method makes is easy to match on a large number of variables.<sup>270</sup> The reason for this is that the variables are all combined to a single matching variable, known as the propensity score. The propensity score is defined as each person's probability of receiving treatment based on his or her characteristics. This probability is estimated using Cox regression with time-varying variables. Since the match is based on the propensity score only, bisphosphonate users and nonusers will not be matched exactly. However, the study groups will still be comparable because of the balance property of the propensity score.<sup>270</sup> This remarkable property means that matching on the propensity score alone will lead to an overall balance in the confounders between the treatment group and the control group.<sup>270</sup>

The second advantage of time-dependent propensity score matching is that it does not use future data.<sup>269</sup> This means that, in contrast to the exact matching method described above, the study cohort was not divided into bisphosphonate users and controls based on whether they ever received treatment during the study period. Instead, matching was done sequentially in pairs,<sup>270</sup> starting with the first person to receive bisphosphonates. This person is matched to the most similar of the other persons (including those who might later receive treatment) at the time of his or her treatment initiation. Similarity is assessed by difference in propensity scores. Next, among the remaining patients, the second to receive bisphosphonates is matched to the most similar of the still untreated patients or never treated patient. This process continues until no more matches are possible, and it makes the study groups comparable at treatment initiation in the treated group.

The argument for letting the control group consist of both never-treated and later-treated patients is that excluding later-treated patients (that is, using data on their future medication use) means that the control group might consist of those who never need treatment.<sup>269</sup> In other words, the control group might become healthier than the treatment group. We expected this bias to be low in Studies 1 and 4, where we used exact matching, because few people received bisphosphonate treatment, so few of these would have been matched as controls.

## **Baseline and follow-up**

In each of the four studies, baseline was defined as the date of treatment initiation in the bisphosphonate group and the corresponding date in the control group. The two groups were then followed up for the study outcomes (fracture, death, or osteonecrosis).

According to the STROBE reporting guidelines for cohort studies,<sup>271</sup> the duration of follow up should be reported so that readers can get a sense of the how long the study was. The recommended way to calculate follow-up duration is by taking the difference between the baseline date and the date of death, outcome occurrence, or study end date (whichever came first).<sup>271</sup> This is how we calculated follow-up duration in Studies 1 and 4. However, this method has a limitation in that the study can look short just because the outcome is common and occurs early. Therefore, I left outcome occurrence out of the calculation of follow-up duration in Study 2. In Study 3, the definition was not an issue because death was the outcome.

## **Statistical analysis**

We measured outcome occurrence using incidence rates (the number of persons with the outcome divided by the total number of person-years of follow-up). The use of incidence rates rather than risks had two advantages. First, incidence rates take into account unequal follow-up durations among patients. Second, incidence rates can easily be calculated for specific periods of follow-up (such as Year 1, Year 2, etc.). This flexibility makes it easy to see trends in outcome occurrence. A disadvantage of incidence rates is that they are more difficult to interpret than risks, so in Studies 2-4 we also estimated risks using the Kaplan-Meier method.

It has been recommended that observational studies imitate the intention-to-treat analysis that is commonly performed in clinical trials.<sup>257,262,272</sup> This can be done by defining treatment as collecting just one prescription and ignoring what happens after that. In clinical trials, a per-protocol analysis is sometimes performed instead, and this type of analysis can also be imitated in an observational study, for example by censoring upon treatment discontinuation in

the treated and treatment initiation in controls.<sup>257</sup> Some researchers advocate a per-protocol analysis in observational studies because the intention-to-treat analysis can underestimate the treatment effect while not having the benefit of randomization.<sup>273</sup> Others have said that both analyses can be used, although a per-protocol analysis may require adjustment for post-baseline variables, which is more advanced (and beyond my skill).<sup>257</sup> We used the intention-to-treat principle in Studies 1 and 3. In Study 2, controls were censored if they received treatment. In Study 4, we analyzed the treatment period and the post-treatment period separately.

Because of varying follow-up times, the associations between bisphosphonate use and the study outcomes were mainly assessed using hazard ratios, estimated using Cox regression. In Study 3 however, we used relative risks because these are easier to interpret. The Cox models were adjusted for confounders in Studies 1 and 4 but not in Studies 2 and 3, where all confounders were used for matching. When running Cox models, we took into account the matching of the data by using robust standard errors. An alternative approach would have been to run Cox models stratified by matched pairs, but a simulation study has shown that robust standard errors performed better (had a lower variance).<sup>274</sup> Effect modification was tested using treatment-by-effect modifier product terms in the Cox models. P-values less than 0.05 were considered statistically significant.

We conducted sensitivity analyses in all four studies, as has been recommended for observational studies.<sup>264</sup> One particular type of sensitivity analysis that has been recommended is to examine the potential influence of unmeasured confounders.<sup>265</sup> I did not conduct this type of sensitivity analysis because it was beyond my skill.

## **Ethics**

This research was approved by the former Regional Ethical Review Board in Umeå (approval numbers 2013-86-31M, 2013-304-32M, and 2017-100-32M). This board is now part of the national Swedish Ethical Review Authority, which replaced all regional ethical review boards in the country in 2019.

Although this project was approved, one ethical issue should be mentioned. This issue is that the people who were studied did not provide informed consent. Register-based research is not exempt from the general requirement of obtaining informed consent, but the Declaration of Helsinki permits research without consent if collecting it would be impractical or impossible.<sup>275</sup> This is arguably the case in the current dissertation, which involved data on millions of people.

Research without consent is also permitted by Swedish law if the research involves negligible risks for participants.<sup>276</sup> This is also arguably the case here, where the research was based entirely on preexisting data. However, there is still risk that people's privacy is violated, which is why we received data without personal identifiers. As previously discussed however, the amount of detail in the data means that it can be possible to identify individuals. Therefore, we are still required to handle the data confidentially, which implies that the original data cannot be made publicly available. The downside of this is that the transparency of the research is lower than would ideally be the case.

# Results

## Study 1: bisphosphonates after a fracture

In Study 1, my coauthors and I examined whether bisphosphonates reduce the risk of new fracture after a previous fracture in older adults. My role in this first study was to analyze the data and to draft the manuscript, but I did not conceive the study, collect the data, or design the study. We proceeded as follows.

We identified every resident of Sweden who was aged 50 years or older on December 31, 2005. Next, we selected everyone who was diagnosed with a fracture between 2006 and 2011 and who was not treated with bisphosphonates at the time, which was defined as not having collected a bisphosphonate prescription since July 2005. Finally, each patient who received a bisphosphonate was matched to one, two, or three untreated patients (controls) on sex and year of birth. The final study cohort consisted of 83,104 matched patients.

The results of this study were not straightforward, so they require a careful explanation. The results showed that bisphosphonate use was initially associated with an *increased risk* of new fracture, but this association diminished over time; after 12-18 months, there was no association between bisphosphonate use and fractures. The initial increase in risk appeared to be explained by the fact that high-risk patients were more likely to receive treatment, as these also had an increased risk of sustaining new fracture in the period before starting treatment.

The subsequent decrease in risk can be explained in at least two different ways. One way is that the decrease was a beneficial treatment effect, where bisphosphonates gradually eliminated the high risk of fracture seen in treated patients. This interpretation was our conclusion in the published article. However, we mention another explanation in the limitations section, namely that the decrease could be due to a bias known as depletion of susceptibles.<sup>277</sup> Depletion of susceptibles means that the association would have diminished over time because the high-risk patients, who were disproportionately bisphosphonate users, had already sustained fractures, leaving lower-risk treated patients to be compared with controls.

Despite the presence of these two contradictory explanations, one in favor of treatment effect and the other in favor of bias, we concluded that the results were consistent with a beneficial treatment effect. This conclusion, I must admit, is unjustified: it is skewed in favor of the most desirable interpretation of the data,

as we did not explain why the results were more likely to be treatment effects than biased associations.

Even without bias or confounding, the results would have been difficult to interpret from a clinical perspective because we did not know whether treatment decisions were based on the patients' BMD. If most patients did undergo a BMD test, then our results would not have answered the main research question, which was whether bisphosphonates reduce the risk of new fractures in fracture patients who are not selected based on low BMD. In other words, the lack of data on BMD was a major limitation, not only in terms being an important confounder but also in terms of understanding the study cohort.

In summary, the results of this study were ambiguous, in part because of confounding, in part because we used a biased method to compensate for confounding. Even so, I made a second attempt to estimate the effects of bisphosphonates on fractures: Study 2.

## **Study 2: bisphosphonates during glucocorticoid therapy**

Study 2 was an attempt to estimate the effect of bisphosphonates on fractures in patients taking glucocorticoids. We limited the analysis to alendronate, the most commonly used bisphosphonate. My role in this study was to design the study, analyze the data, and draft the manuscript. I did not conceive the study or collect the data. Because of the difficulties we encountered in Study 1, I set out to make this study more methodologically rigorous than Study 1.

We started by identifying every resident of Sweden who was aged 50 years or older on December 31, 2005. We then selected those who had started long-term glucocorticoid therapy (defined as  $\geq 3$  months with prednisone or equivalent,  $\geq 2.5$  mg/day) during 2006 to 2011. Next, we used time-dependent propensity score matching to obtain an alendronate group and a control group, matched in pairs on age, sex, diagnoses, medications, glucocorticoid dose, and prior glucocorticoid duration. The final study cohort comprised 33,780 bisphosphonate users and controls, who were followed-up for fractures.

In contrast to Study 1, Study 2 showed that bisphosphonate use was associated with a lower risk of fracture. This association was similar to the effects seen in meta-analyses of clinical trials that have been conducted in postmenopausal (that is, primary) osteoporosis or glucocorticoid-treated patients, although the effects in glucocorticoid-treated patients were not statistically significant. Therefore, we concluded that alendronate appears to have comparable effects in postmenopausal osteoporosis and glucocorticoid-induced osteoporosis.

Another difference with Study 1, which explains the difference in results, is that the study groups appeared to be comparable at baseline, as they had an initially similar risk of fracture. This finding suggests that there was little or no confounding, perhaps because glucocorticoid-treated patients are more homogeneous than fracture patients are. However, another analysis suggested that some amount of confounding was still present in the study, because bisphosphonate use was associated with *increased* risk of fracture among patients who had received bisphosphonates after three or more months of glucocorticoid therapy. This increased risk suggests that the patients treated after 3 or more months were patients discovered to have, or be at risk of, osteoporosis.

Even so, the overall results still showed that bisphosphonate use was associated with a lower risk of fracture. The reason for this was that patients who were treated with bisphosphonates within the first two months of glucocorticoid therapy had a lower risk of fracture than controls. It is possible that this result was also due to confounding but in the opposite direction, where healthier, lower-risk patients were prescribed bisphosphonates for the prevention of glucocorticoid-induced osteoporosis. However, such confounding would conflict with what we learned from Study 1, so a likelier explanation is that bisphosphonates that were prescribed during the first two months of glucocorticoid therapy were closer to being randomly assigned (for example, assigned without the information of a BMD test). Therefore, my overall assessment is there is reason to believe that the results reflect a true reduction in fractures. However, this reduction is probably underestimated because of confounding in later-treated patients.

As this discussion shows, the results are more uncertain than the conclusion of the original article suggests. Overall, the results do suggest that bisphosphonates reduce the risk of fractures in glucocorticoid-treated patients, but the magnitude of the effect is probably confounded by BMD. Furthermore, the similarity with meta-analyses of clinical trials is not a strong argument for causality because, although this type of argument is common,<sup>278–281</sup> it implies that the quality of research can be judged by how well it confirms current evidence, which is obviously wrong. To illustrate how difficult it is to obtain robust evidence of the effects of bisphosphonates in an observational study, I proceeded by conducting Study 3.

### **Study 3: bisphosphonates and mortality**

In Study 3, we examined whether confounding explains why numerous observational studies have shown that bisphosphonate use is associated with lower mortality. My role in this study to conceive and design the study, analyze the data, and draft the manuscript. I assisted in data collection.

As mentioned in the Introduction, the background to the study was that many observational studies,<sup>172–184</sup> but only one clinical trial,<sup>153</sup> had shown that bisphosphonate use is associated with lower mortality. Although most of the authors of these observational studies interpreted the results as evidence of an effect,<sup>172–175,177–184</sup> the authors of one study were more skeptical.<sup>176</sup> These authors argued that the association may be confounded because their study showed a lower mortality rate in patients who had received only one prescription for a bisphosphonate (that is, at most 3 months of treatment), which they argued was unlikely. I thought that the authors' conclusion could be made more convincing if their approach was taken to its logical extreme: examining whether mortality is lower from the first day of treatment. I decided to examine this in a study of my own.

To give the observational study an honest chance to produce robust results, I set out to conduct the most rigorous observational study I could. Therefore, I used data from the Hip Fracture Register, which contains more patient information than any other register that our research team uses. Another advantage of studying a single patient group like hip fracture patients is that homogeneity reduces confounding.<sup>282</sup> To reduce confounding further, I emulated the eligibility criteria of the one clinical trial that has shown that a bisphosphonate reduced mortality.<sup>153</sup> Doing so has been recommended to improve the quality of observational studies.<sup>257,262,278</sup> Emulating the eligibility criteria also reduced the likelihood that any differences in results would be due to differences in study population.<sup>257,262,278</sup> As regards data analysis, I used time-dependent propensity score matching on age, sex, diagnoses, medication use, type of hip fracture, type of surgical procedure, and physical status. To verify that the choice of analysis was unimportant, I also ran a Cox regression on all eligible persons.

The results showed that bisphosphonate use was associated with lower mortality, and the association was the same regardless of whether regression or matching was used. Furthermore, a lower mortality rate could be seen from the second day treatment, which was statistically significant from the second month. We reasoned that such an early treatment effect is not impossible, but it is unlikely, so confounding is likely. As previous observational studies also showed early associations, our results suggest that these results should be interpreted with caution.

The results also suggest that confounding is not necessarily eliminated even if advanced statistical methods and thorough study design are used. Although the results have scientific value by pointing to an uncertainty in the results of previous studies, they have little clinical relevance because bisphosphonates are not prescribed to reduce mortality.

There is a discussion in the epidemiology literature that observational studies of adverse effects are less likely to be confounded than studies beneficial treatment effects, such as mortality.<sup>283–286</sup> Consistent with this discussion, an adverse effect of bisphosphonates was the topic of the final study in this dissertation: Study 4.

## **Study 4: bisphosphonates and osteonecrosis**

In Study 4, we examined whether bisphosphonates are associated with an increased risk of non-jaw osteonecrosis. We also included another type of bone-strengthening medication, denosumab, but I will leave denosumab out of most of the discussion here because it is beyond the scope of this dissertation and because only 3% of the treatment group used it. In contrast to the other studies in this dissertation, my role was limited to reviewing the literature and drafting the Introduction.

The study was designed as follows. Just as in Studies 1 and 2, we identified every resident of Sweden who was 50 years of age or older on December 31, 2005. Using exact matching, we then matched everyone who received a bisphosphonate during 2006–2017 to an untreated control on sex, year of birth, Swedish background (defined as being born in Sweden or having two parents born in Sweden), history of hip fracture, and (if applicable) type of hip fracture and type of surgery. Cox regression was used to control for additional confounders, which were in part selected based on the results of a previous study of ours, which examined risk factors for osteonecrosis.<sup>251</sup> We excluded those who had been diagnosed with osteonecrosis or who had received a bisphosphonate before baseline (the start of bisphosphonate treatment and the corresponding date in controls).

The results showed that osteoporosis treatment was associated with an increased risk of non-jaw osteonecrosis. In the Discussion section of the article, we mention additional results that support a cause-and-effect explanation: the highest risk was seen in patients receiving the most potent medications (denosumab or zoledronic acid), the risk decreased after treatment was stopped, and the analysis included many confounders. Nevertheless, we conclude the article by stating that the results could not be evaluated for causality, as unmeasured confounding was still a possibility.

The cautiousness of this conclusion may be scientifically wise, but it ignores the clinically relevant question: Should we be concerned? Any answer to this question is to some degree subjective, but I believe several factors should mitigate concerns.

First, although osteoporosis is not an established risk factor for osteonecrosis,<sup>222</sup> there is evidence that it is a risk factor.<sup>225,287,288</sup> If so, then osteoporosis would be a confounder that would explain not only the overall association with osteonecrosis but also why the most potent medications were associated with a highest fracture risk, as these might be given to those with the severest osteoporosis.

Second, although a decrease in risk was seen after treatment discontinuation, such a decrease could also be seen during treatment. The latter is more difficult to see because it is not presented in the same type of figure, but it is noticeable upon a close look at Figure 1, which shows that the slope of the risk curve decreases. This makes the apparent decrease in risk after bisphosphonate treatment less convincing as an effect of discontinuation.

Third, whereas osteonecrosis of the jaw was discovered in case reports, there are few case reports of non-jaw osteonecrosis.<sup>289–291</sup> Nevertheless, non-jaw osteonecrosis is much more common, as we explained in the original publication, so an increased risk might not be noticeable to clinicians.

Fourth, although jaw osteonecrosis and non-jaw osteonecrosis may sound the same, they may in fact be two different conditions. For example, bacterial infection is common in osteonecrosis of the jaw but not in non-jaw osteonecrosis.<sup>220</sup>

Fifth, bisphosphonates have actually been used to treat non-jaw osteonecrosis. In these cases, treatment is given to reduce pain and to prevent progression, although evidence of progression prevention is scarce.<sup>292,293</sup> This makes it less plausible that osteonecrosis is an adverse effect.

For these reasons, I conclude that the results of Study 4 are ambiguous. It is possible that bisphosphonates increase the risk of osteonecrosis, but the risk of confounding is high. Therefore, I believe there is little reason for concern at this time.

# Discussion

As the previous chapter explained, the four studies showed that bisphosphonate use was associated with

1. an initially increased risk of new fracture after a previous fracture, which diminished over time. The initial increase appeared to be due to high-risk patients' receiving treatment;
2. a lower risk of fracture during glucocorticoid therapy;
3. a lower mortality rate within days of bisphosphonate treatment;
4. an increased risk of non-jaw osteonecrosis.

As the previous chapter also explained, most of these results are difficult to interpret as true benefits or harms of bisphosphonates, primarily because of the high risk of confounding by BMD and life expectancy. The exception to this is Study 2, in which there is reasonable chance that bisphosphonates reduced the risk of fractures among glucocorticoid-treated patients.

In Study 1, confounding was apparent in the data because the initially increased risk of fracture was also observed before treatment initiation. We tried to solve this problem by showing that the increased risk diminishes over time, which we concluded in the published article is consistent with a gradual treatment effect. However, previous research has explained that this type of analysis is biased because an increased risk can diminish because high-risk patients, who are disproportionally found in the treatment group, have already sustained fractures, leaving lower-risk treated patients to be compared to controls.<sup>277</sup> In other words, the problem of confounding in Study 1 seems to have been replaced with a problem of bias.

In Study 2, confounding was not as apparent as in Study 1. However, there was still evidence of confounding because bisphosphonate-treated patients had an increased risk of fracture if they had received their treatment after three or more months of glucocorticoid therapy. The likeliest explanation for this finding is that treatment was prescribed to patients who were discovered to have, or be at risk of, osteoporosis (that is, confounding by BMD). In contrast, bisphosphonate treatment was associated with a lower risk of fracture in patients who received it within two months of glucocorticoid therapy, perhaps because treatment was initially closer to being randomly assigned. This lower risk result is also more difficult to explain by confounding, because it is unlikely that low-risk patients were more often treated. Due to the apparent confounding in later-treated patients, the overall results were probably an underestimated effect of bisphosphonate treatment on fractures.

In Study 3, the lower mortality rate observed within days of treatment initiation is consistent with confounding. Although such an early treatment effect cannot be ruled out, the consistency with confounding implies that the results of this study, as well as those of similar observational studies, should be interpreted with caution.

In Study 4, confounding was again likely because BMD was missing. Although some of the results do support a causal link between bisphosphonates and osteonecrosis, there are alternative explanations for these results, which make it less plausible that non-jaw osteonecrosis is an adverse effect of bisphosphonate treatment.

Confounding is always a theoretical possibility in an observational study, so a natural question to ask is whether the risk of confounding inevitably made the results ambiguous or whether it could have been minimized by study design or analysis. This matter will be discussed in the next few sections. After that, I will discuss the scientific and clinical implications of this dissertation. The chapter ends with recommendations for future research.

## **Could confounding have been prevented?**

The high risk of confounding is not surprising if one considers the epidemiology literature. According to this literature, studies such as Studies 1 and 2, which examine the intended beneficial effects of a treatment (fracture reduction), are most prone to confounding.<sup>283–286</sup> The reason for this is that patients receive treatment based on their risk of developing the outcome, which creates confounding when they are compared to untreated patients on this outcome. Furthermore, since disease risk is assessed by the partially subjective judgements of physicians, confounding can be difficult or even impossible to measure and control. Therefore, a standard epidemiology textbook concludes that, “Only infrequently can nonrandomized studies provide a valid estimate of the efficacy of a treatment” (p. 650).<sup>283</sup> This conclusion is not new. Back in 1979, a researcher stated that, “The non-experimental methods used in epidemiologic research are of little value in efficacy research”.<sup>284</sup> Others have made similar statements.<sup>285,286</sup>

Studies such as Study 3, which examine the unintended beneficial effects of treatment (mortality reduction) may be less prone to confounding. This is because physicians are less likely to be influenced by a patient’s predisposition for the outcome when deciding whether to treat the patient.<sup>284</sup> However, this assumption is controversial because some researchers argue that unintended beneficial effects are biologically unlikely.<sup>286</sup> In any case, the argument is questionable in Study 3 because there is evidence that a shorter life expectancy,

in terms of older age and poorer general health, makes physicians' less likely to prescribe bisphosphonates.<sup>119,122</sup> Therefore, confounding is probable in Study 3.

Studies such as Study 4, which examine an unexpected harmful effect of a treatment (osteonecrosis), are considered least prone to confounding.<sup>283–286</sup> The reasoning is this: Since the effect is unexpected, physicians are unlikely to be influenced by a patient's predisposition for it when deciding whether to treat the patient. Although osteonecrosis is not a well-established adverse effect of bisphosphonates,<sup>222</sup> there is evidence that osteoporosis is associated with an increased risk of developing osteonecrosis.<sup>225,287,288</sup> If so, then osteonecrosis would be associated with bisphosphonates even though it is an unexpected event. Therefore, confounding is still likely in Study 4.

This discussion suggests that confounding would have been difficult or even impossible to prevent, regardless of the study design or analysis. However, it is important to consider whether the cited literature is stating a sound scientific principle or whether it is simply repeating a scientific dogma. Indeed, some literature is more optimistic about observational studies.<sup>257,262,264,272,278–281,294–296</sup> Although this literature does not dispute the importance of confounder control, it places less emphasis on it, arguing that (1) well-designed observational studies can yield robust results, which are similar to those of randomized trials and that (2) randomized trials have limitations that observational studies do not. These arguments have weaknesses, however, which will be examined in the next two sections.

## **Was poor study design the problem?**

Many recommendations have been proposed to improve the quality of observational studies - to make them well-designed. Among these recommendations are to exclude previously-treated persons and include only the newly treated (a new-user design),<sup>256</sup> to correctly handle pre-treatment follow-up time,<sup>266–268</sup> to imitate the eligibility criteria of a randomized trial,<sup>257,262,278</sup> to control for confounders,<sup>257,262,264,265,278</sup> to run an intention-to-treat analysis,<sup>262,278</sup> to mimic the outcome of a randomized trial,<sup>257,262</sup> to use a grace period (similar to a run-in period in a randomized trial),<sup>257</sup> and to conduct sensitivity analyses.<sup>264,265</sup> Most of these recommendations have been summarized into the broader recommendation of designing observational studies to imitate randomized trials (real or hypothetical ones).<sup>257,262,278,297</sup>

Many of these recommendations were also incorporated into the four studies included in this dissertation (see the Methods section). Study 3 was specifically designed to imitate a real trial.<sup>153</sup> However, studies that lack data on important confounders are not considered by this literature to be well-designed, as the

above-listed methods only provide valid results if data on important confounders are available.<sup>257,297</sup> Since at least one known and important confounder was missing in the studies here, namely BMD, these studies do not appear to meet the criteria of being well-designed.

## **Were previous observational studies well-designed?**

My studies are not the only ones that fail to meet the criteria for well-designed observational studies. Out of 44 previous observational studies of bisphosphonates and fractures that I am aware of,<sup>172,176,177,259,298–338</sup> only 13 had data on the essential confounder of BMD.<sup>177,321–325,327,329,330,332</sup> What is more, these 13 studies all had substantial limitations: examining the effect of a recommendation of bisphosphonate treatment, but lacking data on the number of patients who actually started treatment (as well as having a surprisingly early association of bisphosphonate use with lower fracture risk);<sup>321</sup> being too small to estimate effects on fractures;<sup>177,322,323,330</sup> not having a new-user design;<sup>332</sup> having a high risk of residual confounding due to categorization of BMD;<sup>324</sup> or having a lot of missing data on BMD (63% or 38% of the cohorts).<sup>325,331</sup>

Although two of the studies did not have the mentioned limitations, these had other limitations.<sup>327,329</sup> The first showed contradictory and surprising results: a lower vertebral fracture risk with bisphosphonate use without adjusting for confounders, despite a lower baseline spine BMD, a higher mean age, and a greater reduction in spine BMD in the treatment group.<sup>327</sup> The second study, which compared bisphosphonates to raloxifene (another bone-strengthening medication), was poorly reported, as the number of fractures was not stated (only the percent with fracture was stated) and the confounders that were adjusted for (if any) were unspecified.<sup>329</sup> In other words, these observational studies lacked or had inadequate data on BMD, were too small, or had other methodological or reporting problems.

Previous studies of non-jaw osteonecrosis in bisphosphonates have also lacked data on BMD.<sup>224,225</sup> As mentioned for Study 3, it is difficult to measure physicians' assessments of patients' life expectancy when deciding whether or not to prescribe a medication, which means that it is difficult to determine if a specific variable was missing in these studies.

In summary, both the studies in this thesis and previous observational studies fail to meet the criteria of well-designed observational studies. The main reasons are that the key confounder of BMD is either missing or poorly measured or that the studies have other substantial limitations in design or reporting. This means that even though there is disagreement about the potential for well-designed observational studies to produce robust results, well-designed studies of

bisphosphonates and fractures, mortality, and non-jaw osteonecrosis do not seem to have been conducted.

## **Do the limitations of randomized trials justify observational studies?**

Despite the limitations of observational studies, some researchers argue that these are justified on the grounds that randomized trials also have limitations.<sup>257,262,278,280</sup> The limitations of randomized trials are well known: their high costs, ethical problems (blinding, randomization, and use of placebo), and logistical difficulties (recruiting and retaining participants) can make them infeasible. Even when they are feasible, these limitations mean that trials can be small, short, and selective in participant recruitment.<sup>262,284</sup> Consequently, trials might miss rare or delayed adverse effects, examine surrogate outcomes instead of clinically relevant outcomes, and not be generalizable to the average patient seen in clinical practice.<sup>262,284</sup> For these reasons, it is often said that trials do not provide real-world evidence.<sup>281,294,339</sup>

These limitations have led to the suggestion that observational studies be conducted to complement randomized trials.<sup>257,262,278,280</sup> This has also been suggested in the research on bisphosphonates.<sup>281,294,312</sup> Indeed, it is easier to conduct large and long observational studies in representative populations, especially when using register data. However, there are two problems with the argument.

The first problem is a logical one: the fact that randomized trials have limitations does not mean that observational studies are a viable alternative, because observational studies have their own limitations, so they might create more problems than they solve (instead of providing “real-world evidence”, they might provide “no-world evidence”). The second problem is an empirical one: several of the limitations of randomized trials appear to be overestimated when it comes to trials of bisphosphonates, as my colleagues and I have previously argued.<sup>340</sup>

One limitation that appears to be overestimated is that many trials of bisphosphonates have been large and long enough to study clinically relevant outcomes, that is, fractures (Supplemental Tables 1-3). Nevertheless, plenty of trials of bisphosphonates have used the surrogate outcome of BMD. These trials include the extensions of the original trials, where follow-up was extended to up to 6 or 10 years,<sup>214–216</sup> and trials conducted in certain groups. For example, the 4 trials that have been conducted specifically in men have used BMD or morphometric vertebral fractures, but not clinical fractures, as the primary endpoint,<sup>162,190–192</sup> although one still detected significant a reduction in non-vertebral fractures.<sup>191</sup> The same goes for glucocorticoid-treated patients, where

all trials had BMD as the primary endpoint and no study showed a significant reduction in clinical fractures.<sup>194–204</sup> However, due to the problems of observational studies mentioned above, it might be safer to judge the effects of bisphosphonates on BMD in clinical trials, where at least these effects are certain and where the effects on fractures have been shown in other patient groups, instead of relying on the uncertain results of observational studies.

A limitation that is not overestimated is that clinical trials missed two rare and long-term side effects of bisphosphonates, namely osteonecrosis of the jaw and atypical femur fractures. However, observational studies also missed these effects. The adverse effects were instead detected through case series.<sup>209,226</sup> As my colleagues and I have previously argued,<sup>340</sup> what stood out about these adverse effects is that they are otherwise very rare, which raised suspicions of causality.<sup>211,228</sup> It is difficult to see how these very specific conditions could have been detected in observational studies, especially when these conditions did not have ICD-10 codes at the time (atypical femur fractures still do not have an ICD-10 code; osteonecrosis of the jaw is now included in the broader category of inflammatory conditions of the jaw, *K10.2*).<sup>341</sup>

Another limitation that may be overestimated is the problem of non-representative populations. Non-representative populations can cause generalizability problems because the effect of the medication might change with changes in patient characteristics, such as disease severity, comorbidity, and comedication, or because adherence is often poorer in clinical practice.<sup>284,296</sup> Indeed, studies have shown that many, or even most, osteoporosis patients would not have been eligible for the trials, primarily because they are men, are too young or too old, have comorbidities (e.g., cancer or gastrointestinal disease), or use other medications (e.g., glucocorticoids).<sup>339,342</sup>

This selectivity in trials makes it difficult to test empirically whether the trials of bisphosphonates are misleading because of unrepresentative populations. However, as my colleagues and I have previously pointed out,<sup>340</sup> large trials of zoledronic acid have been conducted in more diverse populations than other trials bisphosphonates have, and these have shown quite similar reductions in clinical fractures: 27% in women with osteoporosis or osteopenia,<sup>163</sup> 33% in women with osteoporosis,<sup>161</sup> 35% in men and women with a previous hip fracture,<sup>153</sup> and 43% in men with osteoporosis (this trial was smaller than the others).<sup>162</sup> This comparison is far from ideal because the trials had different designs and because the results are prone to random fluctuation. However, there is at least no signal that treatment effects vary substantially. It should also be recognized that representability can even be harmful in observational studies because it increases heterogeneity, which increases the risk of confounding.<sup>282</sup>

In clinical practice, many, or even most, patients discontinue bisphosphonate treatment prematurely.<sup>343,344</sup> This goes for both oral and intravenous bisphosphonates.<sup>343,344</sup> However, the argument that this fact calls for observational studies of real-world treatment effects is questionable because it mixes of two different study questions (“Does the medication work?” and “Do patients take the medication?”). This mixing means that the results will be uninterpretable if no association is detected (does the medication not work or are patients not taking it?). To answer the question of whether lower adherence lowers the effect, a separate study should be conducted comparing a lower to a high dose or a shorter to a longer duration. After all, a drug that is not taken should not be expected to work.

In summary, the argument that observational studies of treatment effects are needed to complement randomized trials is questionable both logically and empirically. From a logical perspective, the argument is flawed because simply listing the limitations of both study types without weighing their relevance is insufficient. From an empirical perspective, several of the limitations also appear to be overestimated in research on bisphosphonates.

## **What do observational studies contribute?**

As the above discussion has argued, observational studies have not provided robust evidence of the effects of bisphosphonates on fractures, mortality, or non-jaw osteonecrosis. In addition, they are not sufficiently justified by the limitations of randomized trials. This does not mean that observational studies contribute nothing to our knowledge of bisphosphonates. On the contrary, trials cannot or should not be conducted for some research questions, and in other situations, they can complement them. Here are a few examples.

Observational studies have been useful for determining how common suspected adverse effects are. For example, observational studies have often,<sup>232–235</sup> but not always,<sup>235</sup> shown a strong association between bisphosphonates and atypical femoral fractures, which increases with the duration of treatment. They have also shown that atypical femoral fracture are rare, with estimates such as 0.2, 1.7, and 5.5 cases per 10,000 treated patients per year, as compared with 0.1 in controls.<sup>232–235</sup> Some of the results even support causality. For example, patients who sustain atypical femoral fractures do not seem to have worse BMD or be in poorer general health,<sup>232–235</sup> and bisphosphonates are much more strongly associated with atypical femoral fractures than other femoral shaft or subtrochanteric fractures.<sup>234</sup> Therefore, it is difficult to think of another explanation. Even if all or part of the association is confounded, the studies are useful because they tell us that atypical femoral fractures are rare.

Similarly, observational studies of osteonecrosis of the jaw have shown that most cases have been treated with intravenous bisphosphonates for cancer, not for osteoporosis.<sup>345–350</sup> Furthermore, although the association is strong, osteonecrosis is rare,<sup>349–352</sup> occurring in an estimated 1 in 100,000 to 1 in 10,000 treated patients per year.<sup>208</sup> These studies are limited in that few studies included a control group.<sup>347,351</sup> Another limitation is that the studies used data from health care instead of dental care,<sup>345–348,350</sup> which could lead to an underestimation of the number of cases.<sup>347</sup>

Despite the limitations, the fundamental difference between these studies and the ones that are part of this dissertation is that the former are useful even if the results are confounded, because they estimate an upper limit for the occurrence of atypical femoral fractures and osteonecrosis of the jaw. As mentioned, they also provide stronger evidence of causality because plausible alternative explanations are harder to find.

For these types of research questions, which concern adverse effects, observational studies may be useful but still suboptimal from a scientific point of view. For other research questions, observational studies can be more appropriate or even the only appropriate choice. For example, only observational studies have told us that 2–3 fractures occur per 100 adults over the age of 50 in some communities,<sup>2,5,72</sup> that most of these people do not have osteoporosis,<sup>8,60,61</sup> that osteoporosis is undertreated,<sup>115,117,119,120</sup> and that many bisphosphonate-treated patients discontinue their treatment prematurely.<sup>343,344</sup> In each of these examples, observational studies are more appropriate than randomized trials because the objectives are descriptive rather than causal, so the important feature of the studies is representability, not confounder control.

## **Clinical and scientific implications**

There are several scientific implications of the results. First, most of the results should not be interpreted as evidence of the effects of bisphosphonates, because such interpretations are no more likely to be true than to be wrong. The exception is the results of Study 2, where there is a reasonable chance that bisphosphonates reduced the risk of fractures during glucocorticoid therapy. Even so, none of the four studies meet the requirements to be considered well-designed, because the essential confounder of BMD is missing.

Second, it can be discussed whether observational studies of the effects of bisphosphonates on fractures, mortality, and osteonecrosis may need to be conducted more judiciously (or not conducted at all). It seems clear, however, that if similar observational studies are conducted in the future, their quality needs to be improved. In particular, observational studies of the effects of

bisphosphonates on fractures or non-jaw osteonecrosis should start incorporating data on BMD, and they should follow generally accepted principles for design (e.g., a new-user design), unless there are good arguments against doing so. For studies of mortality, it is more difficult to give recommendations because physician-judged life expectancy is difficult to measure. Therefore, such studies should probably not be conducted.

Third, this research points to a need for a more balanced reporting of observational studies because, with the exception of Study 3, the conclusions in the original publications differ from my conclusions here. In Studies 1 and 2, we hinted that the results were causal, although we did not state this directly. In Study 4, we drew no conclusion at all, although the abstract did hint that bisphosphonates might increase the risk of osteonecrosis. Although the limitations sections of the articles mentioned the alternative explanations presented here, the conclusions in the original publications largely ignored these limitations, instead being skewed in favor of causality. This problem is phrased as follows by the CONSORT guidelines for reporting the results of clinical trials: “The discussion sections of scientific reports are often filled with rhetoric supporting the authors’ findings... and provide little *measured argument* of the pros and cons of the study and its results” (my italics).

Since most of the results are not scientifically robust, they have few clinical implications. Nevertheless, they suggest that bisphosphonates reduce the risk of fractures in glucocorticoid-treated patients. In addition, health care professionals should not expect that bisphosphonates reduce mortality based on the results of observational studies.

## **Future research**

Since this dissertation did not clarify the potential effects of bisphosphonates on fractures after a previous fracture or the potential effects of bisphosphonates on mortality or non-jaw osteonecrosis, further research is needed to answer these questions. In an attempt to do so, my research team launched a clinical trial in February of 2022. In this trial, the main research question is the same as in Study 1 of this dissertation: “Do bisphosphonates reduce the risk of new fractures in older adults who have a history of fracture?” The full study protocol can be found in Appendix 2.

In brief, the trial is multicenter, randomized, and double blind. It is designed to recruit 2900 older adults across Sweden who sustained a non-hip non-vertebral fragility fracture in the past 2 years and who were 65 years of age or older at the time. Participants are randomized to receive two infusions of zoledronic acid (5 mg) or placebo (normal saline), one at baseline and one at two years. Each

participant will be followed-up by study staff for four years and followed-up through registers for 10 years. The primary outcome is new fracture. Mortality and non-jaw osteonecrosis are secondary outcomes. Glucocorticoid-treated patients are excluded for ethical reasons (they have a strong indication for bisphosphonate treatment).

There is no guarantee that this trial will be completed successfully or show clear evidence of benefits and harms (or clear evidence of a lack of benefits and harms). The possible pitfalls include logistical problems, such as not recruiting the required number of participants, and scientific problems, such as unexpected statistical uncertainty. Due to its thorough design however, it should have a good chance to advance current knowledge of the benefits and harms of bisphosphonates.

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**Appendix 1: Supplemental Tables**

**Supplemental Table 1.** Description of the 10 largest trials of the 3 most common bisphosphonates

<b>Study</b>	<b>BP</b>	<b>N</b>	<b>Age (mean/med.)</b>	<b>Sex</b>	<b>T-score</b>	<b>Fracture history</b>
Black 1996 <sup>155</sup>	AL	2,027	55-81 (71)	W	≤ -1.6 FN	≥1 vert.
Cummings 1998 <sup>156</sup>	AL	4,432	55-80 (68)	W	≤ -1.6 FN	No vert.
Pols 1999 <sup>157</sup>	AL	1,908	39-84 (63)	W	≤ -2 LS	-
Harris 1999 <sup>158</sup>	RI	1,641*	≤85 (69)	W	≤ -2 LS (required if 1 vert.)	Vert. (≥1)
Reginster 2000 <sup>159</sup>	RI	816*	≤85 (71)	W	-	Vert. (≥2)
McClung 2001 <sup>160</sup>	RI	9,331	Group 1: ≥70 (74) Group 2: ≥80 (83)	W	Group 1: ≤-4 FN or ≤-3 FN (if non-skeletal risk factor) Group 2: ≤ -4 or ≤-3 FN (if hip-axis length ≥11.1 cm) or no requirement (if other non-skeletal risk factor)	-
Black 2007 <sup>161</sup>	ZO	7,765	65-89 (73)	W	≤ -1.5 FN	≥1 vert. (if T>-2.5)
Lyles 2007 <sup>153</sup>	ZO	2,127	≥50 (74)	W/M	-	Hip fracture
Boonen 2012 <sup>162</sup>	ZO	1,119	50-85 (66)	M	≤ -1.5 TH/FN	1-3 vert. (if T>-2.5)
Reid 2018 <sup>163</sup>	ZO	2,000	≥65 (72)	W	-1.0 to -2.5 TH/FN and ≥ -3 LS	TH/FN/LS

*Abbreviations:* AL, alendronate; BP, bisphosphonate; FN, femoral neck; LS, lumbar spine; med, median; M, men; RI, risedronate; TH, total hip; vert., vertebral fracture; W, women; ZO, zoledronic acid

\*The risedronate 2.5 mg/d group is not included in this count because this group was discontinued

**Supplemental Table 2.** Duration of the 10 largest trials of the 3 most common bisphosphonates

Study	BP	Duration, y (mean/median follow-up)
Black 1996 <sup>155</sup>	AL	3.5 (2.9)
Cummings 1998 <sup>156</sup>	AL	(4.2)
Pols 1999 <sup>157</sup>	AL	1 (-)
Harris 1999 <sup>158</sup>	RI	3 (-)
Reginster 2000 <sup>159</sup>	RI	3 (-)
McClung 2001 <sup>160</sup>	RI	3 (2.3)
Black 2007 <sup>161</sup>	ZO	3 (-)
Lyles 2007 <sup>153</sup>	ZO	(1.9*)
Boonen 2012 <sup>162</sup>	ZO	2 (-)
Reid 2018 <sup>163</sup>	ZO	6 (-)

*Abbreviations:* AL, alendronate; BP, bisphosphonate; RI, risedronate; ZO, zoledronic acid

\*This trial was stopped early due to efficacy

**Supplemental Table 3.** Effects on fractures in the 10 largest trials of the 3 most common bisphosphonates

Study	BP	Hazard ratio (95% confidence interval)				
		Morph. vert.	Clinical vert.	Hip	Any clinical	Non-vert.
Black 1996 <sup>155</sup>	AL	0.53 (0.41-0.68)	0.45 (0.27-0.72)	0.49 (0.23-0.99)	0.72 (0.58-0.90)	0.80 (0.63-1.01)
Cummings 1998 <sup>156</sup>	AL	0.56 (0.39-0.80)	-	0.79 (0.43-1.44)	0.86 (0.73-1.01)	0.88 (0.74-1.04)
Pols 1999 <sup>157</sup>	AL	-	-	-	-	0.53 (0.30-0.90)
Harris 1999 <sup>158</sup>	RI	0.59 (0.43-0.82)	-	-	-	0.60 (0.39-0.94)
Reginster 2000 <sup>159</sup>	RI	0.51 (0.36-0.73)	-	-	-	0.67 (0.44-1.04)
McClung 2001 <sup>160</sup>	RI	-	-	0.7 (0.6-0.9)*	-	0.8 (0.7-1.0) <sup>†</sup>
Black 2007 <sup>161</sup>	ZO	0.30 (0.24-0.38)	0.23 (0.14-0.37)	0.59 (0.42-0.83)	0.67 (0.58-0.77)	0.75 (0.64-0.87)
Lyles 2007 <sup>153</sup>	ZO	-	0.54 (0.32-0.92)	0.70 (0.41-1.19)	0.65 (0.50-0.84)	0.73 (0.55-0.98)
Boonen 2012 <sup>162</sup>	ZO	0.33 (0.16-0.70)	0.3 (0.0-3.3)	-	0.6 (0.2-1.5)	0.6 (0.2-2.0)
Reid 2018 <sup>163</sup>	ZO	-	0.41 (0.22-0.75)	0.66 (0.27-1.16)	0.73 (0.60-0.90)	0.66 (0.51-0.85)

*Abbreviations:* AL; alendronate; BP, bisphosphonate; morph. vert., morphometric vertebral fracture; RI, risedronate; vert., vertebral fracture; ZO, zoledronic acid

\*This hazard ratio is for both study groups combined. Group 1: 0.6 (0.4-0.9). Group 2: 0.8 (0.6-1.2)

†This hazard ratio is for Group 1. No hazard ratio was reported for Group 2

**Supplemental Table 4.** Suspected adverse effects in the 10 largest trials of the 3 most common bisphosphonates

Study	BP	Suspected adverse effects	Incidence (%)	
			BP	Placebo
Black 1996 <sup>155</sup>	AL	None		
Cummings 1998 <sup>156</sup>	AL	None		
Pols 1999 <sup>157</sup>	AL	None		
Harris 1999 <sup>158</sup>	RI	None		
Reginster 2000 <sup>159</sup>	RI	None		
McClung 2001 <sup>160</sup>	RI	None		
Black 2007 <sup>161</sup>	ZO	Post-infusion symptoms	31.6	6.2
		Arrhythmia	6.9	5.3
		Serious atrial fibrillation	1.3	0.5
		Transient increase in serum creatinine >0.5 mg/dl	1.2	0.4
		Transient serum calcium <2.075 mmol/l	1.3	0.0
		Inflammatory ocular events, mainly conjunctivitis	3.3	2.7
Lyles 2007 <sup>153</sup>	ZO	Post-infusion symptoms		
		Myalgia	3.1	0.9
		Pyrexia	6.9	0.9
Boonen 2012 <sup>162</sup>	ZO	Post-infusion symptoms		
		Myalgia	24.3	4.1
		Pyrexia	24.3	3.8
		Headache	13.9	4.4
		Arthralgia	20.9	11.1
		Myocardial infarction		
Reid 2018 <sup>163</sup>	ZO	None	1.5	0.3

*Abbreviations:* AL, alendronate; BP, bisphosphonate; RI, risedronate; ZO, zoledronic acid

**Supplemental Table 5.** Confounders used in Studies 1-4

<b>Confounder</b>	<b>Study</b>			
	<b>1</b>	<b>2</b>	<b>3*</b>	<b>4†</b>
<b>Demographics</b>				
Age	X	X	X	X
Sex	X	X	X	X
<b>Diagnoses</b>				
Angina pectoris			X	
Arteriosclerosis			X	
Asthma		X		
Atrial fibrillation/flutter			X	
Cancer	X		E	X
Crohn's disease				X
Chronic kidney disease	X	X	E	X
Chronic obstructive pulmonary disease	X	X	X	X
Dementia	X	X	X	
Depression	X	X		
Diabetes	X	X	X	X
Fracture	X	X	X	X
Heart failure			X	
Hypercalcemia			E	
Hypercholesterolemia/hyperlipidemia			X	
Hyperparathyroidism			E	
Mental/behavioral disorder due to alcohol use		X	X	X
Myocardial infarction	X	X	X	X
Osteogenesis imperfecta			E	
Osteomalacia			E	
Osteomyelitis				X
Osteoporosis			X	X
Paget's disease of bone			E	
Psoriasis		X		
Renal/kidney failure	X	X	X	X
Rheumatoid arthritis	X	X	X	X
Solid organ transplantation			E	
Stroke	X	X	X	X
Ulcerative colitis				X
<b>Medications and other treatments</b>				
Antidiabetics			X	
Antithrombotics			X	
Calcium and vitamin D		X	X	
Chemotherapy				X
Denosumab			X	

<b>Confounder</b>	<b>Study</b>			
	<b>1</b>	<b>2</b>	<b>3*</b>	<b>4†</b>
Dialysis				X
Glucocorticoids		X	E	X
Immunosuppressants				X
Lipid-lowering agents			X	
Parathyroid hormone			E	
Radiotherapy			E	X
Raloxifene			X	
Strontium ranelate			E	
<b>Socioeconomics</b>				
Disposable income				X
Early retirement	X			
Educational attainment	X			X
Foreign background‡				X
Homemaker care service				X
Marital status	X			X
Nursing home			X	X

*Abbreviations:* E, exclusion criteria; X, controlled for by matching or regression

\*Study 3 included additional confounders: pathologic hip fracture, immobility prior to hip fracture, length of hospitalization, type of hip fracture, type of hip fracture surgery, walking aid, walking ability, and physical status (according to American Society of Anesthesiologists Physical Status score).

†Study 4 included one additional confounder: type of hip fracture surgery

‡Foreign background was defined as being foreign born or having two foreign born parents



## Appendix 2: Fragility Fracture Trial

### CLINICAL TRIAL PROTOCOL

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**The Fragility Fracture Trial (FFT): A randomized, double-blind, placebo-controlled trial to investigate whether zoledronic acid prevents new fractures in older adults with a recent non-hip, non-vertebral fragility fracture**

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EudraCT number:	2019-004766-17
Version number:	8
Date:	2022-03-24
Authors:	Jonathan Bergman Peter Nordström
Sponsor/Coordinating Investigator:	Peter Nordström
Funding:	Swedish Research Council

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This protocol was developed to comply with the *Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)* guideline (BMJ 2013;346:e7586). The protocol is based on a template of the National QA Network at Clinical Studies Sweden (<https://gothiaforum.com/mallar-f%C3%B6r-planering-och-genomf%C3%B6rande-av-kliniska-studier>).

Study Name: Fragility Fracture Trial  
Version No: 8  
Date: 2022-04-28  
EudraCT No: 2019-004766-17

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## Signature Page

### Sponsor/Coordinating Investigator

As sponsor and coordinating investigator, I am aware that I am responsible for ensuring that this protocol includes all essential information for the conduct of the trial. I agree to conduct the trial in compliance with this protocol, the Declaration of Helsinki, ICH GCP (International Council for Harmonization, Good Clinical Practice), and Swedish and European Union regulations.

I will submit this protocol and all other essential study-related documents to the principal investigators and other staff involved in this study, so that they can conduct the study correctly. I am aware that this study will be monitored by an independent monitor and possibly inspected by the Swedish Medical Products Agency.

---

Sponsor's/Coordinating Investigator's signature

Date

Peter Nordström

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Printed name

Study Name: Fragility Fracture Trial  
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Date: 2022-04-28  
EudraCT No: 2019-004766-17

## Protocol Revision History

Date	Version	Main revisions
2020-04-28	1	
2020-10-04	2	<p><b>Sections 7.3 and 9:</b> Data on physical activity and hand grip strength will be collected at all study centers, not just at those that currently have access to the necessary equipment.</p> <p><b>Sections 3.3, 7.3, 9, and 13.6:</b> Health-related quality of life outcomes have been added.</p> <p><b>Section 3.3:</b> The exploratory objective of comparing the effects of one versus two infusions has removed, as such an analysis may be biased when it is based on a comparison of more and less adherent participants.</p> <p><b>Section 3.3:</b> An exploratory objective has been added to investigate a possible interaction effect between zoledronic acid and FRAX score.</p> <p><b>Sections 7.1-7.2:</b> Non-vertebral fracture has been added as a secondary outcome. The outcome of fall without fracture has been redefined to include only falls from standing height or less. International Classification of Diseases (ICD) codes have been included for all primary and secondary outcomes.</p> <p><b>Sections 5.1 and 13.2:</b> The definition of fall from standing height or less has been specified with ICD-10 codes. Falls on</p>

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		<p>stairs or steps have been excluded from the definition.</p> <p><b>Section 9:</b> All baseline testing has been moved to the screening visit so that baseline data will be collected for all patients who provide written informed consent, instead of only for those who are eligible and randomized. This change also simplifies the randomization visit. Similarly, all testing at Visit 2 (time of second infusion) has been moved to Visit 1 to simplify Visit 2 and to ensure that follow-up data are collected for patients who withdraw from the study because of ineligibility for the second infusion.</p> <p><b>Section 9:</b> Renewal of vitamin D prescriptions may be done at every follow-up contact. Each investigator will decide whether a participant has taken enough monthly vitamin D not to require a second loading dose of vitamin D.</p> <p><b>Section 13.6:</b> The treatment-by-baseline value interaction terms have been removed from the analysis of covariance models, as their inclusion is not customary.</p> <p><b>Section 13.7:</b> Post-infusion symptoms occurring <math>\leq 3</math> days after each infusion will be reported.</p> <p><b>Section 13.1:</b> The reporting of the recruitment process has been expanded.</p> <p><b>Section 6.1:</b> Premature unblinding will not lead to automatic discontinuation of treatment.</p> <p><b>Sections 10 and 15.9:</b> Participants will be informed of their treatment assignment when they complete follow-up or when</p>
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		<p>they withdraw from the study, instead of at the end of the Main Phase of the trial, which may be two years later.</p> <p><b>Sections 9 and 15.4:</b> Participants will have the option of letting a next of kin act as a proxy respondent in follow-up interviews if the participant is unable to respond himself or herself.</p>
2021-01-15	3	<p><b>Section 4 and 17:</b> The start of the trial has been delayed.</p> <p><b>Sections 4 and 9:</b> The End of Trial has been redefined as the 10-year registry follow-up.</p> <p><b>Section 5.1:</b> An inclusion criterion has been added to ensure that principle investigators are authorized to verify self-reported outcomes through medical records.</p>
2021-05-06	4	<p><b>Sections 6 and 9:</b> Monthly vitamin D will not be prescribed. Instead, all participants will receive a loading dose of vitamin D before each infusion. Participants will also be recommended to have a sufficient intake of calcium and vitamin D. Participants will not receive advice about nutrition and exercise for preventing fractures, due to limited evidence of effectiveness.</p> <p><b>Section 6.1:</b> Participants with hypocalcemia or hypercalcemia will be disqualified from receiving the second infusion.</p>

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		<p><b>Section 6:</b> The ingredient list for zoledronic acid is redundant and has been deleted.</p> <p><b>Sections 7.1 and 7.2:</b> ICD-10 code T08 has been added for vertebral fractures.</p> <p><b>Sections 7, 9, 13.6, and 15.4:</b> To increase the efficiency of the study, all outcome events will be collected through registries and medical records, instead of through participant interview. Participants will not be able to opt out of the 10-year registry follow-up, unless they withdraw from the trial entirely. Data will not be collected from SWEDEHEART, the Swedish Stroke Register, or the Swedish Cancer register, as data on myocardial infarction, stroke, and cancer are all available from the National Patient Register.</p> <p><b>Section 7.2 and 13.6:</b> Falls will be analyzed as a time-to-event outcome, since registry-data provide exact dates of falls.</p> <p><b>Sections 9 and 15.4:</b> Participants who develop cognitive or physical disabilities that prevent continued in-person follow-up or telephone interview will be followed-up through registries and medical records only. Next of kin will not be interviewed.</p> <p><b>Section 11:</b> The routines for excluding participants during the trial have been clarified.</p>
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		<p><b>Section 7.4:</b> Possible cases of atypical femoral fracture or osteonecrosis of the jaw will be verified by medical record review. ICD-10-SE codes have been included for pre-specified safety outcomes. Serious atrial fibrillation has been removed as a safety outcome, as data on adverse event severity will not be collected. The five different post-infusion symptoms have been collapsed to one safety outcome.</p> <p><b>Section 8.1:</b> It has been clarified that actions taken in response to adverse events are actions that concern the investigational products, not other actions.</p> <p><b>Sections 3.3, 9, 12.2, 13.2, 13.8:</b> For simplicity, baseline data on physical activity will not be collected.</p> <p><b>Sections 3.3, 13.2, 13.8:</b> For simplicity, the exploratory objective to investigate a possible interaction effect between zoledronic acid and the FRAX score has been removed. The FRAX score is less useful when, as in the current study, bone mineral density is not assessed.</p> <p><b>Section 13.2:</b> The baseline variables have been updated.</p> <p><b>Section 13.3:</b> The analysis of investigational products has been simplified.</p> <p><b>Section 5.1:</b> The inclusion criterion requiring that participants consent to</p>
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		<p>medical-record review of their self-reported outcomes has been removed, as this requirement is covered by the criterion on informed consent. It has been clarified that “age <math>\geq 65</math>” refers to age at the time of fracture.</p> <p><b>Section 11:</b> During recruitment, it will be optional for investigators to follow up postal invitations with telephone calls.</p> <p><b>Section 7.2:</b> Non-melanoma skin cancer will be excluded from the cancer outcome, so that this outcome is consistent with the outcome in a previous trial (also see Section 3.2).</p> <p><b>Section 12.1:</b> It has been clarified that registry data will be pseudo-anonymized using participant ID codes.</p> <p><b>Section 16:</b> A Clinical Trial Report will be compiled at both the end of the Main Phase and the end of the Secondary Phase (the End of Trial). The main results will be disseminated at the end of the Main Phase.</p> <p><b>Section 4:</b> The sponsor/coordinating investigator will set up a Coordinating Center.</p> <p><b>Sections 9 and 11:</b> Central follow-up will not be conducted due to the risk of logistical problems.</p> <p><b>Section 5.1:</b> ICD-10-SE codes have been added for fractures.</p>
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		<p><b>Section 5.2:</b> Hypercalcemia and malabsorption of calcium and/or vitamin D have been added as exclusion criteria.</p> <p><b>Sections 10 and 13:</b> The randomization and analysis will be stratified by study center.</p> <p><b>Section 9:</b> The number of follow-up contacts has been reduced to simplify the trial. We do not believe this poses a safety risk, as zoledronic acid is widely used and participants will be able to report adverse events by telephone throughout the Main Phase.</p> <p><b>Sections 7.3, 9, 13.6:</b> Due to the reduction in the number of follow-up contacts, the EQ-5D-5L will be administered less frequently.</p> <p><b>Section 9:</b> Participants will be given a card with study information to carry in their wallet.</p> <p><b>Section 3.2:</b> The possibility of a greater effect on new clinical fractures in women than in men, rather than just a difference in effect, will be investigated.</p>
2021-06-24	5	<p><b>Section 6.1:</b> Adverse events should only lead to discontinuation of treatment if the sponsor/principal investigator so decides. It has been clarified that premature unblinding is not a criterion for discontinuing treatment.</p>

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		<b>Section 10:</b> The procedure for emergency unblinding has been described in greater detail.
2021-11-30	6	<b>Section 15.4:</b> Upon participant withdrawal, all previously collected data must be retained for archiving purposes. <b>Section 8.1:</b> It has been clarified that the definition of adverse event does not include those events that are part of the study's primary or secondary outcomes.
2022-01-31	7	<b>Sections 5.2, 6.1, 9, 12.3, 13:</b> Serum calcium has been replaced with plasma calcium (both values and reference values). <b>Section 8.4:</b> The Development Safety Update Report must be submitted to the Swedish Ethical Review Authority. <b>Section 11:</b> Randomization staff are permitted to have contact with participants prior to randomization. <b>Section 13.3:</b> Batch numbers will be recorded for zoledronic acid.
2022-04-28	8	<b>Section 9:</b> Baseline tests do not need to be repeated if randomization is delayed. <b>Sections 11, 12.2:</b> Information about pre-screening has been added. It has been clarified how patient lists from the Swedish Fracture Register will be handled. <b>Sections 6, 10:</b> Routines for infusions have been updated.

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## Contributions and Contact Information

Name and occupation	Role	Contributions	Contact Information
Peter Nordström, Professor and Chief Physician	Sponsor/ coordinating investigator	<ul style="list-style-type: none"> <li>- Conceived the study</li> <li>- Designed the study</li> <li>- Coauthored this protocol</li> <li>- Applied for funding</li> </ul>	<ul style="list-style-type: none"> <li>- Address: Unit of Geriatric Medicine, Department of Community Medicine and Rehabilitation, Umeå University, 90187 Umeå, Sweden</li> <li>- Phone: +46 70 8996599</li> <li>- Email: peter.nordstrom@umu.se</li> </ul>
Jonathan Bergman, PhD student	Protocol coauthor	<ul style="list-style-type: none"> <li>- Designed the study</li> <li>- Planned the statistical analysis</li> <li>- Coauthored this protocol</li> </ul>	<ul style="list-style-type: none"> <li>- Address: Unit of Geriatric Medicine, Department of Community Medicine and Rehabilitation, Umeå University, 90187 Umeå, Sweden</li> <li>- Email: jonathan.bergman@umu.se</li> </ul>

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## Roles and Responsibilities

Role	Responsibilities
Sponsor/Coordinating investigator	<ul style="list-style-type: none"> <li>- Overall responsibility for the trial, including the protocol and monitoring plans</li> <li>- Ensure that the trial follows ICH GCP, the Declaration of Helsinki, and regulations</li> <li>- Set up a Coordinating Center</li> <li>- Ensure that the trial is uniformly conducted across study centers</li> <li>- Guarantee that participants are insured</li> <li>- Obtain funding</li> <li>- Delegate responsibilities</li> <li>- Recruit study centers (principal investigators)</li> <li>- Publish results</li> </ul>
Principal investigators (one per study center)	<ul style="list-style-type: none"> <li>- Ensure that the trial is conducted according to this protocol</li> <li>- Ensure that participants have provided written informed consent</li> <li>- Ensure that eCRFs are complete and accurate</li> <li>- Protect the integrity and safety of participants</li> <li>- Ensure that participants get necessary medical care</li> <li>- Recruit clinical staff</li> <li>- Ensure that staff are adequately trained</li> </ul>
Trial statistician	<ul style="list-style-type: none"> <li>- Write a computer program for generating a randomization list</li> </ul>

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	<ul style="list-style-type: none"><li>- Develop an electronic case report form (eCRF)</li><li>- Continuously monitor incoming data for accuracy, completeness, and compliance with the protocol</li><li>- Conduct a blind review of the trial database</li><li>- Report to the sponsor when the trial database is accurate and complete</li><li>- Draft the Clinical Study Report</li></ul>
University Hospital of Umeå Clinical Research Center	<ul style="list-style-type: none"><li>- Generate and store a randomization list</li><li>- Monitor the trial for adherence to GCP, regulations, and ethical guidelines</li><li>- Assist in reporting SUSARs</li><li>- Assist in writing DSURs</li><li>- Assist in developing and maintaining the eCRF</li><li>- Assist in writing an agreement with a pharmaceutical company</li><li>- Assist in developing a monitoring plan</li></ul>

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## Acronyms and Abbreviations

Acronym/Abbreviation	Explanation
AE	Adverse event
COVID-19	Coronavirus disease 2019
DSUR	Development safety update report
eCRF	Electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
GCP	Good clinical practice
ICD-10-SE	International Classification of Diseases, 10 <sup>th</sup> revision, Swedish Version
ICH	International Conference/Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Council of Medical Journal Editors
ID	Identification
SEK	Swedish Krona
SUSAR	Suspected unexpected serious adverse reaction

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## 1. Synopsis

**Background:** The incidence of fracture is high among older adults, and older adults who sustain one fracture are at high risk of sustaining new fractures. No clinical trial has examined whether bone-protective therapy is effective in preventing new fractures among older adults with a recent non-hip, non-vertebral fragility fracture, without prior measurement of bone mineral density.

**Primary objective:** To investigate whether zoledronic acid (a widely used antiresorptive) reduces the risk of new clinical fractures, as compared with placebo, in older adults with a recent non-hip, non-vertebral fragility fracture.

**Study design:** 10-year, phase IV, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial. The 10 years will be divided into a double-blind Main Phase of 4 years and an open-label Secondary Phase of 6 years.

**Study population:** Persons with a non-hip, non-vertebral fragility fracture in the past 2 years and who were aged 65 years or older at the time of fracture. Fragility fracture is defined as a fracture occurring after a fall from standing height or less.

**Number of participants:** 2900.

**Investigational products:** Two infusions of zoledronic acid (5 mg) or placebo, one at baseline and one at 24 months. Prior to each first infusion, participants will receive a loading dose of oral vitamin D (100,000 IU or 2.5 mg).

**Primary outcome:** Time to first new clinical fracture.

**Study period:** 2021 – 2033.

## 2. Introduction

About 95,000 individuals suffered a major fracture in Sweden in 2017.<sup>1,2</sup> In comparison, less than half that number, about 40,000, suffered a stroke or myocardial infarction.<sup>1</sup> The most serious type of fracture is the hip fracture, which is regarded as an end stage disease because 25% of hip fracture patients die within a year.<sup>3,4</sup> Of surviving hip fracture patients, only a minority regain their pre-fracture level of physical functioning and quality of life.<sup>5</sup> High mortality rates and reduced quality of life are also seen in patients with vertebral fractures.<sup>6,7</sup> Thus, hip and vertebral fractures are serious threats to the health and independence of older people.

Despite the seriousness of hip and vertebral fractures, these do not constitute the majority of fractures, as they occur in about 28,000 persons per year in Sweden.<sup>1,2</sup> Far more common are fractures of the arm or lower leg, which occurred in about 58,000 people in Sweden in 2017.<sup>1,2</sup> Furthermore, according to government data we have on hand, individuals with a previous fracture of the arm or lower leg have 2.6 times the risk of sustaining a fracture as do individuals without a previous fracture. The data also show that fractures of the arm and lower leg occur at a mean age of 71 years, compared to 77 years for vertebral fractures and 83 years for hip fractures. These facts suggest that health care professionals may be able to prevent hip and vertebral fractures by targeting interventions to older adults with a non-hip, non-vertebral fracture.

Bone-protective agents, such as bisphosphonates, are currently available for reducing fracture risks in older adults.<sup>8</sup> However, the efficacy of these agents after a fracture has not been studied in clinical trials other than after a hip or vertebral fracture.<sup>9</sup> Most trials have recruited participants on the basis of osteoporosis or low

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bone density (with or without a vertebral fracture),<sup>9</sup> but this approach has the disadvantage that physicians often have limited access to bone densitometry,<sup>10</sup> which complicates treatment decisions in clinical practice. Furthermore, many fracture patients, especially male fracture patients, do not have osteoporosis. The actual percentage of patients who have osteoporosis varies among studies, but hip or spine osteoporosis (T-score  $\leq -2.5$ ) has been reported in 36%,<sup>11</sup> 44%,<sup>12</sup> and 56%<sup>13</sup> of female fracture patients and in 13-15%<sup>11</sup> and 21%<sup>12</sup> of male fracture patients. Another study, which examined appendicular osteoporosis (T-score  $\leq -2.5$  in the heel, finger, or forearm), showed that osteoporosis was present in 18% of women with an osteoporotic fracture.<sup>14</sup> Another difficulty in fracture prevention is that health care systems often are not organized to identify patients with osteoporosis; while fractures are initially treated in emergency rooms and orthopedic wards, bone densitometry is usually located in other departments (if available at all) and primary care is often responsible for making treatment decisions.

Given the high incidence of non-hip, non-vertebral fractures, the high risk of recurrent fractures, and the seriousness of hip and vertebral fractures, which occur later in life than other types of fractures, it would be of high interest to study whether bone-protective therapy is effective in older adults who are selected solely for having a history of non-hip, non-vertebral fracture (that is, without prior assessment of bone mineral density). Increased treatment of this patient group is feasible because only around 10% of Swedish fracture patients aged 50 or older receive treatment.<sup>15,16</sup>

Zoledronic acid is a well-known and well-studied bone-protective agent, which was approved in the European Union in 2005.<sup>17</sup> Zoledronic acid reduces bone resorption and belongs to the

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bisphosphonate class.<sup>18</sup> In three large clinical trials, zoledronic acid was shown to reduce the risk of clinical fracture in women with osteoporosis, in women with osteopenia, and in men and women with a hip fracture.<sup>19–21</sup> Although a fourth trial conducted in men with osteoporosis did not show a significant effect of zoledronic acid on clinical fractures, this trial was smaller and it did show a significant effect on radiologically detected vertebral fractures.<sup>22</sup>

The most common adverse effects of zoledronic acid are transient post-infusion symptoms (pyrexia, myalgia, headache, arthralgia, and influenza-like symptoms), which occur in about one third of patients in the first 3 days following an initial infusion.<sup>19</sup> These symptoms are less common after subsequent infusions.<sup>19</sup>

Zoledronic acid and other bisphosphonates have been associated with two rare but serious adverse effects: atypical femoral fractures and osteonecrosis of the jaw.<sup>23,24</sup> However, osteonecrosis of the jaw does not primarily occur in osteoporosis patients but in cancer patients, who receive much higher doses of zoledronic acid to reduce the adverse skeletal effects of cancer (e.g., bone metastases).<sup>23</sup> In osteoporosis patients, the incidence of osteonecrosis of the jaw is estimated to be 1 in 100,000 to 1 in 10,000.<sup>23</sup> Atypical femoral fractures are also rare, and they are typically reported after long treatment periods of 7 or more years.<sup>25,26</sup> It should also be noted that no increased risk of these adverse events was reported in the four largest trials of zoledronic acid that have been conducted to date.<sup>20–22,26</sup>

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## **3. Objectives**

### **3.1. Primary objective**

The primary objective is to investigate whether zoledronic acid reduces the risk of new clinical fractures, as compared with placebo, in older adults with a recent non-hip, non-vertebral fragility fracture.

### **3.2. Secondary objectives**

The secondary objectives are to investigate whether zoledronic acid, as compared with placebo:

1. has a greater effect in reducing the risk of new clinical fractures in women than in men
2. reduces the risk of cancer
3. reduces the risk of cardiovascular disease (stroke or myocardial infarction)
4. reduces the risk of death
5. reduces the risk of falling

Although it is conventional to designate subgroup analyses as exploratory, we designated the subgroup analysis by sex as a secondary objective because no clinical trial has shown that bone-protective therapy significantly reduces clinical fractures in men.<sup>8</sup> This fact may explain part of the low rates of osteoporosis treatment in men.<sup>16,27</sup> Cancer was selected as a secondary outcome to confirm the results of a phase IV trial, which showed a significant reduction in cancer (a pre-specified safety outcome, excluding non-melanoma skin cancer) in osteopenic women treated with zoledronic acid.<sup>21</sup> Cardiovascular disease was selected because both clinical trial data and observational data have suggested that bisphosphonates protect against stroke and myocardial infarction.<sup>21,28–30</sup> Death was selected to confirm the results of a phase III trial that demonstrated significantly reduced

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mortality in hip fracture patients treated with zoledronic acid.<sup>20</sup> Falling was selected as an outcome to confirm the results of two trials, one of denosumab and one of zoledronic acid, which showed significant reductions in falls.<sup>20,31</sup>

### **3.3. Exploratory objectives**

The exploratory objectives are as follows:

1. To investigate whether the effect of zoledronic acid on new clinical fracture decreases with age
2. To investigate the time-to-onset of effect of zoledronic acid on clinical fractures
3. To investigate whether zoledronic increases muscle strength, as compared with placebo
4. To investigate whether zoledronic acid reduces height loss, as compared with placebo
5. To investigate whether zoledronic acid improves health-related quality of life, as compared with placebo
6. To investigate whether zoledronic acid reduces the risk of death, cancer, clinical fractures, falls, and cardiovascular disease, as compared with placebo, over 10 years

Efficacy by age was selected as an exploratory objective because some researchers suggest that bone-protective therapy is less effective in the oldest age groups, perhaps because the high incidence of falls in these groups offsets beneficial skeletal effects.<sup>32,33</sup> Low treatment rates of osteoporosis have also been observed in the oldest age groups.<sup>34</sup> Muscle strength is included as an explanatory outcome because this is a possible mechanism for a beneficial effect of zoledronic acid on falls. Such a mechanism is supported by the known crosstalk between osteocytes and muscle cells, which is mediated by pathways influenced by bone-protective

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agents.<sup>35</sup> Height loss was selected because it reflects efficacy in reducing vertebral fractures. Height loss was designated as an exploratory outcome because it will only be assessed halfway through the Main Phase but not at the end. A reduction in height loss with zoledronic acid was observed in two previous trials of zoledronic acid.<sup>19,21</sup> Health-related quality of life will be used to assess whether participants perceive any health benefits from zoledronic acid treatment. Health-related quality of life outcomes were specified in the protocol of three previous trials of zoledronic acid.<sup>20-22</sup> The results of one of these trials have been published,<sup>36</sup> and these showed a significant improvement in the EuroQol-5 Dimensions-3 Levels (EQ-5D-3L) visual analogue scale, in which respondents rate their overall health on a scale from 0 to 100 (from worst to best imaginable health). An improvement was not, however, observed in the EQ-5D-3L summary score of the 5 dimensions.<sup>36</sup>

## **4. Trial Design**

The study will be a 10-year, phase IV, multicenter, parallel-group, randomized, double-blind, placebo-controlled trial. The 10-year follow-up period will be divided into a double-blind Main Phase of 4 years, followed by an open-label Secondary Phase of 6 years. During the Main Phase, participants will actively participate in the study by receiving investigational products and by being followed-up through study contacts (telephone interview and in-person visits). A 4-year duration was selected because this is anticipated to capture the greatest anti-fracture efficacy of 2 infusions of zoledronic acid administered at baseline and at 24 months (see Section 6). The Secondary Phase will be a 10-year follow-up through registries and medical records, without study contacts.

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The trial will be multicenter so that a sufficient number of participants can be recruited. Study centers (one per principal investigator) will be located in major hospitals in Sweden. We anticipate that approximately 10 centers will be needed. The sponsor/coordinating investigator will also set up a Coordinating Center. A parallel-group, randomized, and double-blind design was selected to enable the study to produce substantial confirmatory evidence of efficacy. The trial will be placebo controlled because there is currently no standard treatment for fracture patients who do not have a hip or vertebral fracture and who have not undergone bone densitometry.

The study is anticipated to take 12 years to complete (2021 – 2033). Participants will be recruited during the first 2 years. The following 4 years will be spent completing the Main Phase for each participant. The final 6 years will be spent completing the Secondary Phase for each participant. The End of Trial is defined as the date when registry data are obtained for the 10-year follow-up (that is, 10 years after the last participant has been recruited).

The initial plan was to start enrolling participants in the first quarter of 2021. This start has been delayed until the second half of 2021. The start may be delayed further if the sponsor considers participant enrollment to be unsafe due to the coronavirus disease 2019 (COVID-19) pandemic, which broke out in 2020 (see Section 17).

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## **5. Eligibility Criteria**

### **5.1. Inclusion criteria**

To be included in the trial, patients must meet all of the following criteria:

1. Willing and able to provide written informed consent
2. Ambulatory (i.e., able to walk without the assistance of another person; canes, walkers, and other assistive devices are permitted)
3. Community dwelling (i.e., living in own home or with friends or relatives)
4. Sustained a non-hip, non-vertebral fragility fracture in the past 2 years
5. Age  $\geq 65$  years at the time of fracture

Fragility fractures are defined as fractures occurring after a fall from standing height or less.<sup>10</sup> In particular, these falls include the following International Classification of Diseases, 10<sup>th</sup> Revision, Swedish Version, (ICD-10-SE) codes:

1. Fall on same level involving ice and snow (W00)
2. Fall on same level from slipping, tripping and stumbling (W01)
3. Other fall on same level due to collision with, or pushing by, another person (W03)
4. Fall while being carried or supported by other persons (W04)
5. Other fall on same level (W18)

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If the type of fall is unknown, it will be assumed *not* to have occurred after a fall from standing height or less.

Non-hip, non-vertebral fractures will include all fractures other than of the face, skull, hands, and feet, as these are not generally considered osteoporotic.<sup>10</sup> In particular, the following fractures will be included (ICD-10-SE):

1. Ribs/sternum/bony thorax (S22.2-S22.8)
2. Pelvis (S32.1-S32.5)
3. Shoulder/upper arm (S42)
4. Forearm (S52)
5. Femur, excluding hip (S72.3-S72.4)
6. Lower leg (S82)

The limit of no more than 2 years since the fracture is based on two considerations. First, the risk of sustaining a new fracture is highest soon after the initial fracture.<sup>37,38</sup> Therefore, we expect zoledronic acid to have the greatest effect if it is administered as soon as possible. However, setting a short time limit would reduce the number of potentially eligible participants, making the trial more difficult to carry out. Therefore, the second consideration is that the time limit should not be set too short for pragmatic reasons.

A minimum duration between time of fracture and time of recruitment has not been set, because no delay in fracture healing was observed in a phase III trial of zoledronic acid in hip fracture patients.<sup>20</sup>

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## 5.2. Exclusion criteria

Patients will be excluded from the trial if they meet any one of the following criteria:

1. History of hip fracture or vertebral compression fracture
2. Undergone bone density scanning since the fragility fracture
3. Severe renal impairment (estimated glomerular filtration rate of  $<35$  ml per minute per  $1.73\text{ m}^2$  of body surface area)
4. Remaining life expectancy of  $<1$  year, according the investigator's judgement
5. Hypocalcemia/hypercalcemia (plasma calcium  $<2.15$  or  $>2.50$  mmol/L)
6. Sarcoidosis (contraindication for vitamin D)
7. Previous use of bone-protective drug (e.g., bisphosphonate, teriparatide, denosumab, raloxifene, or strontium ranelate; calcium and vitamin D are acceptable)
8. Use of systemic glucocorticoids at a dose of  $\geq 5$  mg (prednisolone or equivalent) for  $\geq 3$  months in the past year
9. Malabsorption of calcium and/or vitamin D (e.g., due to gastric bypass)
10. Other medication or medical condition for which bone-protective therapy is indicated (e.g., bone metastases or use of aromatase inhibitor; osteoporosis is permitted)

Patients with a hip or vertebral fracture will be excluded because these patients should receive bone-protective therapy according to current Swedish national guidelines.<sup>39</sup> Patients who have undergone bone density scanning will be excluded because the inclusion of these patients might skew the study population toward low-risk patients who do not qualify for treatment according to current guidelines, which would reduce the statistical power of the trial.

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## **6. Investigational Products**

Zoledronic acid (5 mg) or placebo (normal saline) will be given as a 15-minute intravenous infusion at baseline and at 2 years. Each infusion will contain 6.25 ml of zoledronic acid concentrate or normal saline diluted in 100 ml of normal saline. A flush of 3-5 ml of normal saline will be given before administration, resulting in a total of ~110 ml of intravenously infused fluid. See Section 10 for more information on the administration of infusions.

Zoledronic acid can cause post-infusion symptoms (pyrexia, myalgia, headache, arthralgia, or influenza-like symptoms) within the first 3 days.<sup>19</sup> Participants will be informed that these symptoms may be uncomfortable but are not dangerous and can be eased with paracetamol.

To prevent hypocalcemia, all participants will receive a loading dose of oral vitamin D (100,000 IU or 2.5 mg) before each infusion. The first loading dose will be taken 1 to 4 weeks before the first infusion, but the second loading dose will be taken on the same day as the second infusion, as the risk of hypocalcemia will be lower if the first infusion was administered without causing hypocalcemia. Participants will be recommended to have a sufficient daily intake of calcium ( $\geq 1$  g/d) and vitamin D ( $\geq 20$   $\mu$ g or 800 IU/d) throughout the Main Phase, and they will be reminded of this before the second infusion.

In two previous trials, a loading dose of vitamin D was given only before the first infusion of zoledronic acid or placebo.<sup>20,21</sup> In the first trial, the loading dose of 50,000-125,000 IU was followed by daily vitamin D and calcium supplements.<sup>20</sup> In the second trial, a loading dose of 100,000 IU was followed by monthly vitamin D

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supplements (with a recommendation for a calcium intake of  $\geq 1$  g/d).<sup>21</sup> A third trial used no loading dose but provided daily calcium and vitamin D.<sup>19</sup> We believe that a loading dose of 100,000 IU before each infusion will be sufficient to prevent hypocalcemia, with little or no additional benefit of continued vitamin D supplementation. There is also evidence that high doses of vitamin D increase the risk of falls and fractures.<sup>40</sup>

The above-mentioned dose and administration route for zoledronic acid were selected based on the design of previous phase III trials and on standard use in clinical practice.<sup>17,19,20</sup> The treatment interval of 2 years is not standard, however, as 1-year intervals were used in the phase III trials and are commonly used in clinical practice.<sup>17,19,20</sup> Our decision to extend the treatment interval is based on evidence from a phase IV trial that found similar efficacy with an 18-month treatment interval.<sup>21</sup> A smaller trial also demonstrated that the effect of zoledronic acid on bone mineral density peaks at least 24 months after an initial infusion.<sup>41</sup> Furthermore, a post-hoc analysis of two large clinical trials demonstrated similar reductions in clinical fractures in patients who had received only 1 instead of 3 infusions of zoledronic acid.<sup>42</sup> Based on these findings, we expect a 24-month interval to be optimal.

Zoledronic acid and placebo must be stored securely, meaning that it is accessible only to authorized persons and that it is kept in the conditions specified in the Summary of Product Characteristics. The drugs may only be used for the purposes specified in this protocol. At the end of the study, any remaining products will be handed over to pharmacies for destruction. A Drug Accountability Log will be used to follow the pathway of the study medications throughout the study.

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## **6.1. Discontinuation of treatment**

The investigators and the sponsor can at any time decide that a participant should not receive the second infusion due to, for example, adverse events. A participant will be automatically disqualified from receiving the second infusion if any one of the following criteria is met:

1. Wish of participant
2. Decision of sponsor/principal investigator due to adverse event
3. Initiation of bone-protective therapy (other than the assigned investigational product)
4. Severe renal impairment (estimated glomerular filtration rate of <35 ml per minute per 1.73 m<sup>2</sup> of body surface area)
5. Hypocalcemia/hypercalcemia (plasma calcium <2.15 or >2.50 mmol/L)
6. Decision of sponsor/principal investigator for other reason

It should be noted that premature unblinding is *not* a criterion for discontinuing treatment. A participant's follow-up will continue even if treatment is discontinued, unless the participant wishes to withdraw from the study.

## **6.2. Concomitant medications**

The use of non-investigational bone-protective medications during follow-up will be assessed. The use other medications will not be assessed, because this is a post-marketing trial and no adverse drug interactions are known to exist.<sup>17</sup>

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## **7. Outcomes**

### **7.1. Primary outcome**

Due to the high clinical relevance of most fractures, the primary outcome will be time to first new clinical fracture. Clinical fracture will be defined as any fracture that comes to medical attention, excluding fractures of the facial bones, skull, hands, and feet, which are not generally considered osteoporotic.<sup>10</sup> For the same reason, pathological fractures (e.g., due to cancer or osteomyelitis) will be excluded. High-energy fractures will be included because these are also associated with low bone mineral density.<sup>11,43</sup>

Fractures will be traced centrally by the sponsor through the National Patient Register using ICD-10-SE codes S12-S52, S72, S82, M48.5, M49.5, M80.0A, M80.0J, M80.0K, and T08. The National Patient Register records all diagnoses made in inpatient care in Sweden since 1987 and all outpatient secondary (i.e., non-primary) care since 2001.<sup>44</sup> Data on fractures will also be collected locally at each study center using medical records and the Swedish Fracture Register (same ICD-10-SE codes as above). Fractures identified through registers will be verified through medical records.

### **7.2. Secondary outcomes**

The secondary outcomes are as follows (ICD-10-SE):

1. Time to first non-vertebral fracture (S22.2, S22.3, S22.4-S22.8, S32.1-S32.5, S42, S52, S72, S82)
2. Time to first new non-hip, non-vertebral fracture (S22.2-S22.8, S32.1-S32.5, S42, S52, S72.3-S72.4, S82)

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3. Time to first hip fracture (S72.0-S72.2)
4. Time to first new forearm fracture (S52)
5. Time to first clinical vertebral fracture (S12, S22.0, S22.1, S32.0, M48.5, M49.5, M80.0A, M80.0J, M80.0K, T08)
6. Time to death
7. Time to first new cardiovascular event (stroke or myocardial infarction) (I21, I60-I64)
8. Time to first new cancer diagnosis, excluding non-melanoma skin cancer (C00-C43, C45-C97)
9. Time to first fall from standing height or less (W00, W01, W03, W04, W18) not resulting in fracture

Hip fractures are included among non-vertebral fractures, and forearm fractures are included among non-hip, non-vertebral fractures. However, hip fractures and forearm fractures will also be assessed separately because these are common and classic osteoporotic fractures.

Fractures, myocardial infarction, stroke, cancer, and falls will be traced through the National Patient Register using the above-mentioned ICD-10-SE codes. Fractures will also be traced through medical records and the Swedish Fracture Register (same ICD-10-SE codes). Deaths will be identified centrally by the sponsor through the Swedish Cause of Death Register<sup>45</sup> and locally at study centers through medical records and reports from family members. Apart from fractures, the secondary outcomes will not be verified through medical records, so that the burden on investigators is reduced.

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### **7.3. Exploratory outcomes**

Four exploratory outcomes will be assessed:

1. Change in body height (cm) from baseline to 24 months
2. Change in non-dominant hand grip strength (kg) from baseline to 24 months
3. Change in EQ-5D-5L summary score from baseline to 24 and 48 months
4. Change in EQ-5D-5L visual analogue scale from baseline to 24 and 48 months

Body height (without shoes) will be measured in centimeters using stadiometers at baseline and at 24 months. Hand-grip strength will be measured in kilograms using dynamometers. Each participant will make two attempts, and the maximum value will be analyzed. Values will be rounded to one decimal place. These outcomes will not be assessed at 48 months because the last follow-up visit will be a telephone interview instead of a physical visit due to budget constraints (see Section 9).

The EQ-5D scale will be used to assess health-related quality of life because it is short, generic (rather than disease-specific), and widely used. Two previous trials of zoledronic acid used the 3-level version the EQ-5D (i.e., the EQ-5D-3L).<sup>22,36</sup> We will use the 5-level version (EQ-5D-5L) so that smaller differences in patient-reported health status can be detected. The summary score will be derived from the Swedish Time Trade-off, experience-based value set.<sup>46</sup> The term “experience-based” refers to the instruction that respondents rate their current health state, rather than a hypothetical health state.<sup>46</sup> Both the summary score and the visual analogue scale will be rounded to 2 decimal places.

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#### **7.4. Safety outcomes**

Based on previous trials of zoledronic acid and the Summary of Product Characteristics of Aclasta, the brand name of zoledronic acid,<sup>17,19-21</sup> the occurrence or worsening of the following pre-specified safety outcomes will be assessed:

1. Post-infusion symptoms (T88.7)
2. Osteonecrosis of the jaw (K10.2)
3. Osteonecrosis (avascular necrosis) not of the jaw (M87)
4. Atypical femur fracture (S722-S724)
5. Atrial fibrillation (I48)
6. Re-operation of fracture
7. Delayed fracture healing (M84.2)
8. Renal failure (N17-N19)
9. Hypocalcemia (E835)
10. Ocular event (H10-H22)

During the Main Phase of the trial, data on safety outcomes will be self-reported, and investigators will ask only open-ended questions about adverse events (see Section 8). The above-mentioned ICD-10-SE codes will be used to trace adverse events in the Swedish National Patient Register at the 10-year follow-up. Medical records will be examined to assess whether femur shaft fractures have atypical features and whether an inflammatory conditions of the jaw are cases of osteonecrosis of the jaw. These assessments will be made by physicians who are blind to treatment assignment.

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## 8. Safety

### 8.1. Adverse events

An *adverse event* will be defined as is done by the International Council/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH):<sup>47</sup>

*Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.*

However, the following events will *not* be considered adverse events, as they are primary or secondary outcomes:

1. Fractures (apart from atypical femur fractures, which are adverse events)
2. Myocardial infarction
3. Stroke
4. Falls (fall-related injuries are adverse events, however)

Of note, deaths (and their causes) are will be considered adverse events, although death is also a secondary outcome.

Participants will be inquired about adverse events at study contacts. The questions will be open-ended, instead of directed at particular events. Participants will also have the possibility of reporting adverse events by telephone between the scheduled contacts. Participants who withdraw will be asked if they wish to report adverse events before they formally withdraw.

The following information will be collected about adverse events:

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1. Description (free text or pre-specified text [see Section 7.4])
2. ICD-10 code (if available)
3. Duration (start date and, if applicable, stop date)
4. Causality (suspected/not suspected to be related to zoledronic acid or placebo)
5. Seriousness (serious/non-serious)
6. Expectedness (expected/unexpected) (applicable only if the event is suspected to be causally related to zoledronic acid or placebo)
7. Actions taken with respect to investigational products (zoledronic acid or placebo)
8. Outcome
9. Comments/other actions

The severity of the adverse event (e.g., mild, moderate, or severe) will not be recorded, because this information is not legally required and is unlikely to be analyzed. Causality will be assessed as a binary variable (suspected/not suspected), because more detailed assessments are not needed to flag potential adverse drug reactions.<sup>48</sup>

Participants who have been affected by an AE will be followed-up according to the clinical practice of the study center until the adverse event is resolved or stable. Participants with AEs that are suspected to be related to an investigational product will be followed-up until they have recovered or are well taken care of and on the way to good recovery.

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## 8.2. Serious adverse events

As recommended by the ICH,<sup>47</sup> an adverse event will be classified as a *serious adverse event* if it

- *results in death,*
- *is life-threatening,*
- *requires inpatient hospitalization or prolongation of existing hospitalization,*
- *results in persistent or significant disability or incapacity,*
- *or is a congenital anomaly or birth defect.*

As stated by the ICH, adverse events may also be serious for other reasons:<sup>47</sup>

*Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.*

## 8.3. Adverse drug reactions

An adverse event will be considered an *adverse drug reaction* (i.e., a causal link is suspected) if either the sponsor or the investigator considers there to be a reasonable possibility, based on evidence or arguments, that the event is causally related to an investigational product (zoledronic acid or placebo).<sup>47</sup> This definition of adverse

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drug reaction excludes adverse reactions to non-investigational products, such as concomitant medications. If an adverse drug reaction meets the criteria for seriousness, it will be classified as a *serious adverse drug reaction*.<sup>47</sup>

#### **8.4. Unexpected and serious unexpected adverse reactions**

An adverse reaction will be classified as an *unexpected adverse reaction* if its nature or severity is inconsistent with the Summary of Product Characteristics.<sup>49</sup> If the unexpected adverse reaction is serious, it will be classified as a *suspected unexpected serious adverse reaction* (SUSAR).<sup>49</sup>

In accordance with EU guidelines (Paragraph 29),<sup>50</sup> investigators must report serious adverse events to the sponsor within 24 hours of becoming aware of them. If the adverse event is a SUSAR, the sponsor will report it to the Swedish Medical Products Agency and to the Swedish Ethical Review Authority.<sup>49</sup> SUSARs that are fatal or life-threatening will be reported within 7 days, and relevant follow-up information will be reported within an additional 8 days. Other SUSARs will be reported within 15 days. The sponsor will inform all principal investigators of SUSARs that occur.

#### **8.5. Development Safety Update Report**

With the help of the University Hospital of Umeå Clinical Research Centre, the sponsor will submit to the Swedish Medical Products Agency and the Swedish Ethical Review Authority an annual Development Safety Update Report (DSUR), listing all serious adverse events and evaluating participant safety, as required by regulations (8 kap. 10 §).<sup>51</sup> The DSURs will comply with the ICH E2F guidelines.<sup>52</sup>

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## 9. Participant Timeline

A participant timeline for the 4-year Main Phase can be found in Table 1. As shown, potential participants will be invited to a screening visit (Visit 1) to provide written informed consent, to be assessed for eligibility, to be assigned a participant identification (ID) code, to undergo baseline testing, and to receive a loading dose of vitamin D. Of these steps, informed consent must come first, followed by the assignment of a participant ID code. The baseline tests will include the EQ-5D-5L, a self-administered health/lifestyle questionnaire (see the variables in Section 13.2), and measurements of body height and body weight (using a stadiometer and a medical scale). In addition, baseline tests of hand-grip strength will be conducted using hand dynamometers. Participants will receive a card with study information (e.g., contact information to the center, the participant's participant ID) to carry in their wallet. All participants will also take home a loading dose of oral vitamin D (see Section 6). They will be instructed *not* to take the vitamin D until study staff have notified them that this is safe to do based on the results of their blood tests. Participants must take the loading dose 1 to 4 weeks prior to the randomization visit (see below).

Approximately 10 days after the screening visit, participants will return for a randomization visit (Visit 2). The randomization visit may be cancelled by telephone if the results of the blood tests indicate that the participant does not meet the eligibility criteria. In this case, the patient will be informed that his or her participation ends here (without follow-up of any kind). If, on the other hand, the participant is still eligible, he or she will be randomized and be infused with zoledronic acid or placebo. Participants will be

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encouraged to report adverse events by telephone throughout the Main Phase (48 months).

One week before the second infusion (at 24 months), participants will undergo new blood tests of plasma calcium and creatinine clearance (Visit 3). Investigators may instead choose to refer participants to primary care for blood tests.

At 24 months, participants will visit their study center to receive a second loading dose of vitamin D and a second infusion of zoledronic acid or placebo (Visit 4). They will also take the EQ-5D-5L, undergo measurements of body height, body weight, and hand-grip strength, and be interviewed about adverse events and non-investigational bone-protective therapy.

The final study contact, at 48 months, will be a telephone interview about adverse events and use of non-investigational bone-protective therapy. The participant will also be asked to complete the EQ-5D-5L through an e-mail link. This link will save the participant's responses directly to the eCRF, so that sensitive information is not transferred via e-mail. Participants who are unable to complete the EQ-5D-5L online will receive a paper version by postal mail.

Investigators must do their best to ensure that study contacts occur in the designated time windows by scheduling the study contacts in good time. The procedures performed at screening (Visit 1) do not need to be repeated if randomization (Visit 2) is delayed. Each visit is anticipated to take 1 hour and each telephone interview 30 minutes.

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**Table 1.** Participant Timeline for the 4-Year Main Phase

<b>Timing/ procedure</b>	<b>Visit 1</b>	<b>Visit 2</b>	<b>Visit 3*</b>	<b>Visit 4</b>	<b>Tel.</b>
Time point	-10 d	0	23 m + 3 w	24 m	48 m
Time window	-4 to -1 w	0	±4 w	±4 w	±4 w
Informed consent	X				
Participant ID	X				
Inclusion/exclusion criteria	X				
Health/lifestyle questionnaire	X			X	
Body height	X			X	
Body weight	X			X	
Blood samples	X		X		
Vitamin D loading dose	X			X	
Randomization		X			
Infusion		X		X	
Use of other bone- protective therapy				X	X
Adverse events				X	X
Hand-grip strength	X				
EQ-5D-5L	X			X	X

Abbreviations: D, day; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; M, month; tel., telephone interview; W, week

\*This visit may be replaced with a referral to primary care for blood tests

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## **10. Treatment Allocation and Blinding**

Participants will be randomized according to a 1:1 permuted-block design, with randomly varying block sizes and stratification by center. The trial statistician will not reveal the block sizes to anyone else directly involved in the trial (e.g., the sponsor, principal investigators, or investigators' staff).

The trial statistician will use a computerized random number generator to create a randomization list. To maintain the trial statistician's blinding, the randomization program will be run by staff at the University Hospital of Umeå Clinical Research Centre, who will also select a random seed for the program. The Clinical Research Centre will be responsible for uploading the randomization list to the electronic case report form (eCRF), which will have a randomization feature. The randomization list will be stored by the Clinical Research Centre in a locked and safe location. Access to the randomization list will be granted to independent monitors and inspectors upon request, but not to anyone directly involved in the study. The Clinical Research Centre will also restrict access to the randomization feature of the eCRF to designated staff members.

The study medications will be purchased as marketed (i.e., in the original packaging). Therefore, principal investigators are responsible for enforcing strict routines to ensure that the trial is double blind. This will be done by designating particular staff members (randomization staff) to be responsible for randomizing participants and preparing infusions. Zoledronic acid will be prepared by adding 5 mg/6.25 ml of zoledronic acid concentrate, which is colorless, to an infusion bag containing 100 ml of normal saline. For the placebo group, 6.25 ml of normal saline will be

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added to the same type of infusion bag, making it visually identical to a bag of diluted zoledronic acid.

The randomization staff will be responsible for concealing the content of the infusion bottles from all other staff members and from participants. They are permitted to have contact with participants before, but not after, randomization. In other words, they are permitted to collect baseline data but not follow-up data. All other study staff will be blind to treatment assignments, which includes the sponsor/coordinating investigator, the principal investigators, the trial statistician, research nurses, and administrative staff.

It will not be possible for randomization staff to predict future treatment assignments, because the randomization list will not be accessible to them. In addition, the randomization feature on the eCRF will not include information about future treatment assignments.

Emergency unblinding can be performed if knowledge of a participant's treatment is essential for ensuring his or her safety. Decisions to emergency unblind a participant are made by the principal investigator or the sponsor/coordinating investigator. In such cases, the principal investigator or sponsor/coordinating investigator will contact the randomization staff at the participant's study center or designated staff at the Clinical Research Centre (the latter will have access to the treatment assignment of all participants). These staff members will have around-the-clock, online access to participants' treatment assignment through the eCRF. Investigators will be responsible for registering instances of intentional and unintentional unblinding on the eCRF.

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Participants will be informed of their treatment assignment when they have completed 48 months of follow-up (the Main Phase) or when they withdraw from the study. This information will be provided by the randomization staff. The randomization staff will not spread this information to other staff members, who will be blinded until the end of the trial, when the randomization list is unlocked by the Clinical Research Centre. This will be done when the sponsor/coordinating investigator and the trial statistician have confirmed that the trial database is accurate and complete and when an analysis dataset has been compiled.

## **11. Recruitment, Pre-Screening, and Exclusion**

Potentially eligible patients will be identified through the Swedish Fracture Register. This register was established in 2011 to monitor fracture occurrence, fracture care, and health outcomes after fracture.<sup>53</sup> All patients in this register have agreed to the use of their information in research, although they have provided written consent, as this is not required by Swedish law.<sup>53</sup>

Patient lists will be downloaded from the Fracture Register (see Section 12.2). When potentially eligible patients are found on these lists, they will be contacted through postal mail. The letter will include information about the study, a link to an online informational video, and contact information for reporting interest in participating. To increase participation rates, investigators may follow-up postal invitations with a telephone calls.

Patients who are interested in participating in the trial will be pre-screened for eligibility. The purpose of pre-screening is to avoid

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inviting patients who clearly do not meet the eligibility criteria (see Section 5). The results of pre-screening will be entered in a deidentified pre-screening log (see Section 12.2).

Recruitment through the Swedish Fracture Register has two advantages. First, we consider it to be more respectful than approaching patients in clinics, such as emergency rooms, where they are in pain and in need of medical attention. Second, it will make it easier to recruit the required number of participants. If the Swedish Fracture Register has insufficient coverage of fracture patients at a participating hospital, potentially eligible participants may instead be identified through local patient records (e.g., emergency ward records, X-ray records, or fracture liaison services [*Swedish: “frakturkedjor”*])).

The principle investigator or the sponsor/coordinating investigator can at any time exclude a participant from the entire trial. A participant may also be excluded from specific parts of the trial (infusions, in-person visits, telephone interview, or follow-up through registries or medical records). Reasons for exclusion may be adverse events (e.g., cognitive disability), death, loss to follow-up, termination of the study center, or participant withdrawal. Discontinuation of infusions is not a sufficient reason for excluding a participant from continued follow-up (see Section 6.1).

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## **12. Data Collection**

### **12.1. Participant identification codes**

Participants who provide informed consent will be assigned a sequential participant identification (ID) code, indicating the participant number. Once assigned, ID codes will not be reused for new participants. At each study center, participants will also be registered in a participant log, which will link participants' ID codes to their first name, last name, e-mail address, postal address, telephone number, date of informed consent, and Swedish Personal Identity Number. Of this information, only the participant ID codes will be used during data collection and analysis, in order to protect participants' integrity. Participant lists will be sent encrypted to the sponsor to enable registry follow-up. The registry data will be pseudo-anonymized using the participant ID codes.

### **12.2. Patient list, pre-screening log, and electronic case report form (eCRF)**

Patient lists will be downloaded from the Swedish Fracture Register during participant recruitment (see Section 11). These lists will be merged into a single patient list per study center. On this list, the study staff will note which patients have been contacted by postal mail, have accepted or declined to participate, and have been pre-screened. Patient lists will be anonymized and retained after the end of the Main Phase of the trial.

The results of pre-screening (see Section 11) will be entered into an electronic pre-screening log. The pre-screening log will be kept separate from patient lists. Furthermore, it will not contain personal

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information, as patients will not have provided informed consent at the time of pre-screening.

The data on consenting participants that are required to be collected according to this protocol will be entered by investigators into an eCRF, which will be pseudo-anonymized with participant ID codes. The exception to this rule is registry data on secondary outcomes, which will be collected centrally by the sponsor. However, fractures outcomes will be recorded on the eCRF, as these data will be verified through medical records.

All efficacy outcomes and adverse events will be recorded using the ICD-10-SE system. The eCRF will be appended to the Clinical Study Report. To ensure that the system is secure, the eCRF system will be set up in collaboration with the University Hospital of Umeå Clinical Research Centre and the Department of ICT Services and System Development at Umeå University.

Investigators must ensure that eCRFs are correct and complete and that reporting takes place within the predefined time windows. Any corrections made to an eCRF should be signed, dated, and (if needed) explained.

### **12.3. Biological specimens**

Samples of peripheral venous blood will be collected for analyses of plasma calcium and creatinine clearance (i.e., estimated glomerular filtration rate). The total volume of blood taken from each participant will be a maximum of 20 ml (10 ml at the screening visit and 10 ml 1 week before the 24-month follow-up). Further blood samples may be taken to ensure a participant's

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safety. The samples will be analyzed locally at the accredited department of clinical chemistry at each study center's institution. The samples of venous blood will be destroyed immediately after analysis, but the results will be archived as source documents (see below).

#### **12.4. Documentation**

The sponsor will keep a Trial Master File and investigators will keep an Investigator Site File containing the essential documents of the trial, as defined in ICH GCP.<sup>54</sup> These documents will be archived in accordance with each institution's local rules, but for a minimum of 15 years.

As stated in the ICH GCP,<sup>54</sup> investigators must keep source documents, which include (but are not limited to) eCRFs, questionnaires, laboratory reports, and registry data to enable reconstruction and evaluation of the trial's results. Investigators will also keep a drug accountability log so that investigational products can be tracked and a screening log of persons screened, invited to a screening visit and the number attending a screening visit. The investigator must ensure that all source documents are accessible for monitoring and inspection.

#### **12.5. Data management**

The trial statistician will continuously monitor eCRFs for accuracy and completeness (including range and logical checks) and for compliance with this protocol. Any inaccuracies, inconsistencies, or deviations will be reported to the appropriate study center, with a

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request for correction or explanation. The trial database will be backed up regularly. The sponsor/coordinating investigator may also appoint staff to conduct on-site monitoring to verify eCRFs with source documents. A detailed plan for data management has not been developed at the time of writing, but it will be attached to the Clinical Study Report.

## **13. Statistical Analysis**

Statistical analyses will be performed using the latest version of R software. All statistical hypothesis tests that can be two-sided will be two-sided. P-values  $<0.05$  will be considered statistically significant, unless otherwise specified. P-values will be rounded to two decimal places if  $\geq 0.01$  and rounded to three decimal places if  $<0.01$  but  $\geq 0.001$ . P-values  $<0.001$  will be expressed as “ $<0.001$ ”.

The zoledronic acid and placebo groups will be defined according to randomization. Baseline date will be defined as the date of randomization. In the Main Phase, follow-up time will be defined as 48 months or the date of death or withdrawal (whichever came first) minus the date of randomization plus 1 day (to account for the possibility of an event later in the day of randomization).

Incomplete follow-up will be defined as follow-up time that ends before the last study contact at 48 months. In the Secondary Phase, follow-up will be extended to 10 years.

### **13.1. Description of recruitment process**

The recruitment process will be described in terms of the number of persons invited to a screening visit, the number who attended a

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screening visit, the number who provided informed consent, the number who met all eligibility criteria, the number excluded at screening (in total and by reason for exclusion), and the number randomized.

### **13.2. Baseline characteristics**

All randomized participants (i.e., the intention-to-treat population) will be included in an analysis of baseline characteristics, in which the zoledronic acid and placebo groups will be compared. An analysis of baseline characteristics will also be performed for all participants who provide written informed consent but are not randomized. Baseline values will be defined as the last measurement made prior to randomization. The following numeric, binary, and multi-level categorical baseline characteristics will be analyzed:

Numeric:

1. Age, years
2. Body height, cm
3. Body weight, kg
4. Body mass index, kg/m<sup>2</sup>
5. Age at quitting smoking, years (if former smoker)
6. Number of cigarettes smoked on an average day (if current smoker)
7. Age at time of most recent stroke, years
8. Age at time of most recent myocardial infarction, years
9. Age at most recent cancer diagnosis, years
10. Number of bone fractures in adulthood (age  $\geq$  18 years)
11. Date of baseline fracture

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12. Creatinine clearance (estimated glomerular filtration rate),  
ml/min/1.73 m<sup>2</sup>
13. Plasma calcium, mmol/L
14. Hand-grip strength, attempt 1, kg
15. Hand-grip strength, attempt 2, kg
16. Hand-grip strength, maximum of attempts 1 and 2, kg

Binary:

1. Sex (man, woman)
2. Ever undergone bone density scanning (yes, no)
3. Provided written informed consent (yes, no)
4. Ambulatory (yes, no)
5. Community dwelling (yes, no)
6. Sustained a non-hip, non-vertebral fragility fracture in the  
past 2 years (yes, no)
7. Age  $\geq 65$  years at the time of fracture (yes, no)
8. Undergone bone density scanning since the baseline  
fracture (yes, no)
9. History of hip fracture (yes, no)
10. History of vertebral compression fracture (yes, no)
11. Ever diagnosis of osteoporosis (yes, no)
12. Remaining life expectancy  $< 1$  year (yes, no)
13. Ever use of antidepressant (yes, no)
14. History of stroke (yes, no)
15. History of myocardial infarction (yes, no)
16. Use of systemic glucocorticoids at a dose of  $\geq 5$  mg  
(prednisolone or equivalent) for  $\geq 3$  months in the past year  
(yes, no)
17. Previous use of bone protective drug (yes, no)
18. Malabsorption of calcium and/or vitamin D (yes, no)

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19. Other medication or medical condition for which bone-protective therapy is indicated (yes, no)
20. Place of the most recent non-hip, non-vertebral fragility fracture (indoors, outdoors)
21. Severe renal impairment (yes, no)
22. Hypocalcemia/hypercalcemia (yes, no)
23. Ever smoker, i.e. smoked  $\geq 100$  cigarettes in lifetime (yes, no)
24. Current smoker (yes, no)
25. Non-dominant hand (left, right)

Multi-level categorical:

1. Type of fall that led to the baseline fracture (fall on same level involving ice and snow; fall on same level from slipping, tripping and stumbling; other fall on same level due to collision with, or pushing by, another person; fall while being carried or supported by other persons; other fall on same level)
2. Frequency of alcohol consumption (never,  $\leq 1$  time/month, 2-4 times/month, 2-3 times/week,  $\geq 4$  times/week)
3. Number of glasses of alcohol on a typical day of drinking (1-2, 3-4, 5-6, 7-9,  $\geq 10$ )
4. Diabetes mellitus (type 1, type 2, no)
5. Cancer (current, previous, no)
6. Skeletal site(s) of baseline fracture (femur excluding hip, shoulder/upper arm, pelvis, ribs/sternum/bony thorax, lower leg, forearm)
7. Method of recruitment (Swedish Fracture Registry, local hospital registry, participant initiative, other)

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## 8. Study center

The variables on alcohol consumption are derived from the Alcohol Use Disorders Identification Test. A glass of alcohol corresponds to approximately 12 grams of pure alcohol.<sup>55</sup> The variables on cigarette smoking are based on definitions used in previous studies.<sup>56,57</sup>

Numeric variables will be summarized using means, medians, standard deviations, 25<sup>th</sup> percentiles, 75<sup>th</sup> percentiles, minimums, maximums, and number missing. Binary variables will be summarized as number and percent “yes” and number missing. Categorical variables will be summarized as number and percent in each category and number missing. Numeric values and percentages will be rounded to 1 decimal place (2 decimal places for plasma calcium). All variables will be summarized using number and percent of values out-of-range and, for laboratory values, number and percent outside reference values (see Section 13.7).

### **13.3. Analysis of investigational products**

For each infusion, the following information will be reported by study group for all randomized patients:

1. Receipt of infusion, number (%)
2. Date of infusion
3. Time from randomization to infusion, days/months
4. Receipt of infusion within time window (see Section 9), number (%)

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5. Main reason for not receiving infusion (wish of participant, participant discontinuation, death, exclusion due to adverse event, severe renal impairment [ $<35$  ml/min/1.73m<sup>2</sup>], hypocalcemia/hypercalcemia [plasma calcium  $<2.15$  or  $>2.50$  mmol/L], use of other bone-protective therapy, decision of sponsor/principal investigator for none of the above reasons)
6. Receipt of vitamin D loading dose prior to infusion, number (%)
7. Reason for not receiving vitamin D loading dose, free text
8. Batch number of zoledronic acid (if applicable)

The numeric variables will be summarized using means, medians, standard deviations, 25<sup>th</sup> percentiles, 75<sup>th</sup> percentiles, minimums, and maximums. The categorical variables will be summarized as number and percent in each level. The number with missing values will be calculated for all variables.

### **13.4. Analysis of follow-up**

The number and percent of randomized patients participating in study contacts will be reported for the zoledronic acid and placebo groups at each study contact. The number and percent not completing study contacts will be presented by cause (death, adverse event, loss to follow-up, termination of study center, withdrawal, other). The number and percent not completing registry and medical-record follow-up will also be presented by cause (death or withdrawal). Differential follow-up duration between the zoledronic acid and control groups will be examined by plotting Kaplan-Meier curves and testing for a difference using the log-rank test. Differences in the number and percent

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prematurely unblinded will be examined using Fisher's exact test. Number and percent prematurely unblinded by cause (mistake, adverse event, or other) will be presented.

### **13.5. Analysis of concomitant medications**

The number and percent of participants receiving bone-protective therapy (other than the investigational zoledronic acid) during follow-up will be reported. The study groups will be compared using Fisher's exact test.

### **13.6. Efficacy analysis**

All randomized patients with non-missing outcome data will be included in an efficacy analysis. For time-to-event outcomes, survival time will be calculated as date of event minus date of randomization plus 1 day (to account for the possibility of an event occurring later in the day of randomization). For participants not experiencing the event, time-to-event will be set as the follow-up time (see definition above). If the date of a participant's time-to-event outcome is incomplete, the date will be imputed as was done in a previous trial.<sup>20</sup> Thus, if the day of the month is missing, it will be imputed as the 15<sup>th</sup>. If both the day and the month are missing, these will be imputed as July 1. If the entire date is missing, the time-to-event will be set to 1 day.

For time-to-event outcomes, 4-year cumulative incidence curves will be estimated using the Kaplan-Meier method. The number of participants with an event, the number of events, and the incidence rates (number of events/total person-years at risk) will also be

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provided. The efficacy of zoledronic acid will be determined based on the log-rank test, which will be stratified by center. The relative effect of zoledronic acid versus placebo will be estimated by hazard ratios (with 95% confidence intervals) calculated using Cox regression, with stratification by center. These models will not be adjusted for covariates in the main analysis, so as to be comparable to the log rank test. The proportional-hazards assumption will be assessed using log-minus-log plots and by Wald tests of treatment-by-time product terms. In the case of a clear violation of this assumption, hazard ratios will be computed for time-intervals in which hazard ratios are more stable (e.g. 6-month or 12-month periods). The assumption of no interaction between treatment effect and center effect will be tested using treatment-by-center product terms with a likelihood ratio test.<sup>58</sup>

As an additional analysis, the number of participants needed to treat for 4 years to prevent one fracture will be estimated for each fracture outcome using Kaplan-Meier estimated risks. Ninety-five percent confidence intervals will be provided for numbers needed to treat,<sup>59,60</sup> with variance estimates derived using the method proposed by Kalbfleisch and Prentice (p. 18).<sup>61</sup>

Change-from-baseline outcomes will be analyzed using analysis of covariance. The response variable will be the post-intervention value and the explanatory variables will be baseline value, treatment group, and center. For the EQ-5D-5L exploratory outcomes, which will be measured twice during follow-up, an analysis of covariance will be run with each follow-up value as the post-intervention value. To prevent the problem of multiple testing, the stepwise approach to testing described in Section 13.8 will be used. The assumptions of linearity, constant variance, and normality will be checked using residual plots and normal quantile-

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quantile plots. Clear violations of these assumptions will be dealt with by transformations of the response variable or its baseline value. Clear violations of the assumption of constant variance may instead be dealt with using the method of weighted least squares. Outliers will not be removed. Participants with missing follow-up data on change-from-baseline variables will be excluded.

The hypothesis tests of efficacy will not be adjusted for multiple testing, to avoid a large reduction in the power of the trial.

### **13.7. Safety analysis**

All participants who receive at least one infusion (i.e., the safety population) will be included in a safety analysis. The occurrence of adverse events by the end of follow-up will be analyzed as the number of events and the number and percent of participants reporting at least one event. These data will be presented by study group, seriousness, and causality (suspected/not suspected relation to study medication). The study groups will be compared using Fisher's exact test. For post-infusion symptoms occurring  $\leq 3$  days after infusion, data will be presented for both infusions in total and for events reported to have occurred  $\leq 3$  days after each infusion. In addition to specific adverse events, the composite safety outcomes of any adverse event, any serious adverse event, any serious adverse drug reaction, any unexpected adverse drug reaction, and any suspected unexpected serious adverse reaction will be reported. Laboratory values of plasma calcium (low,  $<2.15$  mmol/l; normal,  $2.15$ - $2.50$ ; high,  $>2.50$ ) will be analyzed in a shift table from before the first to before the second infusion. The number and percent with severe renal impairment (estimated glomerular filtration rate  $<35$  ml/min/1.73m<sup>2</sup>) at Follow-Up Visit 2 will be presented. The

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mean and standard deviation change in estimated glomerular filtration rate from before the first to before the second infusion will be presented and compared between the groups using an independent-samples  $t$  test (Satterthwaite approximation of degrees of freedom).

### **13.8. Subgroup, sensitivity, and exploratory analyses**

Baseline characteristics and efficacy outcomes will be presented in subgroups defined by type of baseline fragility fracture (if a participant has multiple baseline fractures, then the most serious type of fracture in the following descending order of severity will be used: femur excluding hip, shoulder/upper arm, pelvis, ribs/sternum/bony thorax, lower leg, forearm), age group (65-74, 75-84, or  $\geq 85$  year), sex, and study center. In the efficacy analysis, product terms will be included in regression models to assess interaction of treatment with time since fragility fracture, type of fragility fracture, age, sex, and study center. These interaction effects will be tested using Wald tests for numeric and binary variables and likelihood ratio tests for multi-level categorical variables. We do not expect these interaction analyses to show significant differences in effect.

Six sensitivity analyses will be conducted. First, to assess the presence of confounding, regression analyses will be adjusted for the following baseline covariates: age, sex, BMI, time since fragility fracture, and site of fragility fracture (femur excluding hip, shoulder/upper arm, pelvis, ribs/sternum/bony thorax, lower leg, or forearm). Second, the efficacy analysis will be rerun in a per-protocol population (i.e., participants who met all eligibility criteria, either died or completed follow-up, and were both qualified to receive and did receive the 2 assigned infusions).

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Third, efficacy concerning time-to-event outcomes will be analyzed using the Andersen-Gill Cox model for recurrent events,<sup>62</sup> with stratification by study center. Fourth, in the analysis of the primary outcome, the potential effect of informative censoring (including the competing risk of death) will be assessed by rerunning Cox models under the extreme scenarios that all participants who did not complete follow-up either (1) sustained a fracture at the time of censoring (i.e., were at high risk of fracture) or (2) had complete follow-up with no event (i.e., were at low risk of fracture).<sup>58</sup> Fifth, participants with a history of cancer at baseline will be excluded from the efficacy analysis of new cancers diagnosed during follow-up. The same will be done for cardiovascular disease. Sixth, fractures not verified by medical records will be included in the efficacy analyses.

To assess the time-to-onset of treatment effect on the primary outcome, Kaplan-Meier curves will be compared using the center-stratified log-rank test with censoring at months 48, 42, 36, and so on until month 6. To avoid the problem of multiple testing, a fixed-sequence procedure will be used in which the test will first be performed for risk at month 48, then at month 42, and so on until month 6.<sup>63</sup> If a p-value  $\geq 0.05$  is obtained, the results of all subsequent tests will be considered non-significant. Similarly, center-stratified Cox models will be used to estimate hazard ratios and 95% confidence intervals, with administrative censoring at month 48, 42, and so on until month 6.

### **13.9. Interim analysis**

No interim analysis will be performed to determine whether the trial should be terminated early. There are four reasons for this choice in design. First, the risk of large safety concerns is low due to the fact that the effects of zoledronic acid have already been studied, without major safety concerns, in four large trials.<sup>19–22</sup> In

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addition, zoledronic acid will be administered only twice, which is less than is commonly done in clinical practice.<sup>17</sup> It should also be noted that zoledronic acid was approved in the European Union back in 2005.<sup>17</sup> Second, the risk of needing to stop the trial due to futility is low, because zoledronic acid has been shown effective in multiple studies.<sup>19–22</sup> Third, early termination for efficacy is unlikely to result in a substantial increase in the number of patients who receive treatment, as treatment rates are currently low<sup>15,16</sup> and treatment decisions are based on local guidelines, which take time to update. Furthermore, this would reduce the power of the trial to detect effects on secondary outcomes. Fourth, interim analyses are complicated to carry out, as they require unblinding of the data.<sup>64</sup>

No interim analysis will be performed for the purpose of adjusting the sample size upward, because this would not be feasible due to budget constraints.

### **13.10. Sample size and power calculations**

The trial will enroll 2900 participants, of whom 227 will need to sustain a clinical fracture during follow-up for the study to achieve 90% power to detect a 35% reduction in clinical fractures with the log-rank test (2-sided significance level of 5%). This calculation assumes a 4-year fracture risk of 10% in the placebo group and an overall dropout rate of 5% (due to withdrawal or loss to follow-up, i.e., deaths excluded). The details of the calculation can be found in Appendix 1. Appendix 2 provides a table of required sample sizes under varying assumptions. As shown, the required sample size is sensitive to changes in the assumed hazard ratio and the assumed fracture risk in the placebo group, but it is relatively insensitive to changes in dropout rate.

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To put the assumptions of the sample-size calculation in perspective, we note that 3 of 4 previous large trials of zoledronic acid had 90% power,<sup>19,20,22</sup> whereas the fourth had 80% power.<sup>21</sup> Incomplete follow-up (deaths excluded) was observed in 4% of women with osteopenia (6-year follow-up),<sup>21</sup> 8% of men with osteoporosis (1-year follow-up),<sup>22</sup> 13% of women with osteoporosis (3-year follow-up),<sup>19</sup> and 17% of hip fracture patients (1.9-year median follow-up).<sup>20</sup> Three of the trials that were powered to demonstrate effects on clinical fractures, and these showed effects of 27%,<sup>21</sup> 33%,<sup>19</sup> and 35%.<sup>20</sup>

The assumed 4-year fracture risk of 10% was derived from data on the Swedish population that we have previously collected from the Swedish National Patient Register. From this register, we selected adults in Sweden who were aged 65 to 85 years and who suffered an initial fracture of the arm or lower leg in 2006 (ICD-10-SE codes: S42, S52, or S82). There were 10,361 such individuals who were not prescribed bone-protective treatment over the next 4 years. Their mean age was 74.9 years and 73% were women. Over the next 4 years, 10.0% (n=1028) suffered a new fracture at a different skeletal site. We expect the restriction of the analysis to fractures of a different skeletal site to lead to an underestimation of the incidence of new fractures, but this restriction is necessary to avoid counting the same fracture twice. The distribution of fractures by skeletal site was as follows:

1. 457 fractures of the hip
2. 148 fractures of the upper arm
3. 125 fractures of the lower leg and foot joint
4. 117 fractures of the radius or ulna
5. 91 fractures of the lumbar spine

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The risk of a new fracture was similar in women and men, 10.2% in women and 9.6% in men. Assuming a hip fracture risk of  $457/10,361=4.4\%$  in the placebo group and a dropout rate of 5%, recruitment of 2900 participants will give the trial 71% power to detect a 40% reduction<sup>19</sup> in hip fractures and 55% power to detect a 34% reduction<sup>21</sup> in hip fractures (5% significance level).

## **14. Monitoring, Inspection, Deviation, and Early Termination**

Investigators must allow monitoring and inspection by providing direct access to eCRFs, source data, and other study-specific documentation.

### **14.1. Monitoring**

The trial will be independently monitored by the University Hospital of Umeå Clinical Research Centre before, during, and after the Main Phase of the study (see Section 4). The purpose of this monitoring is to ensure that the study is carried out according to the protocol; that the data are collected, documented, and reported in accordance with ICH GCP;<sup>54</sup> and that applicable ethical and regulatory requirements are followed. A Monitoring Plan will be developed jointly by the sponsor/coordinating investigator and the Clinical Research Centre.

The study will not have an independent data and safety monitoring board because no interim analysis is planned (see Section 13.9).

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## **14.2. Inspection**

The Swedish Medical Products Agency may inspect the trial. In this case, any study-related data requested by the Agency must be provided according to Swedish regulations (10 Kap. 1§).<sup>51</sup>

## **14.3. Deviations and serious violations**

Deviations from this protocol, ICH GCP, or regulations will be documented by the sponsor and principal investigators and be described in the Clinical Study Report. Deviations will be considered serious violations if they significantly affect, or are likely to affect, participants' safety, participants' integrity, or the scientific quality of the trial. Such violations will be reported by the sponsor/coordinating investigator to the Swedish Medical Products Agency within 7 days (p. 17-18).<sup>65</sup> It is the sponsor's responsibility to determine whether deviations are serious enough to qualify as violations.

## **14.4. Early termination**

The trial may be terminated early if it appears that zoledronic acid is resulting in a large number of SUSARs. In the case of termination, investigators will immediately inform the participants of this and ensure appropriate treatment and follow-up. The Swedish Medical Products Agency will be informed as soon as possible, but no later than 15 days after the decision to terminate (9 kap 2 §).<sup>51</sup> Decisions about early termination are made by the sponsor.

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## **15. Ethics**

### **15.1. Compliance with the protocol, GCP, and regulations**

The trial will be performed in accordance with this protocol, ICH GCP,<sup>54</sup> the Declaration of Helsinki,<sup>66</sup> and Swedish and European Union regulations. The purpose of this is to ensure the safety and integrity of the participants and the quality of the data.

The Swedish Medical Products Agency will be informed of the study's completion through the submission of a "Declaration of End of Trial Notification" form no later than 90 days after the End of Trial (9 kap., 1 §).<sup>51</sup> The Swedish Ethical Review Authority will also be notified.

### **15.2. Research ethics approval**

Participant recruitment will not begin before this protocol, an informed consent form, and other information provided to participants have been approved by the Swedish Ethical Review Authority. The protocol will also need to be approved by the Swedish Medical Products Agency (5 kap. 1 §).<sup>51</sup>

### **15.3. Protocol amendments**

Substantial protocol amendments must be approved by the sponsor, the Swedish Ethical Review Authority, and the Swedish Medical Products Agency. The Swedish Medical Products agency defines substantial amendments to the study protocol as those that may affect (1) participants' safety or physical or psychological integrity,

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(2) the scientific value of the study, or (3) are substantial in any other way.<sup>51</sup> Substantial amendments will not be implemented until they have been approved, unless doing so is necessary to prevent immediate harm to participants, in which case the amendments will be reported as soon as possible (7 kap. 1 §, 8 kap. 2 §).<sup>51</sup> The opinions of all principal investigators will be sought before substantial changes are made. The sponsor will ensure that principal investigators are aware of approved changes and have access to the latest version of the protocol.

Non-substantial changes (i.e., small administrative changes) require only the approval of the sponsor and will be clearly noted in an amended protocol and in the Clinical Study Report. Non-substantial changes will be reported to the Swedish Medical Products Agency upon End of Trial reporting or earlier, if substantial changes are needed.<sup>65</sup>

## **15.4. Informed consent**

The principal investigator at each site must ensure that participants are given adequate oral and written information about the study. Participants should be given time to consider the information provided and an opportunity to ask questions. The written patient information, the online informational video, and the informed consent form will be approved by the Swedish Ethical Review Authority. These documents will be appended to the Clinical Study Report.

If a patient chooses to participate, both the patient and the investigator will sign the informed consent form. The patient should receive a copy of the written information and the informed

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consent form. The informed consent form must be signed before any study-specific activity is performed. According to Swedish regulations,<sup>65</sup> informed consent must be obtained by a qualified physician. If new information about participants is to be collected after informed consent has been obtained, participants have the right to reconsider whether to continue their participation.

Participants will have the right to withdraw from the study at any time, without justification, and without any consequence to their future medical care. As recommended by ICH GCP however,<sup>54</sup> participants who withdraw will be asked if they want to provide a reason. Participants who request withdrawal will be given the options of just stopping treatment or of stopping both treatment and follow-up. Upon withdrawal, all participant data that have previously been collected must be retained for archiving purposes. The right to retain research data after participant withdrawal is laid down by Swedish law.<sup>67,68</sup>

## **15.5. Medical record registration**

In accordance with Swedish regulations,<sup>65</sup> investigators must register in participants' medical records that the participants are involved in a clinical trial. These entries must include the following information:

1. The trial is randomized and double-blind.
2. The investigational products are zoledronic acid and placebo (normal saline), given as two intravenous infusions at a dose of 5 mg with two years in between.
3. A loading dose of vitamin D (100,000 IU or 2.5 mg) has been given.

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4. Written informed consent has been obtained.
5. Participant ID.
6. Instructions for emergency unblinding.
7. Investigational product received (once unblinded).

## **15.6. Insurance**

Participants will be protected by the Swedish Patient Insurance and by the Swedish Pharmaceutical Insurance.

## **15.7. Confidentiality**

Data collected in the trial, whether in electronic or physical form, will be processed so that only authorized persons have access to it. Datasets used for statistical analysis, eCRFs, and questionnaires will be pseudo-anonymized using participant ID codes (see Section 12.1).

## **15.8. Conflicts of interest**

The sponsor/coordinating investigator and authors of this protocol declare that they have no conflicts of interest.

## **15.9. Post-trial care**

There will be no post-trial care at the end of the Main Phase or Secondary Phase. Instead, participants will be informed of the treatment they received when they have completed the 4-year Main

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Phase or when they withdraw from the study. Participants in the placebo group will not be offered zoledronic acid because of budget constraints and because treatment decisions should be based on individual assessments made according to local guidelines.

### **15.10. Data access**

Principal investigators will have complete access to the data at their center, but they will not have access to the data at other centers. The sponsor and trial statistician will have access to all participant lists and eCRFs. All principal investigators will receive the final, pseudo-anonymized, analysis datasets.

## **16. Dissemination**

A Clinical Study Report of the trial's results will be completed twice in accordance with Annex 1 of the ICH E3 guidelines.<sup>69</sup> The first time will be within a year after the end of the Main Phase. The second time will be at the end of the Secondary Phase (i.e., the End of Trial). The second report will be submitted to the Swedish Medical Products Agency.<sup>65</sup> It will also be posted on the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). Participants will receive a non-technical summary of the study results when the last participant after the Main Phase of the trial. Clinical staff will also receive a summary of the results.

The results of the Main Phase will be published in a peer-reviewed scientific journal after the completion of the Main Phase, regardless of whether or not the results show a significant treatment effect.

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The results of the Secondary Phase will be published similarly. Study centers must not publish their own results, because the results from all centers will be pooled and published jointly. Any exceptions from this rule must be approved by the sponsor.

R code for randomization, data management, and analysis will be made publically available at the time of publication. The Clinical Study Reports will also be made publically available, with possible redaction of individual-level data if this is necessary to ensure the participants' integrity. The pseudo-anonymized analysis datasets will not be made publically available, because these are still considered personal data under the European Union General Data Protection Regulation (GDPR), as the risk of identifying an individual, due to the detail of the data, cannot be ruled out.<sup>70</sup>

Co-authorship of the peer-reviewed journal articles will be determined based on the recommendations of the International Committee of Medical Journal Editors.<sup>71</sup> In good time before publication, the principal investigators and the sponsor/coordinating investigator will each make a list of the members of their staff that want to be included as authors. These lists must include a statement of which ICMJE criteria for apply to each name on the list, as well as an explanation of how each person meets the criteria. The principal investigators and the sponsor will jointly assess who on these lists meet the ICMJE criteria. The investigators and the sponsor will also determine the order in which the names will appear on the published article. The final decision of which names will appear and in what order will be the joint decision of all principal investigators, by consensus if possible, by majority vote if necessary. The sponsor will break a tie should one arise.

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## 17. Risk-benefit evaluation

The main expected benefit of zoledronic acid is a reduced risk of fractures. Based on previous studies, we expect to see a 35% relative risk reduction, corresponding to a 3.5% absolute risk reduction. There are also health economics benefits to consider. Below is an example for hip fractures.

We expect hip fractures to occur in approximately 5% of participants during follow up. With an absolute risk reduction of 1.75% from zoledronic acid (35% relative risk reduction), the numbered need to treat to avoid 1 hip fracture is 57. In clinical practice, the cost of the study drug (two 5 mg infusions of zoledronic acid) is about 300 Swedish Krona (SEK). Additional costs of treatment (e.g., the cost of personnel and blood tests) amount to approximately 500 SEK, meaning that the total cost of treatment is about 800 SEK. Therefore, the estimated cost to avoid one hip fracture is  $800 \times 57 = 45,600$  SEK.

This cost of 45,600 SEK can be compared to the estimated hospitalization cost of 100,000 SEK for each hip fracture patient.<sup>72</sup> Furthermore, in the 12 months following the fracture, each hip fracture patient requires subsequent health care and social care for about 400,000 SEK.<sup>72</sup> Thus, there are substantial health economic benefits based on prevented hip fractures alone. We expect further cost benefits due to reductions in other types of fractures and increased quality-adjusted life years.

There are also risks involved in participating in this trial. One risk is adverse effects. As explained in the Introduction, zoledronic acid causes post-infusion symptoms in about a third of patients, but these symptoms are transient and less common after the second

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infusion.<sup>19</sup> More serious are the adverse effects of atypical femoral fractures and osteonecrosis of the jaw. These effects are rare, however.<sup>23,24</sup> It should also be noted that increased risks of these events were not reported in four previous large trials of zoledronic acid.<sup>20–22,26</sup> In these trials, zoledronic acid was given at more frequent intervals than is planned in our trial, which reduces the risk of adverse effects in our trial.

Another aspect of ethical concern is that some of the patients in the placebo group likely would have received bone-protective treatment had they not been included in the trial. However, only about 10% of fracture patients currently receive treatment,<sup>15,16</sup> and there is currently no standard treatment for fracture patients who (as the patients in the current trial) do not have a hip or vertebral fracture.

There is also a risk of invasion of privacy because we intend to contact potential participants through the registers, primarily the Swedish Fracture Register. However, individuals registered in the Swedish Fracture Register have agreed to the use of their data in research. In addition, we consider it to be more respectful than approaching patients in clinics, such as emergency rooms, where they are in pain and in need of medical attention.

A final risk is the COVID-19 pandemic, which started in 2020 and is ongoing at the time of writing. Due to the participants' age, they are at increased risk of developing severe COVID-19. We believe this risk outweighs any potential benefit of the trial, so participant enrollment will not begin until the pandemic is under control. The sponsor will determine when it is safe to start enrollment. In summary, we consider the benefits of conducting this study to

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outweigh the risks when the COVID-19 pandemic is under control,  
making the trial ethical to perform.

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## 19. Appendix 1: Sample Size Calculation

The first step in the sample size calculation is to calculate the number of fractures that need to be observed in the trial, because the log-rank test is powered by events rather than participants. According to Schoenfeld,<sup>73</sup> the necessary number of fractures (assuming 90% power, a 2-sided alpha of 5%, and a hazard ratio of 0.65) is

$$\frac{4(Z_{1-0.05/2} + Z_{0.90})^2}{\ln(0.65)^2} = 227.$$

Here,  $z_p$  is the  $p^{th}$  quantile of the standard normal distribution and  $\ln(\cdot)$  is the natural logarithm.

The second step is to estimate the required number of participants, ignoring any early dropouts due to withdrawal. According to Schoenfeld,<sup>73</sup> a 10% fracture risk in the placebo group and a hazard ratio of 0.65 corresponds to an estimated risk of

$$1 - (1 - 0.10)^{0.65} = 0.06619$$

in the zoledronic acid group. With 227 fractures, the required number of participants becomes

$$\frac{227}{(0.10+0.06619)/2} = 2732.$$

The third step is to adjust the sample size of 2732 for dropouts. As suggested by Freedman,<sup>74</sup> this can be done simply by dividing the sample size by the proportion of non-dropouts:

$$\frac{2732}{1-0.05} = 2876.$$

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For simplicity, we round this number up to 2900.

20. Appendix 2: Sample Sizes Under Varying Assumptions

Required sample size under varying assumptions (5% significance level)

Power (%)	HR	Risk placebo (%)	Dropout (%)	Required Sample size
80	0.65	15	5	1432
			10	1512
			15	1600
		10	5	2154
			10	2274
			15	2408
	0.70	15	5	2022
			10	2134
			15	2260
		10	5	3040
			10	3210
			15	3398
90	0.65	15	5	1912
			10	2018
			15	2138
		10	5	2876
			10	3036
			15	3216
	0.70	15	5	2708
			10	2858
			15	3026
		10	5	4074
			10	4300
			15	4554

Abbreviation: HR, hazard ratio