Osteoporosis International (2019) 30:1223–1233
https://doi.org/10.1007/s00198-019-04934-7

ORIGINAL ARTICLE

Use of antiosteoporotic medication in the Danish ROSE population-based screening study

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Received: 6 July 2018 / Accepted: 5 March 2019 / Published online: 26 March 2019

Abstract

Summary Use of antiosteoporotic medication in the population-based, risk-stratified osteoporosis strategy evaluation (ROSE) screening study, comparing the use of FRAX followed by DXA with usual care, was examined. Screening increased the overall use of medication. Being recommended treatment by the hospital and higher age increased the likelihood of starting medication, but, nevertheless, a large percentage opted not to start treatment.

Introduction The aim of the study was to examine the impact on medication prescription, adherence, and persistence of osteoporotic medicine in the randomized population-based ROSE screening study for osteoporosis.

Methods The Danish ROSE study included a population-based random sample of women aged 65–81 years randomized to either a two-step screening program consisting of FRAX followed by DXA for high-risk participants or opportunistic screening for osteoporosis (usual care). This sub-study on the intention-to-treat population examined the impact of the screening program on antiosteoporotic medication redemption rates, adherence, and persistence using Danish registers.

Results A total of 30,719 of 34,229 women were treatment-naïve. Significantly more participants in the screening group started on antiosteoporotic medication, but no differences in adherence and persistence rates were found. Higher age was associated with a higher likelihood of starting medication. A low Charlson comorbidity score (= 1) was associated with higher treatment initiation but lower adherence and persistence of antiosteoporotic treatment. A total of 31.7% of participants advised to initiate treatment did not follow the advice.

Conclusions Screening for osteoporosis using FRAX followed by DXA increased the overall use of antiosteoporotic medication in the screening group without differences in adherence and persistence rates. A large percentage of participants advised to initiate treatment did nevertheless fail to do so.

Keywords Adherence · Compliance · Medication · Osteoporosis · Persistence · Population-based screening

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-019-04934-7) contains supplementary material, which is available to authorized users.

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Introduction

One in three women and one in six men will suffer at least one osteoporotic fracture during their lifetime [1]. Osteoporosis is clinically silent until a fracture occurs. To reduce fracture incidence rates, individuals at risk of fractures need to be identified and preventive measures (e.g., antiosteoporotic treatment) need to be administered. Examination rates for osteoporosis even among high-risk populations in Denmark [2] and Norway [3] have previously been shown to be suboptimal. Risk factor–based algorithms such as the Fracture Risk Assessment Tool (FRAX) is a feasible way of identifying potentially high-risk groups/individuals in the general population [4] and might be used in population-based screening, aiming at optimizing osteoporosis care.

An effective prescreening tool would be expected to lead to identification of a higher number of individuals with osteoporosis, either through an increase in overall examination rate or, preferably, through a more effective identification of high-risk individuals, before diagnostic examination [4]. A screening program will not be effective in preventing fractures if increased diagnostic rates are not followed by an increase in the prescription rate of antiosteoporotic drugs [5]. Often, optimal adherence to therapy is taken for granted by health personnel, even though it is well known that adherence to therapy is suboptimal in chronic conditions such as osteoporosis and numerous determinants for non-adherence have previously been identified [6, 7]. Pharmaceutical claims data documents a positive association between compliance with treatment and fracture incidence only in patient groups with medical possession ratio (MPR) above 0.5, with increasing effect above 0.75 [8–10]. However, real world adherence to antiosteoporotic treatment seems less than optimal, with a meta-analysis showing adherence rates in the 50% range already after 6 months treatment [11]. Thus, the prerequisite of an effective prevention program for osteoporosis is a global improvement of one or more of the following factors: screening rate, prescription rate, and adherence to prescribed treatment.

This paper reports the medication rates and adherence to therapy in the Danish ROSE study (risk-stratified osteoporosis strategy evaluation), one of the first population-based screening programs for osteoporosis [12]. The ROSE study consisted of a two-step screening process using the FRAX risk tool as a prescreening tool before diagnostic osteodensitometry by dual x-ray absorptiometry (DXA) in a population-based setting, aiming to reduce overall fracture incidence rates. Compared to usual care, more participants in the screening group were verified with osteoporosis in the intervention group and treatment advice was given to patients and GPs, but it is not known to what extent this advice was followed. This element is of particular importance given that the screening program was dependent upon a well-functioning primary-secondary care interface, with screening initiated in specialist care, but with treatment responsibility being handed over to primary care. Problems in this interface have been known to hamper health care integration [13], which in this setting could lead to lower treatment uptake, adherence, and persistence rates.

Therefore, the aim of this study is to (a) examine whether identification of women with previously unknown osteoporosis led to an overall increase in redemption of antiosteoporotic medicine,

(b) investigate if being randomized to the screening group had an effect on adherence and persistence to therapy, and (c) illuminate whether comorbidity, socio-economic and—demographic factors are associated with the prescription and continued usage of antiosteoporotic medicine.

Methods

The ROSE study (risk-stratified osteoporosis strategy evaluation) examined the effect of a two-step screening process. The study design has previously been described [12]. Briefly, the ROSE study included a population-based random sample of 34,229 women aged 65–81 years living in the Region of Southern Denmark that was randomized to usual care or to the abovementioned two-step screening program for osteoporosis. Treatment of osteoporosis was in concord with Danish national guidelines, stating that treatment of osteoporosis should primarily take place in primary care.

Inclusion period was from February 2010 to November 2011. The index date was defined as the date the questionnaire was mailed to the participant. Participants were stratified according to area of residence and age and randomized 1:1 to either a control group or an intervention group before entering the study. Participants were mailed a 25-item questionnaire about risk factors for osteoporosis, useable to calculate the FRAX 10-year fracture risk. The intervention group was afterward invited to participate in a screening program for osteoporosis. Participants completing the questionnaire (79%, [14]), agreeing to partake in further examinations and with a calculated FRAX 10-year risk of major osteoporotic fractures above 15%, were invited to a diagnostic DXA scan. All scanned participants were informed about DXA results by mail, and participants diagnosed with osteoporosis were urged to visit their GP to initiate treatment. The GP in question was also informed by mail about the results, including recommendations for treatment of osteoporosis in concord with the Danish national guidelines [15]. These guidelines state that treatment of osteoporosis should primarily take place in primary care and in most cases through the prescription of oral alendronate once weekly. As the aim of the ROSE study was to examine only the effect of the screening program, treatment and follow-up of patients in both the screening and control arm were in line with national guidelines and therefore the responsibility of the GPs. Thus,

treatment, choice of treatment, and patient information to ensure proper use of treatment were still at the discretion of the individual primary care provider.

Participation in the study was voluntary and free of charge, as all other health services in Denmark that are funded via the public taxation system. Co-payment exists for medication, with gradually lowering of the co-payment with higher use of prescription medication. The first choice for treatment of osteoporosis is generic alendronate 70 mg once weekly with a yearly co-payment of on average DKK 200 (approx. 30 USD).

DXA scans were performed using Hologic Discovery, Hologic Delphi, or Lunar Prodigy scanners as earlier described [12]. The scanners used in the study were the only available scanners covering the included geographical area of the health region of interest.

Data sources and variables

This study includes questionnaire data and registry data from several national health and socio-demographic registers.

Questionnaire data

The self-administered questionnaire contained items on anthropometry as well as risk factors for and history of fractures and osteoporosis. It had previously been validated in a similar setting [16]. On the basis of the questionnaire, the FRAX 10-year probability of major osteoporotic fractures was calculated and used for screening participants in the intervention arm with moderate to high risk of future fractures, to whom further examination by DXA was recommended, as previously reported [17].

National Health Registers

The entire Danish population is registered either at birth or at time of migration to Denmark in the central person register. Using the central person register, it is possible to link the information from all other population-registers, e.g., containing individualized information about education, employment, income, inpatient and outpatient visits, cause of death and prescription medicine registers, the completeness of which is previously described [18].

The Danish National Patient Registry (NPR)

The NPR contains data on all patients admitted to Danish hospitals since 1977. The register covers both inpatient and outpatient records and indicates the main medical reason for diagnostic procedures or treatment (since 1994 according to the tenth version of the International Classification of Diseases (ICD-10)) [19]. For this study, we extracted data from NPR from 1995 to February 2016.

Danish national prescription registry

Data on prescription rates of antiosteoporotic drugs were accessed through the Danish National Prescription Registry. The registry contains complete information from January 1995 and onwards on all prescriptions filled by Danish residents at outpatient pharmacies [20]. For every individually filled prescription, drug type, quantity, and date of purchase are registered. Drug type is categorized according to anatomic therapeutic chemical (ATC) index. The quantity dispensed for each prescription is expressed as the defined daily dose (DDD) measure developed by WHO [21]. The registry is reported to have high completeness and validity [20].

Comorbidity data

Data on comorbidity data were drawn from the NPR [19]. Comorbidity data were used to derive Charlson comorbidity index as previously defined [22]. All registered comorbidity codes on each participant from 1995 until the date of entry into the study were applied retrospectively, categorizing the Charlson index into 0, 1, and ≥ 2.

Outcome: prescription of antiosteoporotic medicine

Data on prescription rates of antiosteoporotic drugs were accessed through the Danish National Prescription Registry. Treatment in the ROSE study was prescribed by GPs in accordance with national guidelines. The national guidelines recommend the use of oral antiresorptive drugs, preferably alendronate, as the first-line drug of choice. Therefore, drug types of interest for this examination were M05 subgroups (bisphosphonates and strontium ranelate) (shown in Table 2). Calcium and vitamin D formulations (ATC groups A11CC, A12A) were not included, as most sales of these formulations in Denmark are prescription free, and they are considered to be dietary supplements and thus not linked to the central person register. Participants who filled a prescription for one or more of the drug classes mentioned within the last 24 months prior to the index date were deemed active users of antiosteoporotic treatment prior to the study, and treatment not regarded as initiated as a consequence of study participation. As participants in the intervention group with DXA-score close to the guideline-defined intervention threshold T-score of −2.5 (− 2.0 to − 2.5) were rescanned after 1 year, and as there was an average delay between entrance in the study (returning questionnaire) and initial DXA of 205 days (IQ range 118–315 days), prescriptions filled within 2 years of the start of the study participation were likely to be related to the screening program and included in the analysis.

In line with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)'s recommendations [23], the following measures were extracted:

Adherence: through the expression of DDDs compared with duration of time between prescription fills, continuous measure of adherence ratio (CMA) could be calculated using the formula: CMA = number of days of medication supplied over several refill intervals/number of days within refill intervals [24]. Acceptable medication adherence was defined as CMA > 0.8.

Medication persistence: number of days a patient was in possession of a medication to the first gap in the therapy of greater than 90 days [23]. Participants switching from one drug to another during the study period were regarded as adherent as long as CMA was retained above 80% and persistent until the first refill gap exceeding 90 days, in line with earlier studies showing documented effect on fracture rates [8, 10]. Refilling a prescription before the previous refill interval has been exceeded will lead to "hypercompliant values", with MPR exceeding 1 and negative refill gaps, but as definitions of adherence and persistence were based on several refill intervals, such values had no impact on reported measurements.

Socio-demographic data

Data on socio-demographic factors were retrieved from different registers through Statistic Denmark [25]. The maximally achieved level of education on the International Standard Classification of Education [26] was obtained from the population education register categorized into basic school (≤ 10 years), vocational or upper secondary (11–15 years), and further/higher education (> 15 years). Marital status was extracted from the Civil Registration System [27] and classified as married/living with a spouse/living in a registered partnership/cohabiting vs. living alone. Income was extracted from the Income Statistics Registry [28], displaying disposable income after tax and interest (including salaries, retirement benefits, welfare payments, remuneration, company profits), categorized into tertiles (lowest, medium, highest).

The socio-demographic data were extracted with regard to the index year for each woman.

Statistical analyses

To investigate between-group differences in prescription rates of overall antiosteoporotic treatment), chi-squared tests were employed. Logistic regression was used to elucidate which factors that could influence overall prescription rates, both in an unadjusted and a mutually adjusted model. To investigate differences in medication use, we produced graphs of cumulative incidence of adherence (CMA ≥ 0.8) and persistence (permissible gap of 90 days) among the screening and control groups, comparing these with each other. Taking into account the relatively high proportion of participant experiencing death during follow-up, individual adherence (until CMA < 0.8) in the two groups, were modeled using a Fine and Gray competing risk regression model reporting subdistribution hazards. In this way, inferences about the effect of covariates on the incidence of stopping treatment early were possible [29]. FRAX risk score was not included as a correlation-factor in the regression models described as participants were randomized on a population-level, and therefore information about risk factors necessary for the calculation of FRAX risk score was not available for participants not returning the questionnaire.

Ethics

The ROSE study was performed according to the declaration of Helsinki and approved by the local Ethics Committee (jr.nr S-20090127) and the Danish Data Protection Agency (jf.nr. 2008-58-0035). Furthermore, the study was registered in clinicaltrials.gov (NCT01388244).

Results

A flowchart of the overall study design is illustrated in Fig. 1. A total of 30,719 participants of the total population of 34,229 (89.7%) were treatment-naïve at time of randomization and thus possibly eligible for preventive therapy for osteoporosis (intention to treat population). Characteristics of participants are shown in Table 1, with non-significant differences between the screening and control arms regarding age, comorbidity index, income, marital status, and education. As shown in Figs. 1, 827 received treatment as part of the ROSE study in the screening arm, and 507 participants were treated with antiosteoporotic therapy by the GP outside of the ROSE study protocol. Furthermore, a total of 384 participants in the screening group were advised to start treatment but never redeemed a prescription for antiosteoporotic medicine. This equates to 31.7% of the participants in the screening arm advised to start treatment. Use of antiosteoporotic treatment by chosen drug classes is shown in Table 2. In the control group, a total of 608 women started antiosteoporotic therapy during the study period, significantly lower numbers than in the screening group ($p < 0.001$). In line with the national guidelines, the majority of initiated treatment was bisphosphonates, with only 21/10 receiving strontium ranelate in the screening/control groups ($p = 0.046$).

The results of the logistic regression analyses including factors that could influence redemption rates of antiosteoporotic medication in the ROSE study are shown in Table 3. Being randomized to the screening arm was associated with an OR of 2.33 (95% C.I 2.11–2.57) for initiating antiosteoporotic medication in the ROSE study. Women above 70 years of age had significantly higher ORs of starting treatment than women below this age (70–74 years of age, OR 1.23 (95% CI 1.1.0–1.38), 75–81 years, OR 1.36 (95% CI 1.21–1.52)). Women with some comorbidities (Charlson

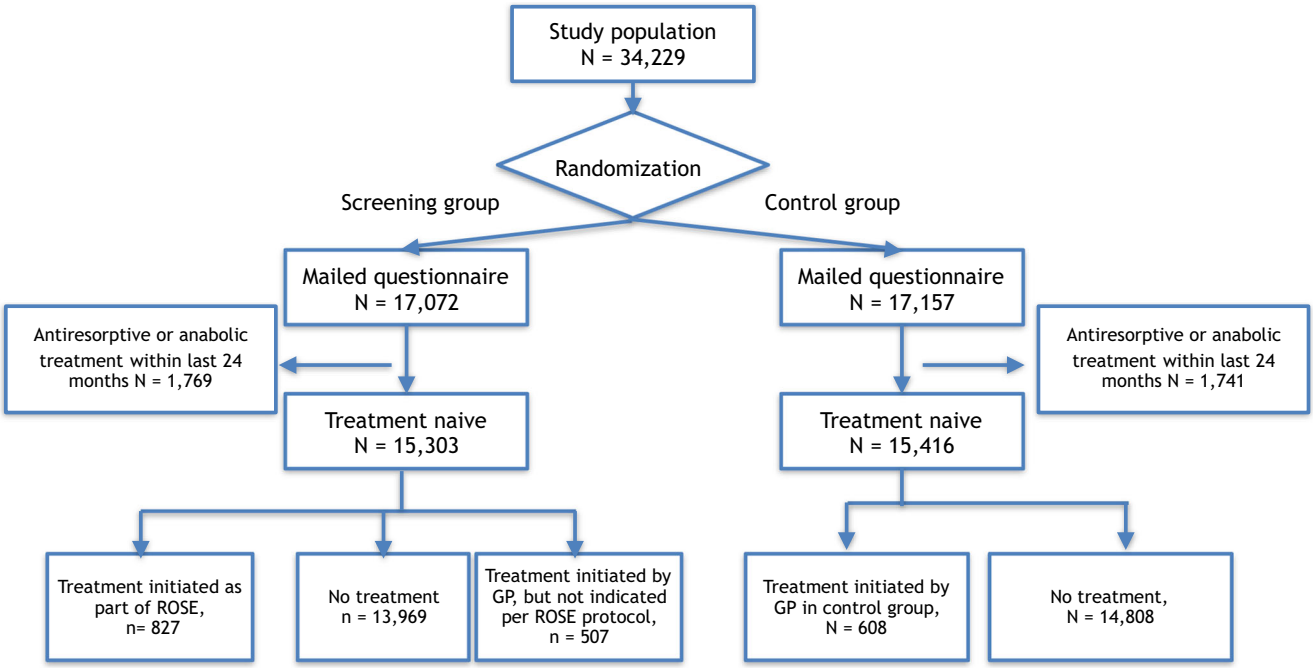

Fig. 1 Overview of study design and proportions initiating antiosteoporotic treatment during the ROSE study, mean follow-up time 5.0 years

comorbidity index equal to 1) had statistically significant higher OR of initiating treatment than women without comorbidity. Among women with more comorbidities (Charlson comorbidity index ≥ 2), a trend towards higher initiation rates was also seen; however, this difference was not statistically significant. No associations on marital status, education, and income in relation to treatment initiation rates were seen. Mutually, adjustment for included risk factors did not change the reported ORs in a significant way.

Figure 2 shows the cumulative incidences of non-adherence (CMA < 0.8) on the basis of a competing risk model. A similar figure for non-persistence (permissible gap of 90 days) can be found in the supplement, as the information provided in these figures is quite similar. As shown, 1-year

Table 1 Characteristics of the 30,719 treatment-naïve women included in the ROSE study

	Intervention (n = 15,303)	Control (n = 15,416)	p value
Age (median, IC range)	71 (68; 75)	71 (67; 75)	0.161
Comorbidity			
Charlson index= 0	11,619 (76%)	11,591 (75%)	0.310
Charlson index = 1	1218 (8%)	1276 (8%)	
Charlson index ≥ 2	2466 (16%)	2549 (17%)	
Income per year (disposable)			0.188
Lowest tertile	5044 (33%)	5195 (34%)	
Intermediate tertile	5179 (34%)	5038 (33%)	
Highest tertile	5078 (33%)	5181 (34%)	
Unknown	< 5	< 5	
Marital status			0.622
Married/living together with spouse	8940 (58%)	8937 (58%)	
Living alone	6362 (42%)	6477 (42%)	
Unknown	< 5	< 5	
Education			0.928
Basic school	8360 (55%)	8476 (55%)	
Vocational or upper secondary	4563 (30%)	4575 (30%)	
Further or higher education	2106 (14%)	2095 (14%)	
Unknown	274 (2%)	270 (2%)	

Table 2 Use of antiosteoporotic medication among the30,719 women. Number of participants filling one or more new prescriptions from study inclusion until 2 years after inclusion

		Intervention ($n = 15,303$)	Control ($n = 15,416$)	p value
Medication groups	Atc codes	N(%)	N (%)	
Total		1334 (8.7%)	608 (3.9%)	< 0.001
Bisphosphonates	M05BAxx + M05BBxx	1319 (8.6%)	601 (3.9%)	< 0.001
Strontium ranelate	M05BX03	21 (0.14%)	10 (0.06%)	0.046

and 2-year cumulative adherence were 70 and 62%, respectively. Similarly, persistence was 77% and 69% for 1- and 2-year periods, with no significant differences between the screening and control groups.

The results of the Fine and Gray competing risk model analysis for adherence and persistence- rates to antiosteoporotic treatment is shown in Table 4. As shown, there was no overall difference between the screening and control arms in relation to adherence (unadjusted SHR 0.93 (95% C.I. 0.82–1.06) and persistence (unadjusted SHR 0.95 (95% C.I. 0.83–1.09). As also seen for treatment initiation, however, women with some comorbidity conditions (Charlson comorbidity index equal to 1) had significantly higher SHR of stopping treatment early than women without comorbidity conditions, both measured by adherence (SHR 1.27 95% C.I. 1.07–1.50) and persistence SHR 1.22 (95% C.I. 1.02–1.46). Women with more comorbidities (Charlson comorbidity index ≥ 2) also showed a trend towards lower adherence and persistence rates than women without comorbidity conditions; however, this difference was not significant. No association between age, marital status, education, income, and adherence or persistence to antiosteoporotic treatment was found. Finally, having treatment endorsed per protocol in the screening arm was associated with an SHR of 0.84 (95% CI 0.74–0.95) for treatment non-adherence and 0.87 (95% CI 0.76–0.99) for treatment non-persistence. Mutually, adjustment for included risk factors did not change the reported SHRs in a significant way.

Discussion

In this substudy of the ROSE study, we reported treatment initiation and -adherence rates for treatment naïve participants,

Table 3 Logistic regression using factors that could influence redemption rates of antiosteoporotic medications in the ROSE study among treatment naïve participants

OR for starting treatment	Unadjusted OR (95% C.I.)	Mutually adjusted OR (95% C.I)
Group (control)	2.33 (2.11, 2.57)	2.33 (2.11, 2.58)
Age		
65–69 years	1 (ref)	1 (ref)
70–74 years	1.23 (1.10, 1.38)	1.21 (1.08, 1.36)
75–81 years	1.36 (1.21, 1.52)	1.32 (1.17, 1.48)
Comorbidity		
Charlson index = 0	1 (ref)	1 (ref)
Charlson index = 1	1.77 (1.54, 2.04)	1.77 (1.53, 2.04)
Charlson index ≥ 2	1.12 (0.98, 1.26)	1.10 (0.97, 1.24)
Marital status		
Married/living with a spouse	1 (ref)	1 (ref)
Living alone	1.13 (1.03, 1.24)	1.08 (0.96, 1.21)
Education		
Basic school	1.02 (0.89, 1.18)	0.95 (0.82, 1.11)
Vocational or upper secondary	1.00 (0.86, 1.17)	0.99 (0.85, 1.16)
Further or higher education	1 (ref)	1 (ref)
Unknown	0.78 (0.52, 1.17)	0.74 (0.49, 1.11)
Income per year (disposable)		
Low tertile	0.98 (0.87, 1.09)	1.03 (0.89, 1.18)
Medium tertile	1.04 (0.93, 1.16)	1.03 (0.91, 1.15)
High tertile	1 (ref)	1 (ref)

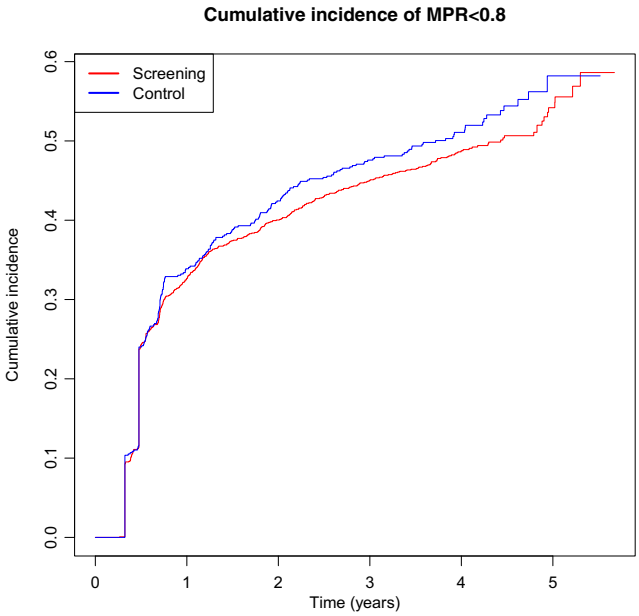

Fig. 2 Cumulative incidence proportion of non-adherence with antiosteoporotic medication in screening and control groups (non-adherence defined as continuous measure of adherence ratio < 0.8)

showing significantly higher overall treatment-rates with antiosteoporotic treatment in the screening group. This is of clinical importance as increasing diagnostic rates for osteoporosis, even after fractures, does not inevitably lead to higher treatment rates [30]. To ensure that differences in treatment initiation rates were indeed related to the screening program, and as some participants were rescanned 1 year after the initial DXA evaluation, and as there was an average delay between returning questionnaires and DXA performance of 205 days (IQ range 118–315), a conservative cutoff for screening-related treatment initiation of 2 years was used in the analyses.

The ROSE study was designed to evaluate the effectiveness of screening for osteoporosis. Thus, while the diagnostic workup in the screening group was hospital-based, the ultimate decision to treat, treatment of choice, and provided information were still at the discretion of the primary physician. Several studies have shown that adherence is higher when treatment is prescribed by hospital-based specialists as compared with GPs [31, 32]. On the other hand, the ROSE study relied on the integration of health care with regard to the primary-secondary care interface, a factor known to be negatively influenced by system complexity [13]. It was thus not known whether the recommendation or advocacy alone of treatment by a hospital specialist, with the prescription of treatment performed by a GP, would have a positive or a negative effect on treatment initiation and adherence.

Adherence rates to antiosteoporotic medicines are suboptimal and vary largely between trials. Thus, a meta-analysis on persistence with denosumab and oral bisphosphonates by Karlsson et al. reports 10–78% one-year and 16–46% 2-year persistence rates [33] for oral bisphosphonates. Using only studies reporting permissible gaps of 90 days or above, the 1 year persistence rates were between 45 and 57%. Kjellberg et al. have previously reported national one-year non-adherence rates with oral bisphosphonates of 29.9% among Danish women aged 55 years and above (derived from prescriptions in the period 2003–2008, using CMA > 70% as a measure of adherence and) [34]. Using data from 1996 to 2008, Hansen et al. examined two-year persistence rates among patients with DXA verified osteoporosis or documented fracture 12 months or less prior to treatment initiation, defining persistence as CMA > 80% [35]. They documented two-year persistence rates of 37% [35]. In contrast to this, Olsen et al. have reported much higher overall persistence rates (CMA > 0.8) of 60% from a Danish nationwide sample of prescriptions with patients starting bisphosphonates in the period of 1997–2006 [10]. Compared to this, Karlsson et al. have reported Swedish 12-months persistence rates on denosumab on 83% (permissible gap of 56 days) [33]. Treatment with denosumab is naturally not directly comparable with bisphosphonates as treatment is physician-based and only requires injections every 6 months. However, it is interesting that even long treatment-intervals are associated with suboptimal persistence rates. For PTH treatment, similar higher numbers have also being reported from a large Danish national registry study (CMA > 80% for 1.5 years, persistence 83% [36]). In Denmark, this treatment is only given to patients with severe established osteoporosis, i.e., either ≥ 1 spinal compression fracture combined with T-score < − 3, alternatively ≥ 2 spinal compression fractures within the last 3 years. As these fractures are often painful and thus clinically apparent to the patient, higher persistence rates are understandable. A large French study of PTH also reported high persistence (permissible gap < 60 days, 1.5 years treatment), but only among participants in an educational program (81.5% vs. national average values of 60%) [37].

Thorsteinsson et al. reported higher PTH adherence rates among married patients and patients still in the labor market [36]. Kjellberg et al. found higher adherence rates among younger patients (55–64 years of age) compared with older patients [34], while studies from Germany [38] and Estonia [39] have found lower adherence rates among younger patients (aged ≤ 60 years). Compared to these results, our adherence- and persistence rates are consistently higher. As rates in the screening- and control group were not statistically significant different, these higher rates of medication adherence and persistence are reassuring.

A not so reassuring finding is the fact that 31.7% of participants advised to initiate treatment in the screening arm did not redeem a prescription for an antiosteoporotic medication, despite willingness to both answer a questionnaire and complete a DXA examination. Reynolds et al. examined the primary non-adherence (PNA) to bisphosphonates among 8454 eligible women aged 55 years and older seen in the Kaiser

Table 4 Fine and Gray competing risk model analysis variables that could influence antiosteoporotic adherence and persistence rates in the ROSE study

SHR for stopping treatment early	Adherence unadjusted SHR (95 %C.I.)	Adherence mutually adjusted SHR (95% C.I.)	Persistence unadjusted SHR (95 %C.I.)	Persistence mutually adjusted SHR (95% C.I.)
Group (control)	0.93 (0.82, 1.06)	0.95 (0.84, 1.09)	0.95 (0.83, 1.09)	0.97 (0.84, 1.11)
Treatment endorsed per protocol (vs. participants in screening group receiving treatment by GP but not indicated per protocol)	0.84 (0.74, 0.95)		0.87 (0.76, 0.99)	
Age				
65–69 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)
70–74 years	0.95 (0.82, 1.11)	0.94 (0.80, 1.09)	0.89 (0.76, 1.05)	0.87 (0.74, 1.02)
75–81 years	1.08 (0.93, 1.25)	1.04 (0.89, 1.22)	1.11 (0.95, 1.29)	1.07 (0.92, 1.26)
Comorbidity				
Charlson index = 0	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Charlson index = 1	1.27 (1.07, 1.50)	1.27 (1.07, 1.50)	1.22 (1.02, 1.46)	1.20 (1.00, 1.45)
Charlson index ≥ 2	1.07 (0.91, 1.27)	1.07 (0.90, 1.26)	0.99 (0.83, 1.18)	0.97 (0.81, 1.15)
Marital status				
Married/living with a spouse vs. living alone	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	1.07 (0.95, 1.21)	1.11 (0.94, 1.30)	1.04 (0.92, 1.19)	1.05 (0.89, 1.24)
Education				
Basic school	0.94 (0.78, 1.12)	0.90 (0.74, 1.10)	1.03 (0.85, 1.24)	0.98 (0.80, 1.21)
Vocational or upper secondary	0.88 (0.72, 1.07)	0.87 (0.71, 1.07)	0.93 (0.75, 1.14)	0.91 (0.74, 1.14)
Further or higher education	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Unknown	1.39 (0.81, 2.39)	1.33 (0.78, 2.29)	1.79 (1.03, 3.09)	1.77 (1.02, 3.08)
Income per year (disposable)				
Low tertile	1.00 (0.86, 1.16)	1.09 (0.90, 1.33)	1.06 (0.90, 1.24)	1.09 (0.89, 1.33)
Medium tertile	0.95 (0.82, 1.10)	0.96 (0.82, 1.13)	1.05 (0.90, 1.23)	1.05 (0.89, 1.24)
High tertile	1 (ref)	1 (ref)	1 (ref)	1 (ref)

Permanente Southern California system from December 2009 to March 2011. PNA was 29.5%, with worse rates among older women and among patients seen by a GP rather than an internist [40]. These numbers are in contrast to PNA rate of 6.5% reported in the Spanish prospective ESOSVAL study [41] for secondary prevention, and 2.8% in the retrospective PREV2FO study of 19,405 patients aged 65 or older patients having experienced a hip fracture (tertiary prevention) [42]. A Danish population-based study has previously examined the primary non-adherence rates of all drugs prescribed by GPs in Denmark in the period from January 2011 to August 2012, finding that overall 9.3% of all prescriptions were not redeemed, with older age and higher income to be associated with lower and polypharmacy with higher rates of PNA. These findings are not directly comparable to our findings, as we did not measure PNA, but instead an aggregate measure of (a) the participant advised to seek information and treatment from her GP actually not doing so, or (b) the GP not prescribing any antiosteoporotic medicine, or (c) true primary non-adherence. The important clinical question to answer is why this large percentage of participants where treatment was clinically indicated did not start the treatment. Kalluru et al. have earlier documented much higher individual fracture risk thresholds for considering preventive medication among patients than what medical societies find appropriate [43]. This, in combination with earlier findings from the ROSE study suggesting a general underestimation of personal fracture risk in the age-group in question [44], might lead to the patient not following the recommendations and thus falling into category a or c. Another factor could be reduced commitment to preventive treatment on behalf of the participant's GP, as the GP himself had not been involved in the decision process to recommend diagnostic examinations or indication for treatment. The present study design precludes us from giving a definitive answer on which of these two reasons is of most importance. Reassuringly, however, is that long-term adherence and persistence rates among patients starting treatment in the screening group are no different from adherence rates in the control group, perhaps indicating that both the patients and the GPs were just as committed to treatment for these patients as in the control group, where both diagnostic examination and treatment were positively endorsed by the GPs. Still, this questions

the sustainability of a screening program where treatment initiation and prescription of medication is not actually being performed by the same person who evaluates the diagnostic examination and concludes with recommending treatment but hands over the responsibility of this treatment to a colleague. Another finding in the present study is that 31.7% of participants given treatment recommendation actually did not start treatment. However, having treatment endorsed by protocol seemed to increase the likelihood of persisting with and adhering to treatment in the screening group, even though this effect was rather small. This should be regarded as a positive finding, though, as this strengthens the notion that the transfer of treatment responsibility to the primary care did not have a large adverse effect on treatment adherence.

Another finding of interest is the fact that some degree of comorbidity increases the likelihood of treatment initiation with antiosteoporotic therapy, but with higher levels of comorbidity, this positive effect disappears. A little puzzling, the same degree of comorbidity (Charlson comorbidity index = 1) increases the risk of early treatment non-adherence, an effect that again cancels out with a higher degree of comorbidity. As the group with Charlson comorbidity index ≥ 2 was much larger (17% with ≥ 2 in Charlson comorbidity index vs. 8% with 1 in the index), it is unlikely that a lack of power is an explanation for this finding. One can consider whether it is in fact positive for initiation rates to be accustomed to regular treatment for other diseases, but at the disease burden goes up, patients might prioritize medications for diseases that are more symptomatic than the often asymptomatic state of disease for osteoporosis. This is a question that needs more exploration and might be important for the clinician discussing treatment adherence with patients suffering from chronical diseases.

Strengths and limitations

A major strength of this study is that it is based on data generated from the ROSE study, a large randomized population-based effectiveness study, minimizing selection bias through the random sampling from the background population of the Region of Southern Denmark and minimizing confounding through the randomized study design with similar sociodemographic baseline characteristics in the screening and control group. The completeness of Danish registries [18] and the possibility of coupling these through the use of the unique central person registry number is a clear strength of the study.

A limitation to the current substudy is the limited overall power as it includes a large number of participants not eligible for treatment in the analyses. Due to the ITT approach,

participants not returning questionnaires and participants in the screening group with FRAX risk score < 15% were not evaluated and thus not eligible for treatment.

A limitation of the study is the lack of uniform cutoff values for defining adherence and persistence making it more difficult to put our results into perspective. However, we have used the terms in accordance with ISPOR definitions [24]. Prescriptions issued does not always imply that the patient is also taking the medicine, but in this study, we report on prescriptions filled rather than prescriptions issued, thus minimizing the potential error. A further limitation is that we did not include intravenous bisphosphonates and PTH treatment in the statistical analyses, as these data were not available from the National Prescription Registry. We would have been able to include this information from the National Health Insurance Service Register, but as intravenous bisphosphonates and PTH are nearly solely being used by hospital departments, and as the treatment of osteoporosis was administered by GPs in accordance with Danish national guidelines, the extra information gathered from this registry is not likely the change in the findings of our study.

Conclusion

In conclusion, this study revealed significantly higher redemption rates of antiosteoporotic drugs in the screening arm of the ROSE study compared with the control arm, with overall no significant differences in adherence and persistence rates between the screening and control arm. A Charlson comorbidity index equal to 1 seemed to increase the likelihood of treatment initiation, combined with smaller negative effects on adherence, while socioeconomic factors did not seem to have any effect on treatment adherence and persistence. Even so, nearly a third of all patients advised to start treatment did not follow the advice and this questions the sustainability of this type of screening program, where responsibility for treatment indication is separated from actual treatment initiation.

Acknowledgments The authors would like to thank the participants in the ROSE study and technical staff in the four involved hospitals: Odense University Hospital, Odense; Hospital of Funen, Nyborg; Hospital of Southwest Denmark, Esbjerg, and Sygehus Lillebælt Hospital, Kolding, Denmark.

Funding The ROSE study was supported by INTERREG 4A, the Region of Southern Denmark, and Odense University Hospital. The funding agencies had no direct role in the conduct of the study, data collection, analysis, and interpretation of the data or the preparation, review, and final approval of the manuscript.

Compliance with ethical standards

Conflict of interest All authors have completed the authorship and disclosure form. S Möller, T Holmberg M Bech, J Gram, KH Rubin have no conflict of interest. MJ Rothmann has received speaker fee from Eli Lilly. M Hoiberg is a full-time employee of Boehringer-Ingelheim Norway KS (currently). AP Hermann serves on advisory boards for Eli Lilly, Amgen, and she has received research funding from Eli Lilly, speaker fee from Eli Lilly, GSK, Genzyme, Amgen; and K Brixen received funding from Merck, Sharpe, Dohme, Amgen, Novartis and NPS, all outside the submitted work.

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