Osteoporosis, identification and treatment in fracture patients

de Klerk, Gijsbert

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Chapter 1

Introduction
Osteoporosis: definition, risk factors, osteoporotic fractures and burden

Osteoporosis is defined by the World Health Organization (WHO) as a systemic disease of the bones characterized by a low bone mineral density (BMD) and loss of micro-architecture, resulting in an increased risk of developing a fracture[1]. BMD is the result of the peak bone mass (reached around the age of thirty), as well as the subsequent rate of bone loss. Genetic factors strongly contribute to peak bone mass, but environmental factors in intrauterine life, childhood, and adolescence modulate the genetically determined pattern of skeletal growth[2,3]. Bone loss is a result of estrogen deficiency, as well as estrogen-independent age-related mechanisms (for example: reduced mechanical loading, underweight, malabsorption syndromes, and inflammatory diseases)[4]. There are several risk factors associated with a low BMD. By assigning a risk score to every risk factor, it is possible to identify which patient might benefit from BMD measurement (table 1)[5]. Furthermore, every fracture patient older than 50 years should be assessed.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk score</th>
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<tr>
<td>Weight &lt;60kg and/or BMI &lt;20kg/m²</td>
<td>1</td>
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<tr>
<td>Age &gt;60 years</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;70 years (do not count risk score &gt;60 years)</td>
<td>2</td>
</tr>
<tr>
<td>Previous fracture after 50 years of age</td>
<td>1</td>
</tr>
<tr>
<td>Immobility¹</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatic Arthritis</td>
<td>1</td>
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<td>History of falling (&gt;1 fall in preceding year)</td>
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Table 1. Risk factors associated with an increased fracture risk and associated risk score. BMD measurement is advocated in patients with a risk score ≥4[5].

¹ Use of aids or not able to walk for >4 weeks in the preceding year
² Risk factor for secondary osteoporosis:
- Untreated hypogonadism (bilateral orchidectomy or ovariectomy, anorexia nervosa, treatment of carcinoma of breast or prostate, hypopituitarism)
- Inflammatory bowel disease
- Chronic malnutrition, malabsorption
- Other chronic inflammatory diseases
- Organ transplant
- Type 1 diabetes
- Thyroid diseases: untreated thyreotoxicosis, or overtreated hypothyreoidism
- Use of anti-epileptic medication
- Hyperparathyroidism
- Chronic Obstructive Pulmonary Disease
- M Cushing
- Use of glucocorticoids
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   - Chronic Obstructive Pulmonary Disease
   - MCushing
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Introduction

This is an increasing problem, because the average age of the world’s population increases. From 2010 to 2040, the world’s population ≥65 years of age will double from about 506 million to 1.3 billion, accounting for 14% of the world’s total population[6]. In the Netherlands the population ≥65 years of age is expected to increase from 1 million to 1.5 million in 2020[7]. This will result in an increase of individuals with osteoporosis, due to the age related decline in bone mass. Because osteoporosis is a systemic bone disease, the risk of almost all types of fractures is increased[8]. In white populations, about 50% of women and 20% of men older than 50 years will suffer from a fracture related to osteoporosis in their remaining lifetime[4]. Typical osteoporotic fractures are fractures of hip, vertebrae, humerus, ankle and wrist[9]. In white women, the 16% lifetime risk of hip fracture is greater than the 11% lifetime risk of developing breast cancer[10].

Of all osteoporotic fractures, hip fractures and vertebral fractures have the biggest impact in patients. Hip fractures are the most devastating result of osteoporosis, requiring the patient to be admitted to hospital and causing excess mortality and serious disability[4]. Table 2 shows the sex specific relationship between hip fracture incidence and age. There is a steep rise in fracture incidence above 50 years of age, which results in 96% of all hip fractures occurring in this older age group. Below 50 years of age, there is a slight preponderance of men over women and above 55 years a strong preponderance of women over men, which results in 71% of all hip fractures occurring in women[4].
Table 2. Age and sex specific incidence of hip fractures in the Netherlands per year (2007)[11].

The in-hospital mortality rate for hip fracture patients is up to 11% and the 1 year-mortality as high as 31%[12,13]. Mortality risk is highest in the first 3 months after a hip fracture and is greater in men than in women[14]. A recent meta-analysis identified 12 factors that are associated with an increased risk of mortality following a hip fracture (table 3)[15]. These prognostic risk factors could help to identify patients at different degrees of risk and therefore can be used to optimize treatment for these patients. Following hip fracture a considerable loss of quality of life is observed, especially in the first year. There is some improvement in the second year, but not to baseline values[16]. Within one year following a hip fracture nearly one third of patients is discharged to a nursing home and only one third has regained their pre-fracture level of function[19]. Five years after a hip-fracture one quarter of survivors are found bedridden and 45% were not able to walk outside[17].
The other osteoporotic fracture with high impact is the vertebral fracture. Most vertebral fractures result from routine daily activities such as bending or lifting light objects, and only a quarter due to falls[4]. The lifetime risk of a vertebral fracture for a 50 year old white women is 32%, which is higher than the lifetime risk of a hip fracture[18]. The incidence increases with age. Above 70 years of age 30% of women and 25% of males suffer from at least one vertebral fracture[19]. Despite the high prevalence of vertebral fractures only one third to one quarter are clinically recognized and few are admitted to hospitals[20-23]. Under diagnosis of vertebral fractures is a multicausal phenomenon (table 4)[18]. In patients presenting with a non-vertebral fracture the prevalence of vertebral fractures differs substantially depending on the site of the non-vertebral fracture (figure 1)[19,9]. The prevalence appeared to be significantly higher in hip fracture patients compared to patients with a non-hip fracture (p<0.009) (figure 1)[9]. An explanation for this high prevalence in hip-fracture patients might be the relationship between incidence and age[19]. Hip fracture patients are on average elderly patients and the incidence of vertebral fractures increases with age.

| Advanced age |
| Male gender |
| Nursing home or facility residence |
| Poor preoperative walking capacity |
| Poor activities of daily living preoperatively |
| Higher American Anesthesiologists Society Score |
| Poor mental state |
| Multiple co morbidities |
| Dementia or cognitive impairment |
| Diabetes |
| Cancer |
| Cardiac disease |

**Table 3.** Factors that are associated with an increased risk of mortality following a hip fracture[15]

| Only 1/3 of patients have acute complaints[24] |
| Presentation is often not specific, resulting in different diagnosis[24] |
| Vertebral fractures are often overlooked in radiographs, false negative rates vary between 27% and 50%[25,22] |
| Ambiguous terminology in radiology reports[26] |
| The diagnosis is overruled by another diagnoses (for example malignancy)[18] |
| Missing the clinical relevance of vertebral fractures by individual doctors[18] |

**Table 4:** Reasons why vertebral fractures are under diagnosed[18].
Excess mortality following both an asymptomatic and a symptomatic vertebral fracture has been reported[27-29]. After a symptomatic vertebral fracture 1-year mortality rates up to 42% are described[30]. Mortality risk is highest in the first year after the fracture, but an increased risk greater than that of the general population extends up to 22 years[30]. Recently, van der Jagt showed that elderly patients with vertebral fractures are at very high risk for developing new vertebral fractures (40%)[31]. The number of vertebral fractures raises the odds ratio of 3-year mortality up to 3.07 (95% CI: 1.61-5.84) in patients with three or more vertebral fractures[31]. After multivariate analysis the presence of three or more vertebral fractures was independently associated with mortality (P=0.002)[31]. Besides mortality, vertebral fractures are associated with a significant loss of quality of life[16,32]. Increasing kyphosis results in a decline in physical function, worsening mobility, falls and fractures[6]. Lumbar vertebral fractures had more impact on quality of life than thoracic vertebral fractures[16]. After diagnosing a vertebral fracture, the risk for a hip fracture is doubled and the risk for a new vertebral fracture even quadrupled[33,34]. Diagnosing (a)symptomatic vertebral fractures is thus beneficial for patients in terms of anti-fracture treatment and perhaps can reduce mortality.

Because the burden of osteoporotic fractures as outlined above, it is important to diagnose and treat osteoporosis in patients.

The golden standard in establishing osteoporosis

A simple way of being informed about the BMD might be the interpretation of a radiograph. Although osteoporosis can be suspected when structural abnormalities such as thinned cortices, endosteal resorption and a reduction in trabecular numbers are seen on radiographs, identification of osteoporosis on radiographs is imprecise and the diagnosis is not evident until a substantial amount (30-40%) of bone mass has been lost (figure 2)[35].
The established modality worldwide for diagnosing osteoporosis is the measurement of BMD with Dual Energy X-ray Absorptiometry (DXA) of the hip and/or spine[37]. Absorptiometry for measuring BMD was first introduced in 1963[38]. In single-photon absorptiometry a 125I radionuclide photon source was used. Limitations were the decay of the radionuclide and therefore the need for replacement, and the slow scanning time. By replacing the radionuclide with a low-dose X-ray tube, photon absorptiometry developed into DXA. DXA was introduced in 1987 and uses X-ray beams of two peak energies (30-50 keV and >70 keV). These energies are selected to optimise separation of the mineralised and soft tissue components of the sites scanned. DXA is a well standardized and easy to use technique that has a high precision (maximum acceptable precision error, 2%-2.5%) and low radiation dose (1-6μSv), equating to only a few hours of natural background radiation (2400 μSv per annum)[39,35]. DXA BMD correlates well with the biomechanically determined bone strength, explaining approximately 70% of bone strength. The BMD measured by DXA is expressed as a T-score, which is the number of standard deviations above or below the mean BMD of young women[1]. For each decrease in BMD of 1SD, the fracture risk is doubled. Patients with a T-score ≤-2.5SD are considered to be osteoporotic[1]. But, DXA has some disadvantages. It is a two-dimensional measurement, which only measures density area in grams per square centimeter and not the volumetric density in milligrams per cubic centimeters[39]. Therefore BMD is overestimated in large bones and underestimated in small bones (figure 3)[35].
Figure 3. DXA is size dependent. As DXA generates a 2D image of a 3D structure, the depth of the bone cannot be taken into account. This representative figure shows two cubes of material that have the same volumetric BMD. However, cube A has a smaller volume; therefore, the projected area means that the areal BMD measured using DXA would be lower than that in cube B. As a result, areal BMD measured by DXA would be underestimated in small bones and overestimated in large bones[35].

Spine and hip DXA are also influenced by degenerative changes, and individuals with substantial degenerative disease will have an increased areal density, which will suggest a lower fracture risk than is actually present[39]. In addition, DXA has limitations in measuring BMD in patients with a body mass index >25 kg/m²; in obese patients, superimposed soft tissue will elevate measured BMD owing to attenuation of the x-ray beams[40].

Although DXA is the golden standard in diagnosing osteoporosis there are other imaging techniques to quantify bone architecture, of which the following technologies are capable of predicting both site specific and overall fracture risk: Quantitative computed tomography (qCT), quantitative ultrasound densitometry (qUS), and peripheral dual energy x-ray absorptiometry[41].

QCT measures BMD in milligram per cubic centimeter. The attenuation values (expressed in Hounsfield units; HU) corresponding to the bone tissue are converted into bone mineral equivalents by calibration with a hydroxyapatite calibration phantom and dedicated analysis software[42]. QCT was developed in the late 1970’s but was superseded by the introduction of DXA. Advantages of qCT over DXA are that qCT allows true volumetric measurements, which makes it independent on the size of the measured bone, and that qCT enables separate measurements of cortical and trabecular BMD. Trabecular bone is metabolically more active, making it more sensitive to change. Disadvantages of qCT are a higher radiation dose (0.06-2.9 mSv), lack of commercially available software programs for analysis of hip qCT, and the limited access to whole body CT scanners. Moreover, T-score thresholds defined by the WHO for diagnosis osteoporosis do not apply to qCT results. This, together with the limited number of longitudinal scientific studies assessing how qCT predict fractures, limits the use in daily clinical practice[39,35].
qUS is a low cost technique to measure BMD. It measures the propagation of ultrasound waves through the bone. However, qUS devices are technologically diverse, measure and report variable bone parameters in different ways, examine different skeletal sites, and have different levels of validating data for association with DXA-measured BMD and fracture risk[43]. This created many problems in applying qUS for use in clinical practice[43]. Moreover, qUS cannot be used to diagnose osteoporosis in terms of the WHO definition or to monitor the effectiveness of therapy[35].

Peripheral DXA devices might play an interesting role in measuring BMD. In this thesis we describe the use of the DXL-Calscan, which is a peripheral dual energy x-ray Absorptiometry device. The DXL-Calscan (Demetech, Solna, Sweden) measures the BMD at the calcaneus, which consists for 90% of trabecular bone, making it ideal for measuring osteoporotic changes[44]. Previous studies already showed similar predictive abilities for osteoporotic fractures of calcaneal BMD measurement, as compared to BMD measurement of hip or spine[45–47]. The Calscan adds a laser beam to conventional DXA technology which makes it possible to measure bone mineral content without the influence of adipose tissue both inside and outside the measured bone[48]. The absorption of X-rays in adipose tissue, bone mineral and lean soft tissue is different, which gives rise to accuracy errors up to 20% in measurements of BMD with DXA[49,48]. As the volume of marrow adipose tissue increases with age especially in patients with osteoporosis the Calscan might even measure BMD more accurately than DXA[50]. By comparing the Calscan T-score to DXA T-scores it is possible to calculate thresholds for the Calscan T-score to diagnose or exclude osteoporosis in terms of the WHO definition, using these Calscan T-scores.

**Case finding osteoporosis**

The specificity for diagnosing osteoporosis with DXA is high, but the sensitivity is only about 50%, which implies that BMD measurement can only be advocated in those patients with a high fracture risk (case-finding)[12]. A general screening program for osteoporosis (primary prevention) can therefore not be recommended but selective screening for people at high risk might be worthwhile (secondary prevention)[5,46,51]. An important high risk group for osteoporosis are fracture patients above 50 years[5]. In 2011, the third revision of the Dutch guideline on osteoporosis and fracture prevention was published[5]. This guideline clearly describes the diagnostic pathway for patients at high risk for osteoporosis (figure 4). Because vertebral fractures increase fracture risk strongly and appear to do this independently from BMD, vertebral fractures are considered a reason for initiating anti-osteoporotic treatment without BMD measurement (figure 4) [52,24,5].
Timing of screening for osteoporosis is an important issue to discuss. Osteoporosis screening has a low priority in most hospitals as well as for the general practitioner. The screening is delayed until fracture patients are more mobile, and often discouraged by family or doctors in elderly patients with a lot of co-morbidity. However one should realize that most subsequent fractures occur in the first year after the initial fracture and fractures are associated with significant mortality, morbidity and costs[53,54]. Recently, van de Glind calculated the time to benefit (TTB) of alendronate for the prevention of subsequent fractures from the original data of the Fracture Intervention Trial (FIT trial). The TTB appeared to be 11 months[55]. The FIT trial was performed in postmenopausal women (55–80 years of age). It has been suggested that the TTB in an elderly population (over 80 years) might be considerably shorter because of a higher risk of falling and fractures in...
this older patient group[55,31]. These arguments lead to the conclusion that screening for osteoporosis should be done as early as possible to prevent subsequent fractures, especially in the elderly population.

The Fracture Liaison Service: a historic perspective
In the late 20th century osteoporosis assessment and treatment rates were low. Anti-osteoporotic treatment was prescribed in only 5-28% of patients after a distal radial fracture, in 4% after a hip-fracture, and in 39% after a vertebral fracture [56,57]. Even repeated presentations with a fracture did not guarantee patients to be treated for osteoporosis, as only 33% of women presenting with their second fracture received anti-osteoporotic medication[58]. To increase assessment rates, a program of open- or direct-access DXA services to which primary care clinicians could refer fracture cases was set up in Glasgow[59]. Nonetheless, only 2.7% of distal radial fractures and 11.6% of hip fracture cases were referred for assessment by DXA[58]. Because of this limited success the program further evolved. Having confirmed that osteoporosis assessment was rarely offered, it was agreed with primary care clinician and orthopedic surgeons that not the primary care clinician nor the patient should be responsible for initiating the assessment for osteoporosis but the trauma – or orthopedic surgeon should take care of this. Initiating case-finding osteoporosis became part of the fracture management, which was offered by the trauma – and/or orthopedic surgeon. This resulted in what nowadays is called the Fracture Liaison Service (FLS). An FLS is a coordinated care system headed by an FLS coordinator (a nurse practitioner, physician assistant, nurse or other health professional) who ensures that individuals who suffer a fracture receive appropriate diagnosis, treatment and support[60]. The FLS includes the following 5 basic elements: case-finding, risk assessment, medical history + clinical examination + laboratory tests, treatment decision, and follow up (figure 5)[61-63].

![Flowchart diagnosis, treatment and follow-up in fracture patients older than 50 years](image)

Figure 5. Five basic elements of an FLS

The first FLS began operating in West Glasgow in 1999 and in South Glasgow in 2000, and was very successful as 67.4% of the West Glasgow patients and 73.4% of South Glasgow patients were considered for bone mineral testing[59]. The initial situation in
the Netherlands was not different from that in Scotland. Hegeman showed that at the University Medical Center of Groningen (UMCG) in 2001 only 14% of fracture patients were screened for osteoporosis and bisphosphonates were only prescribed in 1% of these patients[64]. Van Helden described that in the province of Limburg, in 2005, in hospitals without an FLS only 6% of elderly fracture patients were screened for osteoporosis[65]. This was the reason that in 2003 the first Dutch FLS was set up at the UMCG by the department of Traumasurgery in collaboration with the departments of Internal medicine and Geriatric medicine[66]. Patients over 50 years who were admitted to the emergency department with fractures resulting from low-energy traumas were, after initial treatment of the fracture, offered further diagnosis and treatment at this FLS (figure 6).

**Figure 6.** Flowchart for patients over 50 years of age presenting at the emergency department with a low-energy fracture[66].

1 Emergency Department

The work at the FLS was carried out by a specially trained nurse, under supervision of the traumasurgeon and the internist. If secondary osteoporosis was suspected, the internist carried out further examination. For primary osteoporosis general recommendations were given. In patients with a low BMD and insufficient Calcium and/or vitamin D intake,
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Van Helden and Huntjens further improved osteoporosis care in the Netherlands. They emphasized the importance of the combination of bone-related risks other than low BMD, and fall-related risks, all contributing to fracture risk (table 5)[68].

<table>
<thead>
<tr>
<th>Bone related risk factors other than low BMD</th>
<th>Fall related risks</th>
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<td>a previous fracture after the age of 50</td>
<td>more than one fall in the past year</td>
</tr>
<tr>
<td>a vertebral fracture after the age of 50</td>
<td>the use of psychoactive drugs</td>
</tr>
<tr>
<td>a mother with a fracture history</td>
<td>a low level of activities of daily living before the current fracture</td>
</tr>
<tr>
<td>a body weight of &lt;60kg</td>
<td>articular symptoms</td>
</tr>
<tr>
<td>severe immobility</td>
<td>impaired vision</td>
</tr>
<tr>
<td>the use of glucocorticoids</td>
<td>urine incontinence</td>
</tr>
<tr>
<td></td>
<td>Parkinson disease</td>
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</table>

Table 5. Bone- and fall related risk factors related to fracture risk[68]

In the study by van Helden osteoporosis was only present in 35% of all fracture patients older than 50 years screened at the FLS, while bone related risk factors other than a low BMD where present in 51-53% and fall-related risk factors even in 60-75% of these patients (figure 7)[68,69].
Huntjes showed in an univariable analysis that the risk of a subsequent fracture was significantly higher in patients with the combination of fall- and bone related risk factors (HR 1.99 (95% CI: 1.18-3.36), a conclusion which was no longer valid after adjusting for age, sex and baseline fracture location[69]. In contrast, other studies showed that in patients with fall-related risk factors, the relative risk for hip fractures and proximal humeral fractures was significantly higher[70-72]. The realization that fall related risk factors are important in calculating fracture risk resulted in the development of the GARVAN fracture risk calculator in Australia (http://www.garvan.org.au/bone-fracture-risk). The GARVAN fracture risk calculator incorporates non-invasive risk factors (fall related risk factors, age, sex and in case the BMD is unknown weight) to predict 5-year and 10-year absolute fracture risks[72]. The disadvantage of the GARVAN risk calculator is that it is only suitable to patients over 60 years and does not include other bone-related risk factors than BMD. Another Fracture Risk calculator which includes bone-related risk factors together with age and if known BMD is FRAX®. This is a computer based algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of a hip-fracture or major osteoporotic fracture (proximal humerus fracture, spine fracture, and distal forearm fractures) (figure 8)[73]. When the 10-year probability of a hip fracture is ≥3% or the 10 year probability of a major osteoporotic fracture is ≥20% a patient can be considered osteoporotic[74,75]. Limitations of FRAX® are that fall related risk factors are not included at all.
A fracture liaison service has been a proved instrument to improve the percentage of patients being screened for osteoporosis substantially (from 5 to 51%), results in a high persistence to anti-osteoporotic drug treatment (up to 88% after 1-year treatment), and decreased the rate of subsequent fractures (2% after 1 year, instead of previously described 6.5%) [76,53]. Nonetheless, besides all improvement being made in the screening for osteoporosis, today, still almost half the patients do not respond to the invitation to attend the FLS[76]. The most important reasons of non-responding are: not-interested (37%), already screened/under treatment for osteoporosis (15.7%), physically unable to attend the clinic (11.5%), and death (5.2%) [76]. A frequently mentioned reason for not attending the FLS is the patients’ opinion that they were too old to visit the outpatient clinic and that treatment would not be useful anymore [76]. It also appears that the mean age of non responders is significantly higher than the mean age of responding patients [76]. Thus the elderly fracture population is not attending the FLS, while this group of patients greatly benefit from fracture prevention. Therefore, it remains challenging to further improve the percentage of patients being screened for osteoporosis, and thus decrease fracture risk.
Content of this thesis

The studies of this thesis were performed at the department of Surgery of the Ziekenhuisgroep Twente, location Almelo, the Netherlands. The rationale behind the thesis is described in Chapter 1. Many patients suffer from osteoporosis although most of them are unaware of this. The ultimate consequence of osteoporosis is a fracture. It is well known that these fractures result in an increased morbidity, mortality, and medical costs. However, in the beginning of the 21th century the number of patients being screened for osteoporosis after they suffered from a fracture was still low. This resulted in the organization of the screening for osteoporosis by means of an FLS and with a specialized nurse as the case manager. Although, this resulted in an improvement of the percentage of patients being screened for osteoporosis, as well as a better compliance to osteoporotic treatment, still half of all patients does not attend the FLS. These patients are withheld adequate treatment, putting them at increased risk of a subsequent fracture, and increasing morbidity and mortality, which is not acceptable. The aim of this thesis was to improve the number of patients being screened for osteoporosis and analyze different aspects of our FLS protocol. If there are valid other ways of screening for osteoporosis instead of DXA, the total number of patients being screened for osteoporosis might increase. In Chapter 2 we describe the incidence of vertebral fractures in patients screened for osteoporosis. Vertebral fractures are known to be a reason, independent on BMD, to initiate anti-osteoporotic treatment. Therefore BMD measurement is not perse necessary in those patients who suffer from a vertebral fracture. In Chapter 3 the relationship between AO-classification of distal radial fractures and bone mineral density is described. The hypothesis was that a comminuted intra-articular fracture would suggest osteoporosis. In Chapter 4 and 5 the use of the Calscan in measuring BMD is described. The Calscan is a peripheral dual energy X-ray Absorptiometry device, which measures BMD at the calcaneus. The big advantage of the Calscan is that it is easy to use and results are immediately available. However, Calscan T-scores cannot be used with WHO definition of osteoporosis. Therefore we compared Calscan T-scores with T-scores measured with DXA to calculate thresholds on the Calscan T-score in a way that 90% of osteoporotic patients and 90% of non-osteoporotic patients could be classified correctly by the Calscan. In Chapter 6 we described in a prospective study the use of the thresholds calculated for the Calscan T-score in a group of elderly patients admitted to the hospital because of a fracture. Chapter 7 focused on the value of the panel of laboratory tests used in the screening for secondary osteoporosis at our FLS. Finally, Chapter 8 encompasses the general discussion with conclusions and future perspectives.
References:
55. Van de Glind EM Treatment in geriatric patients: is there time to benefit? submitted


