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EDITORIAL

Short time horizons for fracture prediction tools: time for a rethink

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Prior fracture increases risk of future fracture in a time-dependent manner

Prior fragility fracture is a well-established risk factor for a future fracture [1–4]. The population relative risk of having a subsequent hip fracture or other osteoporotic fracture is approximately 2-fold higher for most types of prior fracture. However, many studies suggest that the increase in risk is not constant with time or age. Indeed, the risk of a subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively over the next 2 years [4–9] but thereafter remains higher than that of the general population (Fig. 1). The early phase of particularly high risk has been termed imminent risk [9]. This transiency, which is not currently accommodated in any of the available fracture risk assessment tools, 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.

Determinants of short-term risk also determine long-term risk

Confusion has arisen, however, about the use of the term imminent risk which has been variously used to imply a transient high risk or simply a high risk in the short term, regardless of transiency. Irrespective of its description, the view has arisen for the need for shorter timeframes over which to express fracture risk. This is illustrated by a number of studies, many of them recently published

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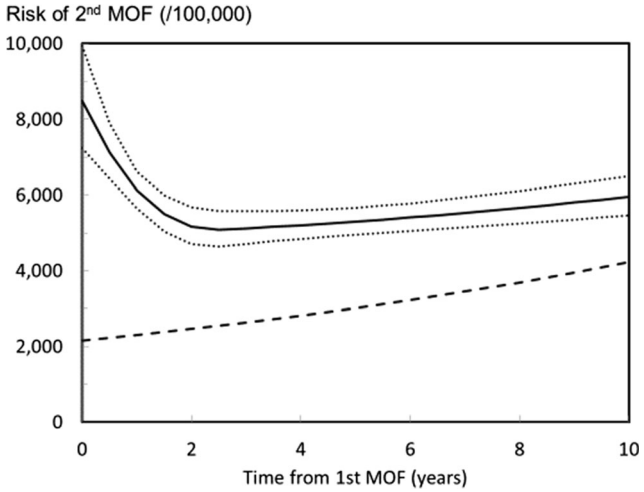

Fig. 1 Risk per 100,000 (95% CI) of a second major osteoporotic fracture (MOF) after a first MOF for a woman at the age of 75 years at her first fracture. Knots for the spline function are set at 0.5, 2.5 and 15 years of follow-up after the first fracture. The dashed line is the risk of first MOF in the whole population (n=18,872) for a woman 75 years at baseline [9] (with kind permission from Springer Science+Business Media B.V)

(Table 1), that seek to identify risk factors associated with incident fractures over a short time horizon, usually up to 2 years after a sentinel fracture. Some derive associated risk prediction algorithms, and, as expected, many of these studies confirm an increased fracture risk associated with a prior fracture, but in many, the mean absolute risk at 2 years is low (<10%), while in others that considered patients with recent fractures, the mean absolute risks were still around 10–15% (see Table 1). Apart from the known heterogeneity of fracture risk between countries [31], a source of heterogeneity may be the site of index fracture which in turn will be age-dependent [32]. In addition, some of the latter studies showed no convincing evidence of imminency of risk in that the relative risk at 2 years is no greater than the relative risk at 5 years [14, 27, 29].

Shorter time horizons yield lower magnitude absolute fracture risks

The rationale behind the need to express fracture risk over a 2-year time horizon as opposed to a longer term to determine intervention requires examination. The most lucid arguments state that tools such as FRAX predict risk over the long term and do not explicitly provide short-term risk estimates necessary to identify patients likely to experience a fracture in the next 1–2 years [10]. This logic implies that there are special characteristics in individuals at high short-term fracture risk not shared by those at long-term risk [33]. There is however no evidence that risk factors for short-term recurrent fractures differ from those identified for fracture irrespective of the time horizon [12–14, 17, 21, 25, 34–37] though this is not easily assessed in studies using machine-learning techniques where the drivers of risk remain opaque [38]. Moreover, a plethora of studies indicates that a heightened risk at 1 or 2 years persists for 5 to 10 years after the event [6, 8, 11, 14–16, 23, 27, 29, 39] (see Table 1). In other words, a high short-term risk aligns with a very high longer-term risk. Thus, the sole impact of choosing a 1- or 2-year time horizon is to decrease the magnitude of the absolute risk estimate produced by the algorithm (to oversimplify, e.g. a 10-year risk of fracture of 50% can be expressed as a 1-year risk of 5%). The oversimplification is that the relationship between time horizon and fracture risk is not linear [39] (Fig. 2). For example, in women with a prior fracture, the ratio between the 10- and 2-year probabilities is much smaller at older ages than younger ages; for example, at the age of 50 years, the 10-year probability is 8 times the 2-year probability, whereas at the age of 90, the ratio is 2.3:1. Note that neither of these ratios is 5:1, reflecting the non-linear relationships of fracture risk and death risk with age. For a 5-year timeframe, the respective ratios to 10-year probabilities are 3:1 and 1.25:1 at the same ages. The lower ratios at older ages are particularly important to appreciate and arise because the 10-year probability is calculated by taking into account the risk of fracture and the risk of death. As the latter exceeds the former at very old age, the probability of fracture actually decreases while remaining high, and the 10-year probability approaches the 2-year and 5-year probabilities (Fig. 2). At these advanced ages, the tool is calculating a 'remaining life-time' risk of fracture and, indeed, can usefully be expressed to patients and their carers in this way.

Given the difficulty that many patients (and indeed healthcare professionals) have in the interpretation of risk, being presented with a fracture risk which is low simply because it is over 2 years, may well be rather less convincing with regard to the need to commence treatment, compared with a substantially larger value pertaining to a 10-year time horizon. Despite a large literature on communication of risk [40, 41], there is relatively little empirical information on the optimal time horizon for expressing risk. The available information would suggest that longer rather than shorter time horizons are preferred in postmenopausal women [41, 42].

Adjusting 10-year probability to account for fracture recency

As stated previously, none of the current fracture risk calculators take account of the heightened fracture risk

Table 1 Studies of short-term (2 years or less) fracture risk following a sentinel fracture

Source	Country	Study size	Age (years)	Time horizon (years)	Outcome fracture	Incidence at 2 years[a] (%)	Reversibility of risk[c]	External validation	Population or predictive factors (notes)
Almog 2020 [10]	USA	>1,000,000	≥50	1, 2	Fracture	6.5	Unknown	No	Primary care records using all ICD codes (black box; incidence estimated from 'time windows' rather than individuals)
Balasubramanian 2019 [11]	USA	377,561[b]	≥65	1, 2, 5	Clinical	18	na	No	Recent clinical fractures (1, 2, 5 yr incidence 10, 18, 31% respectively; evidence for imminent risk)
Banefelt 2019 [12]	Sweden	242,108[b]	74	1, 2	Osteoporotic	12.0	Yes	No	Recent clinical fractures (I yr =7.1%; older age and vertebral fracture associated with increased risk)
Bonafede 2016 [13]	USA	163,186	≥50	1, 2	Osteoporotic	–	No	No	Retrospective case control study (no determination of imminency of risk; similar risk factors for both time horizons)
Chapurlat 2003 [14]	USA	632[b]	75	Up to 13	Hip	4.6	Partly	No	Recent hip fracture (Kaplan-Meier showing 2.3% risk per year; small study; no evidence of imminency)
Giangregorio 2010 [6]	Canada	39,991	67.0	Up to 10	MOF MOF	Major 10.2 Minor 6.1	na	No	Recent major or minor fracture (data presented for 1–5 years rather than 2 years; evidence of imminent risk for both major and minor fractures)
Henry 2006 [15]	Australia	679[b]	≥60	2	MOF	5.3	Yes	No	Case control study
Huntjens [16]	Netherlands	1921	≥50	1, 2, 5	Non-vertebral	10.0	na	No	Retrospective hospital database. 1,2, 5 yr incidence 6.4, 10 and 17.6% respectively; evidence for imminent risk
Iconaru 2021 [17]	Belgium	3560[b]	70.1	1, 2	Osteoporotic	19.9	Yes	No	Prospective cohort of postmenopausal women
Ioannidis 2017 [18]	Canada	29,848	≥18	1	Hip	10.4	No	Yes (Negm 2018) [19]	Long-term care residents (extrapolated from 1-year data; mean risk 5.2% at 1 yr; decision tree analysis identified 8 levels of risk 0.6–12.6%)
Jung 2021 [20]	Korea	4.417	≥50	1, 2, 3, 4	MOF	8.4	na		Recent distal forearm fracture (1,2, 3, 4 yr incidence 4.0, 8.4, 11.6 and 14.7%, respectively; evidence for imminent risk)
Miller 2004 [21]	USA	57,421[b]	66.8	1	Osteoporotic	Overall 4.0 Prior fracture 8.2	Partly	No	Postmenopausal women, without osteoporosis diagnosis (extrapolated from 1-year data)
Möller 2021 [22]	Canada	74,828	≥45	1–2	Hip MOF	M 0.4, W 0.4 M 2.4, W 2.1	No	–	Clinical population undergoing BMD (ICD codes in previous 10 years)
Nymark [23]	Denmark	9122	>50	1, 2, 5	Hip	M 0.63, W 0.55	na	No	Retrospective register database. 1,2, 5 yr incidence 0.49, .63 and 0.86%in men and 39, 0.55 and 0.85 in women, respectively; evidence for imminent risk

Table 1 (continued)

Source	Country	Study size	Age (years)	Time horizon (years)	Outcome fracture	Incidence at 2 years[a] (%)	Reversibility of risk[c]	External validation	Population or predictive factors (notes)
Rubin 2018 [24]	Denmark	2,495,339	≥45	1–2	Hip MOF	M 0.4, W 1.0 M 1.2, W 2.8	No	Yes (Möller 2021) [22]	Population of Denmark (ICD codes over a 14 year period prior to 2013; extrapolated from 1-yr incidence for 2013)
Sheer 2020 [25]	USA	1,287,354	67–87	1, 2	Fragility Hip Spine	M 4.4, W 8.3 M 0.9, W 1.7 M 1.7, W 3.0	Partly	No	Medical insurance database (risk factors in 2014 with incident fractures over 2015–2016 inclusive). Age, fracture, female and comorbidities predictive
Shim [26]	Korea	73717	≥50	1, 2	Osteoporotic	17.9	na	–	South Korean Health Insurance Review and Assessment Service. 1 year incidence = 11.6%; evidence for imminent risk
Söreskog 2020 [27]	Sweden	278,949[b]	79.3	1, 2, 3, 4, 5	MOF	10.7	–	No	All with ≥1 clinical fragility fracture (each matched to 3 controls without history of fracture). Overall 2-yr fracture incidence estimated. Similar increase in fracture risk noted at all time points, especially at younger ages, i.e. no evidence of imminent risk
Toth 2020 [28]	Sweden	35,146[b]	73.8	1, 2	Fragility Fragility Fragility Fragility	Fragility 11.3% Hip 13.7% Spine 17.6% Humerus 11.4%	–	–	Index fragility fracture in 2013. Outcome fragility fracture incidence at 2 yrs by index fracture type
Van Staa 2002 [29]	UK	222,369	≥20	1, 2, 3, 4, 5	Hip Spine Hip	Forearm 3.0% Hip 1.6% Spine 4.5%	–	–	Men and women with fracture in register database (rates shown for women only—estimated from chart). Similar increase in fracture risk noted at all time points, i.e. no evidence of imminent risk
Wong 2019 [30]	Hong Kong	7039	≥50	1, 2	MOF	6.5	–	–	Men and women with hip, forearm or proximal humerus fracture in register database. 1-year incidence = 3.8%

[a] Includes clinical risk factors with reversibility of risk (yes/no/partly)

[b] Includes women only

na not assessed, *MOF* major osteoporotic fracture

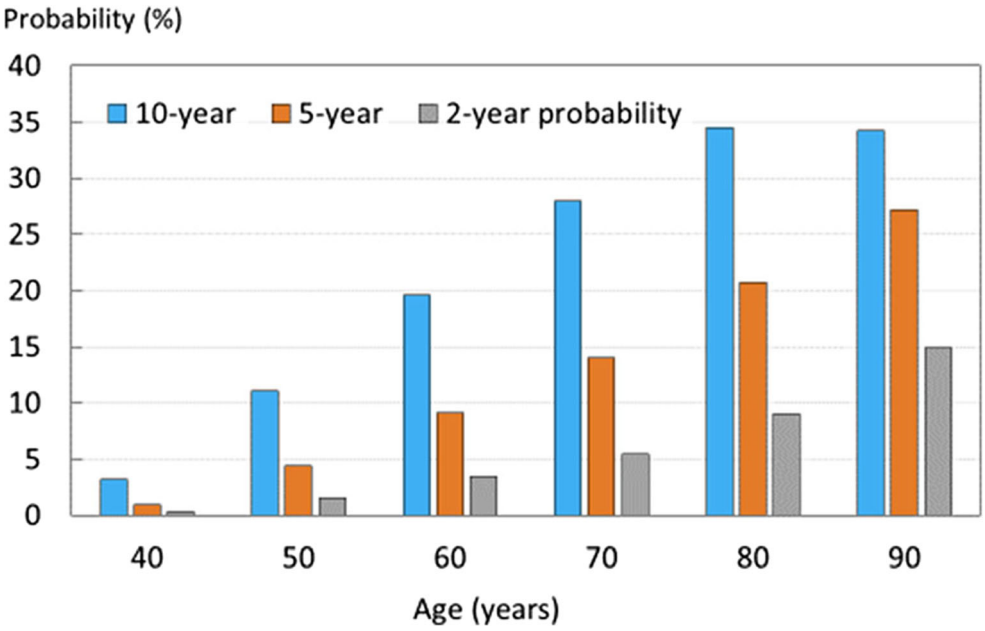

Fig. 2 Probabilities of a major osteoporotic fracture (MOF) in Icelandic women with a prior fracture (of any recency) by age and time horizon [39] (with kind permission from Springer Science+Business Media B.V)

associated with a recent major osteoporotic fracture. However, recent analyses demonstrate that estimates of 10-year fracture probability derived from the FRAX tool can be adjusted according to the recency and site of sentinel fractures; this is shown for the outcome of major osteoporotic fracture in Table 2 [43]. For example, a woman age 70 years from the UK with a prior fragility fracture and no other clinical risk factors has a 20% 10-year fracture probability for a major osteoporotic fracture calculated with FRAX. Where the prior fracture was recent (within 2 years) and was a clinical spine fracture, the adjusted fracture probability would be upward adjusted to 30% (20 × 1.50). Thus, many but not all such adjustments substantially increase fracture probability and could change the category of risk from high to very high, depending on the thresholds selected, and thereby merit consideration of anabolic interventions [44].

Summary and conclusion

Multiple studies of short-term fracture risk have identified similar risk factors to those already well-established in fracture prediction tools over the longer term. High short-term risk is usually associated with a very high long-term risk. Although tools that calculate short-term risk may be superficially attractive, the substantially lower absolute risk generated compared with a 10-year time horizon and the absence of guidelines through which to interpret these outputs are clear limitations to their use in clinical practice. In contrast, the uplift in risk arising from recent discrete events such as fracture can be readily accommodated in FRAX over a 10-year time horizon and linked to established national intervention thresholds that are already widely embedded in clinical guidelines for the management of osteoporosis. That very high risk requires rapid and effective intervention, with combinations or sequences

Table 2 Multipliers for the adjustment of conventional estimates of 10-year probability of a major osteoporotic fracture for a recent fracture (within 2 years) in men and women at the sites shown [43]

Age (years)	Spine		Hip		Humerus		Forearm	
	Men	Women	Men	Women	Men	Women	Men	Women
40	4.18	7.14	5.31	6.77	3.08	4.79	2.61	3.53
50	1.92	2.62	2.28	2.38	1.56	1.96	1.33	1.46
60	1.57	1.84	1.73	1.60	1.42	1.54	1.23	1.16
70	1.48	1.50	1.46	1.23	1.45	1.39	1.33	1.09
80	1.24	1.23	1.08	0.95	1.25	1.26	1.22	1.01
90	0.89	1.01	0.72	0.74	0.85	1.08	0.80	0.81

of pharmacological approaches and/or physical interventions (e.g. falls risk reduction), which is also easily appreciated.

Declarations

Conflicts of interests JAK, NCH, ML and EVM are responsible for the creation and maintenance of FRAX but derive no financial benefit. EVM has received consultancy/lecture fees/grant funding/honoraria from AgNovos, Amgen, AstraZeneca, Consilient Healthcare, Fresenius Kabi, Gilead, GSK, Hologic, Internis, Lilly, Merck, Novartis, Pfizer, Radius Health, Redx Oncology, Roche, Sanofi Aventis, UCB, ViiV, Warner Chilcott and I3 Innovus. FB is employed by and is a shareholder of Quantify Research, a health economic research consultancy. CC reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. NCH has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Radius Health, Servier, Shire, UCB, Consilient Healthcare and Internis Pharma. MKJ declares no conflicts of interest. ML has received lecture fees from Amgen, Lilly, Meda, Renapharma and UCB Pharma and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma and Consilient Health, all outside the presented work. JAK reports no additional competing interests.

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