Anti-osteoporosis drug use: too little, too much or just right?

The HUNT study, Norway

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Mini abstract

Use of anti-osteoporotic treatment (AODs) was examined in a Norwegian population 50-85 year. Among them with FRAX-score for major osteoporotic fracture ≥20, 25% of the women and 18% of the men received AODs. The strongest predictors for AODs were high age in women and use of glucocorticoids among men.

ABSTRACT

Purpose: To examine the use of anti-osteoporotic treatment (AODs) and to identify predictors for prescriptions.

Methods: Data were obtained from the Nord-Trøndelag Health Study (HUNT3) performed in 2006-2008 and the Norwegian Prescription Database, including 15,075 women and 13,386 men aged 50-85 years. Bone mineral density (BMD) in the femoral neck was measured in a subgroup of 4,538 women and 2,322 men.

High fracture risk was defined as a Fracture Risk Assessment Tool score (FRAX) for major osteoporotic fracture (MOF) ≥20%; in the sub group with BMD, high risk was in addition defined as $FRAX_{MOF}$ ≥20% or T-score ≤-2.5.

Hazard ratios (HRs) for predictors of incident use of AODs within 2 years after HUNT3 were estimated by Cox' proportional hazards model.

Results: Among individuals with FRAX MOF ≥20%, 25% of the women and 18% of the men were treated with AODs. Among those with FRAX MOF <20%, 4% and 1% were treated, respectively. In the subgroup with BMD measurement, 24% of the women and 16% of the men at high risk of fractures were treated, compared to 3% and 1% in women and men not fulfilling the criteria.

In women, high age was the strongest predictor for treatment (HR 3.84: 95% confidence interval 2.81-5.24), followed by use of glucocorticoids (GCs) (2.68:1.84-3.89). In men predictors were use of GCs (5.28: 2.70-10.35) followed by multimorbidity (3.16:1.31-7.63) In the subgroup with BMD, T-score ≤-2.5 was the strongest predictor (women 3.98:2.67-5.89; men 13.31:6.17-28.74).

Conclusions: This study suggests an undertreatment of AODs in individuals at high risk of fracture.

BACKGROUND

Osteoporosis is a major health problem [1], and Norway has the highest incidence of osteoporotic fractures worldwide [2-4]. 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 [5] According to the World Health Organization (WHO) osteoporosis is diagnosed as a bone mineral density (BMD) of 2.5 standard deviations (SD) or more below the young adult mean; T-score ≤-2.5 [6]

Intervention with anti-osteoporotic drugs (AODs) has been found to reduce the relative fracture risk for vertebral and non-vertebral fractures by 40-80 % and 20-60 %, respectively [7, 8]. Despite the high incidence of osteoporotic fractures in Norway, the prescription of AODs has been relatively low compared to some other European countries [9-11]. The use has been stable and low regardless of fracture risk, a little less than 5 % among women 40 years and older [9].

Norwegian and European guidelines advise that AODs should be offered to individuals with osteoporosis according to WHO [12, 13]. However, other factors than BMD influence bone strength and most of fractures occur in patients with T-score > -2.5 [14]. Risk scores that combine clinical risk factors have been developed, such as Fracture Risk Assessment Tool FRAX (www.FRAX.com). FRAX predicts the 10-year absolute risk of hip fracture as well as major osteoporotic fracture (MOF), defined as fractures in hip, wrist, humerus and spine (clinical). FRAX can be calculated both with and without BMD [15]. The US National Osteoporosis Foundation and Osteoporosis Canada, recommend offering AODs to subjects with FRAX-score for MOF ≥ 20 % [14, 16-18]. In the US, this threshold was estimated to be cost-effective in postmenopausal women and men above 50 years [14, 18].

The national Norwegian guidelines for prevention and treatment of osteoporosis from 2005 recommend AODs at T-score ≤ -2.5, or ≤-1.5 if previous fragility fracture [12]. The Norwegian Medical Societies of Endocrinology [19] and Rheumatology [20] have both published guidelines in 2015. The first recommend that AODs should also be given to those treated with oral glucocorticoids (GCs) more than 3 months and T-score < -1.0. The Society of Rheumatology in addition advises treatment to all individuals suffering from a fragility fracture in femoral hip or vertebra independent of T-score, as well as those at high risk calculated with FRAX (FRAX hip ≥3 % or MOF ≥20 %).

There is limited knowledge of the extent of under- or overtreatment with AODs. Other factors, unrelated to evidence based practice that may influence treatment. A Norwegian study by Devold et al. concluded that AOD use was related to age, previous hip fracture, number of drugs prescribed and use of oral GCs [10]. This study lacked information on BMD and other risk factors included in FRAX. In a study from US, treatment after the first fracture was dependent on T-score ≤ -2.5, high age, smoking and use of GCs [8].

Overall inequality in health may also be influenced by inequality in treatment and as to osteoporosis, the influence of socioeconomic status is not clear. In the mentioned study by Devold e al. there was an association between use of AODs and middle and low income [10], while a Swedish study concluded that higher education was positively associated with use of AODs in both genders [21].

Even though AODs are shown to prevent fractures in clinical trials, the preventive effect in a population relies on the health service's ability to identify individuals at risk, followed by an optimal use of AODs.

The main aim of our study was to examine if individuals at high risk of fracture in a population received treatment with AODs. The second aim was to identify predictors for starting with AODs.

MATERIALS AND METHODS

We used data from the Nord-Trøndelag Health Study (HUNT) and the Norwegian Prescription Database (NorPD).

The HUNT study

The third survey of HUNT, HUNT 3, was performed from 2006 to 2008 in the county of Nord-Trøndelag which is located in the central part of Norway. The geographic, demographic and occupational structure are considered fairly representative of the country as a whole [22]. All individuals 20 years and older were invited to participate.

In the current study, we included the age group 50-85 years. Of the 43,760 invited, 28,692 (65.6 %) responded, completed a comprehensive questionnaire and underwent a short clinical examination at the screening station. Of these, 231 were excluded due to lack of data on height (N=213) or weight (N=220) (Figure 1), leaving 15,075 women and 13,386 men for the analyses. For all these individuals, FRAX without BMD was calculated.

BMD in the femoral neck was measured in a subgroup of 4,538 women and 2,332 men by dual-energy X-ray absorptiometry (DXA) using Lunar Prodigy Advance (GE Healthcare). BMD was expressed as g/cm^2 and T-score based on BMD for young women calculated. The reference data for T-score estimation were NHANES III. Regular phantom calibration of the densitometer was performed according to the densitometry procedures and quality assessment guidelines in HUNT.

For those having BMD measurement at the femoral neck, FRAX with BMD were calculated.

Estimation of fracture risk

We assessed three sets of risk estimates for fractures:

1) FRAX MOF *without* BMD for the whole group ($FRAX_{MOF}$); 2) FRAX MOF *with* BMD for the subgroup with BMD measured ($FRAX_{MOF\_BMD}$); and 3) T-score for the subgroup with BMD.

The Norwegian FRAX tool was recalibrated based on Norwegian data on incidence of hip fracture and mortality and the FRAX scores were calculated on the basis of FRAX desktop (http://www.who-frax.org/).

Included in the FRAX calculation were:

Gender, age, BMI, use of oral GCs, self-reported previous fracture, parent hip fracture, current smoking, rheumatoid arthritis (RA), secondary osteoporosis and use of alcohol (units per week). Except for drug use (see below), all information was collected from HUNT3 [23]. In line with the guidelines of FRAX, use of at least 5 mg GCs for more than three months prior to the inclusion in HUNT 3, and current use were included in the risk calculation. According to the recommendations from FRAX, missing data were set as "No" in included covariates.

Regarding social status, we included information on education and marital status. High education was defined as occupations demanding college or university education. Marital status was stratified as follows: Married or partnership; widow(er); previously married; or never married.

Norwegian Prescription Database (NorPD)

Data on drug use were collected from the NorPD which contains information on all prescribed drugs dispensed at all pharmacies in Norway to individual patients in ambulatory care, comprising data from 01.01.2004 [24]. Each subject is assigned a unique identifier, which makes it possible to follow chronologically all dispensed prescriptions to each individual. Drugs prescribed to patients during stays at hospitals or other institutions, are not registered in NorPD [25], and therefore the upper age limit for participants was set to 85 years.

All drugs in Norway are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [26]. For each prescription, the amount dispensed measured in defined daily doses (DDD), is registered in NorPD.

The following AODs were included: Bisphosphonates (ATC code M05BA), raloxifene (G03XC01) and teriparatide (H05AA02). Denosumab (M05BX04) was introduced in Norway in 2010, and was not prescribed to our population in the current study.

Further, calcium supplements with or without vitamin D are available without prescription in Norway [27] and were therefore not included.

GCs were classified according to ATC codes H02A and H02B.

In addition, the total number of drugs the last 12 months before HUNT3 was applied as a surrogate measure of comorbidity [9, 28]. Analyses on the number of drugs of ATC groups were based on third-level pharmacological subgroups, which are broad groups of drugs. Examples are insulin (A10A) and antithrombotic agents (J01A).

Hormone therapy (HT) were not defined as AODs due to other indications for use than osteoporosis [12]. However, due to their positive effect on bone, use of HT may influence prescriptions of AOD and were therefore included in an additional analysis. HT was defined as estrogens given as oral medication or patch (G03C), except estriol (G03CA04) which has not been proven to prevent osteoporosis, as well as progestogens and estrogens in combination given as oral medication or patch (G03F).

Definitions:

AODs: Anti-osteoporotic drugs were defined as bisphosphonates, teriparatide, raloxifene and denosumab.

DDD: Defined daily dose. For example 10 mg Alendronate is one DDD and 70 mg Alendronate is seven DDD

Prevalent user**:** Filling at least one prescription for AODs in the first 2 years following the date of HUNT3.

Incident user: A new user who had not been prescribed AODs 365 days before participation in HUNT3 and who had been prescribed AODs in the period of 2 years following her/his participation in HUNT3.

Indication for use of AODs:

1. $FRAX_{MOF} \geq 20$ % for the whole group
2. $FRAX_{MOF\_BMD} \geq 20$ % for the subgroup with BMD
3. T-score $\leq$ -2.5 for the subgroup with BMD

Number of drugs: The total number of dispensed drugs with third level ATC codes 365 days before the fracture, excluding AODs. These were categorized as 0-1 drug; 2-3 drugs, 4-5 drugs and ≥6 drugs.

Analysis strategy and statistical analyses

Descriptive data on prevalence are presented according to our predefined indication ($FRAX_{MOF} \geq 20\%$) and actual treatment with AODs.

In the subgroup of participants with measured BMD, associations between the three indications for treatment ($FRAX_{MOF\ with}$ or without BMD ≥ 20 % and T-score ≤ -2.5) were estimated by Venn diagram and Pearson's correlation coefficient.

Pie charts were made to illustrate treatment gaps for the different indications.

Hazard ratios (HR) for potential predictors of incident use of AODs were estimated by Cox' proportional hazards model. Users of AODs the last year before HUNT3 were excluded. The study population was followed from the date of participating in HUNT3 until date for start of treatment, death or 24 months after participation in HUNT3. The assumption of proportionality was checked by visual inspection of log minus log plots. Crude estimates are presented in addition to two different models 1) adjusted for age, 2) adjusted for all statistically significant predictors.

We chose not to include FRAX in the model since it is composed of most of the risk factors. Association between use of AOD and HT were examined and HT was also included as a predictor for incident use of AOD.

Separate models for men and women are presented. P-values below 0.05 were regarded as statistically significant. All statistical analyses were performed with IBM SPSS version 23.

Ethics

Participants in HUNT 3 gave written, informed consent for use of their data in research including linkage to named registries, such as NorPD. The study was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (2012/1906/REK). Linkage of databases was approved by the Norwegian Data Protection Authority.

RESULTS

Are AODs used by those at high fracture risk?

The baseline characteristics based on indication and treatment with AODs are presented in Table 1.

Among the total group (n=28,461), 3,268 women and 236 men were classified as having a $FRAX_{MOF}$ ≥20 %, 24 % of these were treated with AODs; 810 women (25 %) and 40 men (17 %). In the group with $FRAX_{MOF}$ <20 %, 3.3 % of the women and 0.9 % of the men were treated with AODs. The mean $FRAX_{MOF}$ for individuals with indication for AODs who got treatment was 29.7 (SD 11.8) and the median $FRAX_{MOF}$ was 26.7 (interquartile range 22.1-34.8).

Subgroup with BMD

BMD was measured in 4,538 women and 2,332 men. Based on our three indications for treatment with AODs ($FRAX_{MOF}$with or without BMD ≥ 20 % and T-score ≤ -2.5), 1,502 (22 %) fulfilled our criteria. Of these; 338 (24 %) of the women and 17 (16 %) of the men received AODs.

Among those not fulfilling the criteria (N=5,368), 3 % women and 1 % men were treated.

Of those who met our criteria for treatment (N=1,502), 346 had T-score ≤-2.5 and both $FRAX_{MOF}$with and without BMD ≥ 20; 581 had two of the indications; and 575 fulfilled one, Figure 2.

The correlation coefficient (r) between $FRAX_{MOF}$and T-score was -0.47 (p<0.001) Further, the correlation between the two $FRAX_{MOF}$models (with and without BMD) was 0.88 (p<0.001) and between $FRAX_{MOF_BMD}$and T-score -0.66 (p<0.001).

Figure 3 illustrates the treatment gap. By using both $FRAX_{MOF}$ and T-score, 355 (24%) of those with an indication received AODs. Among the 610 with T-score ≤ -2.5, 157 (26%) were treated.

Predictors for incident use of AODs

After exclusion of those using AODs at baseline, 14,211 women and 13,298 men were included in the analysis (Figure 1). In the follow-up period, 338 women (1.5%) and 67 men (0.5%) were incident users of AODs.

Among individuals classified with $FRAX_{MOF}$≥20%, 161 (6.7 %) of the women and 8 (5.8%) of the men started treatment with AODs during the first 2 years after participation in HUNT 3 (Table 2). In the group with $FRAX_{MOF}$<20%, 1.5 % of the women and 0.4% of the men were treated with AODs.

In the final model, adjusting for all significant predictors, age (>70 years) was the strongest predictor of treatment in women (HR 3.84: 95 % CI 2.81-5.24), followed by use of more than 100 DDD GCs a year (2.68: 1.84-3.89), multimorbidity (HR 2.64: 95% CI 1.80-3.88), previous fracture (2.07: 1.64-2.61), osteoporosis in parents (HR 1.95: 95% CI 1.49-2.54) and BMI< 20 (1.51: 1.09-2.10) (Table 2).

In the corresponding model in men (Table 2), the strongest predictor of treatment with AODs was use of more than 100 DDD GCs a year (5.28: 2.70-10.35), followed by multimorbidity (3.16: 1.31-7.63), self-reported RA (2.49: 1.24-5.00), previous fracture (2.33: 1.30-4.16), age ≥70 years (2.25: 1.16-4.33) and parenteral osteoporosis (2.15: 1.02-4.44).
There was a tendency towards a higher rate of treatment with AODs among those with low education. Marital status did not show any association with initiation of AODs.
In the subgroup with BMD measured, 44.4% of the women and 36.0% of the men with T-score ≤-2.5 received treatment, and this was the strongest predictor for starting AODs in both sexes. In the final model with all other covariates included, the HRs for incident use of AODs for T-score ≤ -2.5 were 3.98 (2.67-5.89) and 13.31 (6.17-28.74), for women and men, respectively (Table 2).

The influence of hormone replacement therapy

Among women 50-85 years, 1067 (7.1%) were treated with HT of which 338 were incident users. By adding individuals using HT to users of AODs, 27% with $FRAX_{MOF}$≥20% were treated. In the subgroup with BMD 26% were treated based on our three indications for treatment with AODs ($FRAX_{MOF}$ with or without BMD ≥ 20 % and T-score ≤ -2.5) .
Further, use of HT the last year before HUNT 3 was a statistically significant negative predictor for starting AODs (HR 0.51: 95% CI 0.28-0.93).

DISCUSSION

In this large population-based study we show that osteoporosis was undertreated according to guidelines. Based on the recommended $FRAX_{MOF}$, only 25 % of the women and 17 % of the men with high fracture risk were treated with AODs. Use of T-score ≤ -2.5 gave similar figures. Accordingly; the use of AODs was low irrespective of whether BMD, $FRAX_{MOF}$ or both were used as criteria for intervention. Among those who did not fulfil the criteria for treatment, less than 5% of the women and 1% of the men used AODs, suggesting that overtreatment is rare.
In Norway, the definition of osteoporosis as well as initiation of AODs are based on T-score ≤-2.5. However, in the guidelines from the Norwegian Society of Rheumatology 2015, FRAX is suggested as a method to find persons with high risk for fracture [20]. FRAX was not in use by clinicians when this study was performed. However, FRAX is a mathematical model calculated from known risk factors for fractures[29], and because we only had BMD for a subgroup, we choose to use FRAX as a tool for identifying patients at high risk for fractures.

The low frequency of AOD use may be influenced by the Norwegian reimbursement system; patients may be qualified to receive medical treatment reimbursed if they are in need of medical treatment due to a severe and chronic illness. In the period this study covers, criteria for reimbursement with bisphosphonates or raloxifene were T-score ≤−2.5 combined with fragility fracture (established osteoporosis) [28]. Teriparatide was reimbursed in those who sustained a fracture during treatment with bisphosphonates.

In our study, using T-score as a criterion for treatment with AODs had only minor impact on the prevalent use. However, T-score ≤−2.5 seemed to be the strongest predictor for initiating AODs as 44 % of the women and 36 % of the men started treatment within two years. This may be attributed to the fact that individuals with low BMD in HUNT 3 were told to contact their GP for further evaluation. This is in line with Siris et al's report from the US where 35 % of women > 55 years were treated with AODs one year after being diagnosed with osteoporosis [30]. Another recent study from US found that both the diagnosis and treatment rates for osteoporosis increased after a fracture. However, while the osteoporosis diagnosis rate in the group 65 years and older increased from 14.3% before fracture to 26.3% after fracture, the respective values for treatment were 11.7% to 15.8%[31] .

Using T-score ≤ -2.5 for diagnosis of osteoporosis is debated. The US National Bone Health Alliance Working Group has suggested that osteoporosis should be diagnosed when an individual has one or more of the following: T-score ≤-2.5; hip fracture; osteopenia and a fracture in vertebra, proximal humerus, pelvic or distal forearm; or a FRAX score of ≥3 % (hip) or 20 % (MOF) [18].

It has been questioned whether treatment with AODs has any effect in those with T-score >-2.5. Little data exist since most clinical trials use T-score ≤-2.5 as an inclusion criterion, but a post hoc analysis of 2-year follow-up data from four large RCTs of postmenopausal women with osteopenia and no prevalent vertebral fractures, showed that treatment with risedronate significantly reduced the risk of fragility fracture compared with placebo [32]. Further, zolendronic acid has also been found to reduce subsequent fractures in women with osteopenia [33, 34], while one study with alendronate showed no significant anti-fracture benefit [35]. However, a recently published guideline from the American college of Physicians states that fracture reduction in patients with osteopenia is likely to be similar across all bisphosphonates [36]. Teriparatide has also been found to reduce subsequent fracture in women with osteopenia [32, 36-38].

There is also a lack of studies examining if treatment according to FRAX criteria without BMD reduces fracture risk. One study looking at the cost-effectiveness of risedronate in the UK, set the threshold for treatment at $FRAX_{MOF}$ without BMD at 18.6%, which is similar to our definition [39]. Further, we have recently validated FRAX without BMD for hip fractures in this cohort and found that the observed number of hip fractures agreed quite well with the predicted number, except for the youngest and oldest men [23]. Based on this, treatment with AODs to women with T-score > -2.5 and high fracture risk seems reasonable.

Increasing age was the strongest predictor for receiving AODs in women, whereas this applied only for those older than 70 years in men. Further, previous fractures and coexistence of other diseases were the strongest predictors for men. This corresponds to the fact that fractures occur ten years later in men than in women, and secondary osteoporosis is more common in men [40]. Almost one third of hip fractures occur in men, and men are twice as likely to die within a year after hip fracture compared to women [40]. Due to the fact that life expectancy the last decade is now increasing rapidly in men, it is important that clinicians diagnose and treat osteoporosis also in men.

Treatment with AODs is recommended in individuals treated with GCs ≥ 7.5 mg for more than 3 months [41]. GCs affect bone quality adversely due to increased apoptosis of osteoblasts and osteocytes; reduced apoptosis of osteoclasts; as well as inhibition of intestinal calcium absorption [41, 42]. The increased risk of fractures at higher BMD during GCs treatment appears to be dose-dependent [41, 43], and FRAX has been criticized for only including GCs as treatment or not [44]. In accordance with previous studies, use of GCs was a strong predictor for incident prescription of AODs among both women and men [10].

HT was the treatment of choice for osteoporosis until 2002, when it was described to have adverse effects when assessing health benefits and risks in the Women's Health Initiative study [45]. In the Norwegian guidelines from 2005 [12], HT is only recommended for osteoporosis in women with postmenopausal complaints and then only for short duration. Thus, in our primary analysis we did not include HT as AOD. In supplementary analyses, adding use of HRT to AOD the percentage treated increased from 25% to 27% based on our definition FRAX MOF 20% and from 24% to 26% in the subgroup with BMD. Use of HT was associated to less incident use of AODs, probably due to its known positive effect on bone.

This study could not confirm that use of AODs was related to middle and low income as previously reported by Devold et al. based on national Norwegian data [10]. This may be due to smaller number of patients in our study. Similarly, we were also unable to confirm Swedish data where an association between use of AODs and high education was found [21].

The results are based on data collected from 2006-2010, and it is not obvious that the data are representative of today's practice. From 2011, reimbursement for alendronate was given to women with T-score ≤ -2.5 without a fragility fracture. However, the total use of AODs in the age group 50-84 in Nord-Trøndelag has been stable from 2006 to 2016 [24]. Among women, 6.8% used AODs in 2006 compared to 7.0 in 2016 (range 6.0-7.0). For men there has been a slight increase from 0.8% in 2006 to 1.6% in 2016 (range 0.8-1.6). Regarding denosumab the use among women has increased from 0.05% in 2011 to 0.3% in 2016, and the respective values for men were 0.01% to 0.05% [24]. We do not have any information regarding who received AODs after 2010. Due to more appropriate prescription as well as more awareness for side effects the last years, the use among individuals with high risk for fracture may have increased at the expense of those without indication. However, the use of AOD is still low.

The strengths of our study are the population-based design, the large registers, complete capture of prescriptions dispensed from Norwegian pharmacies, the follow-up being established through linkage to registries with independent observations, and a reasonably high participation rate (66 %) in HUNT. A survey of 6922 non-participants showed that the most common reason for not attending in HUNT 3 in the age group 40-59 and 60–79 was lack of time, reported by 58% and 37%, respectively. Among those 80 years and older, 23% reported that they were too ill to take part in the study [46]. Based on this, there may be a selection bias due to non-participation of a the frailer individuals among the oldest age group in the study

Although a broad range of data in the HUNT study was available for calculation of FRAX score, we lacked precise information on osteogenesis imperfecta, malnutrition, malabsorption, and chronic liver disease. Next, we were not able to directly retrieve data on hip fractures in parents; Proband reported parental osteoporosis was included in the calculation. Finally, the prevalence of self-reported RA was higher than anticipated [23, 47].

We have not included information concerning events during follow-up such as fractures, use of GCs or comorbidities, but most of this data would rather increase the number that should be offered AODs. Further, we do not have data on BMD measures performed outside the

study as part of regular medical care. Lastly, we do not have information on potential contraindications to AODs such as kidney failure or gastrointestinal ulcer.

Conclusion:

Our data show that although AODs were given to individuals at high fracture risk and comorbidity, there was undertreatment of AODs of subjects at high fracture risk. This finding was consistent whether high fracture risk was defined as T-score ≤-2.5 or $FRAX_{MOF}$, ≥20%. The total use of AODs in Nord-Trøndelag have been stable in the period 2006-2016, indicating a persistent undertreatment. Overtreatment, i.e. treatment with AODs in individuals without indication, seemed to be a minor problem.

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CONFLICTS OF INTERESTS

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Table 1. Baseline characteristics based on indication and treatment defined as FRAX for major osteoporotic fractures without BMD ≥20%. N=28461

	Indication for treatment N=3504		No indication for treatment, N=24957	
	Treated N=850	**Not treated. N=2654**	**Treated N=507**	**Not treated. N=24450**
Women, N (%)	810 (95.3)	2458 (92.6)	392 (77.3)	11415 (46,7)
Age, mean (SD)	73.5 (7.4)	74.2 (7.3)	65.6 (8.2)	62.2 (8.3)
Body Mass index (BMI), mean (SD)	25.9 (4.3)	26.5 (4.3)	27.1 (4.6)	27.8 (4.2)
High EducationN (%)**	147 (17.3)	473 (17.8)	125 (22.7)	7892 (32.3)
Marital status*, N (%)				
-Married/ partnership	419 (49.3)	1299 (48.9)	334 (65,9)	17620 (72.1)
-Widow/ widower	342 (40.2)	1058 (39.9)	83 (16.4)	2072 (8.5)
-Previously married	55 (6.5)	194 (7.3)	59 (11.6)	2927 (12.0)
-Never married	34 (4.0)	103(3.9)	29(5.7)	1820 (7.4)
FRAX major osteoporotic fracture without BMD				
-Mean (SD)	34.2 (13.9)	28.3 (10.6)	12.3 (4.6)	7.4 (4.0)
-Median (25-75 percentile)	31.6 (23.8-41.3)	25.8 (21.7-32.7)	12,6 (8,7-16,3)	6,3 (4,3-9,4)
Previous fracture*, N (%)	542 (63.8)	1367 (51.5)	86 (17,3)	1964 (8,0)
Smoking*, N (%)	199 (23.4)	587(22.1)	108 (21,3)	5495 (22.5)
Alcohol, units per week* (SD)	1.0 (1.6)	1.0 (2.0)	1.4 (2.0)	2.2 (2.8)
Rheumatoid Arthritis*, N (%)	149 (17.5)	320 (12.1)	61 (8,9)	859 (3.5)
Secondary osteoporosis*, N (%)**	215 (25.3)	613 (25.7)	61 (12.0)	1625 (6.6)
Osteoporosis in parents*, N (%)	303 (35.3)	538 (22.5)	106 (18.7)	1848 (7.5)
Glucocorticoids last year before HUNT3, N (%)	206 (24.2)	378 (14.2)	89 (15.7)	1007 (4.9)
Glucocorticoids, defined daily doses last year before HUNT3, N (%)				
-0	644 (75.8)	2276 (85.8)	430 (84.8)	23646 (96,0)
-1-99	42 (4.9)	187 (7.0)	16 (3,2)	595 (2.4)
-≥100	164 (19.3)	191 (7.2)	61 (12.0)	391 (1.6)
Numbers of drugs last year before HUNT3, mean (SD)	8.4 (4.6)	6.0 (4.1)	3,3 (0,9)	2,4 (1,2)

* Self-reported

**High education is defined as occupations with college or university education

*** Secondary osteoporosis defined as: defined as self-reported menopause before 45 years of age or surgical removal of ovaries before 45 years, diabetes mellitus type 1 or hyperthroidism

Table 2. Hazard ratios for incident use of anti-osteoporotic drugs the first 2 years after HUNT3

a) **Women**
b) **Men**

CI: Confidence interval. SD: Standard deviations. BMI Body Mass Index
*Self-reported
**High education is defined as occupations with college or university education

Confidence interval. SD: Standard deviations. BMI Body Mass Index
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a) Women	N 14,211	Treated (%) 338 (2.4)	Crude Hazard ratios	Age adjusted Hazard ratios (95% CI)	Final model Hazard ratios (95% CI)
FRAX MOF without BMD					
<20	11790	177 (1.5)	Reference	Not adjusted	Not adjusted
≥20	2421	161 (6.7)	4.60 (3.72-5.70)		
Previous fracture*					
No	12044	216 (1.8)	Reference	Reference	**Reference**
Yes	2167	122 (5.6)	3.22	2.22 (1.76-2.80)	**2.07 (1.64-2.61)**
Rheumatoid Arthritis*					
No	13488	313 (2.3)	Reference	Reference	
Yes	723	25 (3.5)	1.51	1.28 (0.85-1.93)	
Secondary osteoporosis*					
No	12098	270 (2.2)	Reference	Reference	**Reference**
Yes	2113	68 (3.2)	1.39	1.37 (1.05-1.78)	**1.19 (0.91-1.55)**
Glucocorticoids, last year before HUNT3					
0	13411	296 (2.2)	Reference	Reference	**Reference**
1-99 defined daily doses	476	8 (1.5)	0.73	0.70 (0.35-1.41)	**0.53 (0.26-1.08)**
≥100 defined daily doses	324	34 (10.5)	5.06	3.91 (2.74-5.60)	**2.68 (1.84-3.89)**
Numbers of drugs last year before HUNT 3					
0-1	3442	35 (1.0)	Reference	Reference	**Reference**
2-3	3505	60 (1.7)	1.69	1.53 (1.01-2.32)	**1.60 (1.05-2.43)**
4-5	2954	79 (2.7)	2.64	2.03 (1.36-3.03)	**2.27 (1.52-3.40)**
6-	4310	164 (3.8)	3.81	2.48 (1.71-3.61)	**2.64 (1.80-3.88)**
Age, years					
-50-59	5891	91 (2.7)	Reference	NA	**Reference**
-60-69	4821	98 (2.0)	1.99		**1.84 (1.33-2.55)**
-70-85	3499	179 (5.1)	5.19		**3.84 (2.81-5.24)**
BMI m/kg^2					
<22	1273	63 (4.9)	1.77	1.63 (1.18-2.24)	**1.51 (1.09-2.10)**
22-25	3194	91 (2.8)	Reference	Reference	**Reference**
>25	9744	184 (1.9)	0.67	0.58 (0.45-0.74)	**0.54 (0.42-0.69)**
Marital status*					
-Married/ partnership	9232	183 (2.0)	Reference	Reference	
-Previously married	1700	31 (1.8)	0.90	1.10 (0.75-1.61)	
-Never married	698	15 (2.1)	1.07	1.11 (0.66-1.89)	
-Widow	2574	108 (4.2)	2.20	1.06 (0.81-1.39)	
Education**					
-high	10494	274 (2.6)	Reference	Reference	
-low	3717	64 (1.7)	1.55	1.14 (0.87-1.50)	
Parental osteoporosis*					
No	12564	268 (2.1)	Reference	Reference	**Reference**
Yes	1647	70 (4.3)	1.98	2.35 (1.81-3.01)	**1.95 (1.49-2.54)**
Smoke*					
No	10861	254 (2.3)	Reference	Reference	**Reference**
Yes	3350	84 (2.4)	1.07	1.43 (1.12 -1.85)	**1.20 (0.93-1.55)**
Alcohol units/ week*					
0	5281	166 (3.1)	Reference	Reference	
1-7	8416	162 (1.9)	0.60	0.89 (0.71-1.11)	
>7	270	2 (0.7)	0.22	0.37 (0.09-1.48)	
SUBGROUP with BMD	N=4239	N=133 (2.9)			
T-score >-2.5 SD	4106	74 (1.8)	Reference	Reference	
T-score ≤ -2.5 SD	133	59 (44.4)	7.15	5.85 (3.97-8.61)	**3.98 (2.67-5.89)**

a) Men	N 13,298	Treated (%) 67 (0.5)	Crude Hazard ratios	Age adjusted Hazard ratios (95% CI)	Final model Hazard ratios (95% CI)
FRAX MOF without BMD					
<20	13161	59 (0.4)	Reference	Not adjusted	Not adjusted
≥20	137	8 (5.8)	13.43 (6.42-28..11)		
Previous fracture*					
No	11997	52 (0.4)	Reference	Reference	**Reference**
Yes	1301	15 (1.2)	2.67	2.32 (1.30-4.13)	**2.33 (1.30-4.16)**
Rheumatoid Arthritis*					
No	12807	57 (0.4)	Reference	Reference	**Reference**
Yes	491	10 (2.0)	4.67	4.33 (2.12-8.49)	**2.49 (1.24-5.00)**
Secondary OPO *					
No	13085	66 (0.5)	Reference	Reference	
Yes	213	1 (0.5)	0.92	0.79 (0.11-5.71)	
Glucocorticoids (DDD) last year before HUNT3					
0	12673	48 (0.4)	Reference	Reference	**Reference**
1-99	320	6 (1.9)	4.73	4.27 (1.82-9.99)	**2.69 (1.11-6.48)**
≥100	305	13 (4.3)	11.60	8.43 (4.51-15.78)	**5.28 (2.70-10.35)**
Numbers of drugs last year before HUNT 3					
0-1	4585	7 (0.2)	Reference	Reference	**Reference**
2-3	3303	11 (0.3)	2.18	1.94 (0.75-5.01)	**1.60 (0.60-4.22)**
4-5	2359	12 (0.5)	3.33	2.58 (1.00-6.64)	**1.91 (0,73-5,04)**
6-	3051	37 (1.2)	8.01	5.47 (2.36-12.65)	**3.16 (1.31-7.63)**
Age					
-50-59	5374	14 (0.3)	Reference		**Reference**
-60-69	4616	17 (0.4)	1.42	NA	**0.94 (0.45-1.96)**
-70-85	3308	36 (1.1)	4.35		**2.25 (1.16-4.33)**
BMI m/kg^2					
<22	514	7 (0.4)	2.00	1.79 (0.74-4.33)	
22-25	2479	17 (1.4)	Reference	Reference	
>25	10305	43 (0.4)	0.60	0.66 (0.37-1.15)	
Marital status*					
-Married/ partnership	9921	51 (0.5)	Reference	Reference	
-Previously married	1455	3 (0.2)	0.40	0.54 (0.17-1.74)	
-Never married	1248	8 (0.6)	1.27	1.55 (0.73-3.27)	
-Widower	669	5 (0.7)	1.51	0.85 (0.33-2.18)	
Education**					
-high	8571	15 (0.3)	Reference	Reference	**Reference**
-low	4758	52 (0.6)	1.97	1.71 (0.96-3.04)	**1.41 (0,78-2,53)**
Parental osteoporosis*					
No	12481	59 (0.5)	Reference	Reference	**Reference**
Yes	817	8 (1.0)	2.05	2.40 (1.15-5.04)	**2.15 (1.02-4.44)**
Smoke*					
No	10469	54 (0.5)	Reference	Reference	
Yes	2829	13 (0.5)	0.89	1.03 (0.56-1.89)	
Alcohol* units/ week					
0	2880	27 (0,9)	Reference	Reference	**Reference**
1-7	9350	38 (0,4)	0.43	0.56 (0.34-0.93)	**0,66 (0,40-1,28)**
>7	910	0	NA	NA	**NA**
SUBGROUP with BMD	2314	25 (1.1)			
T-score >-2.5 SD	2289	16 (0.7)	Reference	Reference	
T-score≤ -2.5 SD	25	9 (36.0)	21.31	15.69 (6.52-37.78)	**13.31 (6.17-28.74)**

Figure 1. Flow chart of the included subjects

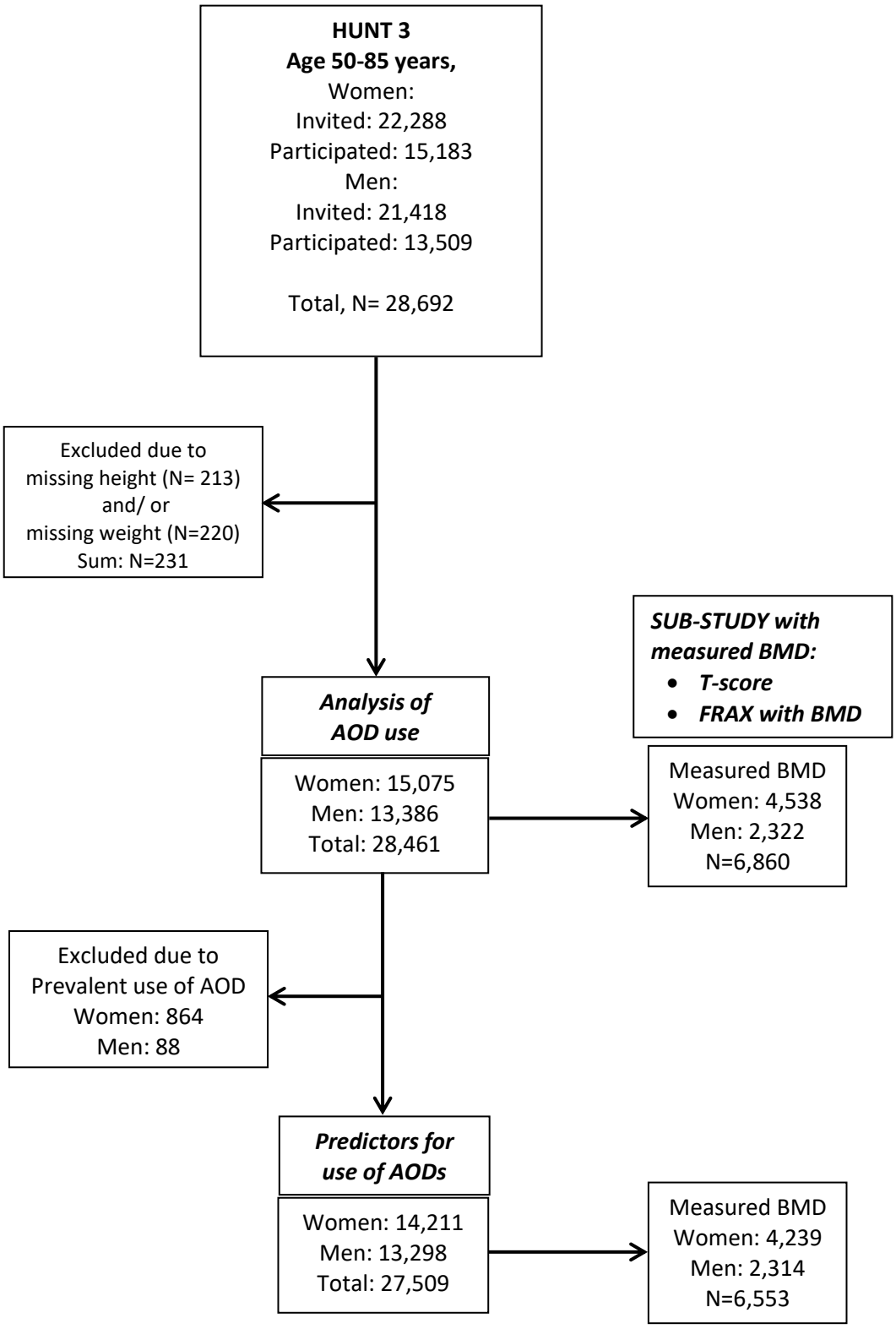

Figure 2. Overlap between FRAX without BMD ≥20, FRAX with BMD≥20 and T-score≤-2.5 among individuals who met the criteria for treatment in the subgroup with BMD measured

Total N= 1,502, numbers refer to individuals in each category.

- $FRAX_{MOF} \geq 20\%$ N=363
- $FRAX_{MOF\_BMD} \geq 20\%$ N=71
- T-score ≤ -2.5 N=141
- $FRAX_{MOF} \geq 20\%$ + $FRAX_{MOF\_BMD} \geq 20\%$ N=458
- $FRAX_{MOF} \geq 20\%$ + T-score ≤ -2.5 N=9
- $FRAX_{MOF\_BMD} \geq 20\%$ + T-score ≤ -2.5 N=114
- $FRAX_{MOF} \geq 20\%$ + $FRAX_{MOF\_BMD} \geq 20\%$ + T-score ≤ -2.5 N=346

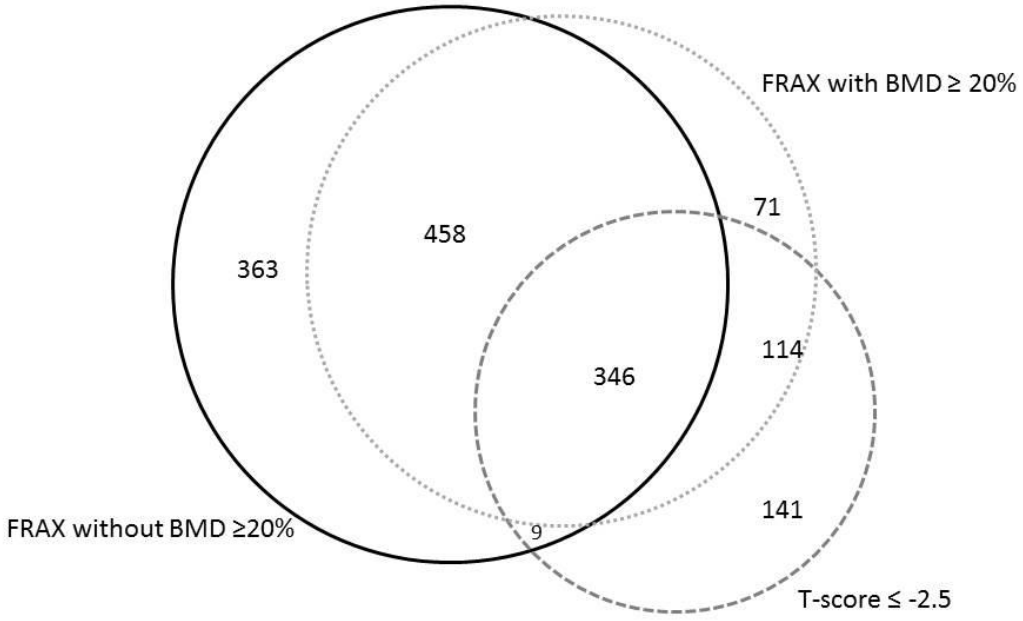

Figure 3. Treatment gap in the subgroup with BMD
24 % with indication were treated with AODs