Osteoporosis International (2025) 36:695–706
https://doi.org/10.1007/s00198-025-07436-x

ORIGINAL ARTICLE

Long-term adherence to anti-osteoporosis medication and determinants of adherence in the population-based screening trial ROSE

Tanja Gram Petersen[1] · Katrine Hass Rubin[1] · Muhammad Kassim Javaid[2] · Anne Pernille Hermann[3,4] · Kristina E. Åkesson[5,6] · Bo Abrahamsen[1,7]

Received: 12 November 2024 / Accepted: 13 February 2025 / Published online: 24 February 2025

Abstract

Summary Screening initiatives for osteoporosis must facilitate treatment of those at elevated fracture risk. In a randomized controlled trial of 24,229 women, those in the screening group with FRAX ≥ 15% were invited for DXA with AOM treatment offered as per national guidelines. Treatment initiation in the following year was 9.5 times higher compared with controls.

Purpose To determine if screened individuals have lower adherence to anti-osteoporotic medication (AOM) than unscreened and to examine determinants for low treatment adherence.

Method In 2010/2011, women aged 65–80 ($N = 34{,}229$) in the Region of Southern Denmark were invited to the risk-stratified osteoporosis strategy evaluation (ROSE) randomized study. Women in the screening group with moderate to high 10-year fracture risk (FRAX® ≥ 15%) were invited for dual-energy x-ray absorptiometry with AOM treatment as per national guidelines. Screened, controls, and an age-matched general population sample were compared for adherence to AOM using 10-year follow-up data on prescription and hospital records.

Results Among ROSE participants with FRAX ≥ 15%, 5864 screened and 5790 controls were eligible for analysis, along with an equal number from the general population. AOM initiation in the first year was 9.5 times higher in screened compared to controls (HR 9.50, 7.16; 12.61). There was no difference in implementation assessed as medication possession ratio. The 5-year persistence rates were similar in screened and controls (51–52%), but lower in the general population (44%). FRAX risk factors partly influenced AOM initiation in the screened, with different patterns in other groups. Immobilization, comorbidities, and co-medications were key determinants of discontinuation in both the short and long term.

Conclusion The ROSE screening programme significantly increased treatment initiation in postmenopausal women. Screened women showed similar treatment adherence levels to non-screened once they started medication. However, frail women were more prone to treatment discontinuation, highlighting the need for targeted support in this subgroup.

Trial registration The original ROSE trial is registered at ClinicalTrials.gov (NCT01388244). The study protocol has been published in Rubin et al. *The risk-stratified osteoporosis strategy evaluation study (ROSE): a randomized prospective population-based study. Design and baseline characteristics. Calcif Tissue Int. 2015;96(2):167–79.*

Keywords Anti-osteoporotic medication (AOM) · Adherence · Osteoporosis screening · Persistence · ROSE

✉ Tanja Gram Petersen
tanja.gram.petersen@rsyd.dk

[1] Research Unit OPEN, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[2] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

[3] Research Unit for Endocrinology, Odense University Hospital, Odense, Denmark

[4] University of Southern Denmark, Odense, Denmark

[5] Clinical and Molecular Osteoporosis Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden

[6] Department of Orthopaedics, SkåNe University Hospital, Malmö, Sweden

[7] Department of Medicine, Holbæk Hospital, Holbæk, Denmark

Introduction

Over one in three women and one in six men over 50 years will experience an osteoporotic fracture [1]. Although anti-osteoporotic medication (AOM) can effectively reduce the risk of osteoporotic fractures, osteoporosis most often remains undiagnosed until an osteoporotic fracture occurs [2, 3]. Adherence to the prescribed treatment regimens is pivotal for reducing the risk of osteoporotic fractures [4]. A 2019 systematic review showed that suboptimal adherence to AOM in postmenopausal women is common, with bisphosphonate persistence rates dropping below 30% after one year of treatment in certain settings [4]. In Denmark, however, the adherence is found to be higher [5, 6].

In 2010, the risk-stratified osteoporosis strategy evaluation (ROSE) randomized study was initiated with the purpose of evaluating the effectiveness of a two-stage screening programme for early detection and treatment of osteoporosis [7, 8]. The programme employed the Fracture Risk Assessment Tool (FRAX®) [9] to identify women with a moderate to high risk of major osteoporotic fractures eligible for dual-energy x-ray absorptiometry (DXA) scans. Screened with an FRAX score of 15% or above were offered a DXA scan with treatment recommended per Danish guidelines if osteoporosis was detected [10]. Although the study showed no overall population effect after 5 and 10 years in the intention-to-treat analysis [8, 11], the 10-year follow-up indicated a preventive effect on fracture incidence among women with moderate to high fracture risk (FRAX ≥ 15%) in the per-protocol analysis [8]. This group represented the intended target population for the intervention, which is why it was more expected to see an effect in this group. Treatment uptake, adherence, and persistence are all crucial for achieving favourable outcomes. In the ROSE programme, the treatment responsibility was transitioned to primary care, potentially affecting treatment uptake and adherence [12]. Moreover, factors like perceived risk, perceived treatment benefits, motivation, and decision-making may differ between individuals who begin treatment through a screening programme versus those who actively seek medical attention from their general practitioners (GPs) and are referred for further assessment, which can impact adherence [12, 13]. In support of this, the C-STOP trial [14] showed that long-term adherence to bisphosphonates was lower in patients assigned to nurse-managed treatment compared to the control group, particularly after regular follow-ups from the nurse were reduced. Consequently, we hypothesized that screened women in ROSE start treatment much faster than unscreened, but after starting treatment, adherence will be poorer among screened.

Most studies on AOM adherence focus on orally administered bisphosphonates therapy [4, 6, 15], which is also the first-line therapy in Denmark per Danish guidelines [10]. However, it is also essential to assess overall adherence to AOM, regardless of whether patients continue with their initial medication or switch to another evidence-based AOM while remaining persistent in treatment. This broader approach is relevant because total exposure to approved AOMs, rather than adherence to a specific medication, is what ultimately reduces osteoporotic fractures risk. Additionally, more evidence is needed on long-term adherence to AOM therapy, particularly beyond 5 years [4, 6, 16].

Thus, the study's primary aim was to examine the effect of the ROSE screening programme on long-term adherence to AOM treatment overall to evaluate the programme's impact on fracture incidence. Secondarily, the study aimed to identify socio-demographic and clinical factors associated with low adherence. To obtain a more natural comparison group, had the screening programme been implemented in routine practice, and to account for potential influences of the osteoporosis risk survey on treatment uptake and adherence among ROSE participants, we used a general population as a secondary comparison group.

Materials and methods

This post hoc study of the ROSE randomized trial assessed adherence and determinants for adherence among ROSE participants and the general population, utilizing survival analyses of clinical data from the ROSE study and data from nationwide registers.

The ROSE study and data sources

Details of the ROSE study have been published [7, 8]. In brief, 98,383 women aged 65–80 residing in the Region of Southern Denmark in 2010 were identified. A random sample of 34,229 women was selected for participation in the ROSE study and randomized to either a screening or control group. All participants (both from the screening group and controls) received an invitation letter by mail in 2010–2011 that contained a questionnaire comprising questions on clinical risk factors for calculating FRAX. Only women in the ROSE screening group with moderate to high fracture risk assessment, assessed as a major osteoporotic FRAX score of ≥ 15%, were offered the intervention, which included a DXA scan of bone mineral density of the lumbar spine (L1–L4) and total right hip. A diagnosis of osteoporosis was based on the lower of the two BMD values. If osteoporosis was identified by bone mineral density (BMD) T-score < − 2.5 SD, treatment advice according to the Danish guidelines [10] was provided to both the women and their GPs, with the GP responsible for the treatment.

The Danish Civil Registration System Register [17] provided baseline demographic data, migration, and vital status. Socioeconomic data came from Statistics Denmark [18]. Prescription data, derived from the Danish National Prescription Registry [19], included data on all filled prescriptions at Danish pharmacies from 1995 and onwards, coded using the Anatomical Therapeutic Chemical Classification System (ATC) and Defined Daily Dose (DDD). Hospital diagnoses (coded according to the International Classification of Diseases, 10th Revision (ICD-10)) and codes for treatment administered during hospital contacts were obtained from the Danish National Patient Register [20], which keeps records of all inpatient and outpatient hospital contacts since 1995. The personal identification numbers were used to link data on an individual level.

Study population

Figure 1 depicts the flowchart of the study population. A total of 17,072 women were randomized to the ROSE screening group (group A) and 17,157 to the ROSE control group (group B). We defined the study-baseline as the date the ROSE participants returned the ROSE questionnaire. We excluded ROSE participants with missing/inadequate data from the questionnaires ($n = 6661/6663$) and participants with self-reported AOM treatment or a record of AOM treatment within 1 year before baseline ($n = 1224/1279$). We also excluded participants with a primary or secondary hospital diagnosis of cancer (ICD10: C00-C99, D00-D48) or Paget's disease (ICD10:M88) within the 5 years preceding the baseline ($n = 1312/1378$) and participants with missing data on sociodemographic factors ($n = 103/104$). These exclusions left 7772 from the screening group (A) and 7733 from the control group (B). We further restricted the population to ROSE participants with FRAX $\geq 15\%$ (i.e. women eligible for the intervention, a DXA scan). This resulted in 5864 women from the screening group (A) and 5790 from the control group (B) constituting the study population.

Participants in the ROSE study represent a selected sample that may not fully reflect the general population [21]. Additionally, responses to the osteoporosis risk survey could potentially have influenced the behaviour of the ROSE participants. To address these limitations, we included a comparison group of age-matched women (group C) from the general population, who were not exposed to the ROSE survey. This comparison group provided a more natural

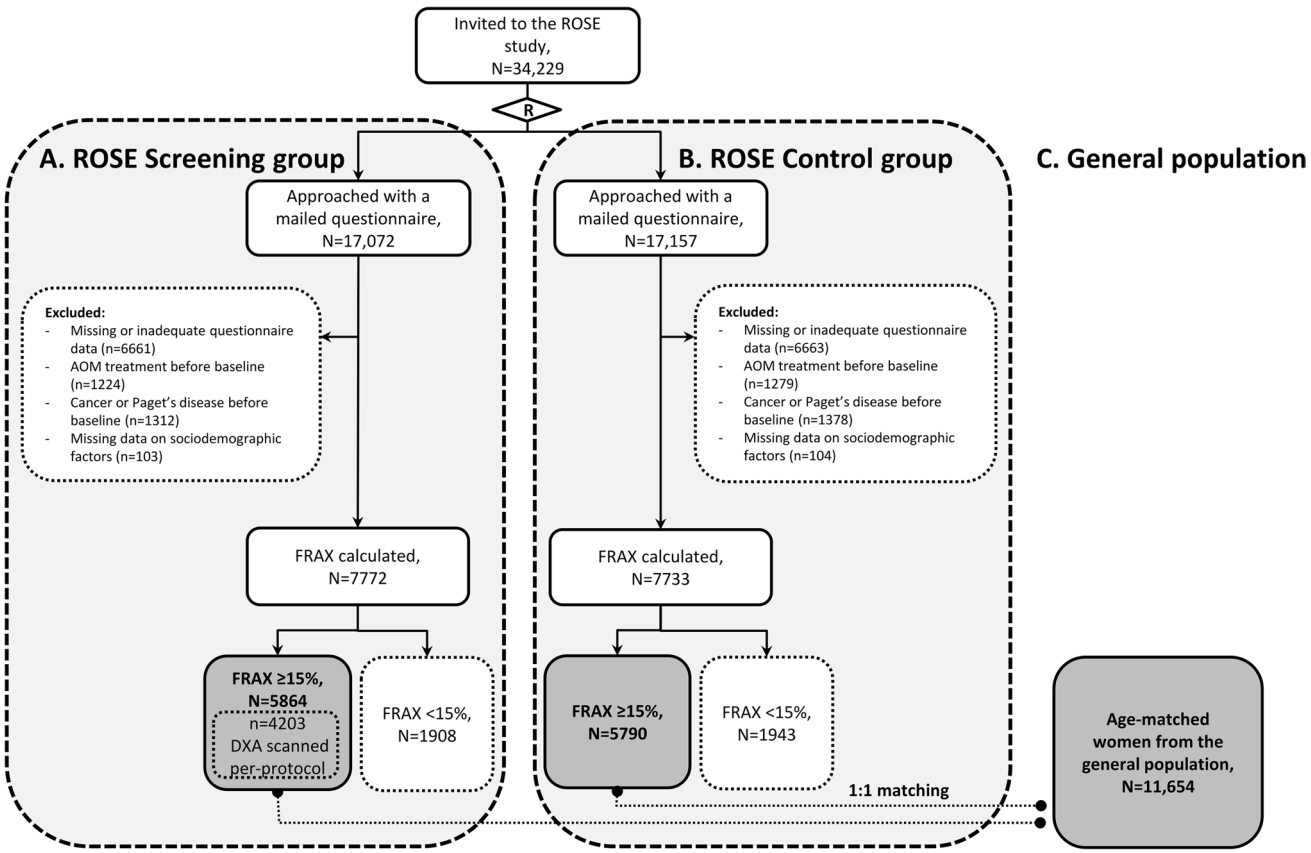

Fig. 1 Flowchart for the (A) ROSE screening group, (B) ROSE control group, and (C) general population. AOM, anti-osteoporotic medication, DXA, dual-energy x-ray absorptiometry

benchmark for assessing adherence, had the screening programme been implemented more broadly, than the ROSE control group. Using the Danish Civil Registration System Register, which keeps information on all residents in Denmark, we extracted this secondary comparator group (C) from the 64,154 women residing in the Region of Southern Denmark in 2010 who were not invited to participate in the ROSE study. These women were age-matched with the ROSE participants (ratio 1:1) and sampled with replacement, allowing the possibility of selecting the same woman more than once. No other matching factors were applied than age, in order to maintain the group's comparability with the general population. Before matching, exclusions concerning AOM treatment, diagnoses of cancer and Paget's disease, and missing sociodemographic data were executed for the age-matched general population (C). The age-matched women from the general population (C) were assigned the same baseline date as their matched ROSE participants (A and B). Similar to the ROSE control group (B), the age-matched women (C) underwent DXA scanning and received treatment based on the standard case-finding approach used in Denmark.

Clinical covariates and determinants obtained from the ROSE questionnaire

Clinical data on ROSE participants was obtained from the baseline questionnaire. We assessed the following clinical determinants for adherence to treatment: previous fractures, parental history of hip fracture, current smoking status, rheumatoid arthritis, condition related to secondary osteoporosis as defined by the FRAX list, body mass index, early menopause, increased fall-risk assessed as > one fall within 12 months, and long-term immobilization. In the ROSE screening group, indication for AOM treatment based on the DXA finding was also evaluated as a determinant for adherence.

Covariates and determinants derived from the national registers

We obtained data on baseline characteristics from the Danish national registers for the entire study population (group A, B, and C), which included age, cohabitation status, disposable family income, and highest obtained educational level in the household. We also obtained information on number of redeemed co-medications (utilizing the first three ATC characters), redeemed systemically acting glucocorticoids (at least one redemption of medicine with ATC code: H02AB01-2, H02AB04-9, H02AB10, H02AB13 disregard dose and duration), and redeemed psychotropic medication (at least one redemption of medicine with ATC code: N05A-C*, N06* disregard dose and duration) in the year preceding baseline. We calculated the Charlson comorbidity index (CCI) [22, 23] based on ICD-10 hospital diagnoses recorded within the 15 years preceding the baseline.

Outcome measures: anti-osteoporosis medications (AOM)

We used a composite measure for AOM treatment that included both treatment with tablets and injections. Information on redeemed prescriptions of AOM was derived from the Danish National Prescription Registry [19] and information on AOM treatment provided during hospital contacts was obtained through the Danish National Patient Register [20]. ATC codes included G03XC01 (SERM), M05BA01, M05BA04, M05BA06, M05BA07, M05BB03 (bisphosphonate), M05BX03, M05BX04 (other antiresorptives/mixed), and H05AA02 (parathyroid hormones analogues). Procedure codes included BWHB40B (ibandronate), BWHB42 (denosumab), and BWHB40A (zoledronate). See Table SI1 for more information on applied codes. We also utilized the date of filled prescription/procedure and the DDDs [24].

We evaluated long-term adherence employing the taxonomy suggested by Vrijens et al. [25]. *Initiation* of treatment was assessed as the date the women claimed their first AOM prescription or had their first hospital-record of AOM treatment during the observational period (until December 31, 2021) and handled as a time-to-event variable. *Implementation* of the dosing regimen refers to the extent to which a patient's actual dosing corresponds to the prescribed daily dose [26]. Implementation was operationalized as *the Medication Possession Ratio (MPR) = total days' supply of medication / number of days in the observation period* [27]. We considered MPR of < 80% as insufficient treatment implementation (yes/no). The MPR was calculated at each recorded treatment based on the cumulative days' supply and the total days in the period up to that point. The first occurrence of MPR < 80% was evaluated as a time-to-event variable. *Persistence* with treatment is the time from initiation of treatment until *discontinuation*, calculated as the number of days a patient was in possession of a medication to the first gap in the therapy of greater than 90 days. We assessed the date of treatment discontinuation as a time-to-event variable.

During hospital admissions, routine treatments is generally continued, but not all treatments administered during hospitalization are recorded in the registers. We considered women as adherent during admissions. When evaluating the overall treatment of AOM, we deemed women who switched from one drug to another as adherent as long MPR was retained above 80% or persistent until the first refill gap

exceeded 90 days. We did not assess adherence during medication re-initiation after MPR < 80% or discontinuation.

Entry date and follow-up

When studying initiation of AOM treatment, we assessed time to first record of AOM treatment. Women in the ROSE screening group who were eligible for a DXA scan (i.e. had a FRAX ≥ 15%) had their scan a median of 195 days after the baseline date. To accommodate this left truncation, scanned women entered the risk set at the scan date. For the remaining women, we imputed an entry date using the median days above. Supplementary Fig. SI1 shows the study diagram.

The analyses assessing the implementation (MPR) of the dosing regimen and treatment persistence/discontinuation were *restricted to women who initiated AOM treatment within 1 year* after they were DXA scanned or an imputed date (defined as the entry date above). For these analyses, the women entered the analyses when they claimed their first AOM prescription or had their first hospital-record of AOM treatment. Supplementary Fig. SI2 shows the study diagram.

In time-to-event analyses, the study population was followed until outcome occurred or the first censoring event: diagnosis of cancer or Paget's disease, death, emigration, or December 31, 2021.

Statistical analysis

When assessing baseline characteristics, frequencies and percentages were used to present binary and categorical variables, while medians with interquartile range (IQR) were used to summarize continuous variables. We calculated the cumulative incidence function (CIF) of initiation of AOM treatment using the Aalen-Johansen estimator [28]. The survival probability of high treatment implementation (MPR ≥ 80%) and persistence over time was computed using the Kaplan–Meier method. We studied the relative differences in adherence between the ROSE screening group (A), the ROSE control group (B), and the age-matched general population (C) using Cox regression models adjusted for age at baseline (included as cubic splines) and CCI (0, 1, ≥ 2). We tested the proportional hazard assumption utilizing log–log plots and by plotting Kaplan–Meier versus predicted survival. To accommodate that the assumption was not met for the Cox model assessing initiation, the analysis-time was split at 1 year, 3 years, and 5 years. We also used multivariate Cox regression models to examine the association of determinants for initiation of treatment within the first year of follow-up and determinants for discontinuation (non-persistence) within the first year and second-tenth year after initiation of treatment. The models were adjusted for potential confounding variables specific to each determinant. Estimates for the Cox regression models are presented as hazard ratios (HRs) with 95% confidence intervals (95% CI). The analyses were performed in StataMP18.

Registration and ethics

The ROSE trial is registered at ClinicalTrials.gov (NCT01388244) and approved by the Regional Committee on Health Research Ethics for Southern Denmark (jr.nr S-20090127) and the Danish Data Protection Agency. The analyses in this publication are post hoc analyses.

Results

Study population

After applying the exclusion criteria and restricting the population to ROSE participants with FRAX ≥ 15%, 5864 from the ROSE screening group (group A) and 5790 from the ROSE control group (group B) were eligible for analyses. An equal number of women from the age-matched general population (group C) were included ($n = 11{,}654$) (Fig. 1). Table 1 presents the study population's characteristics at baseline. Women from the screening group (A) and the control group (B) were similar, except for a slightly higher proportion of women with lower family income in the screening group. The screening group (A) and the ROSE control group (B) differed from women included in age-matched general population (C) in that they were more often married, had higher family income and educational level, and had lower prevalence of psychotropic medicine use and comorbidities.

Effects of the ROSE screening programme on adherence

Initiation of AOM

At 1 year after providing the questionnaire, 535 (9.1%) from the screening group (A) had started AOM treatment. The corresponding cumulative incidence proportion for initiation in screened was 24 per 100 person-years accounting for delayed entry (Fig. 2 and Figure SI3). By contrast, treatment initiation in the same period was 1 per 100 person-years in the ROSE control group (B) and 2.7 per 100 person-years in the age-matched general population (C) (Fig. 2). The initial route of administration of treatment was oral, and the first line medication was almost exclusively alendronate. In relative terms, the screened (A) had a 9.5 times higher AOM initiation rate (adjusted HR 9.50 (95% CI 7.16; 12.61)) compared to controls (B). There was an attenuation of this

Table 1 Baseline characteristic of the study population

	A. ROSE screening: FRAX ≥ 15% *N* = 5864 *N* (%)	B. ROSE control: FRAX ≥ 15% *N* = 5790 *N* (%)	C. Age-matched general population *N* = 11,654 *N* (%)
Information from the registers			
Age, median [IQR]	72.0 [69.0;76.0]	72.0 [69.0;75.0]	72.08 [69.0;76.0]
65–69	1856 (31.7)	1847 (31.9)	3697 (32.4)
70–74	2181 (37.2)	2191 (37.8)	4315 (37.8)
75 +	1827 (31.2)	1752 (30.3)	3413 (29.9)
Unmarried/living alone	2091 (35.7)	2135 (36.9)	4791 (41.1)
Family income, low tertile	1865 (31.8)	1724 (29.8)	4256 (37.3)
Household educational level, lower secondary	2992 (51.0)	2960 (51.1)	6622 (56.8)
Co-medication, median [IQR]	4.0 [2.0;7.0]	4.0 [2.0;7.0]	4.0 [2.0;7.0]
Glucocorticoids	381 (6.5)	373 (6.4)	710 (6.1)
Psychotropic medication	1137 (19.4)	1089 (18.8)	2727 (23.4)
CCI ≥ 2	353 (6.0)	365 (6.3)	867 (7.4)
Information from the ROSE questionnaire			
FRAX (MOF), median [IQR]	23.0 [18.0;29.0]	23.0 [18.0;29.0]	…
Previous fracture	798 (13.6%)	749 (12.9%)	…
Parental hip fracture	1025 (17.5%)	1048 (18.1%)	…
Current smoker	935 (15.9%)	949 (16.4%)	…
Rheumatoid arthritis	370 (6.3%)	388 (6.7%)	…
Condition related to secondary osteoporosis	1437 (24.5%)	1444 (24.9%)	…
BMI, ≤ 19 kg/m^2	397 (6.8%)	439 (7.6%)	…
BMI, median [IQR]	24.8 [22.5; 27.5]	24.7 [22.4;27.5]	…
Early menopause	1375 (23.4%)	1326 (22.9%)	…
Increased fall-risk	386 (6.6%)	434 (7.5%)	…
Long-term immobilization	883 (15.1%)	858 (14.8%)	…

CCI, Charlson comorbidity index; *BMI*, body mass index. Women with missing data on covariates/baseline characteristics were excluded from the study population. Thus, missing data is not presented in the table

difference over the next 3 years. The ROSE controls (B) and age-matched general population (C) were overall comparable with regard to initiation (Fig. 3 and Supplementary Table SI3).

Implementation (MPR) and persistence/discontinuation of AOM

The analysis of treatment implementation (MPR) and persistence/discontinuation included 801 (13.7%) women from the screening group (A) who began AOM medication within 1 year after their DXA scan date. This was alongside 123 (2.1%) women from the control group (B) and 256 (2.2%) women from the age-matched general population (C) (Fig. SI3 and Supplementary Table SI2).

In all groups, more than half maintained an MPR ≥ 80% during the first 5 years after initiation of AOM treatment, and the proportion with MPR ≥ 80% remained above 40% (> 40 per 100 person-years) throughout the study period (Fig. SI4). No statistically significant differences in time to insufficient implementation (MPR < 80%) were found between any of the groups (Supplementary Table SI3).

Moreover, once treatment had been initiated, we observed only minimal differences in persistence between the ROSE participants. Hence, persistence 1 year after initiation was 83% (83 per 100-person years) in screened (A) and 87% (87 per 100 person-years) in controls (B) (Fig. 2). The difference was not statistically significant (Supplementary Table SI3). However, the ROSE participants (A and B) had a 33–51% lower discontinuation rate compared to the age-matched general population (C) during the first year of follow-up (adjusted HR comparing discontinuation in group A vs. C: 0.67 (95%CI: 0.50;0.91) and in group B vs. C: 0.49 (95% CI 0.28;0.86)) (Supplementary Table SI3). All groups had a 5-year persistence of more than 40%, ranging from about 50% (51–52 per 100 person-years) in ROSE participants (A and B) to 44% (44 per 100-person years) in the age-matched general population (C) (Fig. 2 and Fig. 4).

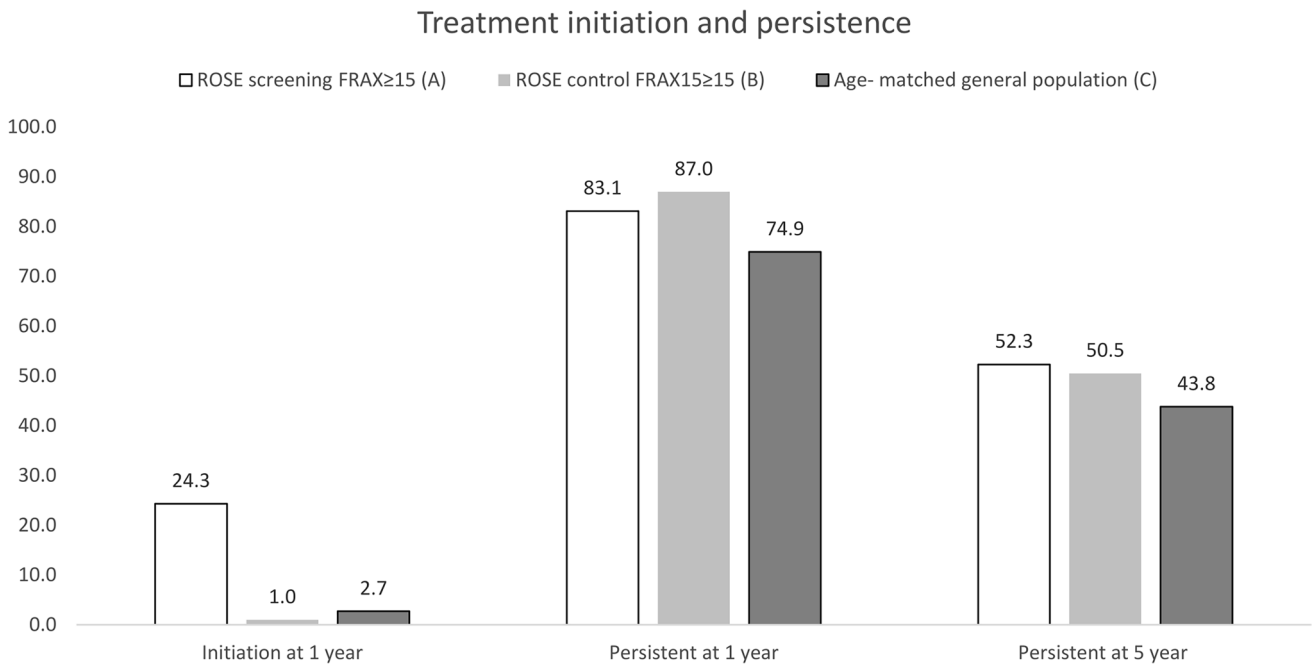

Fig. 2 Initiation of AOM at year one and persistence at years one and five for (A) ROSE screening FRAX ≥ 15 (white bar), (B) ROSE control FRAX ≥ 15 (light grey bar), and (C) age-matched general population (dark grey bar). Treatment initiation was calculated by the cumulative incidence function using the Aalen-Johansen estimator. The analysis was adjusted for delayed entry. The entry date was the DXA scanning date or an imputed date for non-scanned. Thus, only women who did not initiate AOM treatment, die, or emigrate before the entry date were included in the risk set analysing AOM initiation. Persistence was calculated by the survival probability using Kaplan–Meier. Only women who initiated AOM treatment within 1 year after the date of the DXA scan or an imputed date for non-scanned were included in the analyses assessing treatment persistence

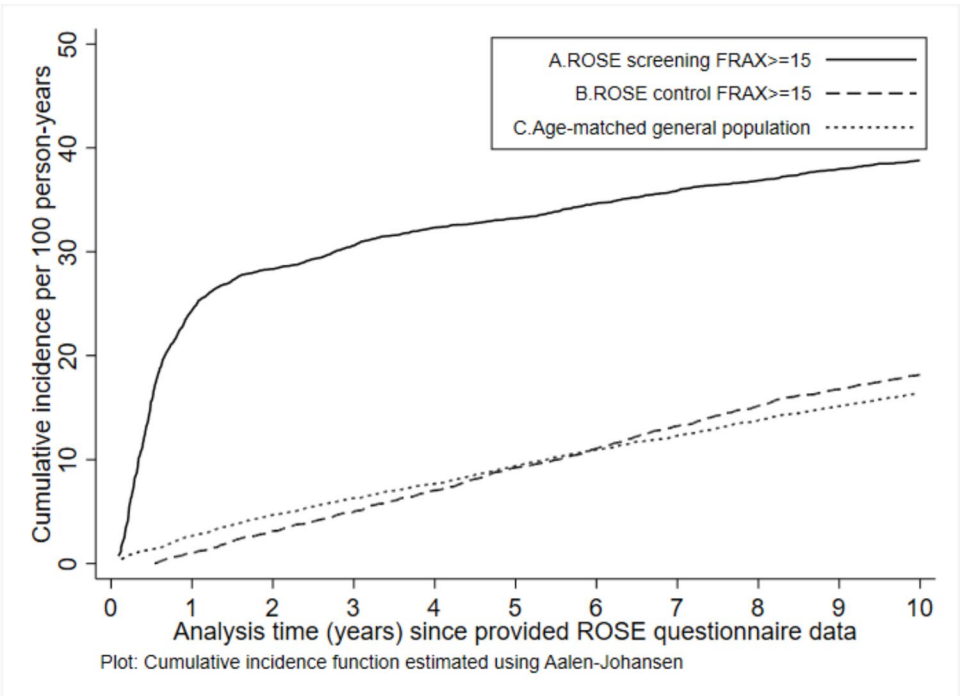

Fig. 3 Cumulative incidence function: initiation of AOM treatment over time for (A) ROSE screening FRAX ≥ 15 (solid line), (B) ROSE control FRAX ≥ 15 (dashed line), and (C) age-matched general population (dotted line)

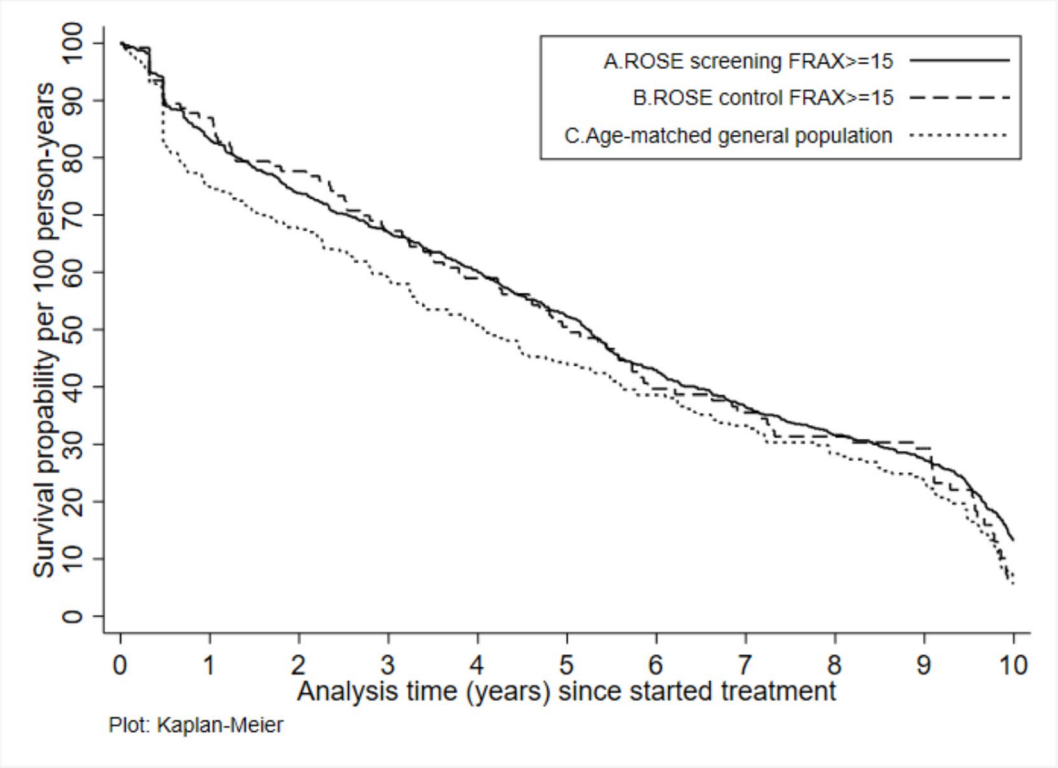

Fig. 4 Kaplan–Meier: probability of persistence of AOM treatment over time for (A) ROSE screening FRAX ≥ 15 (solid line), (B) ROSE control FRAX > = 15 (dashed line), and (C) age-matched general population (dotted line)

Specific factors (determinants) associated with treatment initiation and discontinuation

Determinants for initiation of AOM

We identified the following factors as significantly increasing the rate of AOM initiation after 1 year in the screening group (A) (Supplementary Table SI4): prior fracture, current smoking, BMI ≤ 19, and indication for AOM treatment based on the DXA scan. By contrast, the AOM initiation rate was significantly lower in obese women and in those prescribed four co-medications or more. In the ROSE control group (B) - where DXA was not automatically requested in the presence of FRAX value over 15% - we observed a somewhat different pattern of AOM initiation where the initiation rate was higher in women with seven co-medications or more, glucocorticoid users, those with one or more comorbidities or BMI ≤ 19, with no influence of prior fracture or smoking. In the age-matched general population (C), only glucocorticoid use and having one comorbidity were associated with an increased initiation rate (Supplementary Table SI4).

Determinants for discontinuation (non-persistence) of AOM

Immobilization, comorbidities, and co-medication were the main determinants of short- and long-term discontinuation. Hence, in the ROSE screening group (A), the use of multiple additional medications (≥ 4), the presence of comorbidities (≥ 2), and long-term immobilization were associated with higher discontinuation rates within the first year, indicating early discontinuation. In controls (B), only co-medication was associated with higher discontinuation rates within the first year, while no determinants of early discontinuation were found in the age-matched general population (C), but estimates were imprecise (Supplementary Table SI5). Similar patterns were observed for discontinuation after 2 years in the screening group (A). For the control group (B), no determinants of late discontinuation were found, while in the age-matched general population (C), being unmarried/living alone and co-medication were associated with higher discontinuation rates after 2 years (Table 2).

Table 2 Analysis of determinants for discontinuation of AOM (non-persistence) during year 2–10 after initiation

	A. ROSE screening: FRAX ≥ 15%	B. ROSE control: FRAX ≥ 15%	C. Age-matched general population
Determinants	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age			
65–69	1 (ref)	1 (ref)	1 (ref)
70–74	1.10 (0.88;1.36)	1.16 (0.66;2.02)	1.03 (0.69;1.54)
75 +	1.13 (0.90;1.42)	1.25 (0.73;2.15)	1.18 (0.77;1.80)
Continuous	1.01 (0.99;1.03)	1.01 (0.96;1.06)	1.01 (0.97;1.05)
Unmarried/living alone	0.87 (0.72;1.06)	1.08 (0.68;1.72)	**1.46 (1.03;2.05)**
Family income (percentiles)			
Low tertile	0.99 (0.79;1.24)	0.68 (0.39;1.16)	1.24 (0.82;1.88)
Middle tertile	1 (ref.)	1 (ref.)	1 (ref.)
High tertile	0.81 (0.63;1.03)	0.71 (0.39;1.31)	1.14 (0.73;1.78)
Household educational level			
Lower secondary	0.89 (0.72;1.09)	**0.48 (0.29;0.81)**	**0.62 (0.43;0.88)**
Upper secondary	1 (ref)	1 (ref)	1 (ref)
Post-secondary	1.02 (0.76;1.37)	0.81 (0.39;1.69)	0.73 (0.41;1.31)
Co-medication			
0–3	1 (ref.)	1 (ref.)	1 (ref.)
4–6	**1.33 (1.06;1.66)**	0.55 (0.27;1.13)	1.33 (0.87;2.05)
≥ 7	**1.33 (1.04;1.71)**	1.02 (0.56;1.85)	**1.87 (1.21;2.91)**
Glucocorticoids	0.79 (0.53;1.19)	0.92 (0.49;1.74)	0.68 (0.39;1.20)
Psychotropic medication	1.19 (0.93;1.51)	1.28 (0.72;2.27)	1.29 (0.83;2.02)
CCI			
0	1 (ref)	1 (ref)	1 (ref)
1	**1.51 (1.06;2.15)**	1.24 (0.70;2.21)	1.34 (0.88;2.06)
≥ 2	**1.82 (1.10;3.01)**	1.27 (0.55;2.96)	1.61 (0.76;3.43)
Previous fracture	1.26 (0.97;1.63)	0.51 (0.24;1.10)	
Parental hip fracture	1.03 (0.80;1.33)	1.61 (0.85;3.04)	
Current smoker	1.00 (0.78;1.27)	1.39 (0.75;2.56)	
Rheumatoid arthritis	0.91 (0.59;1.41)	1.07 (0.52;2.17)	
Condition related to secondary osteoporosis	1.04 (0.84;1.29)	0.95 (0.57;1.59)	
BMI			
≤ 19 kg/m^2	1.14 (0.86;1.52)	1.36 (0.64;2.88)	
20–24 kg/m^2	1 (ref.)	1 (ref.)	
25–29 kg/m^2	1.07 (0.86;1.32)	1.23 (0.71;2.14)	
≥ 30 kg/m^2	1.34 (0.93;1.92)	0.96 (0.42;2.20)	
Early menopause	0.98 (0.78;1.22)	1.42 (0.87;2.33)	
Increased fall-risk	1.17 (0.80;1.69)	1.57 (0.67;3.64)	
Long-term immobilization	**1.36 (1.04;1.79)**	1.00 (0.54;1.86)	
Indication for AOM treatment after DXA	1.13 (0.85;1.51)	NE	

CCI, Charlson comorbidity index; *BMI*, body mass index; *NR*, not reported due to insufficient numbers; *NE*, no estimate

Hazard ratios (HR) were estimated using Cox regression. The estimates are presented with 95% confidence intervals (95% CI)

No potential confounders were identified for age, parental hip fracture, and early menopause

Assessing marital status and family educational level as risk factors, the analyses were adjusted for age. Assessing family income as a risk factor, the analysis was adjusted for age and family educational level

Assessing BMI, current smoking status, CCI, and psychotropic medication as risk factors, the analyses were adjusted for age, CCI, and family income

Assessing co-medication, glucocorticoids, previous fracture, rheumatoid arthritis, and condition related to secondary osteoporosis as risk factors, the analyses were adjusted for age, CCI, family income, and family educational level

Assessing fall risk and long-term immobilization as risk factors, the analyses were adjusted for age, CCI, co-medication, family income, and family educational level

Discussion

The population-based screening programme led to a rapid and higher AOM initiation in screened compared to controls, highlighting the ROSE programme's effectiveness in treatment uptake. We hypothesized that motivation to maintain treatment adherence might be lower in those who start treatment due to screening rather than seeking assessment and treatment on their own. Reassuringly, persistence in the ROSE screening group was similar to that in non-screened AOM users, suggesting that screening-initiated treatment does not reduce long-term adherence. Utilization of an age-matched general population as a comparison group, which was not influenced by being invited to the ROSE trial or having completed the FRAX questionnaire, confirmed the programme's findings are applicable to the background population.

An assessment of determinates of AOM initiation in the ROSE study arms revealed distinct patterns. In the screening group, treatment initiation was to some extend influenced by FRAX risk factors, such as smoking, prior fractures, and BMI, which increased FRAX scores, prompting DXA scans and subsequent treatment initiation. In contrast, the ROSE control group generally initiated treatment (following DXA requested by their GP outside the ROSE setup) if they were glucocorticoid users and had multiple co-medications/comorbidities or low BMI. Age was not a significant factor, likely due to the age-homogeneous sample with FRAX ≥ 15%. Furthermore, findings indicated that women in the ROSE population with increased co-medication usage and comorbidities, and who were immobile, in particular, encounter challenges in maintaining high adherence, as these factors occurred as significant determinants for both early and long-term discontinuation. Interestingly, similar findings were not observed in the age-matched women from the general population. Differences in indicated determinants may partly stem from statistical imprecision within specific groups due to few events. In addition, the restriction of ROSE participants to those with FRAX ≥ 15% may affect the generalizability of findings regarding determinants for treatment discontinuation to the general population.

Our study extends Høiberg et al.'s 2019 [6] study on AOM adherence in the ROSE screening programme by doubling the follow-up period to approximately 10 years. This longer follow-up enhances understanding of long-term adherence and provides more resolving power for identifying barriers to effective treatment. Unlike the earlier study, which only assessed tablet forms of bisphosphonates and strontium ranelate (M05 subgroups), we evaluated a broader range of AOM treatments, including tablets and injections, aligning more closely with current clinical practice. Despite these differences, both studies consistently found no adherence differences between the screening and control groups after medication initiation.

In a 2019 study [16], women aged 70–85 from the SCOOP trial, assessing the effectiveness of an osteoporotic screening programme, were followed for 5 years to evaluate self-reported adherence. Like the ROSE study, treatment recommendations were based on FRAX and DXA results, and treatment allocation was not controlled by the trial. However, in contrast to ROSE, screened women showed higher adherence than controls after initiating treatment.

It remains concerning from a public health perspective that over 40% of women meeting the national criteria for osteoporosis treatment failed to complete 5 years of osteoporosis treatment, though adherence rates exceeded expectations from the literature. For oral bisphosphonates, the first line of osteoporosis treatment in Denmark, a systematic review [29] of 89 studies across 15 countries, reported 21–40% 3-year mean persistence, while we found 52% completed 5-year treatment in the screening group. For parenteral osteoporosis therapies, another systematic review [30] found persistence rates of 20–54% for the third dose of zoledronic acid (equivalent to 3 years of treatment) and 55% for the fourth dose of denosumab (2 years of treatment, weighted average of the studies).

Consistent with our findings, the SCOOP study found that FRAX components were associated with increased likelihood of starting on AOM treatment [16]. A nationwide Danish study by Hansen et al. [5], including individuals aged ≥ 35, found that increasing number of co-medications used and the present of comorbidities were associated with increased likelihood of being early quitter of AOM treatment, supporting our findings. However, associations with income, age, and fracture history seen in Hansen et al. [5] were not observed in ROSE. A 2018 systematic review showed that poorer adherence was mainly associated with co-medications, no fall history, therapy-related factors, older age, misconceptions about osteoporosis, care under different medical specialties, lack of patient education and medical insurance, and smoking [12].

A major strength of this study is its large population-based randomized control trial design, which allowed us to assess the ROSE programme's effectiveness in a real-world setting and compare it to standard care. Randomization likely minimized bias from confounding, even though less than one-third of the invited ROSE participants were eligible for the analyses due to subsequent selection and restriction to FRAX ≥ 15%. Another important strength is that the Danish nationwide registers ensured nearly complete follow-up and high-quality data on AOM treatment [19, 31]. Additionally, using dispensing data instead of prescribed drug data may have reduced misclassification, although we cannot confirm whether the subjects actually took the medication as

prescribed. Finally, we could not account for planned drug holidays, which typically occur after 3 to 5 years of bisphosphonate treatment in low-risk patients [32]. This limitation may have led to an overestimation of insufficient implementation and discontinuation rates. On the other hand, persistence beyond 5 years is probably preferable in many high risk patients [33].

Conclusion

In conclusion, the ROSE screening programme significantly increases treatment initiation in postmenopausal women meeting Danish osteoporosis guidelines. Treatment persistence was better than expected. The findings suggest that being identified as a candidate for osteoporosis treatment through a screening programme, rather than by actively seeking an assessment from a general practitioner, does not affect treatment implementation. However, particular attention should be given to the frailer subgroup of women who are on polypharmacy, have significant comorbid conditions, or have long-term immobilization, as these factors link to poorer outcomes in terms of treatment discontinuation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07436-x.

Acknowledgements The ROSE study was jointly funded by INTERREG (4A JNR 08/4177), the Region of Southern Denmark (JNR 08/8133), and Odense University Hospital (JNR 11/5761). We extend our gratitude to the organizations for their financial support.

Funding Open access funding provided by University of Southern Denmark. The study was supported by INTERREG (4A JNR 08/4177), the Region of Southern Denmark (JNR 08/8133), and Odense University Hospital (JNR 11/5761).

Data availability The data underlying this article cannot be shared publicly due to the data-sharing regulations of Statistics Denmark concerning individual data. Aggregated data (results) and do-files can be extracted and shared upon request by emailing the corresponding author.

Declarations

Ethics approval The study is approved by the Regional Committee on Health Research Ethics for Southern Denmark (jr.nr S-20090127) and Danish Data Protection Agency.

Informed consent The Regional Committee on Health Research Ethics approved the data collection for the ROSE trial through questionnaires. Women in the ROSE screening group invited for DXA received both oral and written information before signing informed consent.

Conflict of interest TGP and KHR have no conflict of interest to disclosure. BA has received institutional grants from UCB, Pharmacosmos, and Kuowa-Kirin, consulting fees from UCB and Kuowa-Kirin, and lecture fees from Gedeon-Richter. KEÅ has received lectures without fees from Amgen, UCB, and Honoraria Astellas Pharma. MKJ has received institutional/ personal consulting fees/support from UCB, Amgen, UCB, Abbvie, Besin Healthcare, and Sanofi. APH has received a fee for lectures from UCB, AMGEN, Gideon Richter, a travel grant from UCB, and payment for participation on board from UCB, Gideon Richte.

References

1. Chotiyarnwong P, McCloskey EV, Harvey NC, Lorentzon M, Prieto-Alhambra D, Abrahamsen B et al (2022) Is it time to consider population screening for fracture risk in postmenopausal women? A position paper from the international osteoporosis foundation epidemiology/quality of life working group. Arch Osteoporos 17(1):87. https://doi.org/10.1007/s11657-022-01117-6
2. Vestergaard P, Rejnmark L, Mosekilde L (2005) Osteoporosis is markedly underdiagnosed: a nationwide study from Denmark. Osteoporos Int 16(2):134–141. https://doi.org/10.1007/s00198-004-1680-8
3. Høiberg MP, Rubin KH, Gram J, Hermann AP, Brixen K, Haugeberg G (2015) Risk factors for osteoporosis and factors related to the use of DXA in Norway. Arch Osteoporos 10:16. https://doi.org/10.1007/s11657-015-0220-9
4. Fardellone P, Lello S, Cano A, de Sá Moreira E, Watanabe de Oliveira R, Julian GS et al (2019) Real-world adherence and persistence with bisphosphonate therapy in postmenopausal women: a systematic review. Clin Ther 41(8):1576–88. https://doi.org/10.1016/j.clinthera.2019.05.001
5. Hansen C, Pedersen BD, Konradsen H, Abrahamsen B (2013) Anti-osteoporotic therapy in Denmark–predictors and demographics of poor refill compliance and poor persistence. Osteoporos Int 24(7):2079–2097. https://doi.org/10.1007/s00198-012-2221-5
6. Høiberg MP, Rubin KH, Holmberg T, Rothmann MJ, Möller S, Gram J et al (2019) Use of antiosteoporotic medication in the Danish ROSE population-based screening study. Osteoporos Int 30(6):1223–1233. https://doi.org/10.1007/s00198-019-04934-7
7. Rubin KH, Holmberg T, Rothmann MJ, Høiberg M, Barkmann R, Gram J et al (2015) The risk-stratified osteoporosis strategy evaluation study (ROSE): a randomized prospective population-based study. Design and baseline characteristics. Calcif Tissue Int 96(2):167–79. https://doi.org/10.1007/s00223-014-9950-8
8. Petersen TG, Abrahamsen B, Høiberg M, Rothmann MJ, Holmberg T, Gram J et al (2024) Ten-year follow-up of fracture risk in a systematic population-based screening program: the risk-stratified osteoporosis strategy evaluation (ROSE) randomised trial. EClinicalMedicine 71:102584. https://doi.org/10.1016/j.eclinm.2024.102584
9. Kanis JA on behalf of the World Health Organization Scientific Group (2007) Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization

Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield
10. Dansk Knoglemedicinsk Selskab (2012) Vejledning til udredning og behandling af Osteporose. Available from: https://www.dansk knogleselskab.dk/wp-content/uploads/2019/10/Samlet-osteoporose_180913.pdf. Accessed 2023-11-07
11. Rubin KH, Rothmann MJ, Holmberg T, Høiberg M, Möller S, Barkmann R et al (2018) Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study. Osteoporos Int 29(3):567–578. https://doi.org/10.1007/s00198-017-4326-3
12. Yeam CT, Chia S, Tan HCC, Kwan YH, Fong W, Seng JJB (2018) A systematic review of factors affecting medication adherence among patients with osteoporosis. Osteoporos Int 29(12):2623–2637. https://doi.org/10.1007/s00198-018-4759-3
13. Salter C, McDaid L, Bhattacharya D, Holland R, Marshall T, Howe A (2014) Abandoned acid? Understanding adherence to bisphosphonate medications for the prevention of osteoporosis among older women: a qualitative longitudinal study. PLoS One 9(1):e83552. https://doi.org/10.1371/journal.pone.0083552
14. McAlister FA, Ye C, Beaupre LA, Rowe BH, Johnson JA, Bellerose D et al (2019) Adherence to osteoporosis therapy after an upper extremity fracture: a pre-specified substudy of the C-STOP randomized controlled trial. Osteoporos Int 30(1):127–134. https://doi.org/10.1007/s00198-018-4702-7
15. Friesen KJ, Bugden S, Falk J (2020) Time to benefit and the long-term persistence of new users of oral bisphosphonates. J Bone Miner Metab 38(3):371–377. https://doi.org/10.1007/s00774-019-01069-x
16. Parsons CM, Harvey N, Shepstone L, Kanis JA, Lenaghan E, Clarke S et al (2020) Systematic screening using FRAX(®) leads to increased use of, and adherence to, anti-osteoporosis medications: an analysis of the UK SCOOP trial. Osteoporos Int 31(1):67–75. https://doi.org/10.1007/s00198-019-05142-z
17. Pedersen CB (2011) The Danish civil registration system. Scand J Public Health 39(7 Suppl):22–25. https://doi.org/10.1177/1403494810387965
18. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H (2011) Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health 39(7 Suppl):12–16. https://doi.org/10.1177/1403494811399956
19. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M (2017) Data resource profile: the Danish national prescription registry. Int J Epidemiol 46(3):798–798f. https://doi.org/10.1093/ije/dyw213
20. Lynge E, Sandegaard JL, Rebolj M (2011) The Danish national patient register. Scand J Public Health 39(7 Suppl):30–33. https://doi.org/10.1177/1403494811401482
21. Rothmann MJ, Möller S, Holmberg T, Højberg M, Gram J, Bech M et al (2017) Non-participation in systematic screening for osteoporosis-the ROSE trial. Osteoporos Int 28(12):3389–3399. https://doi.org/10.1007/s00198-017-4205-y
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383. https://doi.org/10.1016/0021-9681(87)90171-8
23. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P et al (2011) Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 173(6):676–682. https://doi.org/10.1093/aje/kwq433
24. Burden AM, Paterson JM, Gruneir A, Cadarette SM (2015) Adherence to osteoporosis pharmacotherapy is underestimated using days supply values in electronic pharmacy claims data. Pharmacoepidemiol Drug Saf 24(1):67–74. https://doi.org/10.1002/pds.3718
25. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T et al (2012) A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol 73(5):691–705. https://doi.org/10.1111/j.1365-2125.2012.04167.x
26. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA et al (2008) Medication compliance and persistence: terminology and definitions. Value Health 11(1):44–47. https://doi.org/10.1111/j.1524-4733.2007.00213.x
27. Rasmussen L, Wettermark B, Steinke D, Pottegård A (2022) Core concepts in pharmacoepidemiology: measures of drug utilization based on individual-level drug dispensing data. Pharmacoepidemiol Drug Saf 31(10):1015–1026. https://doi.org/10.1002/pds.5490
28. Coemans M, Verbeke G, Döhler B, Süsal C, Naesens M (2022) Bias by censoring for competing events in survival analysis. BMJ 378:e071349. https://doi.org/10.1136/bmj-2022-071349
29. Fatoye F, Smith P, Gebrye T, Yeowell G (2019) Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review. BMJ Open 9(4):e027049. https://doi.org/10.1136/bmjopen-2018-027049
30. Koller G, Goetz V, Vandermeer B, Homik J, McAlister FA, Kendler D et al (2020) Persistence and adherence to parenteral osteoporosis therapies: a systematic review. Osteoporos Int 31(11):2093–2102. https://doi.org/10.1007/s00198-020-05507-9
31. Kildemoes HW, Sørensen HT, Hallas J (2011) The Danish national prescription registry. Scand J Public Health 39(7 Suppl):38–41. https://doi.org/10.1177/1403494810394717
32. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F et al (2012) The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 27(2):243–254. https://doi.org/10.1002/jbmr.1494
33. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA et al (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the fracture intervention trial long-term extension (fleX): a randomized trial. JAMA 296(24):2927–2938. https://doi.org/10.1001/jama.296.24.2927