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EDITORIAL

Assessment and management of imminent fracture risk in the setting of the fracture liaison service

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To address the care gap for individuals with a recent fragility fracture [1], service models in post-fracture care, such as fracture liaison services (FLS), are becoming a higher priority for policymakers [2, 3]. The purpose of this editorial is to draw attention to the need for changes in FLS systems to accommodate fracture risk stratification and the streamlining of treatment initiation to optimise the anti-fracture efficacy of FLS services.

A fragility fracture is certainly a well-established major risk factor for further fractures[4, 5]. Furthermore, current evidence suggests a particularly marked increase in risk over the first 2 years after a sentinel fracture; although the excess risk subsequently wanes, it never reverts to the pre-fracture baseline [6]. The time dependency is illustrated by age in Table 1A where, in an Icelandic cohort, the observed 2-year probability of fracture is consistently higher than the 10-year probability divided by 5 [7]. Consequently, in the 10-year period following an index fracture event, around 50% of subsequent fractures were observed to occur within the first 2 years [6].

This time effect, of particular importance in the FLS setting, has been coined "imminent" fracture risk[8], to convey the urgency for appropriate assessment and treatment. High imminent risk is almost always associated with very high long-term risk in those who survive for the long term since the effect of a fracture on future risk never completely disappears, and many other risk factors are not similarly time dependent [7, 9]. Further refinement can be applied, given that imminent fracture risk also varies by the site of the recent fracture, with much higher impact following fractures of the hip, spine, or humerus compared with other sites such as the distal forearm (Table 1B) [7, 10]. Importantly, the impact of fracture recency has received much attention of late, with several published models to estimate short-term risk [9]; the best developed however incorporates adjustment to the outputs from the FRAX® tool, using age, sex, site and recency dependent multipliers [11]. The effect of imminent risk on the absolute 10-year probability can be captured within the FLS setting and readily linked to national guidance predicated on the 10-year time horizon [12]. This is

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Table 1 Observed probability of major osteoporotic fracture in Iceland by age, and site and recency for prior fracture: A: Observed 2- and 10-year probabilities of a major osteoporotic fracture (%) in men and women from Iceland by age following a humeral fracture within the past 2 years. Also shown is the 10-year probability divided by 5, a value that is consistently lower than the 2-year fracture probability; and FRAX 10-year probability of major osteoporotic fracture from the current Iceland model (BMI 22 kg/m^2; prior fracture of any site or recency; no other risk factors), and then, this FRAX probability adjusted for humeral fracture in the previous 2 years; **B**: Observed 2- and 10-year probabilities of a major osteoporotic fracture (%) in men and women age 70 years from Iceland following a sentinel fracture within the past 2 years. Also shown is the 10-year probability divided by 5, a value that is again consistently lower than the 2-year fracture probability, and FRAX 10-year probability of major osteoporotic fracture from the current Iceland model (age 70 years, BMI 22kg/m^2; prior fracture of any site or recency; no other risk factors), and then adjusted for the site of prior fracture in the previous 2 years (Data from Kanis 2021 [7]). Note the decreasing effect of recency on FRAX probability with increasing age, due to the competing effect of mortality. Note also that adjusted FRAX probability calculated with prior fracture (recency and site) uses no other risk factors, whereas the observed probabilities in the cohort reflect a population of individuals with a wide range of risk factors, so observed probabilities are expected to be somewhat higher than predicted in this context

A	**Men**					**Women**				
Age (years)	**Observed 2-year probability**	**Observed 10-year probability**	**Observed 10-year probability/5**	**FRAX 10-year probability**	**FRAX 10-probability adjusted for recency**	**Observed 2-year probability**	**Observed 10-year probability**	**Observed 10-year probability/5**	**FRAX 10-year probability**	**FRAX 10-probability adjusted for recency**
50	3.2	14.3	2.9	7.7	12.0	4.9	21.7	4.3	9.7	19.0
60	4.7	20.0	4.0	12	17.0	7.3	30.1	6.0	18	27.7
70	6.9	25.1	5.0	15	21.8	10.7	39.1	7.8	27	37.5
80	9.4	24.9	5.0	17	21.3	15.0	43.4	8.7	34	42.8
90	11.1	17.5	3.5	16	13.6	19.3	36.9	7.4	30	32.4
					B					
Site of recent fracture	**Observed 2-year probability**	**Observed 10-year probability**	**Observed 10-year probability/5**	**FRAX 10-year probability**	**FRAX 10-probability adjusted for recency**	**Observed 2-year probability**	**Observed 10-year probability**	**Observed 10-year probability/5**	**FRAX 10-year probability**	**FRAX 10-probability adjusted for recency**
Vertebral	8.1	25.5	5.1	15	22.2	13.9	41.9	8.4	27	40.5
Hip	7.9	25.1	5.0	15	21.9	10.2	34.3	6.9	27	33.2
Humeral	6.9	25.1	5.0	15	21.8	10.7	39.1	7.8	27	37.5
Distal forearm	5.2	22.9	4.6	15	20.0	6.9	30.5	6.1	27	29.4

a critical development since more detailed stratification of fracture risk within FLSs informs clinical decision-making about the choice of appropriate treatments. However, the impact of fracture recency is not captured by current fracture risk assessment tools, including FRAX, underestimating fracture risk in the FLS setting.

Given that the current FRAX algorithm does not incorporate the effect of recency or site of prior fracture, the question arises as to whether it might constitute an essential part of risk assessment in the FLS setting. This is reflected by guidelines that recommend anti-osteoporosis treatment after specific major fragility fractures without further risk assessment [13, 14]. However, the value of risk assessment extends beyond the initial treatment decision, as exemplified by the treat to target approach and the more general value of such information for future monitoring of treatment and encouragement of patient adherence [15]. While the bone community awaits algorithms that incorporate IFR and other factors such as the rate of bone loss, fracture while on treatment, and falls, pragmatic solutions for identifying patients at very high imminent risk include combining a high 10-year FRAX score with a major fragility fracture of the hip, pelvis, femur, vertebra or rib in the last 2 years [16]. Indeed, the first steps towards quantifying the associated risk adjustment have already been established, with the recent development of algorithms to modify the output FRAX probability to account for recency and site of prior fracture [6, 7, 11].

The effect of fracture site and recency on FRAX 10-year probability has thus been documented in a series of studies [6, 17, 18], clearly demonstrating the lower probabilities derived where a prior fracture is included without reference to site or recency (current FRAX tool), compared with modifying the output FRAX probabilities to account for the excess risk associated with a fracture in the previous 2 years. The magnitude of the multipliers is age-dependent, being of lower magnitude with increasing age as a result of the association between recency of prior fracture and mortality risk, which is incorporated as a competing hazard in the FRAX tool [11]. At present, the adjustments are based on a single cohort in Iceland, in which the large size and detailed information on timing and site of fractures have facilitated the analysis. Work in additional populations will permit validation and further refinement of these models. Such considerations notwithstanding, comparison of observed 10-year probabilities in Iceland with calculated 10-year probabilities modified for site and recency are congruent, with the observed probabilities tending to be a little greater than the FRAX estimate with no risk factors, reflecting the admixture of clinical risk factors in the cohort. Thus, for example, using calculated FRAX probabilities for Iceland, a woman at 80 years old with a prior fracture at any time in the past has a 10-year probability of major osteoporotic fracture of 34% (no other risk factors and BMI 22kg/m^2), adjusted to 42.8% when the prior fracture is at the humerus within the previous 2 years. In comparison, the observed 10-year incidence from the Iceland cohort (Table 1), for major osteoporotic fracture after a humerus fracture in the preceding 2 years is 43.4%. As a further example, in women at 60 years, the observed probability of major osteoporotic fracture following a humerus fracture in the preceding 2 years in Iceland is 30.1%. The corresponding 10-year probability for a 60-year-old woman (with a prior fracture at any time or site) from the current Iceland FRAX model is 18%, rising to 27.7% when the probability is modified to account for the prior fracture being at the humerus in the preceding 2 years [11]. These comparisons are summarised by age and prior fracture site in Table 1.

Having recognised and accommodated the impact of imminent fracture risk, a critical deliverable for an FLS is to rapidly initiate anti-osteoporosis therapy for patients at sufficiently increased risk of sustaining a further fracture as outlined by organistaional and patient-level performance indicators [3, 19]. Concerns about a lack of efficacy in the very early post-fracture period are not supported by prespecified analyses of a randomised controlled trial of zoledronate following a hip fracture [20], and a sub-analysis of the VERO Trial demonstrated the efficacy of teriparatide compared with risedronate after recent clinical vertebral fracture and low bone density [21]. Local, regional and national guidelines support clinical decision-making for the choice of anti-osteoporosis medication, informed by the magnitude of future fracture risk. Trials have demonstrated clinically important differences between anti-osteoporosis therapies in terms of speed of onset and scale of bone protection [22, 23], and this has influenced clinical guidelines to now prioritise anabolic therapies for those at highest risk [12, 14, 24, 25]. Time to the reduction of fracture risk is a composite of a medication's pharmacology and the onset of action [26, 27] and factors that affect the time from sentinel fracture to the initiation of therapy. The latter component is within the control of FLS, and from a system-related perspective, the goal is to minimise the number of steps which the high fracture risk patient has to negotiate before receiving anti-osteoporosis medication. DXA is a major predictor of fracture risk [28] and most RCTs included low bone density as an inclusion criterion. Hence, DXA is a standard component of fracture risk assessment in many settings. However, at the patient level, there is variable rapid access to DXA availability between countries as well as within countries [29]. Delays to bone density assessment are due to system (e.g. DXA availability) and patient (pain, mobility, accessibility) factors. The system delays have been highlighted by the COVID pandemic [30]. A delay in DXA leads to a delayed treatment recommendation. Fracture risk assessment tools, particularly FRAX, have marked a step-change in clinical assessment by recognising

that BMD was not the only relevant fracture risk predictor. Indeed, many of the non-BMD risk factors in FRAX have a relationship with BMD such that a higher FRAX risk is associated with a low underlying BMD [31]. Age itself remains a significant predictor of imminent fracture risk; for example, the 2-year fracture risk in a 90-year-old individual with a sentinel fracture exceeds the 10-year risk in 50- and 60-year-old individuals [12]. Based on these observations, some have questioned the need for BMD measurements at older ages, an approach that is reflected within NICE guidance [32], and certainly enables the initiation of treatment before a BMD measurement in orthogeriatric patients with a major fracture. Potential benefits from DXA, when it does not delay treatment initiation, are the use of baseline DXA/VFA to provide an assessment for vertebral fracture detection, the presence of which can also influence treatment choice[33], and to monitor subsequent treatment adherence and response such as in the treat to target setting. While a previous DXA scan has been shown to improve initial treatment adherence at least in younger individuals [34], the balance of benefits and costs of repeated DXA imaging and treatment adherence in the FLS setting, where patients have already experienced a clinical event, requires further research.

In summary, practitioners in the FLS setting need to be aware of the impact of recency of fracture on fracture risk and the need for timely interventions. Whereas current fracture risk assessment tools underestimate future fracture risk in the FLS setting, the accommodation of fracture recency within tools such as FRAX should lead to enhanced decision-making in the management of patients attending the FLS. The ability to stratify risk and enable treatment decisions without BMD measurement in some very high risk patients could become standard practice within FLS.

Declarations

Conflicts of interest J.A.K., N.C.H. and E.V.M. are responsible for the creation and maintenance of FRAX but derive no financial benefit. E.V.M. 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. C.C. reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB. N.C.H. 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. M.K.J. reports personal fees from UCB, Amgen and Kyowa Kirin. J.A.K. reports no additional competing interests.

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