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ORIGINAL RESEARCH

Real-Life and RCT Participants: Alendronate Users Versus FITs' Trial Eligibility Criterion

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Abstract We aimed to characterize incident users of alendronate from Denmark and Spain, and investigate their eligibility for participation in the pivotal Fracture Intervention Trial (FIT). This is an international cross-sectional study, where the data were obtained from the SIDIAP database (Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària) from Catalonia (Spain) and the Danish Health Registries (DHR). This study included patients who were incident users of alendronate, ≥40 years old with no history of Paget's disease. Our measurements were the proportion of incident users of alendronate who were not eligible to participate in FIT. 14,316 and 21,221 subjects initiated alendronate in 2006–2007 (SIDIAP) and 2005–2006 (DHR), respectively. SIDIAP and DHR alendronate user cohorts had 2347 (16.4 %) and 5275 (24.9 %) subjects aged >80 years old, reported 9 (0.1 %) and 91 (0.4 %) diagnoses of myocardial infarction, 423 (3 %) and 368 (1.7 %) of erosive gastrointestinal disease, 200 (1.4 %) and 1109 (5.2 %) of dyspepsia, and 349 (2.4 %) and 149 (0.7 %) of metabolic bone disease, all of which were exclusion criteria in FIT. Men [3818 (26.7 %) in SIDIAP and 3885 (18.3 %) in DHR] and

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glucocorticoid users [1229 (8.6 %) in SIDIAP and 4716 (22.2 %) in DHR] were also excluded from the FIT trial. Overall, 3447 (35.4 %) SIDIAP and 6228 (44.5 %) (when not considering men and glucocorticoid users) DHR of incident alendronate users would have been excluded from FIT. One in two real-life users of alendronate exhibited one or more clinical characteristics that would have led to them being excluded from the FIT trial.

Keywords Osteoporosis · Randomized controlled trial · Population characteristics · Alendronate · Observational study

Introduction

Randomized controlled trials (RCT) are the backbone of evidence-based medicine and are considered as the gold standard study design to determine the effect of new or already commercialized medications. While medical doctors are familiar with these studies, the challenge lies in being able to summarize and apply this evidence in their day-to-day practice. The rigorous designs inherent to most RCT confer them high internal validity. However, when applied in a real-world setting, results have been shown on occasion to be much less favorable than expected [1, 2].

Despite considerations about external validity being a pre-requisite for every well-conducted trial [3], this remains a common limitation in RCTs [1], limiting the value of the findings obtained through these studies in real-life practice settings. This has been illustrated in a number of therapeutic areas, including cardiac rehabilitation, where an observational study [2] reported a much less optimistic reduction in mortality than previous Cochrane reviews [4].

Fracture reduction therapies [also called anti-osteoporosis medications] are not an exception; since the first RCT of alendronate (the Fracture Intervention Trial, FIT [5, 6]), observational studies have detected discrepancies between the fracture reduction expected from the RCT findings and what is actually observed in real-life patients [7–10]. Such discrepancies contribute to the debate on the differences between efficacy and effectiveness as well as on potential safety issues not seen in RCTs but possibly present in real-life drug users. The main cause of these discrepancies is likely the strict selection criteria used in most clinical trials.

To illustrate the differences between RCT participants and real-life drug users, we used routinely collected data from two nationwide databases, and compared the FIT's exclusion and inclusion criteria with the baseline characteristics of incident users of alendronate. We hypothesize that a relevant proportion of these subjects will not be eligible for their inclusion in the FIT.

Methods

Study Design and Setting

We conducted an international cross-sectional register-based study using data obtained from the SIDIAP (Sistemad'Informació per al Desenvolupament de l'Investigació en AtenciónPrimària) Database from Catalonia (Spain), and the DHR (Danish Health Registries) from Denmark.

The SIDIAP database is a comprehensive collection of longitudinal records from 274 primary care practices, with the participation of 3414 GPs. It includes primary care electronic medical records for approximately 5 million patients in Catalonia (80 % of the total population in this region). SIDIAP comprises the clinical and referral events registered by primary care health professionals (GPs and nurses 9) and administrative staff in e-records, comprehensive demographic information, prescriptions and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, hospital admissions, and their major outcomes [11]. All this information is anonymized and encoded using the ICD-10 codes and structured forms designed for the collection of variables relevant to primary care professionals. Only GPs who achieve quality control standards can contribute to the SIDIAP database [12].

The DHR comprises by the National Prescriptions Database [13] (Lægemiddelregistret) which contains all filled prescriptions in the country since 1995, the National Hospital Discharge Register [14] (NHDR) (Landspatientsregistret) comprising all diagnosis codes (ICD-8 until the end of 1993 and ICD-10 afterwards) for contacts for inpatients (since 1977) and outpatients (since 1995) and the date of death from the Danish Civil Register [15] (CentralePersonregister, CPR).

Participants

We included all subjects >40 year old registered in the SIDIAP and DHR database between 1/1/2006 and 12/31/2007 and between 1/1/2005 and 12/31/2006 respectively, with an incident use of alendronate within these periods (only naïve subjects to any anti-osteoporosis treatment were included). Incident use of alendronate was defined as no previous alendronate prescription registered from 1/1/2005 for SIDIAP database and from 1/1/1995 for DHR database.

We excluded those with a diagnosis of Paget disease, previous use of any anti-osteoporosis drug in the year prior to the first prescription of alendronate as well as those receiving high-dose bisphosphonates treatment (high dose of risedronate basically for Paget treatment).

Variables

The main study measurements were the inclusion and exclusion criteria reported in the FIT trial: age, sex, bone mineral density (BMD), major illnesses (myocardial infarction, erosive gastrointestinal disease, dyspepsia, metabolic bone disease, cancer, hypertension, unstable angina, malabsorbtion), drug treatments affecting bone turnover (glucocorticoids, estrogen, anabolic steroids, calcitonin, progestin, fluoride) among other variables such as levels of creatinine in blood sample, changes in thyroid hormone dosage, unexplained weight loss, unsuitable anatomy on spinal radiographs, not being ambulatory, history of bilateral hip replacement and alcohol abuse.

For each variable, an operational definition was created adapted to the SIDIAP [16] and DHR databases. When a variable was not available in the participating data sources (e.g., BMD), the related inclusion criteria were assumed to be fulfilled, in order to provide a conservative estimate of non-eligibility. The primary analysis addressed the similarity of real-world alendronate users to the patients permitted to participate in the FIT trial, while a sensitivity analysis broadened the inclusion criteria to allow glucocorticoid users and men to allow for the fact that successful clinical trials with alendronate have been conducted in these patient groups after completion of the original FIT trial.

Statistical Methods

Numbers and proportions of participants fulfilling each of the eligibility criteria were reported for both Spanish and Danish incident alendronate users separately. Further sensitive analyses were carried out without considering male gender and steroid use as criteria of non-eligibility, as these patient groups were included in subsequent alendronate trials [17, 18] where an increase in vertebral BMD was reported.

Results

A total of 14,316 (SIDIAP) and 21,214 (DHR) incident users of bisphosphonates were analyzed which was reduced to 9725 (SIDIAP) and 14,006 (DHR) if not considering men and glucocorticoid users. Baseline characteristics of the real-life incident users of alendronate compared with the exclusion criteria of the FIT pivotal trial are summarized in Tables 1 and 2.

When analyzing strictly the exclusion criteria reported in the FIT trial, among the incident users of alendronate included in the SIDIAP and DHR database, 9.8 and 21.5 % of the subjects respectively were either under 55 or over 80 years old, falling outside the age-range of the FIT trial. The SIDIAP and DHR population also frequently displayed comorbidities such as a history of myocardial infarction, erosive gastro-intestinal disease, dyspepsia and metabolic bone disease, all of which were exclusion criteria of the FIT trial. Men (26.7 and 18.3 % of the Spanish and Danish participants) and systemic glucocorticoid users (8.6 and 22.2 % alendronate users in SIDIAP and DHR respectively) were also excluded from the FIT trial. Overall, 8038 (56.2 %) and 13,443 (63.3 %) incident alendronate users in the SIDIAP and DHR, respectively, had at least one of the previously mentioned exclusion criteria (including men and glucocorticoid users).

Given that men and glucocorticoid users have been included in subsequent RCTs on alendronate [17, 18], a sensitivity analysis was carried out broadening the inclusion criteria to include both variables. When not considering male gender and use of systemic glucocorticoids as exclusion criteria, the proportion of subjects with at least one of the previously mentioned exclusion criteria was reduced to 3447 (35.4 %) and 6228 (44.5 %) in Spain and Denmark.

Discussion

Real-life patients that initiated oral alendronic acid in Spanish or Danish actual practice settings do not resemble the patients included in the alendronate pivotal trial FIT, as just over half of these incident users would have been eligible for this randomized controlled trial.

The population selected for the firsts RCT of alendronate published in the 90s [5, 19] included a large number of exclusion criteria. These limitations were partially compensated, with the publication of further RCTs [17, 18] that included men and oral glucocorticoid users. However, in spite of the proven efficacy for fracture reduction of alendronate [5, 6], some studies have detected differences between the expected effect and the actual effectiveness when applied to the general population [7–10]. Differences in the inclusion–exclusion criteria between trials and these observational studies could partly explain these uneven results.

The real-life population in this study reported many of the FIT's exclusion criteria, mostly considering age and comorbidities. The older subjects are frequently excluded from RCT; in a review published in 2011 [20], the majority of the RCT excluded the aged population either through direct age-exclusion criteria or indirectly by non-age-exclusion criteria focused on comorbidities highly frequent among these subjects. Our population accounted for a large proportion of old people (subjects over 80 years old), which are a target population for bisphosphonate treatment

Table 1 Comparison of the exclusion criteria in the FIT trial with the incident users of alendronate in the SIDIAP and DHR database

FIT exclusion criteria[a]	Operational definition/ICD-10 Codes	Incident users of Alendronate[d]	
		SIDIAP $N = 14,316$ (%)	DHR $N = 21,214$ (%)
Men	Sex according to administrative data	3818 (26.7 %)	3885 (18.3 %)
Age <55 years old	Age at first ALD dispensation	1844 (12.9 %)	1654 (7.8 %)
Age >80 years old	Age at first ALD dispensation	2347 (16.4 %)	5275 (24.9 %)
Major illnesses			
Myocardial infarction[b]	MI[c] (6 months before alendronate initiation date)	9 (0.1 %)	91 (0.4 %)
Serum creatinine >1.6 mg/dl	CKD[c] (Anytime before alendronate initiation date)	300 (2.1 %)	182 (0.9 %)
Erosive gastrointestinal disease within 5 years	K21 (previous 5 years)	423 (3.0 %)	368 (1.7 %)
Dyspepsia requiring daily treatment	K25/K26/K27	200 (1.4 %)	1109 (5.2 %)
Metabolic bone disease	Any of the following at any time before or on date of alendronate initiation: Hyperparathyroidism: E21 OI: Q78.0 Osteopetrosis: Q78.2 Osteomalacia: M83	349 (2.4 %)	142 (0.7 %)
History of cancer	Malignancy[c] (Anytime before or on therapy initiation date)	438 (3.1 %)	2561 (12.1 %)
Treatment affecting bone turnover			
Glucocorticoid[b]	Any use of glucocorticoids[b]	1229 (8.6 %)	4716 (22.2 %)
Other exclusion criteria			
Alcohol abuse	Lifestyle factors in primary care records	99 (0.7 %)	NA

NA Data not available, assumed to be fulfilled, *CKD* Chronic Kidney Disease, *MI* Myocardial Infarction, *OI* Osteogenesis imperfect

Other NA Severe hypertension, unstable angina, malabsorbtion, oestrogens, anabolic steroids, calcitonin, progestin, change in thyroid hormone dosage, fluoride treatment, unexplained weight loss, unsuitable anatomy on spinal radiographs, non-compliance with pre-randomizations study procedures, not ambulatory, history of bilateral hip replacement, unable to give informed consent, participating in another trial, intention to move within 4 years. Data not available: BMD at femoral neck over 3 SD

[a] See Ref. [26]

[b] Within 6 months

[c] See Ref. [16]

[d] Subjects can be included in more than one category

due to the increased risk of fracture with older age, as well as common comorbidities such as gastrointestinal disorders or cancer, which could further increase the risk of fracture. Furthermore, the FIT trial excluded subjects with high alcohol consumption [5] which is considered a risk factor for fragility fracture included in the WHO fracture risk assessment tool FRAX [21].

Lastly, the FIT also included a "run in period" before randomization, during which those subjects with a good-drug adherence or those with fewer side effects were selected for participation. In summation, these choices in the design of the FIT trial are likely to have led to a highly selected population that is very different from the incident real-life users of alendronate, thus limiting the external validity of the findings [1].

The differences between the population selected for RCTs and real-world drug users have been reported previously in other diseases, such as hypertension, cardiovascular disease or chronic obstructive pulmonary disease [22–24]. In a Canadian study published in 2006 [22], only 34–38 % of the real-world population that were taking anti-hypertensive medication would have been selected for the RCTs of these same treatments. This under representation also affects patients with chronic kidney disease,

Table 2 Comparison of the exclusion criteria in the FIT trial with the incident users of alendronate in the SIDIAP and DHR database after excluding men and systemic steroid users

FIT exclusion criteria[a]	Operational definition/ICD-10 Codes	Incident users of Alendronate[d]	
		SIDIAP $N = 9725$	DHR $N = 14{,}006$
Age <55 years old	Age at first ALD dispensation	1442 (14.8 %)	1026 (7.3 %)
Age >80 years old	Age at first ALD dispensation	1525 (15.7 %)	3562 (25.4 %)
Major illnesses			
Myocardial infarction[b]	MI[c] (6 months before alendronate initiation date)	4 (0.04 %)	39 (0.3 %)
Serum creatinine >1.6 mg/dl	CKD[c] (Anytime before alendronate initiation date)	139 (1.4 %)	79 (0.6 %)
Erosive gastrointestinal disease within 5 years	K21 (previous 5 years)	255 (2.6 %)	207 (1.5 %)
Dyspepsia requiring daily treatment	K25/K26/K27	126 (1.3 %)	645 (4.6 %)
Metabolic bone disease	Any of the following at any time before or on date of alendronate initiation: Hyperparathyroidism: E21 OI: Q78.0 Osteopetrosis: Q78.2 Osteomalacia: M83	177 (1.8 %)	107 (0.8 %)
History of cancer	Malignancy[c] (Anytime before or on therapy initiation date)	146 (1.5 %)	1675 (12.0 %)
Other exclusion criteria			
Alcohol abuse	Lifestyle factors in primary care records	34 (0.4 %)	NA
Any exclusion criteria	Any of the above	3447 (35.4 %)	6228 (44.5 %)

NA Data not available, assumed to be fulfilled, *CKD* Chronic Kidney Disease, *MI* Myocardial Infarction, *OI* Osteogenesis imperfect

Other NA Severe hypertension, unstable angina, malabsorbtion, oestrogens, anabolic steroids, calcitonin, progestin, change in thyroid hormone dosage, fluoride treatment, unexplained weight loss, unsuitable anatomy on spinal radiographs, non-compliance with pre-randomizations study procedures, not ambulatory, history of bilateral hip replacement, unable to give informed consent, participating in another trial, intention to move within 4 years. Data not available: BMD at femoral neck over 3 SD

[a] See Ref. [26]

[b] Within 6 months

[c] See Ref. [16]

[d] Subjects can be included in more than one category

who are systematically excluded from most of cardiovascular disease trial, in spite of the great cardiovascular mortality within this particular population [23].

The differences between the final target population and the one selected for the RCT has proven to lead to dangerous results; higher rates of hyperkalemia and mortality due to the increase in the rates of prescription of spironolactone were found in hospitalized patients with heart failure after the aldactone randomized trial was published [24].

We arrive at the same conclusion; real-life users of alendronate in the SIDIAP and DHR databases are markedly different to those included in the FIT trial, even when broadening the inclusion criteria to include men and glucocorticoid users. This underlines the importance that the final population used to study bisphosphonates resembles the end-users, so that medical doctors can predict the effect and properly apply the evidence-based medicine in their daily practice.

Although RCT are the best method to assess, the (effectiveness) efficacy of medical interventions suffers from limitations of external validity, especially regarding the population included. Observational studies, while with different limitations, can however address this issue [25].

The main strength of our study lies in its large, validated and representative population included in the SIDIAP and

DHR databases. Secondly, to the best of our knowledge, this is the first study that carries out an in-depth analysis of the differences between the populations included in the alendronate pivotal trial FIT and the final target population that received this medication. Nevertheless, this study must be analyzed in the light of some limitations; due to the nature of the administrative data in both databases, we were not able to capture some of the exclusion criteria from the FIT trial as, for example, BMD levels (although it would have likely not altered our results), those exclusion and inclusion criterion related to the methodology of RCT (e.g., pre-randomization procedures, informed consent) or certain illness and treatments not routinely collected in primary care. Considering that the missing exclusion criteria such as severe hypertension, unexplained weight loss or changes in the thyroid hormone dosage are frequent reasons for medical consultation in primary care, our results are likely underestimating the proportion of users that would have been excluded from the FIT trial, limiting even more its external validity. We were also not able to account for subjects who had low eGFR, which would contraindicate the initiation of alendronate. Finally, this study used European routinely collected data and since the FIT trial was carried out in the United States, other differences between these two populations could not be accounted, hence our conclusions should be extrapolated with caution.

Conclusion

Patient characteristics used as exclusion criteria in FIT were commonly found among real-life users of alendronate. This severely limits the external validity of this trial. While subsequent RCTs have established the efficacy of alendronate in men and glucocorticoid users, efficacy data are needed for octogenarians, as well as for patients with other common co-morbidities.

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Compliance with Ethical Standards

Conflict of interest P. S, C. R, and A. P declare that they have no conflict of interest; D. P. A: Scientific Coordinator of the SIDIAP Database. Unrestricted research grants from Amgen and Bioiberica; A.D.P: speaker or advisor for Lilly, Amgen, UCB, Active Life Sci; C.C: received consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, Eli Lilly, GSK, Medtronic, Merck, MSD, Novartis, Pfizer, Roche, Servier and Takeda. (outside the submitted work); K.J: personal fees from consultancy, lecture fees and/or honoraria from AMGEN, GSK, Eli Lilly, Novartis, Servier, Medtronic and Roche outside the submitted work; B.A: research grants from or served as an investigator in studies for Novartis, Takeda, NPS Pharmaceuticals and Amgen; T.V.S: advisory boards for GSK and Boehringer and advice to Laser Rx on epidemiological and pragmatic trial methods outside the submitted work.

Human and Animal Rights For this type of study formal consent is not required.

Informed Consent Patient consent was not required (anonymised retrospective data).

References

1. Rothwell PM (2005) External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 365:82–93
2. Taylor RS, Bethell HJN, Brodie DA (2007) Clinical trials versus the real world: the example of cardiac rehabilitation. Br J Cardiol 14:175–178
3. Moher D, Schulz KF, Altman DG (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-grouprandomised trials. Lancet 357: 1191–1194
4. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S (2001) Exercise-based rehabilitation for coronary heart disease. Cochrane Database Syst Rev 1:CD001800
5. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE (1996) Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 348:1535–1541
6. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Palermo L, Prineas R, Rubin SM, Scott JC, Vogt T, Wallace R, Yates AJ, LaCroix AZ (1998) Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 280:2077–2082
7. Cadarette SM, Katz JN, Brookhart MA, Stürmer T, Stedman MR, Solomon DH (2008) Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture. Ann Intern Med 148: 637–646
8. Feldstein AC, Weycker D, Nichols GA, Oster G, Rosales G, Boardman DL, Perrin N (2009) Effectiveness of bisphosphonate therapy in a community setting. Bone 44:153–159
9. Erviti J, Alonso A, Gorricho J, López A (2013) Oral bisphosphonates may not decrease hip fracture risk in elderly Spanish women: a nested case–control study. BMJ Open 3:e002084

10. Abrahamsen B, Eiken P, Eastell R (2010) Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab 95:5258–5265
11. Ramos R, Balló E, Marrugat J, Elosúa R, Sala J, Grau M, Vila J, Bolíbar B, García-Gil M, Martí R, Fina F, Hermosilla E, Rosell M, Muñoz MA, Prieto-Alhambra D, Quesada M (2012) Validity for use in research on vascular diseases of the SIDIAP [Information System for the Development of Research in Primary Care]: the EMMA study. Rev EspCardiol [Engl Ed] 65:29–37
12. Garcia-Gil M, Hermosilla E, Prieto-Alhambra D, Fina F, Rossell M, Ramos R, Rodriguez J, Williams T, Van Staa T, Bolíbar B (2011) Construction and validation of a scoring system for selection of high quality data in a spanish population primary care database [SIDIAP]. Inform Prim Care 19:135–145
13. Kildemoes HW, Sørensen HT, Hallas J (2011) The Danish national prescription registry. Scand J Public Health 39:38–41
14. Lynge E, Sandegaard JL, Rebolj M (2011) The Danish national patient register. Scand J Public Health 39:30–33
15. Pedersen CB (2011) The Danish civil registration system. Scand J Public Health 39:22–25
16. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 43:1130–1139
17. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, Adami S, Weber K, Lorenc R, Pietschmann P, Vandormael K, Lombardi A (2000) Alendronate for the treatment of osteoporosis in men. N Engl J Med 343:604–610
18. Saag KG, Emkey R, Schnitzer TJ, Brown JP, Hawkins F, Goemaere S, Thamsborg G, Liberman UA, Delmas PD, Malice MP, Czachur M, Daifotis AG (1998) Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med 339:292–299
19. Liberman UA, Weiss SR, Bröll J, Minne HW, Quan H, Bell NH, Rodriguez-Portales J, Downs RW Jr, Dequeker J, Favus M (1995) Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 333:1437–1443
20. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA (2011) Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. J Gen Intern Med 26:783–790
21. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19:385–397
22. Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L (2006) Randomized controlled trials: do they have external validity for patients with multiple comorbidities? Ann Fam Med 4:104–108
23. Coca SG, Krumholz HM, Garg AX, Parikh CR (2006) Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. JAMA 296:1377–1384
24. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA (2004) Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 351:543–551
25. Grapow MT, von Wattenwyl R, Guller U, Beyersdorf F, Zerkowski HR (2006) Randomized controlled trials do not reflect reality: real-world analyses are critical for treatment guidelines! J Thorac Cardiovasc Surg 132:5–7
26. Black DM et al (1993) Design of the Fracture Intervention Trial. Osteoporos Int 3(Suppl 3):S29–S39