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Anti-osteoporotic therapy in Denmark—predictors and demographics of poor refill compliance and poor persistence

C. Hansen · B. D. Pedersen · H. Konradsen · B. Abrahamsen

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Abstract
Summary In this study of 100,949 new users of oral bisphosphonates age ≥35 years, "early quitters" were found to differ from others with poor refill compliance in terms of socioeconomic, demographic, and treatment-related characteristics. New risk factors for poor compliance and persistence were identified.

Introduction Poor compliance with anti-osteoporotic therapy is an on-going worldwide challenge. In this study, we hypothesized that "early quitters" differ in socioeconomics, demographics, co-medications, and comorbid conditions from other patients with low compliance.
Methods The study was a register-based nationwide cohort study of anti-osteoporotic therapy comprising 100,949 men and women. Statistical analysis including backward stepwise logistic regression analysis was used to explain causes of treatment failure and Kaplan–Meier survival analysis to estimate persistence of treatment.
Results It was noted that 56.6 % of the patients were persistent and compliant, 4.7 % of the patients were persistent but "low compliant" while 38.7 % of the patients were "early quitters". "Early quitters" were found to differ in socioeconomics from "low compliant" patients. Differences concerning increased risk of "early quitters" were associated with high household income, subjects' age 71.9–79 years, living in the countryside or village, prior treatment with analgesics and anti-parkinson drugs, and dementia. Differences concerning decreased risk of "early quitters" were associated with male, living in an apartment, children living at home, living close to a university hospital, anti-osteoporotic therapy other than alendronate, number of drugs especially above three, pulmonary disease, collagen disease.
Conclusion The results suggest a need for improved support for patients to facilitate the interpretation of the disease and the perception of the benefits and risks of treatment—to reduce the risk of "early quitters". We were able to identify new risk groups that may be candidates for targeted actions.

Keywords Osteoporosis · Persistence · Refill compliance · Register-based · Risk groups · Socioeconomic

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C. Hansen (✉) · B. D. Pedersen
Research Unit of Nursing, Institute of Clinical Research,
Faculty of Health Sciences, University of Southern Denmark,
Campusvej 55,
5230 Odense M, Denmark
e-mail: chansen@health.sdu.dk

C. Hansen
Department of Medicine C, Gentofte University Hospital,
PhD Study Office 2nd floor, Research Unit,
post 284 Niels Andersens Vej 65,
2900 Hellerup, Denmark

H. Konradsen
Research Unit, Gentofte University Hospital,
post 284 Niels Andersens Vej 65,
2900 Hellerup, Denmark

B. Abrahamsen
Department of Medicine F, Gentofte University Hospital,
Niels Andersens Vej 65,
2900 Hellerup, Denmark

B. Abrahamsen
Institute of Clinical Research, Faculty of Health Sciences,
University of Southern Denmark, Campusvej 55,
5230 Odense M, Denmark

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Introduction

Osteoporosis is a considerable public health problem [1–4] affecting hundreds of millions of people worldwide [5]. The consequences of osteoporotic fractures may include hospitalization, need for rehabilitation, lost earnings, early retirement, chronic pain, lost mobility and impaired quality of life [2, 6], as well as high morbidity and mortality [7].

Studies [7–10] have shown that compliance and persistence with bisphosphonate therapy—by far the most widely used treatment for osteoporosis worldwide—is suboptimal and that this may impact on "fracture risk". A Danish register based study of 152,777 patients with recent fractures showed that few patients began osteoporosis treatment, and that one in four patients stopped therapy within the first year [10]. A recent Swedish study [9] demonstrated that about half of osteoporosis patients stop treatment within the first year, with a strong association between treatment discontinuation and subsequent fracture, confirming similar findings from the USA [11]. Accordingly, systematic reviews have also reported that more than 50 % of patients quit treatment during the first year, a spectacular failure of potential fracture prevention [12, 13]. However, the findings depend somewhat on methodology. Thus, the length of treatment pauses (or "grace periods") permitted by the analysis influences findings as some patients who stop bisphosphonate therapy have been found to reinitiate treatment even after extended gaps [1]. The determinants of low compliance and persistence to treatment are still not well understood [9, 14]. Patient compliance stabilizes commonly about 6 months after prescription, and studies have also shown that patients tend to increase compliance just before and a short time after consultation with the physician [15, 16]. Some studies have been carried out in order to gain more insight into causality to compliance and persistence with medication for chronic diseases in general [15, 17–22] and for osteoporosis in particular [1, 23–25]. These studies suggest that personal networks, psychological factors, and relationship to the physician are important factors [17, 18, 20, 23]. Furthermore, research also suggests motivation and health beliefs [25] as well as understanding of the effect of the medication [1] to be important key factors in relation to patients' compliance and persistence towards anti-osteoporotic therapy. The understanding of the phenomenon of low compliance to osteoporosis therapy is still incomplete [14], and there is a need for more detailed knowledge before initiatives to improve compliance and persistence in risk groups can be defined and put into use.

We hypothesized that patients who stop treatment very early differ in socioeconomic demographics, co-medications, and comorbid conditions from other patients with poor compliance. If this could be confirmed, then intervention strategies to improve refill compliance and persistence in the two scenarios may need to be different.

The aim of this study was therefore to obtain epidemiological characteristics of patients in anti-osteoporotic therapy concerning treatment and socioeconomic factors relating to men and women in Denmark. Furthermore, the aim was also to investigate the amount of and the determinants of compliance and persistence as well as medication patterns to see if it was possible to identify potential demographic risk groups based on patterns of refill compliance.

Materials and methods

We used Danish National Registers to identify, characterize, and follow all new users of oral bisphosphonates age ≥35 years in the calendar years 1996 to 2006 with follow-up to the end of 2008. The Danish National Registers are unique national data sources; all admissions are registered from 1977, use of drugs from 1995, and data in the socioeconomic database from 1966 [26]. These databases are linked by individual social security numbers and provide the opportunity to collate information about the same individual from different databases. The National Patient Database, the National prescription Database, and the Socio-Economic Database were used (Statistics Denmark [26], permit 702538). The databases contain key medical, health care, and socioeconomic information concerning citizens in Denmark (approximately 5.5 million individuals).

Age when treatment was initiated was divided into quartiles: first quartile 35–70.1 years, second quartile 70.2–71.8 years, third quartile 71.9–79.0 years, and fourth quartile 79.1–103 years. Education level was classified into three categories: primary school ≤10 years, secondary school >10 years, and bachelor degree or higher. Household income was divided into tertiles.

New users were defined based on at least one prescription for an osteoporosis drug in the period 1/1/1996 to 31/12/2006 in subjects who had not filled prescriptions for anti-osteoporotic drugs during 1 year before inclusion. We excluded those who emigrated in the period as it was impossible to classify their compliance to treatment.

The register contains a dispensing date and the number of doses issued to the patient; repeat prescriptions result in a new record being generated each time the patient makes a purchase, and we used the specific number of tablets bought to calculate the number of doses available in each case. This is fairly simple in osteoporosis as the daily dose does not differ between patients.

The following osteoporosis medications were considered in the study, ATC code: M05BA, M05BA01, M05BA02, M05BA04, M05BA06, M05BA07, M05BB, M05BB01,

M05BB02 (oral bisphosphonates), M05BX03 (strontium ranelate), G03XC01 (raloxifene), H05AA01, and H05AA02 (PTH analogues). Patients who exclusively used intravenous bisphosphonates were not included in the study because of difficulties in tracking compliance as hospital-based infusions and injections do not result in a prescription being filled. Because of this limitation, we only included patients who used oral osteoporosis drugs as these can be accurately tracked through prescriptions. The use of infused or injected osteoporosis drugs at the time was certainly very limited though the exact number of persons who received i.v. treatment is not known. The estimated persistence on treatment was estimated using Kaplan–Meier survival analysis. Information on deaths was collected from The Danish Death Register. The identities of individual patients were blinded to the investigators, and the study did not require ethics committee permission. This was not a clinical trial.

Statistical analysis

In analysis of the socioeconomic data, we used data from the year before the first prescription or, in the case of patients beginning treatment in 1996, the socioeconomic dataset for 1996. Information concerning family status was available from 1/1/1996; municipality of residence and type of housing were available until a data break at the end of 2004 and registered total family income until a data break at the end of 2003. Thus, for patients who entered the study in 2006, family income for 2003 and housing data for 2004 were used in the analysis.

We describe the treated population in relation to the variables presented in Table 1. We used multiple logistic regression analysis, where models A and B were based on prespecified factors chosen on biological and demographic grounds alone. Thus, in model A, covariates immediately driven by the hypothesis were prioritized and mutually adjusted: education level, housing, children, living without a spouse/single, household income, and osteoporosis treatment. In model B, sex and age were incorporated. Model C was mutually adjusted for all other significant or borderline significant covariates selected using stepwise analysis with a critical $P < 0.20$. Thus, the covariates selected for entry into model C were those of models A and B plus a parsimonious subset of additional covariates that had been selected by stepwise backwards regression on the maximum model. The analyses addressed the associations with age, gender, previous fracture, co-medication, comorbidity (ICD-10 codes for hospital contacts, on an in- or outpatient basis), between 1/1/1977 and the date of the first prescription type of anti-osteoporotic medication, education, socioeconomics etc. are described. Persistence estimates were derived using non-parametric survival analysis [27] (Table 2).

Analysis of compliance and persistence

Gaps of more than 56 days (8 weeks) were considered as non-persistence [9]. A sensitivity test was conducted regarding gaps of 84 days (12 weeks). Patients were allowed to change to other osteoporosis drugs without impact on compliance and the persistence estimate as long as the gap in treatment did not exceed 56 days.

Medication compliance was quantified as medication possession ratio (MPR) describing to which extent the patients purchased enough daily doses to fill the need during the treatment period. A critical MPR value of 75 % was predefined as the limit of acceptable refill compliance [11].

Results

The cohort consisted of $N=100{,}949$ subjects (Fig. 1). As 393 emigrated before 1 year of follow-up, the final cohort consisted of a total of $N=100{,}556$: 84.5 % women, mean age 70.4 years, mean time of follow-up 5.2 years, with a total of 520,604 person years of observation time. Table 1 contains detailed information on the baseline characteristics of the study cohort. Briefly, 54 % of the individuals were prescribed alendronate, 40 % were prescribed other bisphosphonates, and only 6 % were prescribed other anti-osteoporotic therapy, mainly raloxifene. A large proportion (52 %) did not have any record of hospital treated comorbid conditions though 81 % had used more than three different medications in the past year. A prior fracture was present in 39 % of the cohort and recent use of glucocorticoids was widespread, with 24 % of patients having been treated with prednisolone in the past year. The educational level of the cohort amounted to 65 % with primary school education only, 21 % with secondary school education and 14 % had a bachelor degree or more. More than two thirds lived less than 50 km from a university hospital. Only 3 % of the study population had children living at home and 48 % lived without a spouse/single. Almost 75 % were retired.

Length of treatment (persistence)

The results of the estimated length of treatment with different anti-osteoporotic therapy are presented in Table 2, showing a mean treatment of 4 years and median treatment of almost 3 years. Ibandronate and risedronate treatment was associated with almost as long treatment duration as alendronate. Treatment with other bisphosphonates was of substantially shorter duration.

We observed a significant linear time trend with better compliance and persistence in later years (see below).

Table 1 Baseline characteristics of 100,556 new users of anti-osteoporosis treatment, with primary osteoporosis, age ≥35 in Denmark 1996–2006: complete information on socioeconomic factors

	Male *N*=15,298 (15.2 %) *N* (% within gender/total)	Female *N*=85,258 (84.5 %) *N* (% within gender/total)	*P* value	Total *N*=100,556 *N* (%)
Age at treatment				
1st quartile (35.0–70.1 years)	4,356 (28.5/4.3)	20,713 (24.3/20.6)	0.0	25,069 (24.9)
2nd quartile (70.2–71.8 years)	3,770 (24.6/3.7)	21,350 (25.0/21.2)	0.3	25,120 (25.0)
3rd quartile (71.9–79.0 years)	3,849 (25.2/3.8)	21,332 (25.0/21.2)	0.7	25,181 (25.0)
4th quartile (79.1–103 years)	3,321 (21.7/3.3)	21,857 (25.6/21.7)	0.0	25,178 (25.0)
Osteoporosis treatment				
Alendronate	9,320 (60.9/9.3)	45,032 (52.8/44.8)	0.0	54,352 (54.1)
Other bisphosphonate	5,746 (37.6/5.7)	34,464 (40.4/34.3)	0.0	40,210 (40.0)
Non-bisphosphonate	232 (1.5/0.2)	5,762 (6.8/5.7)	0.0	5,994 (6.0)
Charlson index (numbers of comorbidity)				
0 (ref)	5,780 (37.8/5.7)	46,724 (54.8/46.5)	0.0	52,504 (52.2)
1	1,297 (8.5/1.3)	5,604 (6.6/5.6)	0.0	6,901 (6.9)
2	3,730 (24.4/3.7)	18,450 (21.6/18.3)	0.0	22,180 (22.1)
3+	4,491 (29.4/4.5)	14,480 (17.0/14.4)	0.0	18,971 (18.9)
Number of drugs (co-medication)				
0	778 (5.1/0.8)	4,676 (5.5/4.7)	0.5	5,454 (5.4)
1–3	2,852 (18.6/2.8)	19,101 (22.4/19.0)	0.0	21,953 (21.8)
4–9	6,063 (39.6/6.0)	36,045 (42.3/35.8)	0.0	42,108 (41.9)
10+	5,605 (36.6/5.6)	25,436 (29.8/25.3)	0.0	31,041 (30.9)
Comorbidity				
Pulmonary disease	4,564 (29.8/4.5)	13,552 (15.9/13.5)	0.0	18,116 (18.0)
Collagen diseases	3,447 (22.5/3.4)	17,033 (20.0/16.9)	0.0	20,480 (20.4)
Hemiplegia	232 (1.5/0.2)	761 (0.9/0.8)	0.0	993 (1.0)
Malignant disease	1,936 (12.7/1.9)	10,266 (12.0/10.2)	0.0	12,202 (12.1)
Dementia	233 (1.5/0.2)	954 (1.1/0.9)	0.0	1,187 (1.2)
Hart failure, any	2,785 (18.2/2.8)	10,873 (12.8/10.8)	0.0	13,658 (13.6)
Fractures after age 50				
Spine	1,046 (6.8/1.0)	4,365 (5.1/4.3)	0.0	5,411 (5.4)
Hip	1,270 (8.3/1.3)	8,703 (10.2/8.7)	0.0	9,973 (9.9)
Forearm	870 (5.7/0.9)	12,831 (15.0/12.8)	0.0	13,701 (13.6)
Humerus	568 (3.7/0.6)	5,834 (6.8/5.8)	0.0	6,402 (6.4)
Any	5,012 (32.8/5.0)	33,806 (39.7/33.6)	0.0	38,818 (38.6)
Type of co-medication				
ACE inhibitor[a]	2,059 (13.5/2.0)	8,120 (9.5/8.1)	0.0	10,179 (10.1)
Anti-coagulation AC[a]	680 (4.4/0.7)	2,101 (2.5/2.1)	0.0	2,781 (2.8)
Antiarhythmics[a]	1,533 (10.0/1.5)	5,686 (6.7/5.7)	0.0	7,219 (7.2)
AT2 antagonists[a]	854 (5.6/0.8)	5,171 (6.1/5.1)	0.0	6,025 (6.0)
Beta blockers[a]	1,877 (12.3/1.9)	10,871 (12.8/10.8)	0.1	12,748 (12.7)
Anti-diabetics[a]	1,031 (6.7/1.0)	3,034 (3.6/3.0)	0.0	4,065 (4.0)
Opposed HRT[a]	2 (0.0/0.0)	4,552 (5.3/4.5)	0.0	4,554 (4.5)
Unopposed HRT[a]	30 (0.2/0.0)	12,552 (14.7/12.5)	0.0	12,582 (12.5)
Lipid lowering[a]	1,475 (9.6/1.5)	6,091 (7.1/6.1)	0.0	7,566 (7.5)
Prednisolone[a]	5,966 (39.0/5.9)	17,888 (21.0/17.8)	0.0	23,854 (23.7)
Analgesics[a]	9,690 (63.3/9.6)	50,020 (58.7/49.7)	0.0	59,710 (59.4)
Anti-epileptics[a]	896 (5.9/0.9)	3,060 (3.6/3.0)	0.0	3,956 (3.9)
Parkinson medications[a]	321 (2.1/0.3)	1,283 (1.5/1.3)	0.0	1,604 (1.6)
SSRI[a]	1,760 (11.5/1.8)	10,153 (11.9/10.1)	0.2	11,913 (11.8)

Table 1 (continued)

	Male *N*=15,298 (15.2%) *N* (% within gender/total)	Female *N*=85,258 (84.5%) *N* (% within gender/total)	*P* value	Total *N*=100,556 *N* (%)
Other antidepressants[a]	1,155 (7.6/1.1)	7,392 (8.7/7.4)	0.0	8,547 (8.5)
Education level				
Primary school	8,106 (53.0/8.1)	57,372 (67.3/57.1)	0.0	65,478 (65.1)
Secondary school	5,198 (34.0/5.2)	15,854 (18.6/15.8)	0.0	21,052 (20.9)
Bachelor degree or higher	1,994 (13.0/2.0)	12,032 (14.1/12.0)	0.0	14,026 (13.9)
Living close to university hospital[b]	9,720 (63.6/9.7)	56,820 (66.7/56.6)	0.0	66,540 (66.3)
Living in countryside or in a village[c]	5,931 (38.8/5.9)	27,919 (32.7/27.8)	0.0	33,850 (33.7)
Children living at home (<25 years)	844 (5.5/0.8)	2,212 (2.6/2.2)	0.0	3,056 (3.0)
Living without a spouse/single	4,604 (30.1/4.6)	43,466 (51.0/43.2)	0.0	48,070 (47.8)
Housing				
Single family house	10,290 (67.3/10.2)	51,723 (60.7/51.4)	0.0	62,013 (61.7)
Apartment	4,461 (29.2/4.4)	31,173 (36.6/31.0)	0.0	35,634 (35.4)
Caravan site/allotment	185 (1.2/0.2)	801 (0.9/0.8)	0.0	986 (1.0)
Institution and other	205 (1.3/0.2)	957 (1.1/1.0)	0.0	1,162 (1.2)
Household income				
Lowest quintile	2,021 (13.2/2.0)	18,010 (21.1/17.9)		20,031 (19.9)
Lowest tertile	4,226 (27.6/4.2)	29,273 (34.3/29.1)		33,499 (33.3)
Middle tertile	4,354 (28.5/4.3)	29,146 (34.2/29.0)		33,500 (33.3)
Highest tertile	6,708 (43.9/6.7)	26,802 (31.4/26.7)		33,510 (33.3)
Retired	11,696 (76.5/11.6)	63,319 (74.3/63.0)	0.0	75,015 (74.6)
Retired but maintain limited work income	1,061 (6.9/1.1)	6,773 (7.9/6.7)	0.0	7,834 (7.8)

[a] Prior use: any use the year before index year

[b] Living close to university hospital: living in a radius of 50 km from a university hospital

[c] Living in countryside or in a village <999 inhabitants

Outcome groups

We pre-specified three non-overlapping groups based on refill compliance and persistence (Fig. 1). Group A: persistent for less than 1 year (early quitters) consisting of individuals with premature medication discontinuation (≤84 DDD during the first 6 months and no further prescriptions). Group B: persistent for more than 1 year but exhibiting a refill compliance of MPR <75 % (less compliant but persistent users). Group C: persistent for more than 1 year with compliance ≥75 % (compliant and persistent users).

In the primary analysis, the 0.1 % (*N*=131) who lacked education and/or income information was excluded. We undertook two sensitivity tests. In the first, we repeated the analysis but assigned individuals without information with an education equal to the mean education level in the study.

Table 2 Survival analysis of time to treatment stopped (years) *N*=100,556: male 15,298 (15.2 %), female 85,258 (84.5 %)

Drug category	Mean (95% CI)	Median (95% CI[a])
Alendronate	4.01 (3.96–4.06)	2.79 (2.74–2.85)
Clodronate	1.46 (0.96–1.96)	0.33 (0.19–0.46)
Etidronate	2.60 (2.56–2.64)	0.95 (0.93–0.98)
Ibandronate	3.86 (3.50–4.22)	2.77 (2.58–2.96)
Risedronate	2.79 (2.69–2.89)	3.14 (2.89–3.38)
Bisphosphonates (any)	3.53 (3.50–3.57)	1.86 (1.82–1.89)
Bisphosphonates (non-alendronate)	2.68 (2.64–2.71)	0.98 (0.95–1.00)
PTH	2.68 (2.46–2.90)	1.99 (1.59–2.38)
Strontium ranelate	1.71 (1.60–1.81)	1.13 (0.91–1.36)
Raloxifene	4.35 (4.23–4.47)	3.28 (3.00–3.56)
Non-bisphosphonates	4.09 (3.98–4.20)	2.56 (2.35–2.77)

[a]Normal approximation by SPSS based on the standard error of the median [27]

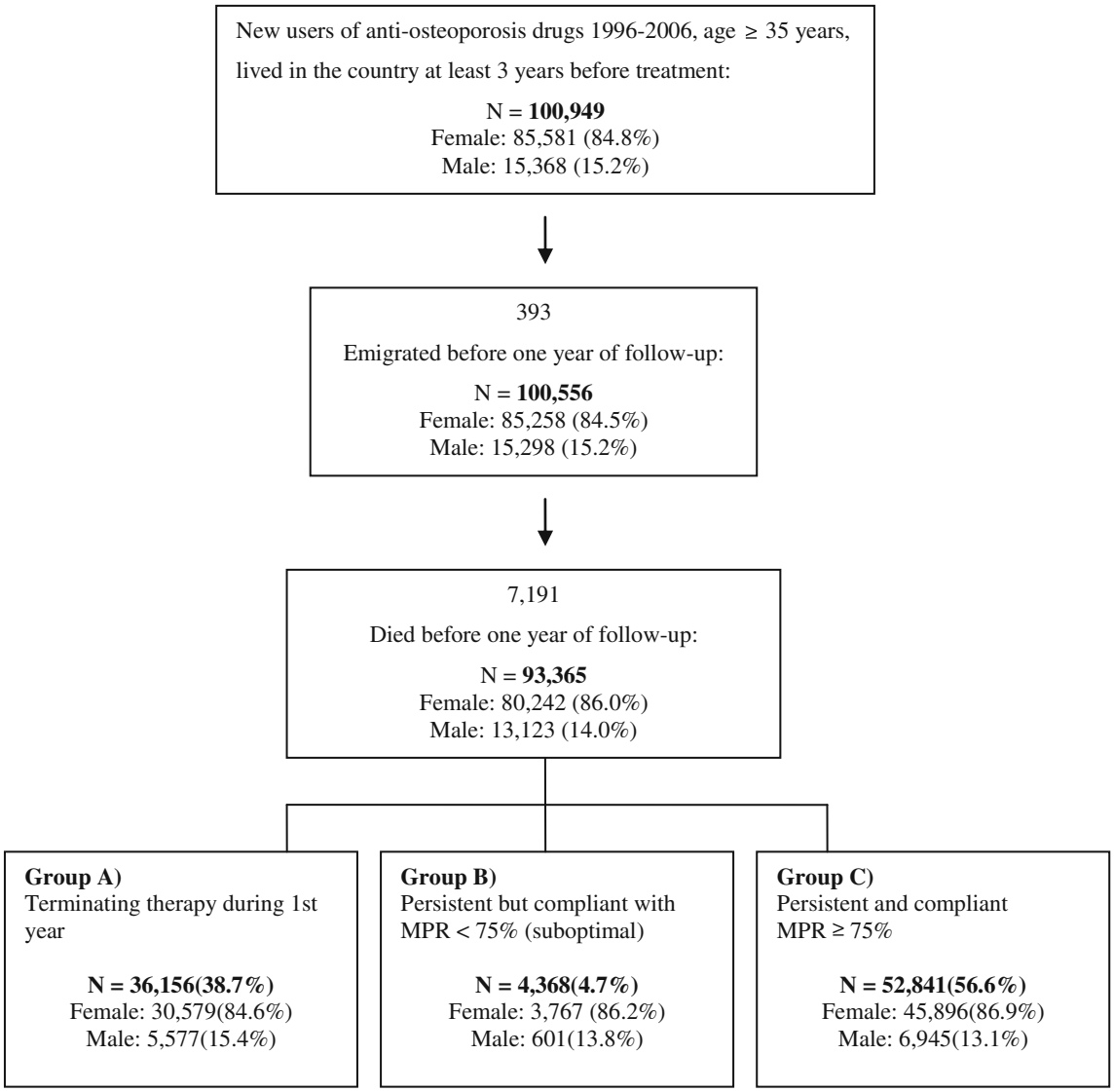

Fig. 1 Cohort consisting of N=100,949 subjects

In the second sensitivity analysis, we assigned individuals without data on income for with an income equal to the average person's income level and if this information was missing we used a median income of the study cohort. As these sensitivity tests yielded the same conclusions as the primary analysis, they were not included in the results section.

Characteristics of early quitters

Within the first year, 38.7 % of users stopped treatment by the definition above. Key factor characteristics of subjects who were persistent for less than 1 year (outcome group A) compared with those who were refill compliant for more than 1 year (group B+C) are presented in Table 3. We observed a significant linear time trend with fewer early quitters in later years (OR 0.92, 95 CI 0.92–0.93, per calendar year).

A decreased risk of quitting during the first year of treatment was associated with household income level above lowest tertile, second (age 70.2–71.8 years), age in the third quartile (age 71.9 – 79.0 years), retirement both with and without maintaining limited work income, living in the countryside or in village, previous fracture of the forearm, and co-medication as ACE inhibitors, lipid-lowering drugs, and analgesics. This was also the case for dementia (Tables 3 and 4). An increased risk of quitting during the first year of treatment was interestingly found to be associated with previous fractures overall when analyzing previous fracture as one category. Other factors statistically associated with increased risk of stopping treatment prematurely were as follows: living in an apartment, children

Table 3 Analysis of predictors of quitting treatment in the first year (group A) versus persisting with treatment beyond 1 year (group B+C)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socioeconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
N=93,365: male: 13,123 (14.1 %), female: 80,242 (85.9 %)			
Effect of the index year—time trend	0.93 (0.92–0.93)***	0.92 (0.92–0.93)***	0.92 (0.92–0.93)***
Education level			
Primary school (ref)	1	1	1
Secondary school	0.98 (0.94–1.01)	0.97 (0.94–1.01)	0.98 (0.94–1.02)
Bachelor degree or higher	0.97 (0.92–0.95)	1.01 (0.96–1.05)	1.01 (0.97–1.06)
Housing			
Single family house(ref)	1	1	1
Apartment	1.16 (1.12–1.19)***	1.15 (1.11–1.18)***	1.10 (1.07–1.14)***
Caravan site/allotment	1.15 (1.00–1.32)	1.14 (0.99–1.31)	1.12 (0.97–1.29)
Institution and other	0.97 (0.85–1.11)	0.92 (0.80–1.05)	0.87 (0.76–1.00)
Children at home (<25 years)	1.63 (1.51–1.76)***	1.48 (1.37–1.61)***	1.47 (1.35–1.59)***
Living without a spouse/single	1.16 (1.12–1.20)***	1.20 (1.16–1.25)***	1.18 (1.14–1.22)***
Household income			
Lowest tertile (ref)	1	1	1
Middle tertile	0.98 (0.94–1.02)	0.94 (0.90–0.97)**	0.94 (0.91–0.98)**
Highest tertile	0.92 (0.89–0.96)***	0.85 (0.81–0.88)***	0.86 (0.83–0.90)***
Osteoporosis treatment			
Alendronate (ref)	1	1	1
Other bisphosphonate	1.71 (1.65–1.76)***	1.76 (1.66–1.77)***	1.73 (1.68–1.79)***
Non-bisphosphonate	1.09(1.03–1.15)**	1.12 (1.06–1.19)***	1.15 (1.09–1.22)***
Sex male		1.39 (1.34–1.45)***	1.33 (1.27–1.38)***
Age at treatment			
1st quartile (35.0–70.1 years) ref.		1	1
2nd quartile (70.2–71.8 years)		0.83 (0.80–0.86)***	0.85 (0.81–0.89)***
3rd quartile (71.9–79.0 years)		0.84 (0.81–0.88)***	0.84 (0.80–0.88)***
4th quartile (79.1–103 years)		1.03 (0.98–1.07)	1.01 (0.97–1.06)
Retired			0.94 (0.90–0.97)***
Retirement but maintain limited work income			0.93 (0.88–0.98)**
Living close to university hospital			1.09 (1.06–1.12)***
Living in the countryside or in a village			0.97 (0.93–1.00)*
Number of drugs			
0 (ref)			1
1–3			1.10 (1.03–1.18)**
4–9			1.23 (1.16–1.32)***
10+			1.33 (1.23–1.43)***
Type of drugs			
ACE inhibitors			0.90 (0.86–0.94)***
Anti-coagulants			1.00 (0.92–1.09)
Beta blockers			0.98 (0.94–1.03)
Anti-diabetics			1.07 (0.99–1.15)
Hormone replacement therapy opposed			1.09 (1.02–1.17)**
Lipid-lowering therapy			0.94 (0.89–1.00)*
Prednisolone			1.08 (1.04–1.12)***
Analgesics			0.97 (0.94–1.00)*
Anti-epileptics			1.01 (0.94–1.08)

Table 3 (continued)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socioeconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
Anti-parkinson			0.98 (0.88–1.10)
Anti-depressants (SSRI)			1.08 (1.03–1.13)**
Other anti-depressants			1.01 (0.96–1.06)
Charlson index			
0 (ref)			1
1			1.05 (1.00–1.12)
2			1.05 (1.01–1.1)*
3+			1.14 (1.08–1.21)***
Comorbidity			
Pulmonary disease			1.05 (1.00–1.10)*
Collagen disease			1.19 (1.15–1.23)***
Hemiplegia			0.94 (0.82–1.09)
Dementia			0.83 (0.72–0.95)**
Cardiovascular diseases			1.03 (0.97–1.08)
Fracture			
Spine			1.05 (0.99–1.12)
Forearm			0.92 (0.88–0.97)**
Humerus			0.99 (0.93–1.05)
Any			1.07 (1.03–1.11)**

Predictors of quitting treatment within the first year (in patients who lived for at least 1 year following initiation of treatment, N=93,365, 14.1 % male)

*p<0.05, **p<0.01, ***p<0.001

[a] Priori covariates due to hypothesis: education, housing, children, living without a spouse/single, income, and treatment

[b] Priori covariates: sex and age

[c] Backward stepwise adjusted for hemiplegia, malignant disease, cardiovascular diseases, hip fractures , humerus fractures, hormone replacement therapy unopposed, analgesics, anti-epileptics, anti-parkinson, other anti-depressants

living at home, living without a spouse/single, osteoporosis treatment with other bisphosphonates or non-bisphosphonates, male gender, living close to a university hospital, number of drugs/being treated with other drugs, and co-medications as hormone replacement therapy, prednisolone, and anti-depressants. Further, we found the presence of more than one—and especially three or more—comorbidities, and presence of pulmonary and collagen diseases to characterize "early quitters" (Analysis of men cf. Table 5).

Characteristics of persistent subjects with low or suboptimal MPR (<75 %)

Out of 57,209 patients who completed the first year on treatment (groups B+C), 25 % (4.7 % of the total study population) showed low refill compliance below 75 %. We observed a significant linear time trend with fewer patients with suboptimal MPR in later years (OR 0.98, 95 CI 0.96–0.99).

Key predictors of low and suboptimal MPR are presented in Table 4.

Factors associated with decreased risk were secondary school, other bisphosphonate or non-bisphosphonate, second age quartile (70.2–71.8 years), and retirement.

Significant factors increasing the risk of low refill compliance included living without a spouse/single, living in the countryside or in village, treatment with analgesics, and the presence of two or more comorbid conditions (Tables 4 and 6) (Analysis of men cf. Table 7).

Characteristics of early quitters compared with the group with suboptimal MPR

The large group of patients who terminated therapy prematurely was found to differ in some of the socioeconomic demographics, co-medications, and comorbid conditions from the smaller group of patients who persisted with low refill compliance (group A vs. group B) (Table 8).

Table 4 Analysis of persistent patients with MPR <75 % (group B) versus persistent patients with MPR ≥75 % (group C)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socioeconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
N=57,209: male 7,546, female 49,663			
Effect of the index year—time trend	0.98 (0.96–0.99)***	0.97 (0.96–0.99)***	0.98 (0.96–0.99)***
Education level			
Primary school (ref)	1	1	1
Secondary school	0.86 (0.80–0.94)**	0.87 (0.80–0.95)**	0.90 (0.82–0.98)*
Bachelor degree or higher	1.02 (0.93–1.13)	1.04 (0.95–1.15)	1.07 (0.97–1.17)
Housing			
Single family house (ref)	1	1	1
Apartment	0.98 (0.91–1.05)	0.97 (0.91–1.04)	1.01 (0.93–1.09)
Caravan site/allotment	0.89 (0.64–1.24)	0.90 (0.65–1.26)	0.86 (0.62–1.21)
Institution and other	1.03 (0.76–1.41)	1.01 (0.74–1.37)	0.91 (0.67–1.25)
Children at home (<25 years)	1.16 (0.96–1.38)	1.07 (0.89–1.29)	1.05 (0.87–1.26)
Living without a spouse/single	1.16 (1.08–1.25)***	1.15 (1.06–1.24)**	1.12 (1.03–1.21)**
Household income			
Lowest tertile (ref)	1	1	1
Middle tertile	1.03 (0.94–1.12)	1.02 (0.93–1.11)	1.02 (0.93–1.11)
Highest tertile	1.07 (0.98–1.17)	1.03 (0.94–1.13)	1.06 (0.96–1.16)
Osteoporosis treatment			
Alendronate (ref)	1	1	1
Other bisphosphonate	0.10 (0.09–0.11)***	0.10 (0.09–0.11)***	0.10 (0.09–0.11)***
Non-bisphosphonate	0.82 (0.73–0.92)**	0.81 (0.72–0.91)***	0.82 (0.73–0.93)**
Sex male		1.02 (0.92–1.12)	0.99 (0.90–1.09)
Age at treatment			
1st quartile (35.0–70.1 years) ref.		1	1
2nd quartile (70.2–71.8 years)		0.79 (0.72–0.87)***	0.84 (0.75–0.93)**
3rd quartile (71.9–79.0 years)		0.91 (0.83–1.01)	0.95 (0.86–1.06)
4th quartile (79.1–103 years)		0.98 (0.89–1.09)	0.99 (0.88–1.10)
Retired			0.90 (0.83–0.97)*
Retirement but maintain limited work income			0.98 (0.87–1.12)
Living close to university hospital			0.96 (0.90–1.03)
Living in the countryside or in a village			1.09 (1.01–1.18)*
Number of drugs			
0 (ref)			1
1–3			0.98 (0.85–1.14)
4–9			0.96 (0.83–1.11)
10+			0.99 (0.85–1.17)
Type of drugs			
ACE inhibitors			0.91 (0.81–1.01)
Anti-coagulants			0.94 (0.78–1.13)
Beta blockers			0.95 (0.86–1.05)
Anti-diabetics			1.11 (0.94–1.31)
Hormone replacement therapy (opposed)			1.07 (0.92–1.24)
Lipid-lowering therapy			0.92 (0.82–1.04)
Prednisolone			0.98 (0.99–1.06)
Analgesics			1.10 (1.03–1.19)**
Anti-epileptics			1.09 (0.93–1.28)

Table 4 (continued)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socioeconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
Anti-parkinson			1.20 (0.96–1.51)
Anti-depressants (SSRI)			1.06 (0.96–1.17)
Other anti-depressants			1.09 (0.98–1.22)
Charlson index			
0 (ref)			1
1			1.11 (0.97–1.27)
2			1.16 (1.05–1.27)**
3+			1.20 (1.05–1.37)**
Comorbidity			
Pulmonary disease			0.92 (0.82–1.03)
Collagen disease			1.04 (0.95–1.13)
Hemiplegia			1.21 (0.90–1.62)
Dementia			1.16 (0.88–1.54)
Cardiovascular diseases			0.93 (0.83–1.05)
Fracture			
Spine			1.06 (0.91–1.23)
Forearm			0.94 (0.85–1.05)
Humerus			1.07 (0.94–1.22)
Any			1.06 (0.97–1.15)

Predictors of quitting treatment within the first year (in patients who lived for at least 1 year following initiation of treatment, N=93,365, 14.1 % male)

*p<0.05, **p<0.01, ***p<0.001

[a] Priori covariates due to hypothesis: education, housing, children, living without a spouse/single, income, and treatment

[b] Priori covariates: sex and age

[c] Stepwise adjusted for malignant disease, hip fractures, anti-arrhythmic, rx_AT2I_max, hormone replacement therapy unopposed

An increased risk of premature termination of treatment compared with group B was associated with high household income (OR 1.24, 95 CI 1.13–1.37), age group 71.9–79 years (OR 1.14, 95 CI 1.02–1.27), living in the countryside or village (OR 1.12, 95 CI 1.03–1.21), prior treatment with analgesics (OR 1.13, 95 CI 1.05–1.22), anti-parkinson drugs (OR 1–39, 95 CI 1.09–1.77), and dementia.

A decreased risk of premature termination of treatment compared with group B was associated with male gender (OR 0.78, 95 CI 0.71–0.86), living in an apartment (OR 0.90, 95 CI 0.83–0.97), children living at home (OR 0.68, 95 CI 0.56–0.82), living close to a university hospital (OR 0.88, 95 CI 0.82–0.94), initial anti-osteoporotic therapy other than bisphosphonate (OR 0.06, 95 CI 0.06–0.07) and non-bisphosphonate (OR 0.73, 95 CI 0.65–0.83), number of drugs especially 4–9 (OR 0.73, 95 CI 0.63–0.85) and 10+, pulmonary disease, collagen disease (Table 8).

Discussion

The present study provided information from a national study of both men and women 35+ years of age, which began osteoporosis treatment. Compliance and persistence with treatment of osteoporosis remains a challenge in Denmark and elsewhere. New risk factors associated with low persistence and low refill compliance emerged in this study.

The findings in this study are based on the three defined non-overlapping outcome groups (Fig. 1). Socioeconomic and demographic factors as well as some co-medications and comorbid conditions were shown to decrease or increase the risk of stopping treatment prematurely. Further, we found some differences between the two groups with low refill compliance. This is consistent with the study hypothesis that patients who terminate treatment early differ from other patients with poor compliance. Specifically, patients who terminated treatment prematurely were shown to differ from other patients with poor compliance (group A

Table 5 Men quitting treatment before 1 year (group A) versus men with persistence after 1 year (group B+C)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics and age[b] HR, mutually adjusted	Model C Socieconomics, age, and major comorbid conditions[c] HR, mutually adjusted
N=13,123 men			
Effect of the index year—time trend	0.94 (0.92–0.95)***	0.93 (0.92–0.95)***	0.93 (0.92–0.95)***
Education level			
Primary school (ref)	1	1	1
Secondary school	0.96 (0.89–1.05)	0.97 (0.90–1.06)	0.98 (0.90–1.06)
Bachelor degree or higher	0.98 (0.87–1.11)	1.02 (0.90–1.14)	1.02 (0.91–1.15)
Housing			
Single family house (ref)	1	1	1
Apartment	1.15 (1.06–1.25)**	1.14 (1.05–1.24)**	1.16 (1.06–1.28)**
Caravan site/allotment	1.29 (0.94–1.78)	1.29 (0.94–1.78)	1.26 (0.91–1.75)
Institution and other	0.77 (0.54–1.08)	0.75 (0.53–1.04)	0.76 (0.54–1.07)
Children at home	1.51 (1.30–1.76)***	1.33 (1.13–1.56)**	1.35 (1.15–1.60)***
Living alone	1.25 (1.15–1.36)***	1.21 (1.11–1.32)***	1.22 (1.11–1.33)***
Household income			
Lowest tertile (ref)	1	1	1
Middle tertile	0.89 (0.80–0.98)*	0.87 (0.78–0.96)**	0.88 (0.80–0.98)*
Highest tertile	0.82 (0.75–0.90)***	0.77 (0.70–0.85)***	0.79 (0.71–0.87)***
Osteoporosis treatment			
Alendronate (ref)	1	1	1
Other bisphosphonate	2.11 (1.94–2.29)***	2.12 (1.95–2.31)***	2.12 (1.95–2.31)***
Non-bisphosphonate	1.34 (1.01–1.78)*	1.32 (0.99–1.76)	1.37 (1.03–1.83)*
Age at treat			
1st quartile (ref)		1	1
2nd quartile		0.79 (0.71–0.87)***	0.79 (0.71–0.89)***
3rd quartile		0.76 (0.68–0.84)***	0.74 (0.66–0.83)***
4th quartile		0.94 (0.84–1.05)	0.94 (0.83–1.06)
Retired			1.01 (0.91–1.11)
Retired but maintains limited work income			0.89 (0.76–1.04)
Living close to university hospital			1.14 (1.05–1.23)**
Living in the countryside or in village			1.08 (0.99–1.18)
Number of drugs			
0 (ref)			1
1–3			1.00 (0.83–1.19)
4–9			1.04 (0.88–1.24)
10+			1.07 (0.89–1.30)
Type of drugs			
ACE inhibitors			0.87 (0.78–0.98)*
Anti-coagulants			1.20 (1.00–1.44)
Beta blockers			1.10 (0.98–1.24)
Anti-diabetics			1.06 (0.91–1.24)
Lipid-lowering therapy			0.92 (0.80–1.05)
Prednisolone			1.12 (1.03–1.22)*
Analgesics			0.94 (0.87–1.02)
Anti-epileptics			1.00 (0.85–1.17)
Anti-parkinson			1.09 (0.85–1.41)
Anti-depressants (SSRI)			1.02 (0.91–1.16)

Table 5 (continued)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics and age[b] HR, mutually adjusted	Model C Socieconomics, age, and major comorbid conditions[c] HR, mutually adjusted
Other anti-depressants			0.99 (0.86–1.15)
Charlson index			
0 (ref)			1
1			0.97 (0.84–1.12)
2			0.93 (0.82–1.04)
3+			1.04 (0.90–1.21)
Comorbidity			
Pulmonary disease			1.07 (0.96–1.20)
Collagen disease			1.10 (1.01–1.20)*
Hemiplegia			0.80 (0.59–1.08)
Dementia			0.63 (0.45–0.88)**
Cardiovascular diseases			1.05 (0.92–1.19)
Fracture			
Spine			1.01 (0.86–1.18)
Forearm			0.80 (0.68–0.95)*
Humerus			1.19 (0.97–1.46)
Any			1.05 (0.95–1.15)

Predictors of quitting treatment within the first year (in patients who lived for at least 1 year following initiation of treatment, N=13,123 male, 14.1 % of total population)

*p<0.05, **p<0.01, ***p<0.001

[a] Priori covariates due to hypothesis: education, housing, children, living alone, income, and treatment

[b] Priori covariates: age

[c] Backward stepwise adjusted for hemiplegia, malignant disease, cardiovascular diseases, hip fractures, humerus fractures, hormone replacement therapy unopposed, analgesics, anti-epileptics, anti-parkinson, other anti-depressants. Models included adjustment for time trends

vs. group B) as described in the above section: characteristics of early quitters compared with the group with suboptimal MPR. The statistically decreasing risk factors of patients terminating treatment prematurely also showed that patients with these characteristics were more likely to continue treatment with low refill compliance than to cease treatment entirely.

However, we also demonstrated that the overwhelming problem was patients quitting treatment early, not the small number who persisted with treatment but had low refill compliance. Thus, intervention in the risk groups identified in Table 3 would be expected to have a greater health impact on the community than intervention based on Table 4. This may have implications for the type of intervention chosen as discussed below.

In the present study, 61.3 % of the population persisted with therapy for more than 1 year and 56.6 % of the population were compliant with MPR ≥75 %. These findings are encouraging and suggest that persistence and compliance to anti-osteoporotic therapy may be rather high in Denmark compared to other countries. A comparable observation was made in a Danish survey [28] where persistence with therapy at two years was found to be between 84 % and 88 % in three different clinics. Studies in other countries have generally found lower compliance and persistence rates. Thus, in Norway [29] an adherence of 45.4 % was reported throughout the study period of 4.2 years. Furthermore, persistence after 1 year was reported to be 51.7 % for alendronate and 50.6 % for risedronate in a Swedish study, where 23 % of subjects terminated treatment early [30]. Together with the results of the present study—with 38.7 % early quitters—this clearly highlights a general need to address the reasons for early termination of therapy. A reason for the fairly good persistence with osteoporosis treatment in Denmark compared with other countries could be the relatively strict criteria for reimbursement of treatment, which restricts reimbursement to patients with low energy fractures or the combination of a risk factor and a BMD T-score below −2.5. This may select patients with a higher motivation for treatment and the reimbursement letter from the Medicines Agency could further reinforce patient beliefs in the appropriateness of treatment in their individual

Table 6 Overview of significant predicting factors of quitting treatment during the first year (group A) and persisting with treatment beyond 1 year with low MPR (group B)

	Group A Predictors of quitting treatment in the first year	Group B Predictors of persisting with low MPR
Factors decreasing the risk	• Middle and highest tertile of household income	• Educational level secondary school
	• Second and third age quartile	• Other bisphosphonate than alendronate
	• Retirement both without and with maintained limited work income	• Non-bisphosphonate
	• Living in the countryside or in a village	• Second age quartile
	• ACE inhibitor, co-medication	• Retirement, full
	• Lipid lowering, co-medication	
	• Analgesics, co-medication	
	• Previous fracture of the forearm	
	• Dementia, comorbidity	
Factors increasing the risk	• Previous fractures overall	• Living without a spouse/single
	• Living in an apartment	• Living in the countryside or in a village
	• Children living at home (<25 years)	• Analgesics, co-medications
	• Living without a spouse/single	• Comorbidity 2 or more
	• Other bisphosphonates than alendronate	
	• Non-bisphosphonates	
	• Being a male	
	• Living close to a university hospital	
	• Number of drugs/being treated with other drugs	
	• Hormone replacement therapy opposed, co-medications	
	• Prednisolone, co-medications	
	• Anti-depressants, co-medications	
	• Comorbidity overall and especially 3+	
	• Collagen diseases, comorbidity	
	• Pulmonary diseases, comorbidity	

case. The increased establishment of patient education specifically targeting osteoporosis could have an impact on compliance and persistence. We observed a significant improvement in compliance and persistence in later study years compared with patients who began treatment earlier. The reasons are not known, but it may be that the introduction of additional treatment options and more convenient dosing regimens contribute to this slow improvement.

Somewhat contrary to our initial expectations, the highest income was found to be associated with a decreased risk of stopping treatment prematurely. We did not expect this finding because the health care system in Denmark is financed by taxes and all citizens have free access to healthcare and some reimbursement of drug costs is provided. However, reimbursement of osteoporosis drugs is not universal in Denmark, and patients contribute to the cost of their medications as reimbursement is typically only 50 % of the price of the medication. As mentioned above, for most osteoporosis drugs, reimbursement requires a specific application from the treating physician. Personal income can also affect compliance and persistence in ways unrelated to medical expenditures. For example, income level may to some extent serve as a proxy for individual health beliefs and perceptions. This assumption is supported by the findings in a systematic review of osteoporosis health beliefs and decisions concerning osteoporosis preventive health behavior in men and women [25]. Further, in Canada patients with fragility fractures [31] have been found to interpret their diagnosis, the information concerning osteoporosis, their fracture risk, and the therapy in ambiguous ways. Further research is needed to obtain an in-depth understanding of these issues. By contrast, once patients were established on treatment, household income did not demonstrate statistical significance in predicting subsequent low refill compliance. Our findings are to some extent confirmed by a Norwegian prospective register-based cohort study [29]. The researcher investigated socioeconomic factors which influenced adherence to alendronate. They found an association between high income and increased adherence concerning women but not concerning men.

In our analysis, about 40 % had a prior hospital-treated fracture. Surprisingly, a prior fracture in general was found

Table 7 Men persistent after 1 year with MPR <75 % (group B) vs. men persistent with MPR ≥75 % (group C)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socieconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
N=7,546 men			
Education level			
Primary school (ref)	1	1	1
Secondary school	0.93 (0.77–1.13)	0.91 (0.75–1.12)	0.93 (0.76–1.13)
Bachelor degree or higher	1.36 (1.06–1.74)*	1.37 (1.07–1.75)*	1.36 (1.06–1.75)*
Housing			
Single family house (ref)	1	1	1
Apartment	1.10 (0.91–1.35)	1.10 (0.90–1.34)	1.10 (0.88–1.37)
Caravan site/allotment	0.51 (0.18–1.40)	0.51 (0.18–1.39)	0.50 (0.18–1.40)
Institution and other	1.13 (0.53–2.40)	1.10 (0.52–2.34)	0.98 (0.46–2.12)
Children at home	1.00 (0.70–1.44)	0.90 (0.61–1.33)	0.90 (0.61–1.33)
Living alone	1.21 (0.99–1.48)	1.19 (0.98–1.46)	1.13 (0.92–1.39)
Household income			
Lowest tertile (ref)	1	1	1
Middle tertile	0.84 (0.65–1.07)	0.83 (0.64–1.07)	0.82 (0.63–1.07)
Highest tertile	1.15 (0.92–1.43)	1.10 (0.87–1.39)	1.11 (0.88–1.41)
Osteoporosis treatment			
Alendronate (ref)	1	1	1
Other bisphosphonate	0.19 (0.14–0.26)***	0.19 (0.14–0.26)***	0.19 (0.14–0.26)***
Non-bisphosphonate	1.72 (1.06–2.78)*	1.70 (1.05–2.74)*	1.55 (0.95–2.55)
Age at treatment			
1st quartile (ref)		1	1
2nd quartile		0.80 (0.63–1.02)	0.84 (0.64–1.09)
3rd quartile		0.90 (0.70–1.15)	0.87 (0.67–1.14)
4th quartile		0.83 (0.63–1.08)	0.77 (0.57–1.03)
Retired			1.06 (0.84–1.34)
Retired but maintains limited work income			0.73 (0.49–1.10)
Living close to university hospital			0.93 (0.77–1.11)
Living in the countryside or in village			1.00 (0.82–1.22)
Number of drugs			
0 (ref)			1
1–3			0.99 (0.66–1.51)
4–9			1.02 (0.68–1.53)
10+			1.00 (0.64–1.57)
Type of drugs			
ACE inhibitors			0.93 (0.71–1.21)
Anti-coagulants			0.72 (0.46–1.13)
Beta blockers			0.93 (0.70–1.23)
Anti-diabetics			1.17 (0.82–1.67)
Lipid-lowering therapy			0.79 (0.59–1.07)
Prednisolone			0.95 (0.77–1.17)
Analgesics			1.06 (0.87–1.29)
Anti-epileptics			0.75 (0.50–1.11)
Anti-parkinson			2.05 (1.28–3.27)**
Anti-depressants (SSRI)			0.88 (0.66–1.17)
Other anti-depressants			1.25 (0.92–1.72)

Table 7 (continued)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socieconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
Charlson index			
0 (ref)			1
1			1.38 (1.01–1.88)*
2			0.95 (0.71–1.25)
3+			0.97 (0.68–1.36)
Comorbidity			
Pulmonary disease			0.96 (0.73–1.27)
Collagen disease			1.15 (0.93–1.42)
Hemiplegia			1.43 (0.82–2.49)
Dementia			1.53 (0.82–2.86)
Cardiovascular diseases			1.24 (0.92–1.66)
Fracture			
Spine			1.09 (0.77–1.54)
Forearm			0.87 (0.60–1.27)
Humerus			1.16 (0.75–1.81)
Any			1.16 (0.94–1.44)

Predictors of quitting treatment within the first year (in patients who lived for at least 1 year following initiation of treatment, N=93,365, 14.1 % male)

*p<0.05, **p<0.01, ***p<0.001

[a] Priori covariates due to hypothesis: education, housing, children, living alone, income, and treatment

[b] Priori covariates: sex and age

[c] Stepwise adjusted for malignant disease, hip fractures, anti-arrhythmic, rx_AT2I_max, hormone replacement therapy unopposed

to have a tendency to increase the risk of terminating treatment early. However, fracture of the forearm seems associated with a lower risk of stopping treatment early. Further research is necessary to obtain deeper understanding of this phenomenon. It may be that it takes a more highly motivated patient to begin treatment after a forearm fracture than after more potentially dangerous fractures such as those of the spine and of the hip. Fracture history did not have any impact on the likelihood of low refill compliance. To our knowledge, there are no other studies investigating risk of prematurely termination of therapy or low refill compliance and the association with pre-existing osteoporotic fractures [6, 7, 9–12].

In the literature, comorbidity is generally considered to be a factor predictive of decreased compliance and persistence [9]. This is to some extent confirmed in the present study where we found Charlson comorbidity index overall and especially 3+ to be associated with an increased risk of prematurely terminating therapy, though not in men. Premature termination of treatment was also associated with the presence of comorbid conditions as pulmonary disease and collagen disease, while dementia seemed protective with less likelihood of terminating treatment early. The latter factor may be due to treatment being administered with help from others or the prescriptions being delivered to the home. In contrary to "early quitters", the probability of continuing treatment but with low refill compliance was not statistically significantly related to any specific comorbid condition.

Co-medications as hormone replacement therapy, prednisolone, and anti-depressants were statistically significant associated with increased risk of early termination of therapy for the entire population. Only ACE inhibitors and prednisolone were statistically significant in analysis of men. Furthermore, increasing numbers of drugs were associated with risk of early termination; this may be in line with findings in the Norwegian study [29], where decreasing adherence was associated with increasing number of drugs prescribed.

Somewhat in contrary to findings in the Swedish study [9], we did find living in the countryside or in a village to be associated with a slightly lower risk of terminating therapy early, but at the same time it was also found to be a factor associated with increased risk of low refill compliance. These findings may, together with the findings of proximity to a university hospital which was associated with a noteworthy increased likelihood of stopping treatment early, be

Table 8 Early quitters (group A) versus low refill compliance (group B)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socieconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
N=40,524 (male 6,178, female 34,346)			
Education level			
Primary school (ref)	1	1	1
Secondary school	1.08 (0.99–1.18)	1.05 (0.97–1.15)	1.04 (0.95–1.14)
Bachelor degree or higher	0.92 (0.83–1.01)	0.92 (0.83–1.02)	0.91 (0.82–1.00)
Housing			
Single family house (ref)	1	1	1
Apartment	1.21 (1.12–1.30)***	1.21 (1.12–1.30)***	1.12 (1.03–1.22)**
Caravan site/allotment	1.28 (0.90–1.80)	1.26 (0.89–1.78)	1.30 (0.92–1.84)
Institution and other	0.91 (0.66–1.27)	0.89 (0.64–1.24)	0.95 (0.68–1.32)
Children at home (<25 years)	1.45 (1.21–1.74)***	1.44 (1.19–1.74)***	1.45 (1.20–1.76)***
Living without a spouse/single	1.01 (0.94–1.09)	1.05 (0.96–1.13)	1.05 (0.97–1.14)
Household income			
Lowest tertile (ref)	1	1	1
Middle tertile	1.00 (0.91–1.09)	0.98 (0.90–1.107)	0.98 (0.90–1.08)
Highest tertile	0.88 (0.91–0.97)**	0.86 (0.78–0.94)**'*	0.85 (0.77–0.93)***
Osteoporosis treatment			
Alendronate (ref)	1	1	1
Other bisphosphonate	18.57 (18.57–16.26)***	18.69 (16.37–21.375)***	18.75 (16.41–21.42)***
Non-bisphosphonate	1.38 (1.23–1.56)***	1.421 (1.26–1.60)***	1.42 (1.26–1.60)***
Sex male		1.25 (1.13–1.37)***	1.24 (1.12–1.38)***
Age at treatment			
1st quartile (ref)		1	1
2nd quartile		1.05 (0.95–1.16)	1.05 (0.95–1.17)
3rd quartile		0.94 (0.85–1.04)	0.91 (0.82–1.01)
4th quartile		1.00 (0.90–1.11)	0.99 (0.88–1.10)
Retired			1.05 (0.97–1.15)
Retired but maintains limited work income			0.84 (0.74–0.97)*
Living close to university hospital			1.14 (1.23–1.23)***
Living in the countryside or in village			0.89 (0.82–0.96)**
Number of drugs			
0 (ref)			1
1–3			1.20 (1.03–1.40)*
4–9			1.39 (1.19–1.62)***
10+			1.50 (1.26–1.78)***
Type of drugs			
ACE inhibitors			0.96 (0.86–1.08)
Anti-coagulants			1.05 (0.86–1.27)
Beta blockers			1.04 (0.93–1.15)
Anti-diabetics			0.96 (0.81–1.14)
Hormone replacement therapy (opposed)			1.10 (0.94–1.29)
Lipid-lowering therapy			0.95 (0.84–1.07)
Prednisolone			1.04 (0.96–1.14)
Analgesics			0.89 (0.83–0.97)**
Anti-epileptics			0.86 (0.73–1.02)
Anti-parkinson			0.72 (0.56–0.92)**

Table 8 (continued)

	Model A Socioeconomics[a] HR, mutually adjusted	Model B Socioeconomics, sex, and age[b] HR, mutually adjusted	Model C Socieconomics, sex, age, and major comorbid conditions[c] HR, mutually adjusted
Anti-depressants (SSRI)			0.99 (0.90–1.10)
Other anti-depressants			0.92 (0.82–1.03)
Charlson index			
0 (ref)			1
1			0.94 (0.81–1.07)
2			0.94 (0.85–1.04)
3+			0.98 (0.85–1.12)
Comorbidity			
Pulmonary disease			1.12 (0.99–1.25)
Collagen disease			1.18 (1.08–1.29)***
Hemiplegia			0.79 (0.58–1.07)
Dementia			0.63 (0.46–0.84)**
Cardiovascular diseases			1.00 (0.89–1.14)
Fracture			
Spine			1.05 (0.89–1.22)
Forearm			0.99 (0.89–1.11)
Humerus			0.93 (0.81–1.06)
Any			0.96 (0.88–1.05)

Predictors of quitting treatment within the first year (in patients who lived for at least 1 year following initiation of treatment, N=93,365, 14.1 % male)

*p<0.05, ** p<0.01, *** p<0.001

[a] Priori covariates due to hypothesis: education, housing, children, living without a spouse/single, income, and treatment

[b] Priori covariates: sex and age

[c] Stepwise adjusted for malignant disease, hip fractures, anti-arrhythmic, rx_AT2I_max. Hormone replacement therapy unopposed

considered as so far not explained proxy to refill compliance and persistence, contributing to the findings that explanations cannot clearly be identified in a register-based study. Treatment thresholds could be lower for patients with easy access to specialist care, and this may lead to patients with lower motivation beginning treatment. To our knowledge, this is the first study investigating the association between risk of stopping therapy early, the risk of low refill compliance, and proximity to a university hospital. Further studies are needed.

We found an association with housing conditions. Living in an apartment increased the risk of terminating therapy early, irrespective of gender. There may be subtle differences between subjects with different housing conditions that contribute to the finding but which cannot clearly be identified in a register-based study. People of the same sex, income, age, and education might function in different ways: both socially and mentally, lived experiences, health belief, and related to social support. It is also possible to imagine that this finding actually describes differences in the quality of health care in various types of housing, such as general practitioners, home care schemes, and other municipal systems.

Children living at home—we included young adults up to age 25—were found to increase the risk of early termination of therapy extensively. However, this may be a chance finding as the number of patients with children still at home was very low. Only one prior study was found addressing the predictive impact of children in the home. This was the cross-sectional study of the National Health and Wellness Survey [32], and here the researchers did not find any association between prescription treatment of women with osteoporosis or osteopenia and children <18 years at home. Other study designs focusing on the individual perspective by using qualitative methods, e.g., in-depth interviews, may be able to provide insight into the mechanism.

Anti-osteoporotic therapy other than alendronate seemed to increase the risk of early termination of therapy, but it was also associated with a reduced risk of subsequent low refill compliance. Physicians may target bisphosphonates other than alendronate to patients who are more likely to stop

treatment, for example because of pre-existing upper GI symptoms.

Regarding age at treatment, subjects 70.2–79.0 years of age were found to be associated with a reduced risk of premature discontinuation of treatment (Tables 3 and 6). While the SARA study and the Danish survey [9, 28] did not report any statically significant association between age and compliance or persistence, the Norwegian study [29] reported higher odds of adherence for women ≥60 years.

Limitations

A register-based study has some shortcomings. Although we have information of the date of dispensing and dosage of drugs dispensed to each individual, we do not know whether the individuals are actually taking the dispensed drugs and to what extend they are using them. Therefore, overestimation of drug use is a possible bias in this study. On the other hand, we do not have information of drug use or medication delivered from the hospital or other institutions or if the patient purchased the medication abroad, which might lead to an underestimation of drug use.

Another limitation regards comorbid conditions diagnosed in general practice, where patients have not required in- or outpatient hospital treatment. We did, however, obtain some indirect information about comorbid conditions through capture of all filled prescriptions issued by general practitioners.

Implications and conclusion

Patients who stop treatment very early differ in sociodemographics from other patients with poor refill compliance. Therefore, interventions aimed at preventing early medication discontinuation should be targeted patient information where the sociodemographic factors are incorporated and adapted to the treatment regimen and interventions aimed to prevent early medication discontinuation, and incorporated extended focus on male patients, pulmonary and collagen diseases, and number of drugs. Also, stopping treatment early was far more frequent than persisting with low MPR. This suggests that interventions aimed at better education and motivation of groups at risk of low persistence may have a larger community impact than addressing persistence with low refill compliance. It may be that technology in the form of reminders and more convenient dosing regimens could improve refill compliance but not necessarily reduce the risk of early quitting. More research is needed.

Further, it might be appropriate to incorporate increased patient participation in the medical decision-making and frequent interactions with the patients with special focus on compliance which can lead to improved compliance rates and outcomes [33, 34].

The strength of the present study is the large population containing all men and women aged 35+ treated for osteoporosis in Denmark, and the ability to draw on extensive population-based health and socioeconomic information.

In conclusion, these results suggest that there may be a need for better support for the patients—to help patients interpret the disease and help modify perceptions about the benefits and hazards of treatment—in order to reduce the risk of patients stopping treatment prematurely. The study provides less information about modifiable risk factors for those patients who remain on treatment but have poor refill compliance which may have an impact on fracture prevention. However, there is a need for more research including socioeconomic and demographic differences in osteoporosis treatment and prevention to identify the underlying pathways. In order to assess the needs of patients for the level of support and content of such, there is a need for research dealing with patients' own perceptions of barriers in relation to premature termination or low compliance towards medical fracture prevention treatment of osteoporosis. The study adds new knowledge useful to identify subgroups for targeted action by subsequent intervention studies.

Conflicts of interest B. Abrahamsen has served as an investigator in clinical trials and on advisory boards and/or speakers panels for pharmaceutical companies that produce osteoporosis drugs. Clinical trials: Amgen, NPS Pharmaceuticals. Advisory boards: Amgen, Takeda-Nycomed. Speakers panels: Amgen, Nycomed, Eli Lilly, Merck.

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