Chapter 7

Main results and general discussion

7.1
Main results in perspective

7.2
General discussion

7.3
Final statement

7.4
Future research
7.1

Main results in perspective
Main results and general discussion

Introduction
The main objective of this thesis was to obtain more knowledge about vertebral fractures among geriatric patients. The methodology of diagnosing vertebral fractures on lateral chest X-rays was studied. To quantify the prevalence of vertebral fractures in geriatric patients visiting an outpatient day clinic, we have studied a large cohort in 2007-2008. To investigate the clinical burden and relevance of vertebral fractures in these patients, we have analysed data from the original cohort at baseline and after follow-up of three years. Furthermore, we studied the relationship between vertebral fractures, a changed posture (due to vertebral fractures) and future falls. Lastly, to examine whether patients with limited life expectancy, such as geriatric patients, will benefit from anti-osteoporosis medication, we have applied statistical process control-a novel method- to determine the exact moment in time when anti-osteoporosis medication becomes effective.

Chapter 2 - Methods discussed
In all studies included in the present thesis, a lateral chest X-rays was used to diagnose vertebral fractures of the thoracic spine, along with a lumbar spine X-ray. Diagnosis of a vertebral fracture was made using the semi-quantitative method of Genant. This method was until recently only validated for lateral X-rays of the (thoracic) spine [1] and CT images [2].

In our study, we compared in 109 patients X-rays of the chest with that of the thoracic spine: we found a high (>90%) intra-observer agreement for the diagnosis of vertebral fractures. Thus, we concluded that the X-ray of the chest could also be used to identify vertebral fractures. This finding is important for clinical practice, since chest X-rays are often part of the standard care at the geriatric outpatient clinic (the Comprehensive Geriatric Assessment -CGA). With the results of this study, vertebral fractures can be diagnosed, without any extra X-rays for patients, thus less discomfort, less radioactive radiations for patients and lower costs.

*Therefore, a (lateral) x-ray of the chest is useful for diagnosing vertebral fractures of the thoracic spine (this thesis-1).*

Chapter 3 - Prevalence of vertebral fractures and risk factors
In our population of geriatric outpatients (mean age 82) who visited the diagnostic day clinic of the Slotervaart Hospital in Amsterdam for a Comprehensive Geriatric Assessment, we found a high prevalence of vertebral fractures, namely 51%. Noteworthy, we found a high amount of moderate (25-40% height loss) and severe (>40% height loss) vertebral fractures (respectively 36% and 33% of all vertebral fractures) (chapter 3.1). In addition, in geriatric males we found a prevalence of vertebral fractures of 48% (chapter 3.2) in our post hoc analysis. In these men with vertebral fractures, 40% had more than one vertebral fracture, and roughly half of them had a moderate or a severe fracture. In an age-comparable population based study in the Netherlands (the Rotterdam-study), the prevalence of vertebral fractures in individuals of the same age (80+) was much lower.
(women 30%, men 22%-data adjusted from figure in original study), and the amount of moderate and severe fractures accounted together for only 30% of the vertebral fractures [3]. Another very large population-based study from Europe shows comparable results to the Rotterdam study [4].

The high numbers of multiple vertebral fractures and the high amount of moderate and severe vertebral fractures in men and women presenting at an outpatient day clinic for geriatrics show the severe underlying osteoporosis in this specific patient group (this thesis-2).

In our cohort (chapter 3.1) we found that previous non-vertebral fractures and former use of glucocorticoids were independently associated with vertebral fractures at baseline. We could not confirm co morbidity or immobility as risk factor for vertebral fractures in our study. Moreover, no risk factors could be identified in our study on vertebral fractures in geriatric males (chapter 3.2).

These results make clear that despite the high prevalence of multiple and severe vertebral fractures, there are no clinical risk factors found in this study for this population that can identify these patients without radiography (this thesis-3).

Chapter 4 - Consequences of vertebral fractures after 3 years
After 3 years of follow-up, 46% of the patients from the original cohort in 2007-2008 were deceased. Mortality rate in this cohort was doubled, compared to the Dutch national statistics of individuals of the same age (28% mortality after 3 years for men, and 19% for women of 82 year old). Analyses showed that mortality after 3 years was related with the presence of any vertebral fracture, and that it was independently associated with the presence of 3 or more vertebral fractures at baseline. The association does not imply causality, since the patients with vertebral fractures were significantly older, had more chronic diseases and used more prescriptions. Age and co morbidity were probably the most important confounding factors.

Only 50 patients of the 395 included patients at baseline were able and willing to return after 3 years. Patients with a prevalent vertebral fracture at baseline, the incidence of a new vertebral fracture over 3 years was 40%, which is statistically higher (p=0.006) than the incidence of 11% in those patients without a prevalent vertebral fracture (Odds ratio 6.4, 95% CI 1.17-32.7) (chapter 4.1). To put these numbers in perspective, a post hoc analysis of the placebo arm of the Horizon Trial showed that women (mean age 72.9) with 63% prevalent vertebral fractures at baseline had 9% incident vertebral fractures [5].

These results show that prevalent vertebral fractures in geriatric patients are highly clinically relevant: patients with prevalent vertebral fractures are at very high risk for developing new vertebral fractures, and when patients have multiple vertebral fractures they tend to die earlier (this thesis-4).
Chapter 5 - Consequences of vertebral fractures on posture, postural control and falls

Falling is one of the major problems in geriatric patients. In the general population, thirty percent of individuals older than 65 years fall at least once per year, and 10% has serious injury from the fall [6-8]. Patients who fall are at high risk for hip and upper arm fractures [9]. Our literature review revealed that osteoporosis as well as the presence of vertebral fractures, increased thoracic kyphosis and/or a flexed posture affects postural control negatively, increasing the risk of falling (chapter 5.1). This means that patients with a vertebral fracture are at higher risk of falling, especially when an increased thoracic kyphosis (as a result of the vertebral fractures in some cases) is present or even a flexed posture has occurred. To test the hypothesis that patients with a vertebral fracture are more likely to fall, we studied in a cohort of independently walking geriatric patients gait pattern and falls prospectively. Of these patients, 39% had at least one vertebral fracture, 55% had a hyperkyphosis (≥50 degrees) and 44% had a flexed posture. Most patients had a combination of two or three of the above-mentioned clinical entities. We showed that vertebral fractures could contribute to the manifestation of an increased kyphosis. Remarkably, in the presence of a hyperkyphosis falls are more likely to occur with an odds ratio of 6.18 (95% CI 1.17-32.7; p=0.03) (chapter 5.2). Vertebral fractures had a trend towards significance in the relation with future falls (p=0.06).

The results of chapter 5 show that vertebral fractures can cause change of posture, which influences postural control and contribute to falling (this thesis -5). Moreover, hyperkyphosis is highly prevalent in geriatric patients and these patients fall more often (this thesis-6).

Chapter 6 - Treatment in geriatric patients: is there time to benefit?

Our literature search on randomized controlled trials in osteoporosis medication, to evaluate whether there is any data on ‘time to benefit’ for the treatment of osteoporosis revealed that only five (of the 325) studies found showed a method to evaluate an early effect of treatment (chapter 6). Other terminology than ‘time to benefit’ was used in these studies. We have applied a novel method to calculate time to benefit. Statistical Process Control (SPC) can detect at which moment processes starts to change [10]. To perform this method on an existing dataset, we received data from The Fracture Intervention Trial [11]. This pivotal trial of more than 6000 women has shown that alendronate (worldwide the number one treatment option to prevent further fractures due to osteoporosis) is effective in postmenopausal women between 55 and 80 years. We included in our analysis the patients with either a prevalent vertebral fracture or a T-score ≤ -2.5. Clinical fracture during follow-up was the outcome measure of interest. SPC showed that the time to benefit in elderly patients (≥ 70 years) treated with alendronate for any clinical fracture is 8 months, although at that moment the absolute risk reduction (ARR) is still small (1.4%) (chapter 6).
The patients in the FIT-trial who were included for the analysis with SPC were younger than geriatric patients in this thesis (FIT had women of mean 70 years versus 82 years in this thesis) and had a confirmed diagnosis of osteoporosis: they had either an existing vertebral fracture (n=2027) or a T score ≤ -2.5. The question is whether the results of the SPC analysis on the FIT-data can be extrapolated to the geriatric population. On the one hand, it can be assumed that the time-to benefit will be shorter in a geriatric population: geriatric patients have, due to more muscular weakness and dysbalance, a higher fall rate, and therefore a higher chance than younger individuals of suffering a fracture [12] (chapter 4). On the other hand, the women included in SPC analysis had all a confirmed diagnosis of osteoporosis. In our cohort we did not perform DXA, consequently we do not know the patients T-score. It is expected that in the cohort of geriatric patients with a prevalence of vertebral fractures of 50%, the diagnosis of osteoporosis will be high, but probably not reaching a 100 percent. For the cohort of geriatric patients it is not sure what the time to benefit would be. But, since we would only prescribe anti-osteoporotic medication for the selected geriatric patients with either a vertebral fracture or a T score ≤ -2.5 it is assumed that these patients will have a higher a priori chance of falling, thus a higher chance for a fracture, and therefore a shorter time to benefit.

Moreover, the analysis was done only for the outcome of clinical fractures. The asymptomatic vertebral fractures were not included in the model used with SPC analysis. This thesis showed the high clinical relevance of these asymptomatic vertebral fractures. Consequently, anti-osteoporosis medication is expected to have clinical impact when incident morphometric vertebral fractures (a new vertebral deformity during follow up without clinical symptoms) are prevented. In other studies with bisphosphonates is it shown that for these morphometric vertebral fractures significance can be reached even within 6 months [13-17].

Therefore, we conclude that alendronate can be worth prescribing to prevent subsequent fractures in geriatric patients with a limited life expectancy of 6 months (this thesis-7).
7.2

General discussion
Main results and general discussion

A. Why do geriatric patients have so many (vertebral) fractures? A theoretical model.

The reason for the observed, almost doubled prevalence of vertebral fractures of 50% for men and women in our cohort compared to the results of population based studies (22% for men and 30% for women [3,4]), and the high amount of severe vertebral fractures among geriatric patients compared to individuals of the same age, is not yet fully clarified. An explanation could be that the patients selected (first time visitors of a geriatric diagnostic day hospital) have more co morbidity than community dwelling elderly from population based studies. The underlying mechanisms of osteoporosis and high fracture risk in geriatric patients are multiple and can vary between patients, which is typical for the geriatric population.

Age is probably of great importance because it affects all organ systems such as bone and muscles. After menopause bone remodelling shows an imbalance with more bone resorption than bone formation [18]. Bone resorption takes place at the surface of trabecular and cortical bone, destructs bone, leaving cavities, which osteoblasts will fill up with bone formation [19]. However, when bone formation stays behind, the total amount of cavities increases, leaving more surfaces, on which bone resorption can take place [19]. As a result of the enlarged surfaces, resorption tends to increase more rapidly [18]. Therefore, the acceleration in bone resorption exceeds to accelerate even more at higher age [20]. Cancellous bone shows thinning of the cortex from within, more porosity and destruction of bone architecture, which results in more fragile bone [18]. Eventually, in old age trabecular bone has decreased and cortical bone has become cancellous. Fragile bone, as a result of porosity, can fracture easily, especially in the vertebrae. In fact, vertebral fractures can occur during normal daily activities, such as climbing stairs, lifting groceries or bending forward [21]. Figure 1 shows the physiological process of ageing on bone, leading to fragility.

In addition to age, there are several known risk factors that can speed up the process of bone resorption in older individuals. In summary, immobility [22], low body mass [23], smoking [24], vitamin D deficiency [25], and the co morbidity of chronic diseases with low inflammatory diseases such as COPD (Chronic Obstructive Pulmonary Disease) [26] and rheumatoid arthritis [27] are well known for their negative effect on bone. Moreover, prior corticosteroid use [28] and previous fracture [29] are also well known risk factors for osteoporosis and subsequent fractures. The last mentioned factors (corticosteroid use and previous fracture) were also independently associated with prevalent vertebral fractures in our cohort (chapter 3.1). Most of the earlier-mentioned factors are often present in the majority of geriatric patients [25]. Figure 2 shows how diseases and co morbidity theoretically add to the cascade of ageing bone. Fractures can occur earlier in life due to the cumulative effect of ageing and other negative factors on bone remodelling. At the moment when fractures occur, they can cause immobility (especially major fractures such as hip or pelvis fractures) and consequently cause loss of muscle mass and function (sarcopenia). Sarcopenia can add to fall risk in this frail population what can result in a fall
Chapter 7.2

and a new fracture. Finally a vicious circle occurs that can undermine rehabilitation and can result in excess mortality in this patient group.

To understand the high rate of non-vertebral fractures in old age, bone strength accounts for only a part of the risk. Falls are important as well, about one third of community dwelling older adults above the age of 65 falls every year [30-32], while 5-10% of the falls in older adults lead to major injuries such as fractures [33]. For example, the rate of hip fractures following a fall is only 1%, but 90% of all hip fractures are caused by a fall [33].

Well-known risk factors for falls in older adults are overlapping with risk factors for fractures. The most important risk factor is higher age due to declines in several physiological systems [32,34,35]. Examples of the decline of physiological systems are slowed postural responses, lower vision, less vestibular function, less proprioception and less coordination, in combination with less strength, less cardiovascular reserves and less cognitive function [36,37]. Furthermore, use of several medications adds to a higher fall risk. Underlying diseases such as cardiovascular and neurologic diseases can increase fall risk [37].

Figure 1: After menopause, bone resorption increases and bone formation decreases, resulting in bone loss over time. Bone loss takes place at the surface of bone, leaving cavities. Due to bone loss, there is destruction of bone architecture, with thinning of the cortex and increased porosity. In old age this process has resulted in more fragile bone that breaks easily.
Main results and general discussion

Figure 2: In addition to the physiological process of ageing, diseases and co morbidities can speed up the process resulting in major fractures earlier in life. Fractures can cause immobility and consequently sarcopenia and falls, which adds to a vicious circle.

Moreover, environmental or extrinsic factors are also important in contributing to fall risk [38]. Lastly, we showed that change in posture due to hyperkyphosis, which might be the result of vertebral fractures in the thoracic spine, results in a higher fall risk (chapter 5.2).

To summarize why geriatric patients have so many (vertebral) fractures, is because in old age several physiological systems decline in function due to the ageing process as well as the result of diseases. This decline results in fragile bones, less muscle mass, and less reserves to keep equilibrium while walking and standing. Fractures (vertebral and non-vertebral) are the ultimate result of ageing (this thesis-8).
B. Rather an atypical presentation than an ‘asymptomatic’ presentation

To the editor: Individuals with vertebral fractures do not often come to medical attention: it has been shown that only about one third seeks acute medical help, of whom 8% is hospitalized for a vertebral fracture [31]. The majority of the individuals with vertebral fractures, who are usually diagnosed based on vertebral deformities on X-rays that have been performed for other medical reasons, (for instance pneumonia), are often referred to as ‘asymptomatic’ [32,33].

In the last decade, many studies have shown that these asymptomatic (prevalent) vertebral fractures may lead to substantial somatic and psychological burden; individuals with vertebral deformities have more back pain and higher immobility [30], lower quality of life and more complaints of anxiety and depression than age- and sex-matched controls [34]. Associations were stronger in individuals with more severe vertebral fractures [35,36]. In addition, vertebral fractures quadruple the risk of a new vertebral fracture and double the risk of a non-vertebral fracture [37,38]. Vertebral fractures were also found to be associated with mortality in several observational cohort studies in various countries [39,40, chapter 4].

A prevalence of vertebral fractures of 50% was recently found in 395 older outpatients (mean age 82); two-thirds of these vertebral fractures were moderate (25-40% height loss) or severe (>40% height loss) fractures (chapter 3.1). In a comparable population-based study in the Netherlands, the prevalence of vertebral fractures in individuals of the same age (≥80) was much lower (30%), and moderate and severe fractures accounted for only 30% of the vertebral fractures [3]. In another study, after 3 years follow-up, 182 (46%) participants had died. Mortality was independently associated with the presence of three or more vertebral fractures at baseline (chapter 4). In individuals with a prevalent vertebral fracture at baseline, the incidence of a new vertebral fracture over 3 years was 40%, which is statistically higher (odds ratio = 6.4, 95% confidence interval = 1.68-24.8, p=0.006) than the incidence of 11% in those patients without a prevalent vertebral fracture (chapter 4). These data clearly emphasize the clinical relevance of these ‘asymptomatic’ fractures in older adults.

Despite the high clinical burden for individuals with vertebral fractures, there is a well-known phenomenon of underdiagnosis of these typical fractures. There are many reasons why these vertebral fractures are so often overlooked [8]. For instance, doctors fail to diagnose vertebral fractures due to the asymptomatic presentation; the recognition rate by radiologists is in various studies approximately 50% [ref 41,42], especially when the reason for performing an X-ray was not back pain; and doctors tend to miss the clinical relevance, which result in failure to start treatment [8]. Treatment in case of vertebral fractures caused by osteoporosis is widely available and have proven to be effective even for the oldest old, and can reduce new (non) vertebral fractures and new non-vertebral fractures [43,44]. Various studies have shown that treatment leads to a relative risk reduction after 3 years of approximately 50% for vertebral fractures and 20% for non-
vertebral fractures [45-49]. These relative risks correspond to a large reduction in fractures, because fracture risk is high in elderly adults. Referring to vertebral fractures as ‘asymptomatic’ seems to underestimate the large consequences these deformities can have for individuals. In addition, the word ‘asymptomatic’ may unintentionally indicate a lack of need for preventive treatment. To enhance the recognition of vertebral fractures with or without acute symptoms, the term ‘atypical presentation’ for prevalent vertebral fractures seems more adequate. ‘Atypical presentation’ is used more frequently in geriatrics, for example when elderly patients present with a pronounced infection but no fever [50], or when a delirium occurs instead of chest pain in case of a myocardial infarction [51]. The atypical presentation is referred to when the classical symptoms for a disease are absent [52]. The consequence of an atypical presentation is a delayed diagnosis or no diagnosis at all, and therefore no or delayed treatment. This letter is a call for action to recognize all vertebral fractures in older adults, to account for their clinical relevance, and to start secondary prevention of fractures, by using anti-osteoporotic drugs. To address the clinical relevance of vertebral fractures in older adults, ‘atypical presentation’ should be used for vertebral fractures rather than ‘asymptomatic’ vertebral fractures (this thesis-9).
Chapter 7.2

C. Geriatricians should screen for vertebral fractures in all patients by performing X-rays of the thoracic spine.
(Accepted for publication in J Am Geriatr Soc 2014)

Introduction
Worldwide, the population of elderly is growing and since the prevalence of fragility fractures is rising with age, it is expected that major fractures due to osteoporosis will increase dramatically over the next decades. The question arises how older individuals can be prevented from subsequent fractures. We suggest to screen for vertebral fractures by performing at least X-rays of the thoracic spine in all individuals referred to specialists in concern for geriatric care. We applied our idea to the criteria of Wilson and Jungner [53] for screening of populations, to offer secondary prevention. The criteria are shown in table 1.

Is osteoporosis an important health problem?
Fractures due to osteoporosis are a serious public health issue: it is estimated that 50% of women and 20% of men will suffer from a fragility fracture during their remaining lifetime [54]. Osteoporosis has great consequences in terms of high rate of fractures in elderly populations, in terms of morbidity as a result of these fractures and accelerated mortality in fractured patients and in terms of costs for society [54,55].

Is there a recognizable latent or early symptomatic stage?
Vertebral fractures are the hallmark of osteoporosis, predict subsequent fractures [38,56] and tend to occur earlier in life than hip fractures [54] and can therefore be seen as an early stage. The prevalence of vertebral fractures is rising with age [54]: recent studies show prevalences of 50% of vertebral fractures in individuals (mean age 82, 63% female) who were referred to a geriatrician [chapter 3]. They had a high amount of moderate or severe vertebral fractures, which are easy to recognize on X-ray. It is known that individuals with vertebral fractures do not often come to medical attention: only about one third seeks for medical help [31]. Consequently, underdiagnosis and undertreatment is common.

Is there a policy on whom to treat as patients?
This is defined in guidelines [55, 65, 66] for the diagnosis and treatment of osteoporosis and an algorithm is used for defining patients who should start treatment.

Is there a target population?
Any new older individual referred to a specialist in concern for geriatric care should be screened for vertebral fractures. An exception for this target population is a patient who will not live long enough to experience the benefits of secondary prevention or is not willing to take secondary prevention medication. The time to benefit from secondary
Main results and general discussion

prevention is in most trials 6 to 18 months [26], depending on which population is studied. Any individual with a diagnosis of osteoporosis and a life expectancy of at least six months should get secondary prevention offered [chapter 6].

Is routine screening a continuing process and not a ‘once and for all’ project? This criterion will be met if screening for vertebral fractures with radiography of the lateral spine is assimilated in guidelines for Comprehensive Geriatric Assessment (CGA).

Table 1: Criteria of Wilson and Jungner applied to screening of vertebral fractures in older individuals referred to a specialist in concern for geriatric care.

<table>
<thead>
<tr>
<th>Wilson and Jungner criteria (numbered) and emerging criteria (italic) for disease screening</th>
<th>Criteria applied to vertebral fractures in geriatric patients. Criteria fulfilled?</th>
</tr>
</thead>
<tbody>
<tr>
<td>The problem</td>
<td></td>
</tr>
<tr>
<td>1. The condition sought should be an important health problem</td>
<td>Yes</td>
</tr>
<tr>
<td>2. There should be a recognizable latent or early symptomatic stage</td>
<td>Yes</td>
</tr>
<tr>
<td>3. The natural history of the condition, including development from latent to declared disease, should be adequately understood.</td>
<td>Yes</td>
</tr>
<tr>
<td>The screening program should respond to a recognised need</td>
<td>Yes</td>
</tr>
<tr>
<td>The objectives of screening should be defined at the outset</td>
<td>Yes</td>
</tr>
<tr>
<td>The screening population</td>
<td></td>
</tr>
<tr>
<td>4. There should be an agreed policy on whom to treat as patients</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Case-finding should be a continuing process and not a “once and for all” project.</td>
<td>Yes, if test will be implemented and assimilated in CGA*</td>
</tr>
<tr>
<td>There should be a defined target population</td>
<td>Yes</td>
</tr>
<tr>
<td>The program should ensure informed choice, confidentiality and respect for autonomy</td>
<td>Not applicable</td>
</tr>
<tr>
<td>The program should promote equity and access to screening for the entire target population</td>
<td>Not applicable</td>
</tr>
<tr>
<td>The test and the treatment</td>
<td></td>
</tr>
<tr>
<td>6. There should be an accepted treatment for patients with recognized disease</td>
<td>Yes</td>
</tr>
<tr>
<td>7. Facilities for diagnosis and treatment should be available</td>
<td>Yes</td>
</tr>
<tr>
<td>8. There should be a suitable test or examination</td>
<td>Yes, if radiologists are trained</td>
</tr>
<tr>
<td>9. The test should be acceptable to the population.</td>
<td>Yes</td>
</tr>
<tr>
<td>There should be quality assurance, with mechanisms to minimise potential risks of screening</td>
<td>Yes</td>
</tr>
<tr>
<td>The costs</td>
<td></td>
</tr>
<tr>
<td>10. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole</td>
<td>Not certain</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>There should be scientific evidence of screening program effectiveness</td>
<td>No</td>
</tr>
<tr>
<td>The program should integrate education, testing, clinical services and program management</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Program evaluation should be planned from the outset</td>
<td>Yes</td>
</tr>
<tr>
<td>The overall benefits of screening should outweigh the harm</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*CGA: Comprehensive Geriatric Assessment
Chapter 7.2

Is there a suitable test? And is this test acceptable to the population?
To detect older individuals with high fracture risk lateral spine radiography is recommended in order to diagnose vertebral fractures. A lateral chest x-ray, which visualises the thoracic spine, is proven to be sufficient to detect vertebral fractures (chapter 2), because most vertebral fractures occur in the thoraco-lumbar region (T11-L1) and mid-thoracic region (T6-T9) [15]. Radiography is cheap, simple, has relatively low radiation load and is available in all hospitals and is therefore acceptable to the population. The semi-quantitative method of Genant [1] to diagnose vertebral fractures is used as gold standard in scientific research, and is more and more implied in clinical settings. The method is nearly error free, with good to excellent intra- and inter-observer reliability when used by physicians with greater experience (respectively 93-99% and 90-99%) in the original study [1]. Consequently this test seems suitable for screening.

Is there an accepted treatment for patients with recognized disease?
Suppletion of dietary calcium, vitamin D suppletion and antiresorptive therapy such as a bisphosphonate is recommended therapy in all guidelines [57-59] to prevent worsening of the underlying osteoporosis and prevent subsequent fractures. Bisphosphonates, which are widely available and relatively cheap and safe [60], have proven to be effective in subpopulations of older individuals with reductions in risk of new vertebral fractures (40-50%) and non-vertebral fractures (20-40%) [56,61].

The costs of screening (including diagnosis and treatment of patients diagnosed) that should be economically balanced in relation to possible expenditure on medical care as a whole, has not yet been proven. Scientific evidence is not yet available and input data are needed.

To conclude, osteoporosis is a serious public health issue and fragility fractures are common in older individuals. Vertebral fractures are highly clinical relevant as early symptom of severe osteoporosis. Vertebral fractures are associated with increased mortality and predict subsequent fractures. To prevent frail individuals from subsequent fractures screening for vertebral fractures in all older individuals who are referred to specialists concerning for geriatric care, is warranted (this thesis-10).
Final statement
Final statement
This thesis shows that vertebral fractures are very common (>50%) in geriatric patients (mean age 82), and additionally, there is a high rate of moderate and severe vertebral fractures among these fractures in women and in men. These fractures are highly clinical relevant: the chance for subsequent vertebral fractures is high, mortality increases when vertebral fractures are multiple, postural changes can occur and with these postural changes (hyperkyphosis), the chance for a fall in the future is increased.

We have proposed a theoretical model for the very high fracture risk in this frail population. To address the clinical relevance of vertebral fractures, we should rather use the term atypical presentation for these vertebral fractures than the term ‘asymptomatic’. Screening for these vertebral fractures is essential in this patient group to protect them from subsequent fractures. Screening can be performed with radiography of the spine, but a lateral chest X-ray is an adequate tool to visualize vertebral fractures. Since most vertebral fractures happen to be in the midthoracic region (T6-T9) or in the thoracic-lumbar region (T11-L2), which are both visualised on the lateral chest X-ray, this radiography is suitable. Screening for vertebral fractures should be incorporated in a comprehensive geriatric assessment, and for this purpose a chest X-ray (posterior/anterior and lateral) can serve more screening goals than vertebral fractures alone (e.g. heart failure, lung problems). At last, anti-osteoporotic treatment should be started even in elderly with a limited life expectancy, to prevent these frail patients from subsequent fractures.
7.4

Future research
Main results and general discussion

Future research
This thesis shows that geriatric patients with prevalent vertebral fractures are at high risk for subsequent fractures, changes in posture and falls. Fractures can be prevented with medication, even if life expectancy is short. We observed that, due to underdiagnosis of prevalent fractures, treatment is often not offered to these frail patients. The first goal for future research is to understand why underdiagnosis and undertreatment is high in these patients. To answer this question, a questionnaire should be done throughout the field of physicians who treat elderly individuals. The questionnaire should focus on why physicians fail to diagnose the vertebral fractures or osteoporosis. Secondly, which underlying mechanisms account for non-treatment decisions. Thirdly, which patient factors are associated with non-treatment decisions. The information from this questionnaire could report on how physicians can be motivated and instructed for higher treatment rate.

The second direction for future research should investigate the effect of an early treatment start after a major fracture. In daily practice anti osteoporotic treatment is started several weeks after the major fracture, such as a hip fracture. The problem is that, despite the effort of fracture liaison services [62], patients with hip fractures do not often come to the service and have treatment started. In fact, Eekman showed that of all patients with a fracture after the age of 50, only 50% attended the fraction liaison service, but only 25% of the patients with hip or pelvis fractures came back for fracture prevention. It can be assumed that these patients did not attend the service due to immobility and due to be still in a rehabilitation program. If anti osteoporotic treatment could be started directly after the fracture in these frail patients, there would be a higher treatment rate and consequently less fractures for these patients in the future. To answer the question of safety of an early treatment start in these geriatric patients with major fractures, a randomised controlled trial should be conducted. The hypothesis is that early treatment (within the first week after major fracture) would not affect fracture healing clinically and is therefore not inferior to starting treatment after six weeks. In the early treatment arm, patients after major fracture start calcium, vitamin D and a bisphosphonate in the first week after the major fracture. In the control arm, calcium and D will be started within the first week of the fracture, and a bisphosphonate after six weeks, when the fracture is healed. Patients should get normal follow-up after their major fracture. This study should focus on non-union of the initial fracture, delayed healing of the fracture and new (clinical) fractures within the first year. Secondary endpoint should be persistence of therapy.

Lastly, to investigate the effectiveness and costs of a screening program in older individuals referred to a specialist in concern for geriatric care, we should conduct a study in which the costs of screening and treatment can be calculated and weighted against the benefit of less subsequent fractures.
Chapter 7.4

References

24. Black 2000

136
Main results and general discussion

Chapter 7.4