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The use of 2-, 5-, and 10-year probabilities to characterize fracture risk after a recent sentinel fracture

J.A. Kanis^{1,2} · H. Johansson^{1,2} · N.C. Harvey^{3,4} · V. Gudnason^{5,6} · G. Sigurdsson⁵ · K. Siggeirsdottir⁵ · M. Lorentzon^{1,7} · E. Liu¹ · L. Vandenput^{1,8} · W.D. Leslie⁹ · E.V. McCloskey^{2,10}

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Abstract

Summary The increase in fracture risk associated with a recent fragility fracture is more appropriately captured using a 10-year fracture probability than 2- or 5-year probabilities.

Introduction The recency of prior fractures affects subsequent fracture risk. The aim of this study was to quantify the effect of a recent sentinel fracture, by site, on the 2-, 5-, and 10-year probability of fracture.

Methods The study used data from the Reykjavik Study fracture register that documented prospectively all fractures at all skeletal sites in a large sample of the population of Iceland. Fracture probabilities were determined after a sentinel fracture (humeral, clinical vertebral, forearm and hip fracture) occurring within the previous 2 years and probabilities for a prior osteoporotic fracture irrespective of recency. The probability ratios were used to adjust fracture probabilities over a 2-, 5-, and 10-year time horizon.

Results As expected, probabilities decreased with decreasing time horizon. Probability ratios varied according to age and the site of sentinel fracture. Probability ratios to adjust for a prior fracture within the previous 2 years were higher the shorter the time horizon, but the absolute increases in fracture probabilities were much reduced. Thus, fracture probabilities were substantially lower with time horizons less than 10 years.

Conclusion The 10-year probability of fractures is the appropriate metric to capture the impact of the recency of sentinel fractures. The probability ratios provide adjustments to conventional FRAX estimates of fracture probability for recent sentinel fractures, adjustments which can readily inform clinical decision-making.

Keywords Fracture probability · FRAX adjustment · Imminent risk · Prior fracture · Risk assessment · Sentinel fracture

Introduction

In 2008, the then World Health Organization (WHO) Collaborating Centre for Metabolic Bone Diseases at

Sheffield, UK, released FRAX®, a fracture risk assessment tool for estimating individualized 10-year probability of hip and major osteoporotic fracture (MOF; hip, clinical spine, distal forearm, or proximal humerus) [1]. The

✉ J.A. Kanis
w.j.pontefract@shef.ac.uk

¹ Mary McKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia

² Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK

³ MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

⁴ NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

⁵ Icelandic Heart Association Research Institute, Kopavogur, Iceland

⁶ University of Iceland, Reykjavik, Iceland

⁷ Geriatric Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

⁸ Department of Internal Medicine and Clinical Nutrition, Institute of Medicine and Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

⁹ Department of Medicine, University of Manitoba, Winnipeg, Canada

¹⁰ Mellanby Centre for Bone Research, Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

FRAX tool integrates seven dichotomous clinical risk factors (CRFs: prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, rheumatoid arthritis, and other causes of secondary osteoporosis) which, in addition to age, sex, and body mass index (BMI), contribute to a 10-year fracture probability estimate independently of bone mineral density (BMD) [1, 2]. BMD at the femoral neck is an optional input variable. FRAX tools are country specific to take account of the heterogeneity of fracture risk and mortality worldwide [3]. Since its release, 71 models have been made available for 66 countries covering more than 80% of the world population [4]. The tool provides metrics which are increasingly used in health technology assessment [5–7], regulatory guidance [8], and clinical guidelines [9].

Prior fragility fracture, a well-established risk factor for a future fracture [10–14], is already accommodated within FRAX [1]. The population relative risk of having a hip fracture or other osteoporotic fracture is approximately 2-fold higher for most types of prior fracture. However, the increase in risk is not constant with time or age [13]. Additionally, the risk of a subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively with time [15–22]. The immediate risk is high and then wanes over time for approximately 2 years. Thereafter, a nadir is reached but the risk remains higher than that of the general population. The early phase of particularly high risk has been termed imminent risk [22].

This transiency, which is not currently accommodated in the FRAX algorithm, suggests that treatment given to patients immediately after a fracture might avoid a higher number of new fractures compared with treatment given at a later date. Despite limited empirical data [23], this reinforces a rationale for very early intervention immediately after fractures to avoid recurrent fractures. Furthermore, it supports the use of the most effective therapies early in the course of treatment, rather than delaying their use to a time of lower fracture risk. Thus, the quantification of imminent risk enables the targeting of anabolic treatments to individuals identified to be at very high risk [24]. The most recent guidelines of the International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases provided multipliers to traditional FRAX estimates of fracture probability to account for the imminent risk associated with a recent vertebral fracture [7]. More recently, algorithms have been provided to adjust FRAX probabilities for a recent hip, spine, humerus, and forearm fracture [25].

These adjustments represent multipliers to 10-year fracture probabilities for individuals with a prior fragility

fracture. For example, the 10-year probability of major osteoporotic fracture (MOF) in women age 60 from the UK with no clinical risk factors (BMI set at 25 kg/m²) is 5.9%. The FRAX-based probability rises to 12% in the presence of a prior fragility fracture. In the presence of a recent spine fracture (0–2 years), the multiplier of 1.84 is used to uplift the 10-year probability to 22% [25]. It has been argued that shorter-term probabilities would be appropriate for clinical messaging because the multipliers would be greater. The counter argument is that despite higher multipliers, shorter time horizons would reduce the absolute fracture probabilities to an extent greater than the increment provided by higher multipliers. That is, for any given scenario, the final absolute fracture probability will always be greater over a 10-year than over a 2-year time horizon.

The aim of the present study was to compare the impact of recency of index fractures on fracture probability as used by FRAX (i.e., over 10 years) with those calculated over a 5-year or 2-year time horizon.

Methods

Methods have been previously detailed [25]. In brief, the study used data from the Reykjavik Study fracture register that documented prospectively all fractures at all skeletal sites in a large sample of the population of Iceland. Fracture probabilities were determined after a sentinel fracture (humeral, clinical vertebral, forearm, and hip fracture) from the hazards of death and fracture [26, 27]. It is important to note that the probability models used were based on purpose-built models similar, but not identical, to FRAX. Fracture probabilities were computed on the one hand for sentinel fractures occurring within the previous 2 years and on the other hand probabilities for a prior osteoporotic fracture irrespective of its site or recency. Probability ratios for the two estimates were determined for time horizons of 10 years (as for FRAX), 5 years, and 2 years. The probability ratios were used to adjust estimates of fracture probability for recent sentinel fractures by age, sex, site of sentinel fracture, and time horizon.

Probability estimates are presented for each sentinel fracture sustained within the previous 2 years. For brevity, a fracture within the previous 2 years is termed a recent fracture unless otherwise noted.

Results

Follow up data were available for 2074 individuals following a hip fracture, 1365 cases of clinical vertebral

fracture, 2364 following a distal forearm fracture, and 1092 cases of fracture at the proximal humerus. Ten-year probabilities of a major osteoporotic fracture and hip fracture in men and women with a prior fragility fracture (any site irrespective of its recency), men and women with a recent sentinel fracture (within 2 years), and the ratio between 10-year probabilities by age are given in the Appendix (Tables 1, 2, 3 and 4).

Ten-year, 5-year, and 2-year probabilities of a major osteoporotic fracture and hip fracture (%) in men and women with a prior fragility fracture (any site irrespective of its recency), probabilities for a recent clinical vertebral fracture (within the previous 2 years), and the ratio between 10-year probabilities by age are provided in the Appendix. We illustrate below the salient features for women from Iceland.

Time horizon

As expected, probabilities decreased with decreasing time horizon. Probabilities of a major osteoporotic fracture (MOF) in women with a prior fracture (of any recency) are shown in Fig. 1. It is important to note that probabilities shorter than 10 years are not a simple fraction of 10-year probabilities, particularly among older women, largely reflecting the effects of competing mortality over the longer time horizon. In the examples in Fig. 1, 5-year probabilities varied from 28% of the 10-year value at the age of 50 years to 79% at the age of 90 years. In the case of 2-year probabilities, the variation with age was from 10 to 43%, respectively.

Similar findings were applied to men and to hip fracture probabilities (see Appendix).

Adjustment ratios

Figure 2 shows adjustment ratios for a recent sentinel spine fracture in women. Adjustment ratios decreased with age but were higher the shorter the time horizon. Of note, the impact of the time horizon on the ratios was most marked at younger ages, and the differences diminished substantially with age. Similar findings applied to men and to hip fracture probabilities (see Appendix).

Probability of MOF

The 10-year probability of major osteoporotic fracture (MOF) in women is shown in Fig. 3 for recent (within previous 2 years) vertebral, hip, humerus, and forearm fracture by age. For each sentinel fracture and each age, fracture probabilities were lowest with a 2-year time horizon, intermediate with a 5-year horizon, and highest for 10-year probabilities. Similar findings were noted in men (Appendix). Probabilities varied according to the

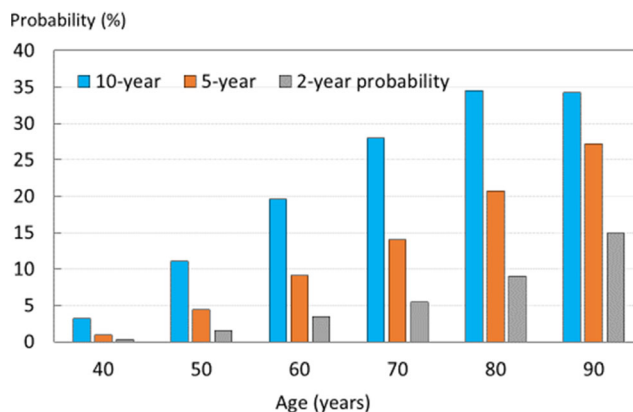


Fig. 1 Probabilities of a major osteoporotic fracture (MOF) in Icelandic women with a prior fracture (of any recency) by age and time horizon

site of sentinel fracture with higher ratios for hip and vertebral fracture than for humerus or forearm fracture.

Probability of hip fracture

The 10-year probability of hip fracture in women is shown in Fig. 4 for recent hip fracture by age. At each age, fracture probabilities were lowest with a 2-year time horizon, intermediate with a 5-year horizon, and highest for 10-year probabilities. Similar findings were noted for all sentinel fractures and in men (Appendix).

Discussion

This analysis indicates that although probability adjustment ratios increase with decreasing time horizon, fracture probabilities calculated over a shorter than 10-year horizon yield markedly lower absolute values, as expected. The low absolute risk with the shorter time horizon

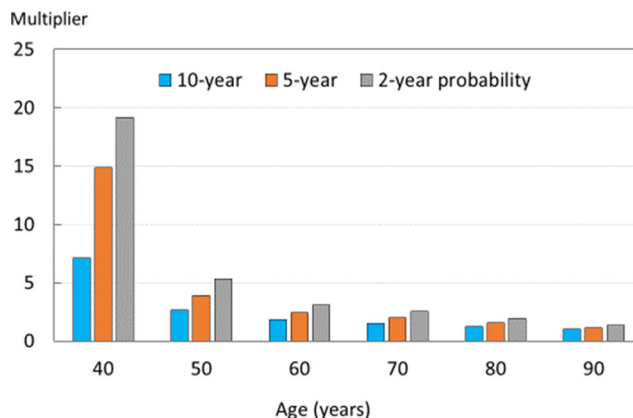


Fig. 2 Spine fracture—MOF multiplier for women with a recent clinical spine fracture according to age and time horizon

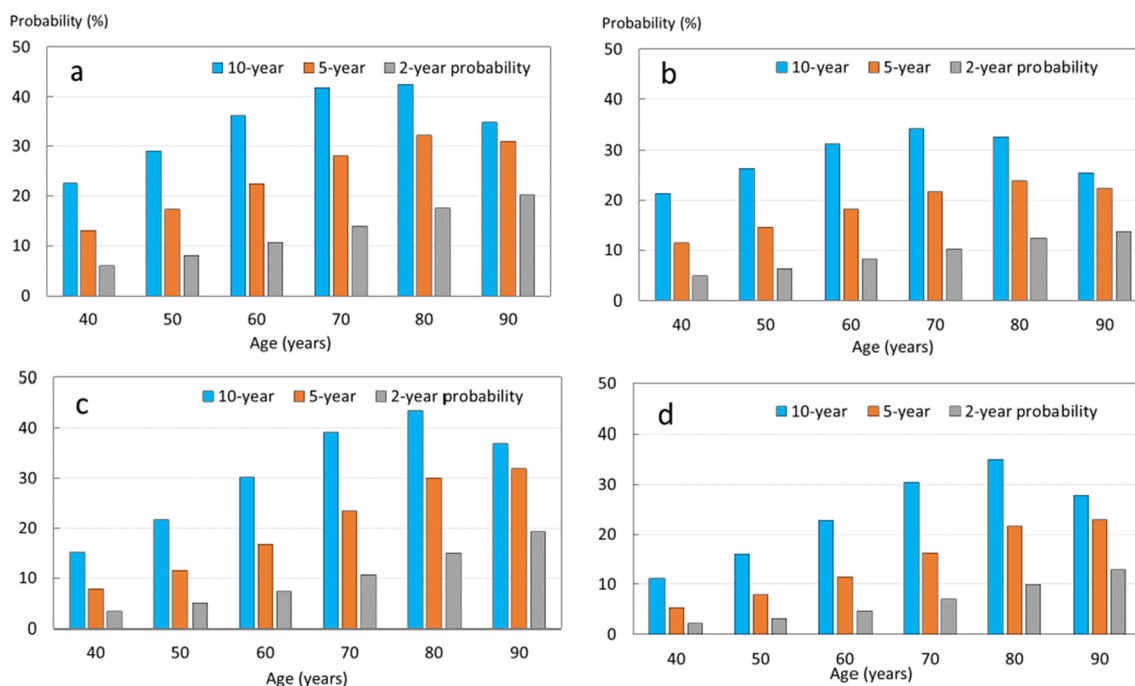


Fig. 3 Ten-year, 5-year, and 2-year probability of major osteoporotic fracture (MOF) in women from Iceland with a recent **a** vertebral fracture, **b** hip fracture, **c** humeral fracture, and **d** distal forearm fracture

attenuates markedly the effect of the multiplier. This suggests that 10-year probabilities are the preferred metric to express recent sentinel fractures for at least three reasons. Firstly, management of fracture risk is a long-term strategy, so that short time horizons undermine NNTs and health economic assessment. Secondly, the larger numbers using the 10-year horizon are more readily appreciated by patients and health care professionals. Thirdly, 10-year horizons are accepted worldwide as a risk measurement for many chronic diseases. For fragility fracture, this holds true not only for FRAX but also for national risk engines such as QFracture, the Garvan calculator, and the American Bone Health algorithm

[28–30]. A counter argument (raised by one of the reviewers of this paper) is that a 2-year probability may be of greater immediate personal significance than a 10-year probability despite the lower probability. The differences are, however, substantial. For example, a woman aged 60 years with a recent vertebral fracture has a 10-year probability of a MOF of 36% and a 2-year probability of 11% (see Table 1 of Appendix).

For the present study, we provided FRAX adjustments for prior fractures within a 2-year interval. The choice of 2 years is somewhat arbitrary but covers the approximate period of imminent risk [22]. Other scenarios are equally possible. For example, the probability ratio for a woman aged 60 years with a sentinel vertebral fracture (that is, at any time in the past 2 years) is 1.84 (Appendix). The probability ratio at the time of fracture (time 0) is 1.96 and at 2 years after the prior fracture is 1.75, differing from the integral value by 5–6% (data not shown). The small differences suggest that the 2-year integral value sacrifices accuracy modestly for a substantial gain in simplicity. Nonetheless, computer-based algorithms will provide a more granular assessment of fracture recency as a continuous variable. An example is shown in Fig. 5 for a sentinel humerus fracture.

The present study also highlights that probability time horizons are non-linear in that, for example, a 5-year probability in individuals is not just half that of a 10-year probability. In large heterogeneous populations,

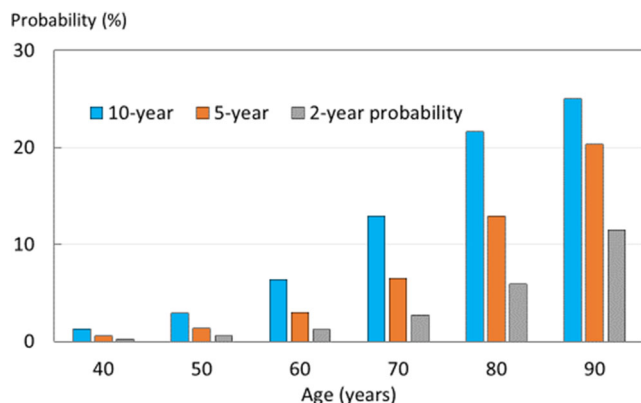


Fig. 4 Ten-year, 5-year, and 2-year probability of hip fracture in women from Iceland with a recent hip fracture

10 year probability of MOF (%)

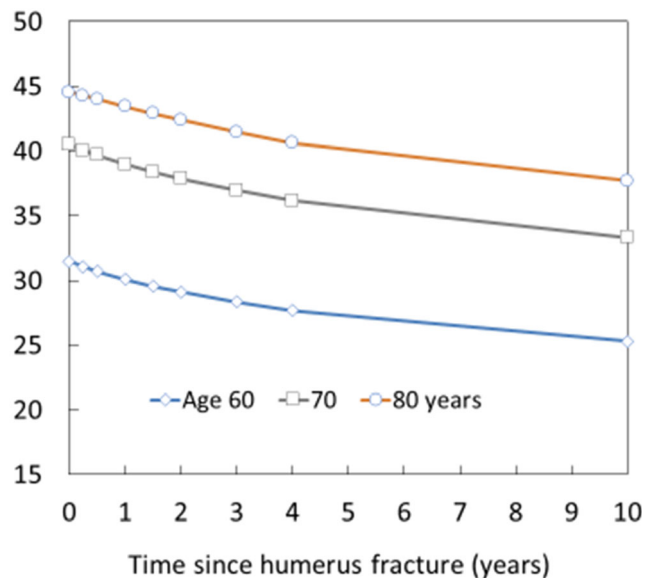


Fig. 5 Ten-year probability of a major osteoporotic fracture (MOF) for women aged 60, 70, and 80 years with a sentinel humeral fracture

this will be approximately true [31] but falls down in individual estimates. As noted previously, 5-year probabilities varied from 28% of the 10-year value at the age of 50 years to 79% at the age of 90 years in women with a prior fracture (Fig. 1). In the case of 2-year probabilities, the variation with age was from 10 to 43%, respectively. However, at the age of 70 years, the 5-year probability was half that of the 10-year value, and the 2-year probability was one fifth that of the 10-year probability. The differences reflect the changing death and fracture hazards with age. For example, at the age of 50 years, an individual is unlikely to die following say a humeral fracture. In this case, the 2-year probability of a MOF (14.4%) in a woman will be close to one fifth of the 10-year probability (3.18%). At the age of 90 years, the competing risk of death is much higher so that the 2-year probability (12%) approaches more closely the 10-year probability (18%) which, in turn, is almost the same as the 5-year probability (16%). This somewhat complex relationship differs according to the site of sentinel fracture since each has a

different impact on subsequent risk of fracture and death. These observations caution the use of short-term probabilities if they do not take these factors into account.

The present results are based on an Icelandic population. There are, however, large differences in age and sex-specific fracture incidence in different countries of the world [3]. Thus, the absolute probability values we observed will not be representative of other populations, but there is no reason to suppose that probability ratios would differ markedly by country. This assumption has not been extensively tested. However, probability ratios following a sentinel vertebral fracture in the present study were very similar to those calculated for the UK [24, 25]. This suggests that the probability ratios derived in the present study can be applied to adjust FRAX estimates of fracture probability in all FRAX models.

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Compliance with ethical standards

The study was approved by the National Bioethics Committee and the Data Protection Authority in Iceland. All the participants gave informed written consent.

Conflicts of interest W Leslie, E Liu and H Johansson, V Gudnason, G Sigurdsson, and Kristin Siggeirsdottir have no competing interests to declare.

N. Harvey has received consultancy, lecture fees, and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Kyowa Kirin, Consilient Healthcare, Radius Health, and Internis Pharma.

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Appendix

Table 1 10-year, 2-year, and 5-year probability of a major osteoporotic fracture and hip fracture (%) in men and women with a prior fragility fracture (any site irrespective of its recency), probabilities for a recent clinical vertebral fracture (within previous 2 years), and the ratio between 10-year probabilities by age

10 year probability		2 year probability						5 year probability							
		Major osteoporotic fracture			Hip			Major osteoporotic fracture			Hip				
Age (years)	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio
Men															
40	3.22	13.47	4.18	0.55	1.17	2.13	0.33	3.43	10.39	0.61	0.24	3.93	0.95	7.65	8.05
50	9.18	17.59	1.92	1.29	2.45	1.90	1.26	4.63	3.67	0.16	0.51	3.19	3.72	10.19	2.74
60	14.08	22.11	1.57	2.80	4.93	1.76	2.57	6.19	2.41	0.37	1.08	2.92	6.74	13.32	1.98
70	17.25	25.54	1.48	6.45	8.93	1.38	3.62	8.11	2.24	1.02	2.24	2.20	9.02	16.63	1.84
80	20.01	24.77	1.24	12.61	13.00	1.03	5.69	10.11	1.78	2.98	4.39	1.47	12.73	18.69	1.47
90	20.67	18.37	0.89	16.50	13.54	0.82	9.64	11.15	1.16	7.74	7.52	0.97	16.96	16.77	0.99
Women															
40	3.15	22.50	7.14	0.83	1.73	2.08	0.31	5.95	19.19	0.091	0.35	3.85	0.88	13.06	14.84
50	11.05	28.98	2.62	1.93	3.62	1.88	1.50	8.00	5.33	0.24	0.75	3.13	4.44	17.26	3.89
60	19.55	36.05	1.84	4.20	7.33	1.75	3.46	10.66	3.08	0.52	1.59	3.06	9.15	22.38	2.45
70	28.00	41.87	1.50	9.70	13.62	1.40	5.46	13.92	2.55	1.32	3.32	2.52	14.04	27.93	1.99
80	34.53	42.49	1.23	19.12	20.96	1.10	9.02	17.50	1.94	3.68	6.60	1.79	20.71	32.08	1.55
90	34.21	34.71	1.01	24.17	23.62	0.98	14.84	20.03	1.35	10.56	11.77	1.11	27.19	30.96	1.14

Table 2 10-year, 2-year, and 5-year probability of a major osteoporotic fracture and hip fracture (%) in men and women with a prior fragility fracture (any site irrespective of its recency), probabilities for a recent clinical hip fracture (within previous 2 years), and the ratio between 10-year probabilities by age

10 year probability		2 year probability						5 year probability							
		Major osteoporotic fracture			Hip			Major osteoporotic fracture			Hip				
Age (years)	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio	Any time	0-2 years	Ratio
Men															
40	3.22	17.09	5.31	0.55	6.51	11.83	0.33	3.88	11.76	0.061	1.37	22.46	0.95	9.09	9.57
50	9.18	20.97	2.28	1.29	9.50	7.36	1.26	5.01	3.98	0.16	2.09	13.06	3.72	11.53	3.10
60	14.08	24.30	1.73	2.80	13.05	4.66	2.57	6.40	2.49	0.37	3.15	8.51	6.74	14.23	2.11
70	17.25	25.16	1.46	6.45	15.87	2.46	3.62	7.94	2.19	1.02	4.62	4.53	9.02	16.55	1.83
80	20.01	21.55	1.08	12.61	15.69	1.24	5.69	9.28	1.63	2.98	6.35	2.13	12.73	16.98	1.33
90	20.67	14.81	0.72	16.50	12.23	0.74	9.64	9.50	0.99	7.74	7.61	0.98	16.96	13.91	0.82
Women															
40	3.15	21.32	6.77	0.83	6.50	7.83	0.31	4.89	15.77	0.091	1.35	14.84	0.88	11.40	12.95
50	11.05	26.34	2.38	1.93	9.64	4.99	1.50	6.32	4.21	0.24	2.07	8.63	4.44	14.52	3.27
60	19.55	31.26	1.60	4.20	13.69	3.26	3.46	8.11	2.34	0.52	3.15	6.06	9.15	18.11	1.98
70	28.00	34.30	1.23	9.70	17.87	1.84	5.46	10.21	1.87	1.32	4.70	3.56	14.04	21.69	1.54
80	34.53	32.69	0.95	19.12	19.88	1.04	9.02	12.35	1.37	3.68	6.72	1.83	20.71	23.88	1.15
90	34.21	25.48	0.74	24.17	17.56	0.73	14.84	13.69	0.92	10.56	8.76	0.83	27.19	22.33	0.82

Table 3 10-year, 2-year, and 5-year probability of a major osteoporotic fracture and hip fracture (%) in men and women with a prior fragility fracture (any site irrespective of its recency), probabilities for a recent clinical humeral fracture (within previous 2 years), and the ratio between 10-year probabilities by age

		10 year probability				2 year probability				5 year probability			
		Major osteoporotic fracture		Hip		Major osteoporotic fracture		Hip		Major osteoporotic fracture		Hip	
Age (years)	Sex	Any time	0-2 years	ratio	Any time	0-2 years	ratio	Any time	0-2 years	ratio	Any time	0-2 years	ratio
Men													
40		3.22	9.91	3.08	0.55	0.52	0.94	0.33	2.13	6.45	0.061	0.081	1.33
50		9.18	14.35	1.56	1.29	1.35	1.05	1.26	3.18	2.52	0.16	0.21	1.31
60		14.08	19.96	1.42	2.80	3.40	1.21	2.57	4.72	1.84	0.37	0.55	1.49
70		17.25	25.07	1.45	6.45	7.91	1.23	3.62	6.86	1.90	1.02	1.42	1.39
80		20.01	24.94	1.25	12.61	14.10	1.12	5.69	9.43	1.66	2.98	3.50	1.17
90		20.67	17.53	0.85	16.50	14.52	0.88	9.64	11.07	1.15	7.74	7.40	0.96
Women													
40		3.15	15.10	4.79	0.83	0.61	0.73	0.31	3.31	10.68	0.091	0.096	1.05
50		11.05	21.70	1.96	1.93	1.58	0.82	1.50	4.94	3.29	0.24	0.25	1.04
60		19.55	30.15	1.54	4.20	4.01	0.95	3.46	7.31	2.11	0.52	0.65	1.25
70		28.00	39.05	1.39	9.70	9.59	0.99	5.46	10.67	1.95	1.32	1.67	1.27
80		34.53	43.45	1.26	19.12	18.76	0.98	9.02	15.03	1.67	3.68	4.18	1.14
90		34.21	36.90	1.08	24.17	22.67	0.94	14.84	19.27	1.30	10.56	9.37	0.89

Table 4 10-year, 2-year, and 5-year probability of a major osteoporotic fracture and hip fracture (%) in men and women with a prior fragility fracture (any site irrespective of its recency), probabilities for a recent clinical forearm fracture (within previous 2 years), and the ratio between 10-year probabilities by age

		10 year probability				2 year probability				5 year probability			
		Major osteoporotic fracture		Hip		Major osteoporotic fracture		Hip		Major osteoporotic fracture		Hip	
Age (years)	Sex	Any time	0-2 years	ratio	Any time	0-2 years	ratio	Any time	0-2 years	ratio	Any time	0-2 years	ratio
Men													
40		3.22	8.39	2.61	0.55	1.31	2.38	0.33	1.60	4.85	0.061	0.24	3.93
50		9.18	12.21	1.33	1.29	2.93	2.27	1.26	2.39	1.90	0.16	0.55	3.44
60		14.08	17.34	1.23	2.80	6.25	2.23	2.57	3.54	1.38	0.37	1.24	3.35
70		17.25	22.91	1.33	6.45	11.87	1.84	3.62	5.18	1.43	1.02	2.74	2.69
80		20.01	24.37	1.22	12.61	16.97	1.35	5.69	7.30	1.28	2.98	5.69	1.91
90		20.67	16.48	0.80	16.50	16.23	0.98	9.64	8.97	0.93	7.74	9.99	1.29
Women													
40		3.15	11.11	3.53	0.83	1.30	1.57	0.31	2.15	6.94	0.091	0.24	2.64
50		11.05	16.08	1.46	1.93	2.92	1.51	1.50	3.20	2.13	0.24	0.54	2.25
60		19.55	22.75	1.16	4.20	6.38	1.52	3.46	4.73	1.37	0.52	2.37	2.08
70		28.00	30.47	1.09	9.70	12.93	1.33	5.46	6.93	1.27	1.32	2.75	2.08
80		34.53	34.96	1.01	19.12	21.62	1.13	9.02	9.88	1.10	3.68	5.92	1.61
90		34.21	27.81	0.81	24.17	25.02	1.04	14.84	12.84	0.87	10.56	11.48	1.09

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