ORIGINAL ARTICLE

The application of FRAX® to determine intervention thresholds in osteoporosis treatment in Poland

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KEY WORDS

fracture epidemiology, osteoporosis, therapeutic thresholds

ABSTRACT

INTRODUCTION FRAX®, an assessment algorithm for estimating fracture probability, has been widely used for the evaluation of osteoporosis since 2008. Its clinical use requires that osteoporotic fracture probability is established at which treatment can be recommended.

OBJECTIVES The aim of the present study was to explore possible treatment thresholds for Poland.

PATIENTS AND METHODS The FRAX-based probabilities were calculated in 1608 unselected postmenopausal women from Białystok using the British model (version 3.1). Intervention thresholds were set at fracture probability equal to women with a bone mass density (BMD) T-score of –2.5 standard deviation (criterion A), equal to women with a prior fracture using a fixed threshold irrespective of age (criterion B), or an age-dependent threshold (criterion C). Additionally, we assumed that all women with a prior fracture would be eligible for treatment plus those with a fracture probability equal to women with a prior fracture using a fixed threshold (criterion D).

RESULTS Mean 10-year probability of a major osteoporotic fracture was 10.9% when BMD was not included in the FRAX calculation and 11.6% with BMD included. In women with a prior fragility fracture, the respective probabilities were 18.0% and 17.4%.
For criterion A, 39% women aged 50 years or more would be eligible for treatment, for criterion D – 35%, and for criteria B and C – 16%. For criteria B and C, women with higher risk would be eligible for treatment compared with criteria A and D. Assuming a relative fracture risk reduction of 30%, the number needed to treat (NNT) to prevent a major fracture was lower for criteria B and C (NNT = 13 and 14, respectively) than for criteria A and D (NNT = 18).

CONCLUSIONS The use of intervention thresholds based on the probabilities equal to women with a prior fracture is most efficient. The use of an age-specific threshold may be more clinically appropriate than a fixed probability threshold for all ages.

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INTRODUCTION The diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD). The disease is defined as a BMD value that lies below 2.5 standard deviations (SD) or more below the young female reference range.[1,2] The World Health Organization and International Osteoporosis Foundation recommend the femoral neck as a reference site and the National Health and Nutrition Examination Survey III (NHANES III) values for Caucasian women aged 20 to 29 years should be used as a reference range.[3,4] The development of diagnostic criteria and the availability of equipment for measuring BMD have resulted in the widespread use of BMD testing to determine eligibility for osteoporosis treatment. In Poland, for example, intervention was recommended for individuals with a low BMD T-score of –2.5 SD.

However, there are limitations in the use of BMD to determine intervention thresholds. Firstly, the BMD T-score decreases progressively with age, so in the elderly, a T-score of –2.5 SD is higher than the average BMD. Secondly, although BMD has high specificity for fracture risk prediction, it has low sensitivity, so the majority of osteoporotic fractures will occur in individuals with BMD values above the osteoporosis threshold.[1,5-8]

In the past 15 years, extensive research has been conducted to identify factors other than BMD that contribute to fracture risk. Examples include age, sex, prior fracture,[9] a family history of fracture,[10] as well as lifestyle risk factors such as physical inactivity[11] and smoking.[12] Some of these risk factors are partially or wholly independent of BMD. Therefore, independent risk factors used with BMD enhance the information provided by BMD alone.[13] Conversely, some strong BMD-dependent risk factors can, in principle, be used for fracture risk assessment in the absence of BMD tests. For this reason, the consideration of well-validated risk factors, with or without BMD, improves fracture prognostication and the selection of individuals at high risk for treatment.

FRAX® is a computer based algorithm (http://www.shef.ac.uk/FRAX) that provides models for the assessment of fracture probability in men and women.[14-16] It was constructed from 9 prospective primary cohorts and validated in further 11 prospective cohorts, including more than 275,000 persons corresponding to 1.4 million person/years with more than 22,000 reported fractures.[13] The approach uses easily obtained clinical risk factors to estimate 10-year fracture probability. The estimate can be used alone or with BMD to enhance fracture risk prediction. For this reason, intervention thresholds are increasingly being based on fracture probability rather than BMD alone.[17-26]

The probabilities of fracture and death vary markedly in different regions of the world,[27] so the FRAX models need to be calibrated to the known epidemiology of fracture and death in any one region. At present, models are available for Argentina, Australia, Austria, Belgium, Canada, China, Colombia, France, Finland, Germany, Hong Kong, Hungary, Italy, Japan, Lebanon, Mexico, the Netherlands, New Zealand, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, the United Kingdom (UK), and United States (US).

In the absence of a FRAX model for a particular country, a surrogate country may be selected. At present, there is no FRAX model available for Poland, largely because of marked differences in fracture rates reported in different studies.[28-30] For this reason, the UK model has been used as a surrogate model for Poland.[31] The aim of the present study was to explore the manner by which FRAX-based intervention thresholds might be developed in the Polish setting.

PATIENTS AND METHODS We studied a cohort of 1608 randomly selected, postmenopausal women living in the region of Białystok, aged 40 to 89 years.[32] They were invited to the Centre for Osteoporosis and Osteo-Articular Diseases in Białystok for BMD testing. BMD was measured by dual-emission X-ray absorptiometry (DXA) at the femoral neck, the proximal femur, and at the lumbar spine (L1–L4 vertebrae) with the use of Hologic QDR4500SL. Apart from BMD screening, height and weight were measured and the women were asked to fill out a questionnaire on the risk factors used in FRAX®. These comprised:

1. a prior fragility fracture above the age of 40 years
2. parental history of hip fracture
3. current tobacco smoking
4. ever long-term use of oral glucocorticoids (>12 months)
5. rheumatoid arthritis
6. other causes of secondary osteoporosis
7. alcohol consumption of 3 or more units daily.

Ten-year fracture probability was assessed with the UK version of FRAX® (version 3.1).[15] For each patient, we estimated the 10-year probability of a major osteoporotic fracture (hip, clinical spine, forearm, or humerus) or of a hip fracture. The estimate of probability was made with clinical risk factors alone and with femoral neck BMD included in the FRAX model.

Intervention thresholds were based on the probability of a major osteoporotic fracture and explored in several ways. The first approach (criterion A) was based on the current guidelines in Poland that recommend treatment in patients with a T-score of –2.5 SD or less. The fracture probability at this T-score could therefore be used as an intervention threshold. The T-score was computed using the NHANES III as a reference for BMD at the femoral neck in Caucasian women aged 20 to 29 years.[4] The calculation of fracture probability at a T-score of –2.5 SD was made at the body mass index (BMI) of 24 kg/m^2. Changes in BMI have little effect on predictive value for fracture risk assessment in the presence of BMD.[10]

A second criterion was to set a fixed intervention threshold equivalent to a mean fracture probability in the cohort of women aged 50 years and older with a prior fragility fracture (criterion B). Since fracture probabilities in women with a prior fracture increase progressively with age, the third approach was to set a similar threshold (equivalent to a woman with a prior fragility fracture in the UK) that was age-specific (criterion C) – an approach used by the National Osteoporosis Guideline Group (NOGG) in the UK[17] and discussed in the Polish setting elsewhere.[31] Finally, we considered a management algorithm whereby women with a prior fragility fracture would be eligible for treatment together with women in whom the fracture probability exceeded

TABLE 1 Baseline characteristics of 1608 postmenopausal women

	Mean/prevalence			
	all women	no prior fracture	prior fracture	two-sided *P* value[b]
number of women	1608	1173	435	
age, y	64.0 ±9.0	63.1 ±9.0	66.5 ±8.5	<0.001
BMI, kg/m²	27.8 ±4.6	27.7 ±4.8	28.0 ±4.2	0.15
previous fracture, %	27	0	100	–
parental history of hip fracture, %	12	11	13	0.25
current smoking, %	15	16	13	0.21
glucocorticoids, %	2	2	3	>0.30
rheumatoid arthritis, %	7	7	7	>0.30
alcohol intake ≥3 units daily, %	0	0	1	0.18
secondary osteoporosis, %	0	0	0	–
femoral neck BMD, g/cm²[a]	0.73 ±0.09	0.74 ±0.09	0.73 ±0.09	0.11
lumbar spine BMD, g/cm²[a]	0.89 ±0.13	0.90 ±0.13	0.87 ±0.13	<0.001
total hip BMD, g/cm²[a]	0.88 ±0.11	0.88 ±0.10	0.87 ±0.11	0.21
10-year probability of major fracture without BMD, %	10.9 ±6.5	8.3 ±4.0	18.0 ±6.6	<0.001
10-year probability of major fracture with BMD, %	11.6 ±7.6	9.3 ±5.2	17.4 ±9.3	<0.001
10-year probability of hip fracture without BMD, %	2.8 ±3.2	1.9 ±2.2	5.2 ±4.1	<0.001
10-year probability of hip fracture with BMD, %	3.0 ±4.8	2.2 ±3.1	4.9 ±7.0	<0.001

a BMD available in 1078 women
b comparison of those with and without a prior fracture, Fisher's permutation test

Abbreviations: BMD – bone mineral density, BMI – body mass index

the average fracture probability of a prior fragility fracture (criterion D).

For each criterion, the number of postmenopausal women aged 50 years or more that exceeded the intervention threshold (and would thus be eligible for treatment) was calculated as a total and in 5 year age intervals using FRAX probabilities that included BMD in the calculation. The expected number of fractures in eligible women was calculated from the 10-year probability of a major osteoporotic fracture. To assess the effect of different management algorithms, we calculated the number of fractures that would be averted assuming a treatment for 10 years with an efficacy of 30% (relative risk = 0.7). This order of efficacy is consistent with a meta-analysis of the effects of bisphosphonates used in the health economic evaluation of treatment strategies.[33,34] For comparative purposes we calculated the number of women who would require treatment to avert 1 major fracture (number needed to treat – NNT).

RESULTS The baseline characteristics of patients are summarized in TABLE 1. The mean age was 64 years and the mean BMD at the spine and femoral neck was 0.89 and 0.73 g/cm², respectively. A history of fracture was reported by 27% of the patients (n = 147). The prevalence of a prior fracture increased with age from 17% between the age of 50 to 54 years to 53% at the age of 80 years and above. The probability of a major fracture was 10.9% when calculated without BMD and 11.6% with the inclusion of BMD. Hip fracture probabilities were approximately 3 times lower than the probability of a major fracture. Fracture probabilities were similar with or without the inclusion of BMD in the FRAX model. The similarity indicates that the cohort was not preferentially enriched by women with low or high BMD for age.

Women with a prior fracture were older than women with no prior fracture and had a lower BMD at the lumbar spine, but did not differ in terms of baseline characteristics in other respects (TABLE 1). As expected, fracture probabilities were approximately 2-fold higher in women with a prior fracture.

The effects of different management algorithms on the population of postmenopausal women who would be eligible for treatment are shown in TABLE 2. If an intervention threshold was set at a femoral neck T-score of –2.5 SD and applied to the Polish cohort (scenario A), then 39% of women aged 50 years or more would be eligible for treatment (TABLE 2).

Note that the proportion of treated women did not vary markedly with respect to age until the age of 80 years and older. In women over the age of 80 years, the vast majority would be eligible for treatment. The reason relates to the BMD T-score, which decreases progressively with age so that in the elderly, a T-score of –2.5 SD is higher than the average BMD. The point is illustrated in the FIGURE, which shows fracture probabilities in women (with no clinical risk factors) at a T-score of –2.5 SD and women with an average T-score for age. At the age of 50 to 54 years, the fracture probability in women at the threshold of osteoporosis was approximately 2-fold

TABLE 2 The effect of different intervention thresholds on the proportion (%) of women eligible for treatment by age

age, y	n	Criterion A T-score = –2.5 SD[b]	Criterion B prior fracture[a]	Criterion C prior fracture[b]	Criterion D prior fracture or probability >17.5%
50–54	104	31.7	0.0	11.5	17.3
55–59	122	32.8	5.7	21.3	25.4
60–64	117	44.4	10.3	22.2	35.0
65–69	198	44.4	18.7	17.2	37.9
70–74	319	32.6	16.9	10.0	34.8
75–79	108	44.4	33.4	13.9	50.9
80–84	15	80.0	80.0	40.0	86.7
85–89	2	100.0	100.0	100.0	100.0
≥50	985	38.5	16.1	15.5	35.1

a fixed threshold at all ages
b age-dependent thresholds calculated from the UK FRAX model

Abbreviations: SD – standard deviation

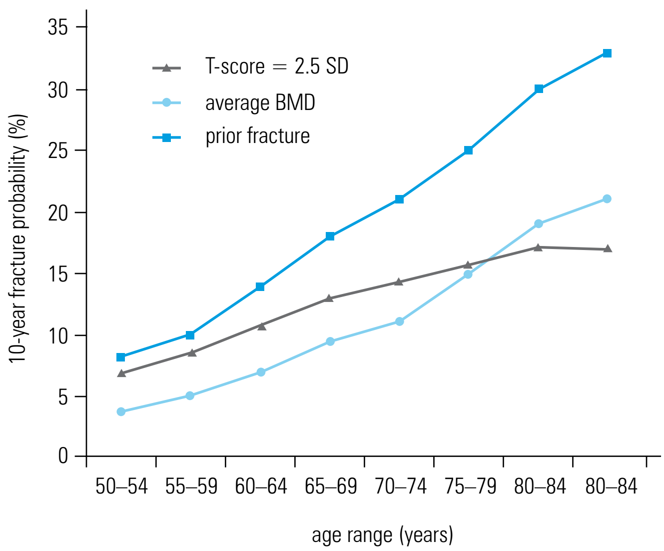

FIGURE Ten-year probability of a major fracture by age in women with an average T-score for age compared with women with a femoral neck T-score of –2.5 standard deviation (scenario A) and women with a prior fragility fracture (scenario C)
Abbreviations: see TABLES 1 and 2

higher than in women with average BMD. The difference in fracture probabilities decreased with age, so that at the age of 60 to 65 years the probability was only 50% higher in women with osteoporosis. Over the age of 75 years, the fracture probability was lower in women with a T-score of –2.5 SD than in women with an average BMD for age.

The second approach to exploring intervention thresholds was to set a fixed threshold equivalent to the mean fracture probability of women in the Polish cohort with a prior fragility fracture. In women with a prior fracture, the average 10-year probability of a major osteoporotic fracture was approximately 17.5%. The implications of using this value as an intervention threshold are shown in TABLE 2, criterion B. At younger ages, much fewer women would be selected for treatment than if the T-score threshold was used. Indeed, with a 17.5% 10-year fracture probability, no women aged 50 to 54 years would be eligible for treatment. The proportion eligible for treatment rose progressively with age. As with the use of a fixed T-score threshold, the vast majority of women aged 80 years or more would be eligible for treatment with a fixed probability threshold because of the progressive increase in fracture probability with age (FIGURE). Overall, 16% of women over the age of 50 years would be eligible for treatment.

The effect of using an age-specific threshold, based on the probability of fracture in the presence of a prior fracture, was to treat more women at younger ages but fewer women at older ages than if using the fixed 17.5% threshold (criterion C, TABLE 2). Overall, 16% of women over the age of 50 years would be eligible for treatment. When all women with a prior fracture were eligible for treatment plus those with a fracture probability that exceeded 17.5% (with no prior fracture), approximately ⅓ of women would be selected for treatment.

The effect of the 4 approaches on intervention thresholds is shown in TABLE 3 and compared with a no-threshold option. If all postmenopausal women aged 50 years or more were to be offered treatment, then 123 fractures would be expected per 1000 women over the next 10 years, equivalent to 121 fractures in the present cohort. If a treatment was offered and taken with an efficacy of 30%, then 36 fractures would be prevented. Treatment would be required in 27 women to prevent 1 fracture (NNT = 27).

As expected, all the threshold scenarios identified high-risk patients. The highest-risk populations were criteria B and C. Consequently, these criteria had the more favorable NNTs, i.e., 27. On the other hand, fewer high-risk women were indentified, and more fractures occurred in the women categorized as low-risk in scenarios B and C than in criteria A and D.

TABLE 3 The effect of 4 different intervention thresholds in postmenopausal women aged 50 years and older

		Criterion A	Criterion B	Criterion C	Criterion D
	no threshold	T-score = –2.5 SD	prior fracture[a]	prior fracture[b]	prior fracture or probability >17.5%
eligible women					
% identified	100	38.5	16.1	15.5	35.1
fracture probability, %[c]	12.3	18.4	25.6	23.7	18.6
expected number of fracture patients in 10 years/1000[c]	123	184	256	237	186
number of fractures expected in the group of eligible women	121	70	41	36	64
fractures saved by treatment/1000[d]	37	55	77	71	56
fractures saved by treatment[d]	36	21	12	11	19
number needed to treat	27	18	13	14	18
ineligible women					
% of population	0	61.5	83.9	84.5	64.9
expected number of fracture patients in 10 years/1000	0	84	97	101	88
number of fractures expected in the group of ineligible women	0	51	80	84	56
population impact					
fracture reduction, %	30	17	10	9	16

a fixed threshold at all ages
b age-dependent thresholds
c in those eligible for treatment
d 30% efficacy (relative risk = 0.3)

Abbreviations: see TABLE 2

DISCUSSION The application of FRAX methodology to clinical practice requires a consideration of an intervention threshold, namely, the fracture probability at which to recommend treatment. Several approaches have been examined to help set probability-based intervention thresholds.[35] Intervention thresholds have been based on cost-effectiveness analyses, e.g., the UK and US,[33-36] but will not be applicable to other countries because the 10-year probability of fracture varies markedly between different countries.[27] Intervention thresholds would also change with differences in costs, particularly fracture costs, which vary considerably across the world. There is also the issue of affordability or willingness to pay for a strategy.[14] For all these reasons, it is important to define intervention and assessment thresholds on a country-by-country basis that takes into account the setting for service provision and willingness to pay, as well as consideration of absolute costs.

In this paper, we examined the consequences of using several clinical approaches to develop probability-based thresholds in the Polish setting. The choice of thresholds was somewhat arbitrary but was modeled on existing guidelines. For example, in Poland, treatment was recommended in women with osteoporosis defined on the basis of a T-score. The same thresholds are used in the US and were previously used in many other European countries.[37,38] The presence of a prior fragility fracture has also been widely used as an intervention threshold.[38,39] In some instances, the presence of either a prior fracture or a low T-score has provided an intervention threshold.[23,38-40]

FRAX® became available in 2008 and since then, new or revised guidelines are accommodating FRAX-based probabilities, often determined on pre-existing guidance. In the UK, for example, previous guidance by the Royal College of Physicians state that treatment can be considered in women with a prior fracture irrespective of BMD.[37,38] New guidance, issued by the NOGG, has set the treatment intervention threshold at a 10-year probability of fracture in women with prior osteoporotic fracture, but in whom BMD is unknown.[17] The NOGG guidance is thus a "translation" of former guidance into a probability-based approach. Thus, the aim of the present study was to determine the manner in which a translational approach could be considered in Poland.

Each of the criterion examined in the present study has merits and disadvantages. The use of a fixed T-score threshold at –2.5 SD (criterion A) or the combination of a prior fracture and a fixed probability threshold (criterion D) seems less satisfactory than others because treatment will be offered to a very large proportion of the population (35%–39%), including women at low risk (e.g., 17%–32% of women aged 50–54 years). In addition, those identified over the age of 75 years would have a fracture probability that was less than the average probability for women of the same age (FIGURE). By contrast, setting an intervention threshold at a probability equivalent to that associated with a prior fracture (criteria B and C) identified fewer women but at a much higher risk, so the number of fractures averted by treatment was greater and the NNT was lower. In a population setting, however, fewer fractures in the community would be prevented (10% vs. 17%, TABLE 3). It is of interest that the use of a fixed threshold (17.5% probability) and an age-dependent threshold had similar performance characteristics, though different women would be treated. In criterion B (fixed threshold), more women with no prior fracture would be treated at younger ages and fewer women with a prior fracture would be treated at older ages than when using an age-specific threshold. Thus, the use of a fixed threshold for all ages may be less clinically intuitive.

The present study has a number of limitations. We have used the cohort to extrapolate to the Polish postmenopausal population. Although the sampling was random, we were unable to assess recruitment bias. It is of interest that mean fracture probabilities were similar with or without the inclusion of BMD in the FRAX model. The similarity indicates that the cohort was not preferentially enriched by women with low or high BMD for age. It is also possible that women from Białystok may not be representative of the general Polish population. A similar calculation was performed in the population of women from the Łódź region but using different criteria. The essential difference is in the evaluation of the proportion of women eligible for treatment on the basis of T-score –2.5 criteria, 38.5% in our cohort vs. 8.5% in the Łódź cohort, probably due to a relatively small number of participants (n = 96), and due to an incomplete recording of all risk factors implemented into the FRAX tool.[41]

It is also important to recognize that we have not modeled scenarios that will necessarily be applied. We have not modeled assessment thresholds, namely, the threshold probabilities at which a BMD test might be used. In addition, most guidelines do not recommend a screening strategy where all women are evaluated as assumed in the present study. Rather, women are identified opportunistically by the presence of clinical risk factors. The effect of this will be that fewer women are identified, but at higher fracture probability. Thus, the strength of the present study lies in the comparison of the criteria and relative consequences rather than in the absolute impact of any management algorithm.

We conclude that the advent of FRAX® will necessitate the development of treatment guidance on the fracture probabilities at which to recommend treatment. Of the examined criteria, the most efficient is the use of intervention thresholds based on the probabilities equivalent to women with a prior fracture. The use of an age-specific threshold may be more clinically appropriate than a fixed probability threshold for all ages.

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ARTYKUŁ ORYGINALNY

Zastosowanie narzędzia FRAX® do wyznaczania progu interwencji leczniczej osteoporozy w Polsce

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SŁOWA KLUCZOWE

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STRESZCZENIE

WPROWADZENIE Narzędzie oceny ryzyka złamania FRAX jest szeroko stosowane w diagnostyce osteoporozy od 2008 roku. Jego kliniczne zastosowanie wymaga jednak ustalenia, przy jakim prawdopodobieństwie złamania osteoporotycznego zalecić leczenie.

CELE Celem badania była analiza możliwych progów interwencji leczniczej w Polsce.

PACJENCI I METODY Ocena prawdopodobieństwa złamania została przeprowadzona na niewyselekcjonowanej grupie 1608 kobiet z Białegostoku w okresie pomenopauzalnym, przy użyciu narzędzia FRAX wzorowanego na modelu brytyjskim (wersja 3.1). Progi interwencji zostały ustalone jako: wartości równe prawdopodobieństwu wystąpienia złamań u kobiet z gęstością mineralną kości (*bone mineral density* – BMD) o *T-score* –2,5 (kryterium A); u osób z przebytym złamaniem niezależnie od wieku (kryterium B); próg zależny od wieku (kryterium C). Ponadto założyliśmy, że wszystkie kobiety z uprzednim złamaniem lub wykazujące takie ryzyko złamania, jakie mają osoby z przebytym złamaniem, powinny zostać poddane leczeniu obejmującego kobiety z przebytym złamaniem (kryterium D).

WYNIKI Średnie 10-letnie prawdopodobieństwo poważnych złamań osteoporotycznych wyniosło 10,9% bez uwzględniania BMD podczas obliczania FRAX i 11,6% z jego uwzględnieniem. Wśród pacjentek z przebytym złamaniem po niewielkim urazie ryzyko wynosiło odpowiednio 18,0% i 17,4%. Do leczenia kwalifikowałoby się 39% kobiet >50 r.ż. przy kryterium A, 35% przy założeniu D i 16% przy założeniach B i C. Przy scenariuszu B i C do leczenia zakwalifikowałyby się kobiety o wyższym ryzyku niż w przypadku A i D. Zakładając redukcję względnego ryzyka złamania o 30%, liczba rekomendowanych do leczenia (*number needed to treat* – NNT) w celu uniknięcia poważnego złamania osteoporotycznego była niższa przy opcji B i C (odpowiednio NNT = 13 i 14) niż w przypadku opcji A i D (NNT = 18).

WNIOSKI Największą efektywność wykazuje próg interwencji równy ryzyku kobiet po przebytym złamaniu. Zastosowanie zaś progu zależnego od wieku może być właściwsze od jednego wspólnego dla wszystkich ze względu na omawiane uwarunkowania kliniczne.

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