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The characteristics of osteoporotic fractures in the region of Bialystok (BOS-2). The application of the WHO algorithm, FRAX®BMI and FRAX®BMD assessment tools to determine patients for intervention

Charakterystyka złamań osteoporotycznych regionu białostockiego (B0S-2). Zastosowanie algorytmu WHO i narzędzi FRAX®BMI i FRAX®BMD do identyfikacji osób wymagających leczenia

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Abstract

Background: The 2007 WHO guidelines for the treatment of osteoporosis require that we know the population risk of an osteoporotic fracture for each country to classify patients requiring treatment.

Material and methods: Studies have been carried out among a random cohort of 1,608 women over the age of 40 to assess a ten-year absolute risk of main osteoporotic fractures (AR-10 m.o.fx.) and hip fractures (AR-10 h.fx.) by using FRAX®BMI and FRAX®BMD based on the epidemiology of fractures in England.

Results: Both methods gave similar results in assessing the probability of fracture, showing the increase of AR-10 m.o.fx. in subsequent life decades to rise from 5% in the fifth decade to 25% in the ninth, mean result 11%, and AR-10 h.fx. to rise over the same period from 0.5% to 13%, mean result 3%. The number of fractures increases up to the seventh and eighth decades, and decreases according to the number of patients in the age group. The commonest fracture risks reported, other than old age and low BMI, were a prior fracture, a family history of hip fracture and smoking.

Conclusions: Comparative analysis of examined parameters of FRAX between people with and without fractures showed considerable differences only in age and AR-10 m.o.fx. This doubled in people with previous fractures (ca. 18% *vs.* 9%) and AR-10 h.fx. (ca. 5% *vs.* 2.5%). The "middle" area between the average population risks (AR-10 m.o.fx. 11% and AR-10 h.fx. 3%) and the risks in patients with fractures (AR-10 m.o.fx. 18% and AR-10 h.fx. 9%) could work as an indicator: below those values the risk is low and no treatment is required; above those values, the risk is high, and intervention is necessary; the middle area implies a BMD examination and reassessment of the fracture risk. **(Pol J Endocrinol 2011; 62 (4): 290–298)**

Key words: *osteoporosis, fracture epidemiology, therapeutic thresholds*

Streszczenie

Wstęp: Schemat Światowej Organizacji Zdrowia (WHO) z 2007 roku postępowania wobec osteoporozy prowadzący do identyfikacji osób potrzebujących leczenia, aby zmniejszyć ryzyko złamania, stawia wymóg znajomości w każdym kraju poziomu populacyjnego zagrożenia złamaniami osteoporotycznymi.

Materiał i metody: Podjęto badania oceny 10-letniego prawdopodobieństwa głównych złamań osteoporotycznych (RB-10 g.z.op.) i złamań biodra (RB-10 b.) na niewyselekcjonowanej grupie 1608 kobiet po 40. roku życia, posługując się narzędziem FRAX®BMI i FRAX®BMD wzorowanym na epidemiologii złamań w Anglii.

Wyniki: Obydwa sposoby podobnie oceniły prawdopodobieństwo złamania i w kolejnych dekadach życia ujawniły rosnące RB-10 g.z.op. od ok. 5% w 5. dekadzie do 25% w 9., średnio 11%, oraz RB-10 b. odpowiednio od 0,5% do 13%, średnio 3%. Liczba złamań rosła do 7. i 8. dekady i malała zgodnie z liczebnością grupy wiekowej. Najczęściej zgłaszanymi czynnikami ryzyka, poza zaawansowanym wiekiem i niskim BMI, były: przebyte uprzednio złamanie, palenie tytoniu i złamanie biodra w wywiadzie rodzinnym.

Wnioski: Analiza porównawcza badanych parametrów FRAX osób z złamaniami i bez nich wykazała znamienne statystycznie różnice wyłącznie pod względem wieku i dwukrotnie wyższe RB-10 g.zop. osób ze złamaniami (ok. 18% *vs.* 9%) i RB-10 b. (ok. 5% *vs.* 2,5%). Przestrzeń „pośrednia" pomiędzy średnim ryzykiem populacyjnym (RB-10 g.z.op. 11% i RB-10 b. 3%) a ryzykiem osób ze złamaniami (RB-10 g.z.op. 18% i RB-10 b. 9%) mogłaby posłużyć jako punkt orientacyjny: poniżej wymienionych wartości — ryzyko małe, niewymagające leczenia, powyżej — ryzyko duże wymagające interwencji, zaś ta „pośrednia" stanowi wskazanie do badania BMD i ponownej analizy zagrożenia złamaniem. **(Endokrynol Pol 2011; 62 (4): 290–298)**

Słowa kluczowe: *osteoporoza, epidemiologia złamań, próg interwencji leczniczej*

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Introduction

Defining osteoporosis on the basis of BMD (T-score of minus 2.5) [1] does not fully reflect its nature or clinical manifestation i.e. susceptibility to low-energy fractures (= osteoporotic fractures) and its consequences. That has been proven by research that judged osteoporotic fractures against BMD. All of the research [2–5] shows that most fractures, including proximal femur ('hip fracture' for short) happen with BMD at the femoral neck above a T-score of minus 2.5, which was the WHO criterion for defining osteoporosis in 1994.

That resulted in intervention being offered only to individuals with low BMD (a T-score of less than minus 2.5). That complied with drugs registration and medical expense reimbursement rules.

It has become clear that factors other than low BMD affect bone strength and susceptibility to fracture. A number of clinical risk factors (CRFs) independent of BMD and individually sufficient to increase the risk have been examined by a series of meta-analyses of fracture epidemiology. They are: old age, low BMI, history of osteoporotic fracture, family history of hip fracture, low BMD, chronic glucocorticosteroids use, rheumatoid arthritis (with possible other secondary osteoporosis), excessive alcohol consumption and smoking [6, 7].

A great deal of global research has taken place to formulate a WHO algorithm determining the risk of fracture and whether there is a need for intervention (intermediate risk: should be verified by a BMD screening, low risk: no intervention required, high risk: treatment required). FRAX® is a risk assessment tool which combines the independent fracture risks into one parameter: a ten-year total (absolute) probability of an osteoporotic fracture (AR-10) [8].

At present, individuals with BMD above a T-score of minus 2.5 with fractures (most cases) or with a high probability of an osteoporotic fracture, are not diagnosed with osteoporosis. This leads to the self-contradictory conclusion that a patient has had an osteoporotic fracture but does not suffer from osteoporosis. Osteoporosis (T-score: minus 2.5) is thus only one of several reasons for excess bone brittleness and looking solely at osteoporosis means ignoring other reasons for lower bone strength. Clinically, it is not the diagnosis of osteoporosis but the assessment of an individual probability of fracture, whatever its cause, that determines for the doctor which patient should be given treatment. Treatment equals decrease of fracture risk.

Who then should be given treatment? Patients with high risk of fracture obviously. But at what AR-10? One criterion is cost effectiveness (which is cheaper: pharmacotherapy or intervention after the first or subsequent fractures?) That means learning the data representative of the whole country as well as pricing the cost of treatment. As drugs are available at a whole range of prices, and aimed at patients with differing BMDs, their effectiveness depends on the degree of BMD lowering. We have no such data in Poland. Applying data from another country would help. If not, we could create our own locally-based points of reference.

The aim of this study was:

— to determine the mean ten-year probability of the main osteoporotic fractures and hip fractures (AR-10 m.o.fx. and AR-10 h.fx.) in women over 40 years of age living in the region of Bialystok, by using FRAX® with BMI (FRAX/BMI) and with BMD (FRAX/BMI) separately;
— to analyse the differences between fracture risk for patients with and without previous osteoporotic fractures;
— to identify intervention thresholds applicable in Poland;
— to identify the most efficient treatment for certain patients and who would not benefit from treatment at all.

Material and methods

The subject of this epidemiological analysis was a cohort of 1,608 non-selected women living in the region of Bialystok, aged 40 to 89, average age 63.9. They underwent epidemiological examination and were diagnosed, for different reasons, in the Centre for Osteoporosis and Osteo-Articular Diseases in Bialystok. Apart from BMD screening, they were asked to fill in a questionnaire on various risk factors, being FRAX components. Figure 1 shows age distribution in the BOS-2 cohort.

Having established the age, weight, height and BMI (kg/m^2), the following were recorded: evidenced low-energy fracture, over 40 years of age, hip fracture in parent, chronic, more than 12 months' glucocorticosteroids use, rheumatoid arthritis, long-lasting smoking and alcohol abuse. All participants were screened for BMD at neck and total proximal femur as well as L1-L4 vertebrae using DXA with Hologic QDR4500SL. Still, only 1107 women held all the documentation necessary for FRAX/BMD calculation. The calculation included a ten-year probability of fracture at the proximal femur (so-called "hip fracture") (AR-10 h.fx.) and altogether at all main sites (AR-10 m.o.fx.), meaning hip, clinical vertebra fracture, Colles' fracture and proximal humerus fracture. A computer-driven form of FRAX® (FRAX-WHO Fracture Risk Assessment Tool) of 2008 was used, with BMI and BMD [8]. It was based on the epidemiology of fracture among women in England and is currently being popularised by the WHO report [6] and the European Guidances from

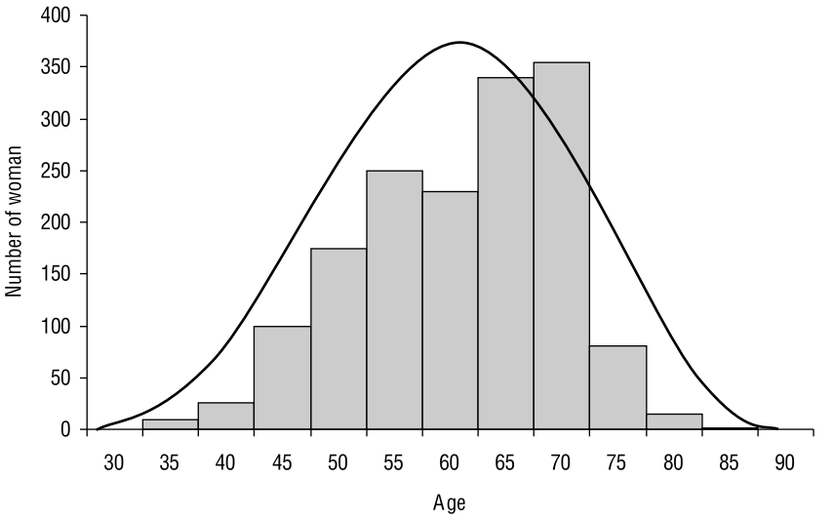

Figure 1. *BOS-2: number of women/observations and age distribution in the population of 1,608 women*
Rycina 1. *BOS-2: liczebność kobiet/obserwacji i dystrybucja wieku w populacji 1608 kobiet*

the ESCEO and IOF [7]. The statistical analysis of the differences in the contrasted groups was made using a *t*-student test.

Results and discussion

The commonest CRFs in the BOS-02 cohort were low BMI at relative risk (RR) below 1.0, history of an osteoporotic fracture, smoking, family history of hip fracture, and rheumatoid arthritis.

The percentage of women who have sustained an osteoporotic fracture increases with age (Figure 2). In the sixth decade, one in six has had a fracture (16.82%), in the seventh decade it is 29.24% and in the eighth decade it is 33.46%. Over the age of 80, almost half of women have suffered a fracture (44.44%), the mean result being that 27.05% of women over the age of 40 suffer a low-energy fracture. The number of fractures complies with the age distribution in the BOS-2 cohort, the lowest over the age of 80, in a group of only 27 females (Figure 3).

Age, BMI and BMD calculations and data from medical history were used to assess an individual, total/absolute ten-year probability of fracture at the main osteoporotic locations (AR-10 m.o.fx.) and hip (AR-10 h.fx.) using the FRAX tool in two versions with BMI and BMD – FRAX/BMI and FRAX/BMD via the internet, as shown in Figures 4 and 5.

The AR-10 m.o.fx. results calculated with BMI and BMD show considerable similarities: there is a four-fold increase between the sixth and ninth decades, with mean results at 11.0–11.8%. There is also a noticeable two-fold increase of risk between the ages of 50 and 70 and another one between the ages of 70 and 90.

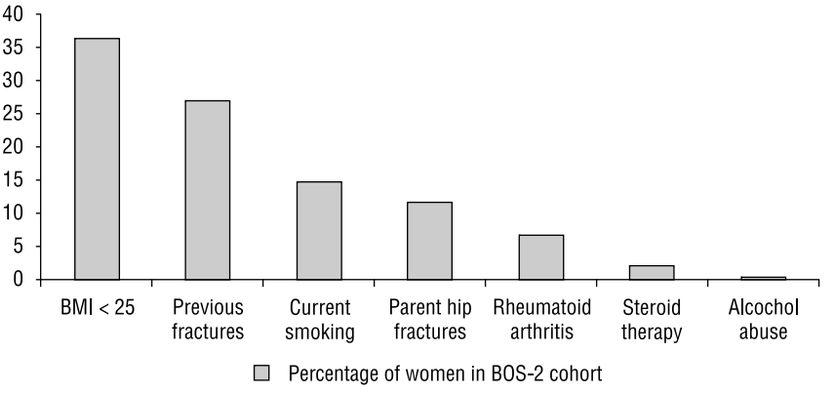

Figure 2. *BOS-2: frequency of clinical fracture risks*
Rycina 2. *BOS-2: częstotliwość występowania klinicznych czynników ryzyka*

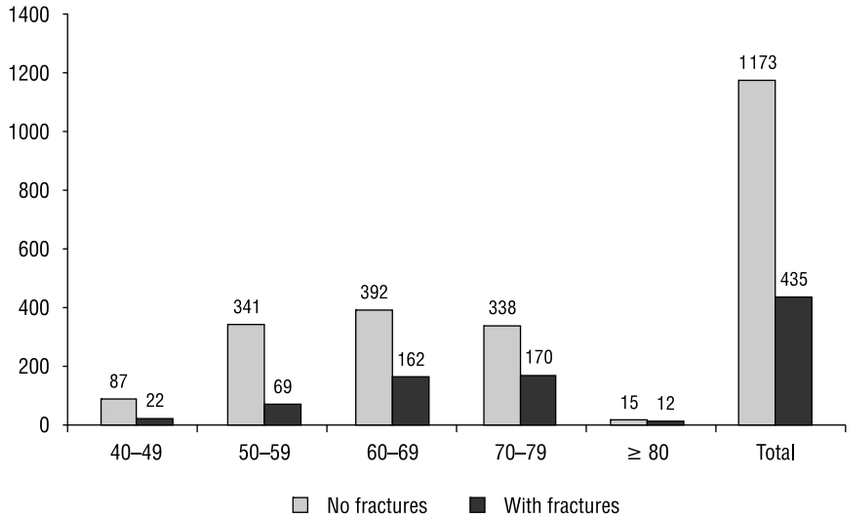

Figure 3. *BOS-2: number of individuals with and without fractures according to life decades in a population of 1,608 women aged 40–89*
Rycina 3. *BOS-2: liczba osób bez i ze złamaniami w poszczególnych dekadach życia w populacji 1608 kobiet w wieku 40–89 lat*

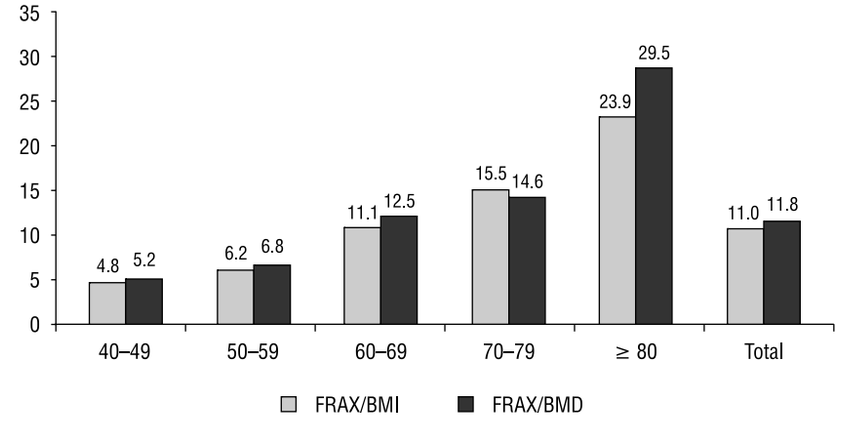

Figure 4. *BOS-2: ten-year probability of main osteoporotic fracture (femoral neck, vertebral column, Colles' fracture) (AR-10 m.o.fx.) calculated with FRAX®BMI and FRAX®BMD*
Rycina 4. *BOS-2: 10-letnie ryzyko głównych złamań osteoporotycznych (szyjki kości udowej, kręgosłupa, k. ramiennej i złamanie Collesa) RB-10 g.z.op. wyliczone narzędziami FRAX®BMI i FRAX®BMD*

Figure 5 illustrates a similar increase in the risk of hip fracture. Every decade of life increases the risk twice; in the ninth decade it is five times higher than the intermediate risk (2.8–3.1%).

Is there a relationship between the current BMD screenings (which manifest results lower than in the past) and the history of an osteoporotic fracture (Figure 6)? The BOS-2 cohort was divided into two groups. One with a T-score for the femoral neck below minus 2.5 (osteoporosis), the other with a T-score above minus 2.5 (norm), where the mean T-score was minus 1.4- minus 1.5, indicating an osteoporosis T-score of minus 3.1. There were 18% of cases with osteoporosis in the group without fracture and 29% in the group with fractures (in 71% of normal BMD readings).

Table I illustrates different parameters in patients with and without fractures. Significant statistical differences were present only in the case of age (63.1 years without fractures, 66.5 years with fractures) and analysis with the FRAX/BMI and FRAX/BMD tools,both in the cases of AR-10 m.o.fx., and AR-10 h.fx. AR-10 was twice as high in individuals with fractures than in those without.

Mean AR-10 results in the whole cohort AR-10 m.o.fx. approx. 11% and AR-10 h.fx. approx. 3% and mean AR-10 of women with previous fractures approx. 18% and approx. 5% respectively can be used as reference values to assess the need for treatment in a population represented by the BOS-2 cohort. What is the significance of the particular CRF? The influence of each reported CRF on the number of females with AR-10 above

Table I. *BOS-2: Statistical differences between women with and without previous fracture in the BOS-2 cohort calculated using FRAX®BMI and FRAX®BMD*

Tabela I. *BOS-2: Analiza statystyczna różnic pomiędzy kobietami z przebytym złamaniem i bez niego w kohorcie BOS-2 oceniana sposobem FRAX®BMI i FRAX®BMD*

	Mean without fractures (n = 1173)	Mean with fractures (n = 435)	P
Age (years)	63.1	66.5	< 0.001
BMI [kg/m^2]	27.7	28.0	NS
BMD Z-score	0.02	–0.05	NS
BMD in femoral neck [g/cm^2]	0.74	0.73	NS
Family history of hip fracture (yes/no)	11%	13%	NS
Rheumatoid arthritis (yes/no)	7%	7%	NS
Glucocorticosteroids use (yes/no)	2%	3%	NS
Smoking (yes/no)	16%	13%	NS
Excess alcohol consumption (yes/no)	0%	1%	NS
AR-10 m.o.fx. FRAX®BMI (%)	8.4%	18.2%	< 0.001
AR-10 m.o.fx. FRAX®BMD (%)	9.4%	17.5%	< 0.001
AR-10 h.fx. FRAX®BMI (%)	1.9%	5.3%	< 0.001
AR-10 h.fx. FRAX®BMD (%)	2.3%	5.0%	< 0.001

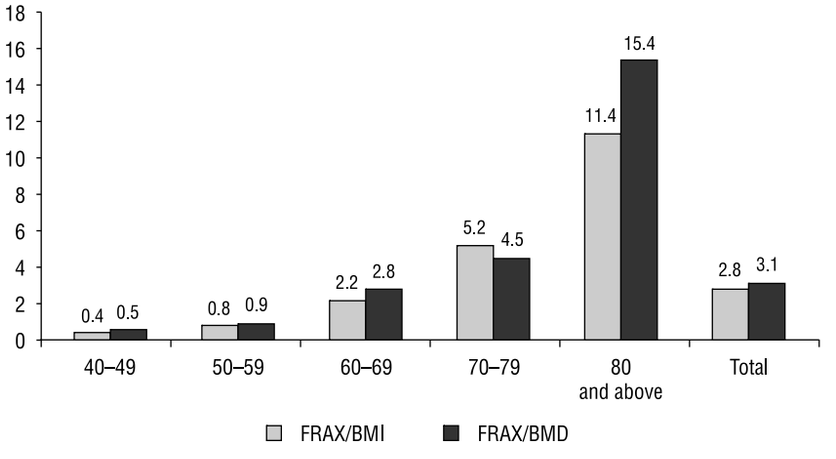

Figure 5. *BOS-2: Ten-year probability of hip fracture (AR-10 h.fx.) calculated with FRAX®BMI and FRAX®BMD*

Rycina 5. *BOS-2: 10-letnie ryzyko złamań b.k.k.u. (biodra) RB-10 b. wyliczone narzędziami FRAX®BMI i FRAX®BMD*

18% compared to those below 18% may be contributory. That could help identify the so-called 'strong CRF' in the whole examined cohort. That is shown in Figures 7–13.

In the population of 1,078 females, approximately 85.8% were burdened with RB-10 below 18% and 14.19% had RB-10 above 18%. The latter figure increases with age; only in the ninth decade does it become inversely proportional.

Every single CRF increases the number of individuals with AR-10 above 18% by 6%.

Family history of hip fracture doubles the number of individuals with AR-10 above 18%.

A previous fracture increases the number of individuals with AR-10 above 18% by 5.5-fold.

Of 14 individuals with chronic steroid use, half were burdened with AR-10 above 18%, which constituted the group with the highest probability of an osteoporotic fracture.

Active smoking and excessive alcohol consumption seem to be weak CRFs. But only seven patients acknowledged these facts in their medical record.

The analysis of the level of significance of particular risk factors proves that long-term glucocorticosteroids use, family history of hip fracture, and

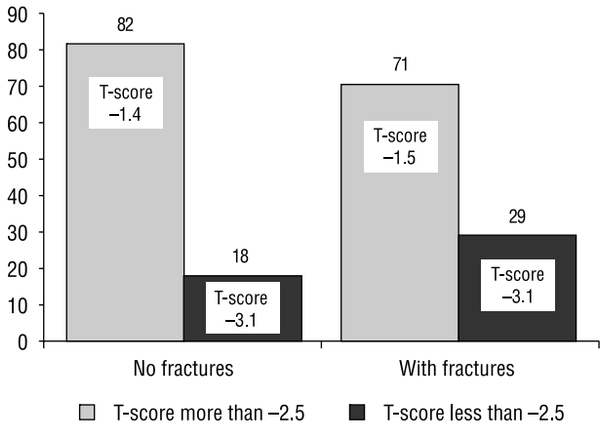

Figure 6. *BOS-2: osteoporotic fractures against "densitometric osteoporosis"*

Rycina 6. *BOS-2: złamania osteoporotyczne* vs. *„osteoporoza densytometryczna"*

past hip fracture represent serious danger, as has long been known.

Discussion

The application of the WHO algorithm is becoming more and more widespread. However, in order to reach an agreement on an appropriate threshold to identify patients for intervention, the data needs to be tailored to national requirements. The algorithm implies the need for AR-10 screening (individual, absolute risk of fracture), and correctly classifies it into low, intermediate and high. High risk requires intervention without any additional screening. Intermediate risk implies a BMD examination and reassessment of fracture risk. With low risk, no intervention is required.

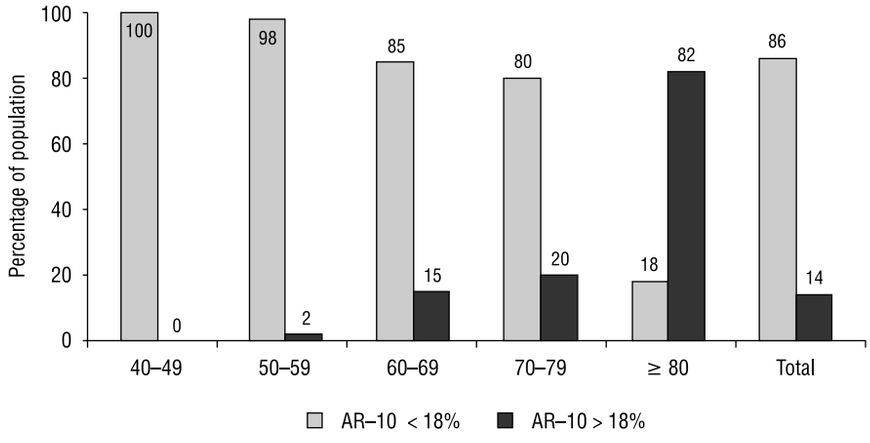

Figure 7. *BOS-2: influence of age (life decades) on the number of individuals with AR above 18%*

Rycina 7. *BOS-2: wpływ wieku (dekad życia) na odsetek osób z RB-10 powyżej 18%*

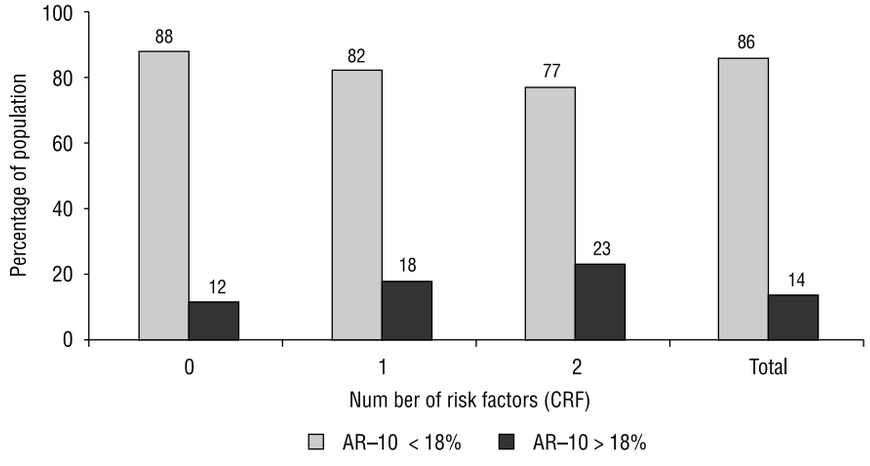

Figure 8. *BOS-2: influence of the number of risk factors on the number of individuals with AR-10 above 18%*

Rycina 8. *BOS-2: wpływ liczby czynników ryzyka na odsetek osób z RB-10 powyżej 18%*

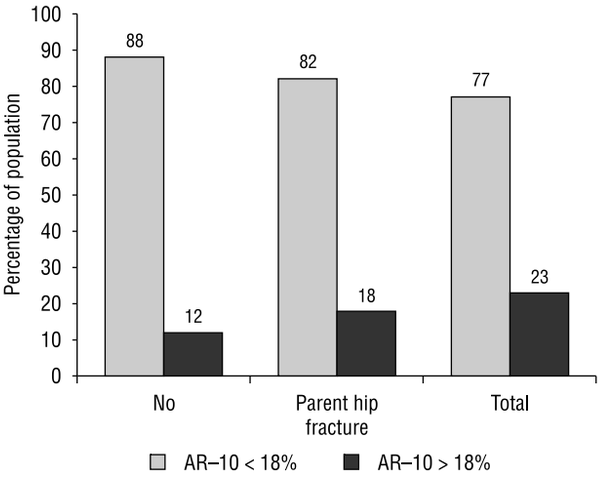

Figure 9. *BOS-2: influence of hip fracture in parent on the number of individuals with AR-10 above 18%*

Rycina 9. *BOS-2: wpływ złamania biodra u rodziców na odsetek osób z RB-10 powyżej 18%*

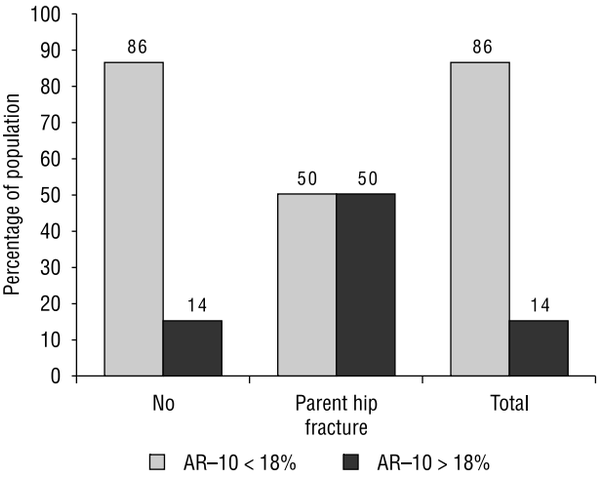

Figure 11. *BOS-2: influence of long-term glucocorticosteroids use on the number of individuals with AR-10 above 18%*

Rycina 11. *BOS-2: wpływ glikokortykoidosteroidoterapii na odsetek osób z RB-10 powyżej 18%*

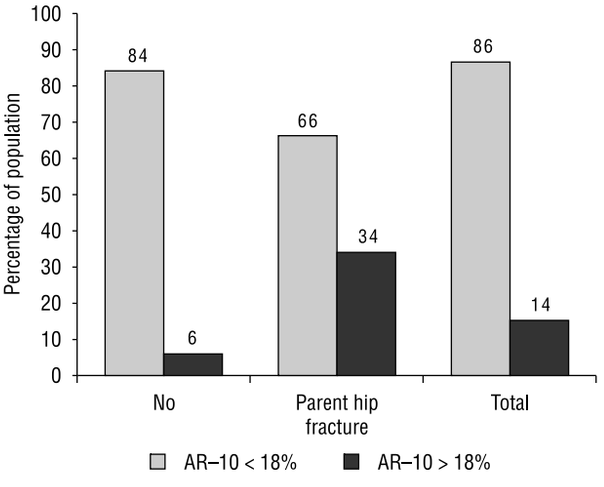

Figure 10. *BOS-2: influence of previous fracture on the number of individuals with AR-10 above 18%*

Rycina 10. *BOS-2: wpływ przebytego złamania na odsetek osób z RB-10 powyżej 18%*

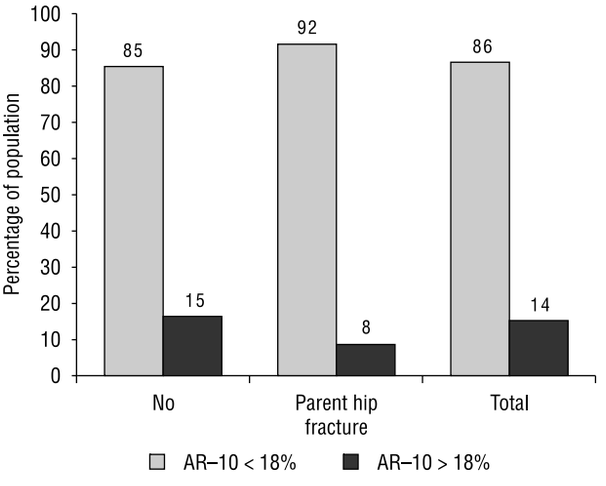

Figure 12. *BOS-2: influence of active smoking on the number of individuals with AR-10 above 18%*

Rycina 12. *BOS-2: wpływ aktywnego palenia na odsetek osób z RB-10 powyżej 18%*.

Our points of reference were the mean AR-10 in the population and the part of the population that had suffered an osteoporotic fracture, which confirms the diagnosis of osteoporosis. The frequency of occurring/reporting particular CRFs and their influence contribute additional information on the Polish population. The analysis was performed on a group of 1,608 women over the age of 40 that we had at our disposal in our database at the Centre for Osteoporosis and could be used ad hoc. The group comprised non-selected females, although not selected by blind choice. All the subjects had been asked questions on CRF, which is a FRAX requirement. The age distribution was typical for a cohort of postmenopausal women and comparable to the BOS-1 [4, 5] screening. AR-10 m.o.fx. and AR-10 h.fx. results calculated with FRAX/BMI and FRAX/BMD proved similar. More significant differences were reported only in the ninth decade of life.

The average value of AR-10 m.o.fx. with and without BMD was approximately 11%, the value of AR-10 h.fx. was approximately 3%. AR-10 m.o.fx. in the case of individuals with past low-energy fractures with and without BMD was above 18% and AR-10 h.fx. was 5%.

The above data were held as reference points.

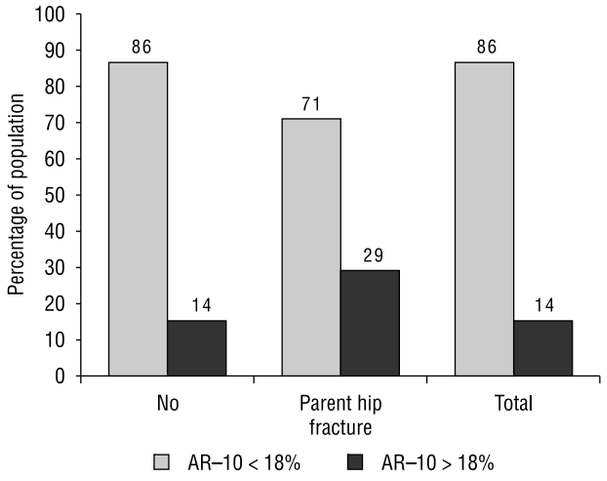

Figure 13. *BOS-2: influence of excessive alcohol consumption on the number of individuals with AR-10 above 18%*

Rycina 13. *BOS-2: wpływ nadużywania alkoholu na odsetek osób z RB-10 powyżej 18%*

We consider AR-10 m.o.fx. and AR-10 h.fx. below the middle population risk in each life decade (i.e. on average below AR-10 m.o.fx. 11%, and/or AR-10 h.fx. 3%) as "low" risk. "High" risk means AR-10 m.o.fx. above 18%, the mean value of AR-10 in women with previous fractures. "Intermediate" risk is then between those values of mean population AR-10 (11%), and the mean value of patients with fractures (18%). These make it possible to classify patients according to those three groups at the first appointment at primary health care level by using mean values and the FRAX®BMI tool without the necessity for BMD screening. AR-10 m.o.fx. higher than 11% and/or AR-10 h.fx. higher than 3% are indications for Hip BMD by DXA measurements and for AR-10 recalculation with FRAX/BMD. Values above AR-10 18% should be considered as "high" probability requiring pharmacological intervention.

There is a lively debate as to whether one intervention threshold for all patients is more justified than one threshold proportionate to each life decade [9, 10]. Most opinion-formers advocate the latter, giving priority to the life risk of a younger individual who will live longer. Therefore, younger people have their intervention thresholds set much lower than older patients. Such a solution is currently supported by the Polish Society for Osteoarthrology, the Polish Foundation of Osteoporosis, and the Multidisciplinary Forum on Osteoporosis, who promote an easy-to-use AR-10 calculator with therapeutic data adequate for each age [11].

Using the FRAX methodology, Johnell points to AR-10 m.o.fx. over 14% as being the cost-effective threshold [12]. In the USA, AR-10 h.fx. above 3% is the threshold for intervention[13, 14]. In Japan, AR-10 m.o.fx. from 5% in the sixth decade to 20% in the ninth [15]. Similar intervention tresholds were considered for Poland in 2007 [11]. In Belgium, a previous fracture suffices to refund the cost of treatment and RB-10 g.z.op. ranges between 7.5% at 50 years of age to 26% at 80 [16]. In England, the cost-effective threshold of risedronate therapy is AR-10 m.o.fx. at 13% [17]. The use of the FRAX tool in the USA classifies 37% of women over 50 for treatment and reduces the number of patients for intervention by 20% in relation to the previous recommendation [18].

27% of postmenopausal women would require intervention if we agreed on AR-10 m.o.fx. above 18% (individuals with previous fracture) as indicating "high" risk. In another Polish analysis, with 94 participants, 20.2% of females aged 55–79 would require treatment if all osteoporotic fractures were intervention indicators [19].

Since 31 May, 2008 it has been the EMEA (European Medicines Agency) condition that if a medicine is to be registered "for treatment of osteoporosis in postmenopausal women with high fracture probability," screenings for the drug's effectiveness in females with overpopulation risk need to be done regardless of BMD [20].

Pharmacotherapy for individuals at high probability of fracture with BMD characteristic of osteopenia poses a problem. Most registered and reimbursed antiresorptives are active only at low BMD, below a T-score of minus 2.5. Consequently, the patient's BMD, as well as the proposed drug's efficacy, need to be identified prior to intervention. For instance, it will not be successful to treat a patient with AR-10 30% and BMD at a T-score for example of minus 1.8 with alendronate, which is a reimbursed drug.

Our BOS-2 population is characterised by the frequency of particular CRFs (low BMI, past osteoporotic fracture, smoking and hip fracture in parent) and the influence grading (previous fracture, glucocorticosteroids use, family history), which makes it easier to identify patients for intervention in outpatient healthcare.

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