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EDITORIAL

Imminent fracture risk assessments in the UK FLS setting: implications and challenges

Rafael Pinedo-Villanueva[1] · Mata Charokopou[2] · Emese Toth[2] · Kerry Donnelly[2] · Cyrus Cooper[1,3] · Daniel Prieto-Alhambra[1] · Cesar Libanati[2] · Muhammad K. Javaid[1]

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Dear Editor,

With an estimated 520,000 fragility fractures every year in the UK, delivering effective and efficient healthcare for this patient group has significant consequences for patients, families, the NHS, and society [1]. A fragility fracture is a major risk factor for further fractures [2], and healthcare systems are now beginning to recognise the benefits of secondary fracture prevention [3]. Despite this, less than 50% of patients receive effective secondary fracture prevention after a fragility fracture [4]. This has led to national [5, 6] and international [7–11] initiatives to improve clinical services by implementing fracture liaison services (FLSs). Successful funding of a new FLS is usually influenced by the number of fractures it is expected to prevent in the first few years after an index fracture. The expected number of fractures prevented is in turn determined by the baseline risk of subsequent fracture, the number of patients at high enough fracture risk to warrant anti-osteoporosis medication (AOM), and the degree of fracture risk reduction by AOMs. Underestimating fracture risk in the post-fracture period will lead to fewer expected fractures prevented and lower perceived benefit of the FLS by payers, and importantly also by patients, families, healthcare providers, and payers. Tools are available to determine the long-term risk of fracture based on patient factors, including previous fracture [12–15]. Of these, FRAX and QFracture have been incorporated within UK NICE clinical guidance [16], and the FRAX-derived intervention threshold is used to guide recommendations for AOM in the NHS [17].

✉ Muhammad K. Javaid
Kassim.javaid@ndorms.ox.ac.uk

[1] Nuffield Department of Orthopaedics, Rheumatology and Orthopaedic Sciences, University of Oxford, Oxford, UK

[2] UCB BioPharma SPRL, Brussels, Belgium

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

The risk of subsequent fracture is time-dependent, with much higher fracture risk in the first 2 years after an index fracture, a period that might be termed as "imminent fracture risk" (IFR) (Fig. 1) [18–20]. Recency of fracture is one of several determinants of IFR. Whereas FRAX and similar models include previous fracture history, the focus of these algorithms has been on use in primary care, and the recency and site of fracture are not considered both of which significantly influence imminent risk. Linear interpolation of FRAX risk, for example by dividing the 10-year probability by 5 to estimate the 2-year probability ("interpolated-FRAX"), thus necessarily underestimates shorter-term risk immediately following a fracture [21]. This is particularly relevant to the FLS population given that by definition, all cases have had a recent fracture [22]. Below, we explore the potential benefits and challenges presented by the concept of IFR for assessing the benefits of an FLS service, and potential implications for clinical assessment in the context of immediate secondary prevention.

Many definitions of IFR or near-term risk have been used, varying by the sites of the index and subsequent fractures included and the period of interest [18, 23, 24]. Given the time dependency of subsequent fracture risk, we suggest IFR in the FLS setting could be defined as the risk of any subsequent fragility fracture within 2 years of the index fracture when the majority of recurrent fractures have occurred [21].

Estimating the IFR within an FLS population is feasible. From observational cohort studies, the rate of subsequent fragility fracture within 2 years in women varies from 7.6 to 23.2% [19, 21, 25, 26]. Important determinants of the absolute IFR include age, gender, fracture site, bone mineral density, and specific comorbidities [18, 21, 23–28].

For IFR to be relevant in the FLS setting, consideration should be given to the therapeutic modalities that can rapidly reduce fracture risk well within the 2 years after an index fracture. Traditional treatment strategies in the UK have used a stepwise approach driven by cost and tolerability [29] with oral bisphosphonates offered as first-line therapy. Significant

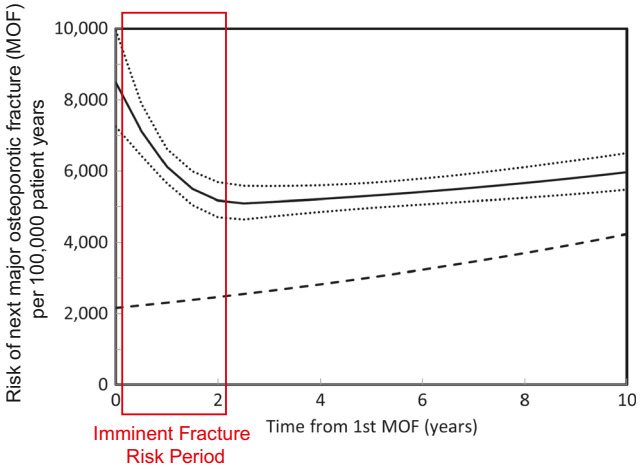

Fig. 1 Time dependency of re-fracture after index fracture adapted from Johansson et al. [15]

fractures occur in the period of IFR despite treatment with oral bisphosphonates as these agents do not provide optimal fracture risk reduction early after initiation, requiring at least 6 to 12 months of adherent therapy before a significant difference in non-vertebral fracture rates is observed [30], with oral agents reaching maximal observed reduction in fracture risk by 36 months [31, 32]. Recently, in head-to-head randomised controlled trials, specific AOMs (teriparatide [33], romosozumab [34], and denosumab [35]—noting the denosumab trial had a randomised open-label alendronate comparator arm) demonstrate both earlier onset of fracture reduction and superiority over oral bisphosphonates within the IFR period of 2 years, and so could be classified as potent AOMs.

For FLSs, the expected number of fractures prevented is directly related to the expected fracture rate in the IFR period and the risk reduction through the use of quicker acting potent AOMs. For example, for a population represented by 1000 UK women aged 75 years with a previous fracture and a femoral neck BMD *T*-score of − 2.9, using interpolated FRAX, the expected number of major osteoporotic fractures within 2 years is 66 (Table 1) [36]. Using fracture reductions from an indirect treatment comparison at 12 and 24 months for specific fracture sites, based on data from all relevant RCTs identified through a systematic literature review [36], the number of major osteoporotic fracture expected to be prevented within 2 years varies from 9 to 33 by AOM per 1000 patients treated immediately following index fracture (Fig. 2). When the same model uses IFR instead of interpolated FRAX, the estimated number of subsequent fractures increases to 107 and the number of fractures avoided almost doubles (mean increase of 91%). Moreover, as IFR applies every time a fracture occurs, potential additional fractures avoided and their consequences can be expected to compound over patients' lifetimes with its corresponding positive impact on patients' quality of life and societal costs [38].

While IFR has clear implications for the planning and justification of FLS services, it also leads to the equally clear message that potent AOMs should be considered promptly following a fragility fracture. The use of potent AOMs in an IFR approach to risk assessment is in line with treat-to-target strategies recommending potent AOMs used first followed by maintenance therapy with bisphosphonates afterwards [39–42]. However, the route to the incorporation of IFR in clinical assessment pathways, as opposed to its use in service planning, is yet to be defined. For example, the specific threshold required for a patient to be recommended potent AOMs might be based on an IFR threshold reached as well as age, gender, bone mineral density, fracture type, number, and recency. In certain situations, the skeletal site of the fracture and the number of previous fractures may suffice. Alternatively, since IFR markedly influences FRAX 10-year fracture probability, a threshold based on a modified form of this metric might offer a further way forward.

There are many apparent challenges of implementing an IFR approach for UK FLSs. For it to be effective, eligible patients need to be identified, investigated, initiated, and adhered to AOM soon after the index fracture. Results from the 2017 UK national audit of FLSs demonstrated that only 6% of submitted patients had a sentinel vertebral fracture, 41% of patients were monitored within 16 weeks of index fracture, and 31% had initiated therapy [5]. Improving detection of vertebral fractures is likely to require integration with radiology systems [43]; reducing the time to treatment is likely to need integration of FLS directly into existing orthopaedic

Table 1 Relationship between index fracture site and subsequent fractures within 2 years in women aged over 50 years [37]

Index fracture type	Post-index fracture at 24 months, *n* (%)					
	Any	Hip	Humerus	Wrist/forearm	Vertebral	Other
Any	4032 (11.4)	1197 (3.4)	632 (1.8)	757 (2.1)	555 (1.6)	1278 (3.6)
Hip	984 (13.7)	289 (4.0)	184 (2.6)	187 (2.6)	124 (1.7)	310 (4.3)
Humerus	564 (11.4)	200 (4.0)	28 (0.6)	134 (2.7)	75 (1.5)	185 (3.7)
Wrist/forearm	813 (8.1)	216 (2.2)	204 (2.0)	69 (0.7)	71 (0.7)	296 (3.0)
Clinical vertebral	498 (17.6)	166 (5.9)	57 (2.0)	66 (2.3)	129 (4.6)	148 (5.2)
Other	1173 (11.1)	326 (3.1)	159 (1.5)	301 (2.9)	156 (1.5)	339 (3.2)

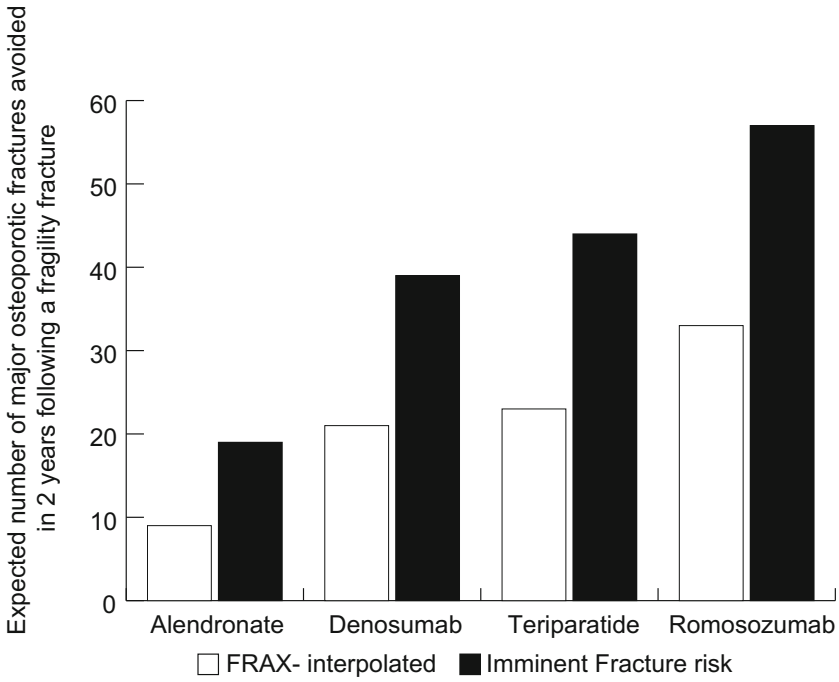

Fig. 2 Expected number of major osteoporotic fractures prevented per 1000 patients treated immediately following index fracture by different anti-osteoporosis medications using interpolated FRAX vs. IFR after an index fracture [36]

pathways, minimising additional clinical workup [44]. While the benefits of potent AOMs in the setting of a recent fracture have not been formally tested, subgroup analyses from studies stratified by recency of fracture have been encouraging [34, 45]. Further, there are no comparative data with intravenous bisphosphonates and the potent AOMs listed above. The data informing IFR calculations and potential benefits mainly come from non-UK sources, where fracture risk may differ due to genetic and environmental factors. The benefits need to be weighed against costs, potential side effects, and the ability of the NHS to rapidly identify, investigate, and initiate therapy in the real-world setting. From a payer perspective, work is urgently needed to simulate the impacts of incorporating an IFR approach into secondary fracture prevention on the clinical and cost-effectiveness of the intervention in a real-world FLS population, considering differences in age, gender, fracture site, and type of AOM administered. This is particularly relevant for FLSs, whose current benefits are usually calculated based on a uniform interpolation of fracture risk using 10-year values and generic alendronate. Consideration of prior fracture location and recency in future versions of FRAX may thus offer a further opportunity to assess these impacts, especially given the global priority for establishing the benefits for sustainable resourcing of effective FLSs [43].

In summary, we recommend the IFR approach to address the need for accurate estimation of the expected number of fractures prevented in the FLS setting and guide recommendation of specific, potent AOMs that demonstrate a rapid onset of fracture protection and superiority over oral bisphosphonates.

Compliance with ethical standards

Conflict of interest The concept for this paper arose from a meeting that was funded by UCB Pharma, with no further funding provided. M Charokopou, E Toth, K Donnelly and C Libanati are employees of UCB. Outside of the submitted work: MK Javaid has received research grants and speaker honorarium from UCB, Lilly UK and Amgen and stock options for Zebra Medical Vision; R Pinedo-Villanueva has been co-applicant in research grants from Amgen; C Cooper has received lecture fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Medtronic, Merck, Nestlé, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB; D Prieto-Alhambra has received research grants from Servier, Amgen and UCB and his department has received speaker and consultancy fees from Amgen and UCB respectively.

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