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Clinical science

Fracture prediction in rheumatoid arthritis: validation of FRAX with bone mineral density for incident major osteoporotic fractures

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Abstract

Objectives: FRAX uses clinical risk factors, with or without BMD, to calculate 10-year fracture risk. RA is a risk factor for osteoporotic fracture and a FRAX input variable. FRAX predates the current era of RA treatment. We examined how well FRAX predicts fracture in contemporary RA patients.

Methods: Administrative data from patients receiving BMD testing were linked to the Manitoba Population Health Research Data Repository. Observed cumulative 10-year major osteoporotic fracture (MOF) probability was compared with FRAX-predicted 10-year MOF probability with BMD for assessing calibration. MOF risk stratification was assessed using Cox regression.

Results: RA patients ($n = 2099$, 208 with incident MOF) and non-RA patients ($n = 2099$, with 165 incident MOF) were identified. For RA patients, FRAX-predicted 10-year risk was 13.2% and observed 10-year MOF risk was 13.2% (95% CI 11.6, 15.1). The slope of the calibration plot was 0.67 (95% CI 0.53, 0.81) in those with RA *vs* 0.98 (95% CI 0.61, 1.34) in non-RA patients. Risk was overestimated in RA patients with high FRAX scores (>20%), but FRAX was well calibrated in other groups. FRAX stratified risk in those with and without RA [hazard ratio (HR) 1.52 (95% CI 1.25, 1.72) *vs* 2.00 (95% CI 1.73, 2.31)], with slightly better performance in the latter (P for interaction = 0.004).

Conclusions: FRAX predicts fracture risk in contemporary RA patients but may slightly overestimate risk in those already at high predicted risk. Thus the current FRAX tool continues to be appropriate for fracture risk assessment in RA patients.

Keywords: rheumatoid arthritis, FRAX, dual-energy X-ray absorptiometry, osteoporosis, fracture risk prediction, rheumatic disease, fracture.

Rheumatology key messages

- Validation of FRAX in modern RA patients was lacking.
- FRAX with BMD predicts incident major osteoporotic fracture well in this RA population.
- A small overestimation of fracture was seen in those at highest predicted risk.

Introduction

The World Health Organization defines osteoporosis as 'a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture' [1]. Many factors contribute to the risk of osteoporotic fracture beyond BMD and the quality of bone, including chronic diseases, medications, falls and lifestyle [2]. To guide treatment decisions, guidelines recommend using risk calculators that consider risk factors in addition to BMD. Most prominent of these is the FRAX score. The FRAX score used data from 12 international prospective cohort studies to develop an algorithm that computes 10-year probability of a major osteoporotic fracture (MOF) (clinical spine, hip, humerus or forearm fracture) and the 10-year probability of hip fracture alone [3].

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Patients with RA experience higher rates of chronic medical complications, including osteoporosis. RA patients have significantly lower BMD and higher FRAX risk compared with healthy controls [4]. Proposed mechanisms include joint damage, systemic inflammation and greater fall risk [5–7]. RA increases fracture risk independent of glucocorticoid use, although RA status was only available in three FRAX development cohorts and relied on self-reports [7]. RA is an input variable in the FRAX tool and can push a patient above treatment thresholds [8].

Since the 1980s there has been a marked improvement in therapy for RA, first with conventional systemic DMARDs (csDMARDs), then with biologics revolutionizing the treatment of RA. Most of the data used in constructing the FRAX algorithm were collected prior to widespread use of biologics [7, 9]. RA patients have become progressively healthier and are at lower risk of downstream consequences of untreated RA [10], raising the question, with RA patients healthier than when FRAX was first developed, does FRAX still accurately estimate fracture risk in RA patients?

FRAX was validated in RA patients by Klop *et al.* [11] using the Clinical Practice Research Datalink (CPRD) database in the UK with an index date of 1 January 2004 and up to 10 years of observation. Klop *et al.* [11] found that the UK FRAX overestimated fracture risk in RA for both MOF and hip fracture, but conclusions regarding MOF were limited by a lack of hospital linkage for MOF. Since BMD was not available, the FRAX score was used without BMD, which does not mirror clinical practice in many high-income countries [12, 13]. Mousa *et al.* [14] validated FRAX for incident MOF in a small retrospective cohort of 662 RA patients (356 RA patients with DXA results available) showing good prediction for MOF without BMD and some underestimation of fracture in those ages 40–59 years with BMD. Parental hip fracture and complete glucocorticoid data were not available, competing mortality analysis was not used and the data index dates are not current (1980–2007).

FRAX has been validated in the general population [15, 16]. The current study is the largest longitudinal direct validation of FRAX with BMD in RA patients. Therefore, this study informs clinical decision making by filling a gap in the literature: validating FRAX with BMD for MOF prediction in the modern era of RA treatment.

Methods

Study design and data sources

This study is an observational cohort study using routinely collected health administrative data.

Manitoba is a province in Canada with a population of ≈1.4 million with a one-tier, single-payer public healthcare system [17]. The Manitoba BMD program oversees all DXA tests in Manitoba, with data available since 1990 [18]. The Manitoba BMD database shows >99% completeness for BMD results and >99% successful linkage to population health databases [19]. The index date is taken as the patient's first BMD. Therefore this database represents a selected, but clinically relevant, population of patients who have been sent for, and received, BMD testing as part of routine clinical care for osteoporosis. The Manitoba Health Information Privacy Committee approved access to the de-identified data and waived the requirement for signed consent (HIPC 2016/2017-29), in accordance with the Personal Health Information Act (PHIA).

Study population

To reflect RA treatment in the biologics era, only patients with a first BMD assessment in 2000 onwards were included [20]. Other inclusion criteria were age >40 years and at least 2 years of observation time before the first DXA.

RA cases were identified using two complementary sources: clinical diagnosis gathered at the time of DXA (intake questionnaire reviewed by medical staff, supplemented with a review of medications and referring physician contact as required) and the validated administrative database definition by Hitchon *et al.* [21] [five physician or hospital visits for RA (if coverage ≥2 years) or three physician or hospital visits for RA (if coverage <2 years)]. RA billing codes were based on the International Classification of Disease version 9 and 10 codes (ICD-9-CM: 714 rheumatoid arthritis and other inflammatory polyarthropathies; ICD-10-CA: M05, M06).

An equal number of unmatched non-RA patients were randomly selected from patients who met the same inclusion criteria but did not satisfy a diagnosis of RA. Patients were not excluded for other health conditions. The non-RA group was used to assess the performance of FRAX in the general population. A deliberate decision was made not to match the comparator patients to RA patients on the basis of age or sex, since this would tend to select for non-RA secondary conditions referred for BMD testing [13]. By not matching, the comparator group largely represents an unselected general population and is more representative of the 'usual use case' for FRAX. Importantly, an unselected comparator group still has enough overlap in FRAX scores with the RA group for useful comparison.

Data linkage

Linkage occurred at the level of the Manitoba Centre for Health Policy, and prior to the dataset being uploaded, 1168 of 158 131 (0.7%) observations were dropped because of non-linkage. Non-linkage generally occurs if the patient did not have a Provincial Health Identification Number (PHIN) due to healthcare funding being provided by an alternate agency (e.g. residents from neighbouring provinces or members of the Department of National Defence).

Bone density measurements and fracture probability

Hip DXA scans were acquired in keeping with the manufacturer's recommendations (Prodigy or iDXA, GE Healthcare, Madison, WI, USA). Instruments have been previously cross-calibrated using anthropomorphic phantoms and shown to have stable long-term performance (coefficient of variation <0.5%).

The 10-year probability of MOF was calculated for the Canadian FRAX using FRAX Desktop Multi-Patient Entry, version 3.8. BMI, age, femoral neck BMD and other variables required for the FRAX calculation were obtained from information and direct measurements (height and weight) and collected from patients through the intake questionnaire; as described elsewhere, this information was supplemented with population-based healthcare data (hospital diagnoses, physician billing claims, provincial pharmacy database), ensuring essentially complete information in effectively all subjects

(Supplementary Table S1, available at *Rheumatology* online) [22]. Before 2005, parental hip fracture was available by self-report, and after 2005, by linkage to parental hospitalization information. Oral glucocorticoid use was defined as >90 days of oral glucocorticoids obtained from the Manitoba Drug Program Information Network dispensed in the year prior to BMD [23].

When femoral neck BMD was missing, FRAX was calculated using clinical risk factors alone (3.6% of patients). In an exploratory analysis, we also calculated the FRAX–MOF–BMD score for the RA group where the RA input was set to absent.

RA medication categories of csDMARD and biologic therapies were defined by the Anatomical Therapeutic Chemical (ATC) classification system captured for 2 years prior to the index date using data from the Manitoba Drug Program Information Network. Codes are based in part on previously published categories and updated based on current drug availability in Manitoba (Supplementary Table S2, available at *Rheumatology* online) [24]. Small molecule RA therapies (e.g. tofacitinib) were considered a biologic equivalent for the purposes of this study.

Outcomes

Fracture was assessed using hospital diagnosis and procedure codes [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) prior to 2004, International Classification of Diseases, Tenth Revision, Canadian Enhancements (ICD-10-CA) thereafter] and physician billing claims (ICD-9-CM) using previously validated definitions that exclude fractures accompanied by high trauma codes (Supplementary Table S3, available at *Rheumatology* online) [25, 26]. The primary outcome was incident MOF (defined as hip, proximal humerus, clinical spine or forearm fracture). Fractures were excluded if there were hospital or physician visits with the same type of fracture in the 6 months preceding an incident fracture diagnosis, to prevent double counting of a single fracture.

Statistical analysis

Statistical analysis was performed using Stata 16 (StataCorp, College Station, TX, USA) [27] and R for graphing (R Foundation for Statistical Computing, Vienna, Austria) [28]. Baseline characteristics were captured at the date of BMD. RA and non-RA between-group differences were calculated using a two-sided *t*-test for continuous normally distributed variables, Wilcoxon rank sum test for continuous non-normally distributed variables and chi-squared test for categorical variables.

The 10-year observed cumulative MOF probability was estimated in the presence of competing mortality as previously described [29]. Calibration was assessed using predicted compared with observed events at 10 years, slope of the calibration plot and intercepts and calibration plots by category of predicted risk [low (<10%), moderate (10–20%) and high (>20%) FRAX scores].

Using Cox proportional hazards regression, ratios per s.d. increase in FRAX score were estimated. FRAX scores were log-transformed due to a skewed distribution. The primary analysis was stratified by RA status and then two-way group-by-FRAX interaction testing was performed. Sensitivity analysis for missing femoral neck T-score, excluding RA from the FRAX score, sex and glucocorticoid exposure were performed.

The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) checklist as recommended by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network was used, with relevant sections referenced in the checklist in Supplementary Table S4, available at *Rheumatology* online [30].

Results

Our study population included 2099 RA patients and 2099 non-RA patients. Characteristics are reported in Table 1. The mean age of the RA patients was 62.5 years (s.d. 11.0), with 16% being men. In the prior 2 years, 10% were prescribed a biologic or small molecule treatment for RA and 81% were prescribed csDMARDs. In the year prior, 28% had glucocorticoid exposure. csDMARDs can be prescribed for diseases other than RA, and exposure in the non-RA group was 4%. In the RA population ($n = 2098$), the 10-year MOF risk was low (<10%) in 996 patients, moderate (10–20%) in 706 patients and high (>20%) in 396 patients. In the non-RA comparator population ($n = 2099$), the 10-year MOF risk was low (<10%) in 1305 patients, moderate (10–20%) in 579 patients and high (>20%) in 215 patients.

Outcomes and observation times are shown in Table 1. A total of 208 first incident MOFs in RA patients (65 in low, 70 in moderate and 73 in high-risk categories) and 165 first incident MOFs in non-RA patients (53 in low, 70 in moderate and 42 in high-risk categories) were observed. During follow-up, RA patients were more likely than non-RA patients to fracture [15.6 (95% CI 13.6, 17.8) *vs* 11.7 (95% CI 10.0, 13.6) fractures per 1000 person-years; $P = 0.006$] or die [25.7 (95% CI 23.2, 28.5) *vs* 20.4 (95% CI 18.2, 22.9) deaths per 1000 person-years; $P = 0.003$].

FRAX calibration

In RA patients, the mean predicted 10-year MOF risk (using FRAX–MOF–BMD) was 13.2% and observed 10-year MOF was 13.2% (95% CI 11.6, 15.0). The slope of the calibration plot was 0.67 (95% CI 0.53, 0. 81) (Fig. 1A), but the difference between predicted and observed risk was not significant except in the lowest decile of predicted risk (Fig. 1A).

In the non-RA population, predicted risk was 10.2% and observed fracture risk was 10.3% (95% CI 8.8, 11.9). The slope of the calibration plot was near unity at 0.98 (95% CI 0.61, 1.34) (Fig. 1B).

When classifying patients by risk categories, 1702 of 2098 RA patients (81%) were in the low (<10%) or moderate risk (10–20%) categories (Fig. 1C), which were well calibrated. In the non-RA population, all risk categories showed calibration that included the line of equality (Fig. 1D).

Cox proportional hazards models

Cox proportional hazards models showed that FRAX significantly predicted risk in those with RA and without RA (Table 2). Clinical FRAX score (without BMD) predicted MOF with a higher HR in non-RA patients [1.93 (95% CI 1.66, 2.24)] than RA patients [1.44 (95% CI 1.28, 1.63)], with a *P* for interaction of 0.003. The addition of BMD to the FRAX–MOF score increased the HR in the RA group to 1.52 (95% CI 1.35, 1.72), which was again lower than the non-RA

Table 1. Baseline characteristics and outcomes

Characteristics and outcomes	RA ($n = 2099$)	Non-RA ($n = 2099$)	*P*-value
Age, years, mean (S.D.)	62.5 (11.0)	65.4 (11.0)	**<0.001**
Male, *n* (%)	328 (16)	224 (11)	**<0.001**
BMI, kg/m^2, mean (S.D.)	28.00 (5.85)	27.47 (5.60)	**0.003**
Prior fracture, *n* (%)	369 (18)	439 (21)	**0.006**
Parental hip fracture, *n* (%)	172 (8)	180 (9)	0.656
Smoker, *n* (%)	287 (14)	225 (11)	**0.003**
Glucocorticoid use, *n* (%)	593 (28)	86 (4)	**<0.001**
Secondary causes of osteoporosis (other than RA) , *n* (%)	240 (11)	338 (16)	**<0.001**
High alcohol use, *n* (%)	13 (1)	17 (1)	0.464
Femoral neck T-score, mean (S.D.)	−1.38 (1.05)	−1.34 (1.01)	0.156
FRAX–BMD–MOF, mean (S.D.)	13.2 (9.5)	10.2 (7.4)	**<0.001**
Diabetes, *n* (%)	293 (14)	247 (12)	**0.034**
RA drug, *n* (%)			
Biologic or small molecule	207 (10)	7 (0)	**<0.001**
csDMARD	1708 (81)	78 (4)	**<0.001**
Ethnicity, *n* (%)			
White	2002 (95)	1991 (95)	0.569
Non-white	57 (3)	63 (3)	
Missing	40 (2)	45 (2)	
MOFs, *n* (%)	208 (9.9)	165 (7.9)	**0.020**
MOF/1000 person-years (95% CI)	15.6 (13.6–17.8)	11.7 (10.0–13.6)	**0.006**
Deaths, *n* (%)	362 (17.2)	300 (14.3)	**0.009**
Deaths/1000 person-years (95% CI)	25.7 (23.2–28.5)	20.4 (18.2–22.9)	**0.003**

Events measured at <10 years observation time.
Bold values are statistically significant.

group [2.00 (95% 1.73, 2.31)], with a *P* for interaction of 0.004.

Sensitivity analysis

In RA patients not exposed to glucocorticoids ($n = 1506$), the mean MOF risk was 12.2% and observed 10-year MOF risk was 13.8% (95% CI 11.8, 16.1) (Supplementary Fig. S1, available at *Rheumatology* online). In RA patients without glucocorticoid exposure, Cox proportional hazards models showed FRAX predicted fracture risk (Supplementary Table S5, available at *Rheumatology* online).

Sex-stratified analyses showed wide CIs for men ($n = 328$) that limits interpretation (Supplementary Fig. S2, available at *Rheumatology* online) and the *P*-value for the two-way interaction of FRAX and sex was not statistically significant for both FRAX–MOF with and without BMD (Supplementary Tables S6 and S7, available at *Rheumatology* online). Analysis for female sex only ($n = 1771$) resembled the results for the entire group (Supplementary Fig. S2, available at *Rheumatology* online).

Omitting RA from the FRAX score led to overall underestimation of fracture (Supplementary Fig. S3, available at *Rheumatology* online). Omitting those with a missing femoral neck T-score did not change the overall results.

Discussion

RA patients were more likely to fracture or die than non-RA patients. FRAX without and with BMD stratifies MOF risk in RA patients, although HRs were slightly lower than in non-RA patients. HRs for MOF prediction were higher for FRAX with BMD than without. A slight overestimation of fracture risk was seen in higher FRAX risk RA patients (particularly in the top two deciles of risk and high FRAX score >20%). For those at low or moderate risk, FRAX was well calibrated. For RA patients in the top two deciles of FRAX risk, the modest overestimation of risk may not have clinical implications since these patients may fall well above treatment thresholds.

Validation of FRAX in the RA population was published by Klop *et al.* in 2016 [11]. That study has many strengths: they considered competing mortality analysis, used an appropriate outcome calculated by survival methods, had appropriate follow-up times and used a large, well-established administrative database (the UK CPRD). Firm conclusions from that study could only be made from hip fracture (247 outcomes) and showed overestimation of FRAX without BMD for hip fracture [5.5% *vs* 4.1% (95% CI 3.6, 4.6)], especially in higher-risk groups, with calibration plots very like the current study, showing overestimation in patients in the highest two deciles of risk. The current study demonstrates reproducibility of some of the findings by Klop *et al.* [11] (overestimation of fracture seen in high-risk patients); the differences in population, risk score and outcomes between the two studies speak to reproducibility.

Our findings are generally consistent with Mousa *et al.* [14], who showed acceptable validation of FRAX for incident MOF with and without BMD in a smaller retrospective cohort, although they did not observe the overestimation of fracture at highest risk. Yu *et al.* [31] studied 493 Taiwanese RA participants over a 3-year period in a prospective cohort study that sought to identify the optimal threshold for FRAX based on receiver operating characteristics curves. The authors suggest a Taiwan FRAX–MOF threshold of 22% for treatment intervention, which generally agrees with guidelines using a 20% FRAX cut-off [32, 33]. However, this study was limited by short follow-up time (less than the 10 years predicted in FRAX) and a lack of competing mortality analysis. Both of these studies have limitations because of low event rates, with 76 MOFs in Mousa *et al.* [14] and 116 MOFs in Yu *et al.* [31].

A major strength of the current study is the use of the outcome measure of 10-year cumulative incidence considering

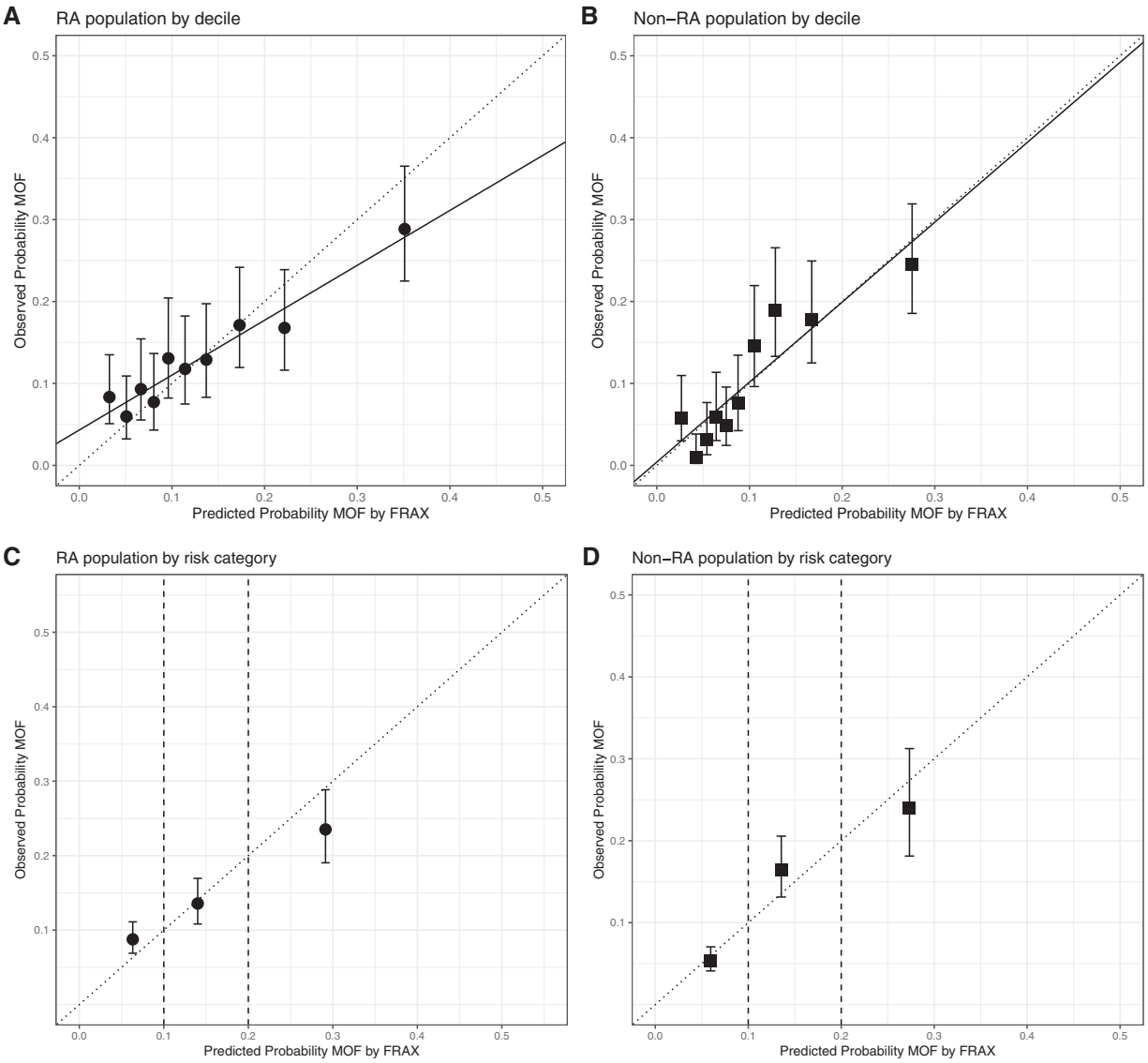

Figure 1. Ten-year observed MOF *vs* predicted probability using FRAX–BMD by decile and risk category. **(A)** RA population ($n = 2099$). **(B)** Non-RA comparator population ($n = 2099$) by decile of FRAX. **(C)** RA population ($n = 2098$): low ($n = 996$), moderate ($n = 706$) and high ($n = 396$) risk. **(D)** Non-RA comparator population ($n = 2099$): low ($n = 1305$), moderate ($n = 579$) and high ($n = 215$) risk. Dotted line represents observed equal to predicted. Solid lines are lines of best fit. Dashed vertical lines denote low (<10%), moderate (10–20%) and high (>20%) FRAX scores

Table 2. HRs for incident MOFs per s.d. increase in FRAX score

Score	RA patients, HR (95% CI)	Non-RA patients, HR (95% CI)	*P*-value for interaction (group*FRAX)
FRAX without BMD	1.44 (1.28, 1.63)	1.93 (1.66, 2.23)	0.003
FRAX with BMD	1.52 (1.35, 1.72)	2.00 (1.73, 2.31)	0.004

competing mortality. This study has an appropriate sample size with 208 outcomes in the RA group and is greater than the 100 outcomes recommended [34, 35]. Risk of bias due to missing data is low, thanks to few missing values and a very high rate of data linkage (99.3%). Klop *et al.* [11] did not have BMD data available; the robust and complete BMD data in this study is a significant strength and mirrors clinical practice in high-income countries [12, 13]. Fracture outcome definitions for this study have been validated [25]. We used a validated administrative definition of RA supported by the high rate of csDMARD use [21].

Limitations are acknowledged. The sample size led to wide CIs that could contribute to uncertainty. The sample size is small in the high-risk group, limiting the precision of our estimates, especially when predicted risk is >20%. Nevertheless, the point estimates suggest that patients falling in this category have an observed cumulative risk >20% (Fig. 1C and D). This dataset represents a population where osteoporosis assessment by way of DXA was arranged by a care provider and, as such, represents a clinically relevant and pragmatic choice of population. This population may be subject to healthy referral bias since patients were well enough to be

referred for and receive DXA testing. From an external validity perspective, this population may also represent an older [62.5 years (S.D. 11.0)], predominantly White population (95%), with higher glucocorticoid exposure (28%) and lower biologic/small molecule exposure (10%) than other RA populations [36, 37]. The original hypothesis of this study was that fracture risk may be lower than predicted by FRAX in patients in the biologic era. The low biologic/small molecule exposure (10%) may have impacted the results, and further study in cohorts of younger RA patients with greater biologic exposure may yield different results.

Conclusions

FRAX was validated to predict fracture risk in modern RA patients but may slightly overestimate risk in those already at high predicted risk, although sample size limits the ability to make firm conclusions in high-risk patients. Clinicians can continue to use FRAX in the osteoporosis management of RA patients.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data sharing is not permitted under the Researcher Agreement with Manitoba Health and Seniors Care (MHASC). However, researchers may apply for data access through the Health Research Ethics Board of the University of Manitoba and the Health Information and Privacy Committee of MHASC.

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Are you using a treatment that addresses all 6 key manifestations of PsA?

The key clinical manifestations of PsA are joints, axial, skin, enthesitis, dactylitis and nails.[1]

Joint relief in PsA:

68% of patients achieved **ACR50** with Cosentyx® (secukinumab) at **Year 1** (observed data)[2]

Results from ULTIMATE (N=166). The primary endpoint of GLOESS mean change from baseline vs placebo at Week 12 was met (−9 vs −6, p=0.004)[2,3]

Click here to visit our HCP portal and learn more

Skin clearance in PsO:

55% of patients achieved **PASI100** at **Week 52** with Cosentyx 300 mg AI (secondary endpoint, observed data, N=41)[4]

Results from MATURE. The co-primary endpoints PASI 75 and IGA mod 2011 0/1 at Week 12 were met for Cosentyx 300 mg (N=41) vs placebo (N=40), (95% vs 10% and 76% vs 8% respectively, p<0.0001)[4]

Axial joint relief in PsA:

69% of patients achieved **ASAS40** at **Week 52** with Cosentyx 300 mg (secondary endpoint, observed data, N=139)[1]

Results from MAXIMISE. The primary endpoint of ASAS20 with Cosentyx 300 mg (N=164) vs placebo (N=164) at Week 12 was met (63% vs 31% respectively, p<0.0001)[1]

Cosentyx is the first and only, fully human biologic that directly blocks IL-17A regardless of its source[5–10]

8 years

A **consistent safety profile** with **over 8 years** of real-world experience[5,6,11]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[5,6]

Cosentyx licensed indications in rheumatology: Cosentyx is indicated for the treatment of active psoriatic arthritis in adult patients (alone or in combination with methotrexate) when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; moderate to severe plaque psoriasis in children and adolescents from the age of 6 years, and adults who are candidates for systemic therapy; active enthesitis-related arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active juvenile psoriatic arthritis in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[5,6]

ULTIMATE (N=166), a multicentre, randomised, double-blind, placebo-controlled, 52-week Phase III trial in patients with PsA. Patients were randomly assigned to receive either weekly subcutaneous Cosentyx (300 mg or 150 mg according to the severity of psoriasis) or placebo followed by 4-weekly dosing thereafter. The primary outcome of mean change in the ultrasound GLOESS from baseline to Week 12 was met (−9 vs −6; p=0.004).[2,3]
MATURE (N=122), a 52-week, multicentre, double-blind, randomised, placebo-controlled, Phase III trial in patients with PsO. Eligible patients were randomised to Cosentyx 300 mg or placebo. The co-primary endpoints were PASI75 and IGA mod 2011 0/1 responses at Week 12. The study met the co-primary endpoints: PASI75 and IGA mod 2011 0/1 response at Week 12 were met for Cosentyx 300 mg vs placebo (95% vs 10% and 76% vs 8% respectively, p<0.0001).[4]
MAXIMISE (N=498) a double blind, placebo-controlled, multicentre, Phase IIIb study in patients with PsA. Patients were randomised in a 1:1:1 ratio to receive Cosentyx 300 mg, 150 mg or placebo. The primary endpoint of the proportion of patients achieving and ASAS20 response with Cosentyx 300 mg at Week 12 vs placebo was met (63% vs 31% respectively, p<0.0001).[1]

ACR, American College of Rheumatology; AI, auto-injector; ASAS, Assessment of SpondyloArthritis International Society; BASDAI, Bath; ankylosing spondylitis disease activity index; EULAR, European Alliance of Associations for Rheumatology; GLOESS, Global EULAR and OMERACT synovitis score; IGA mod 2011 0/1, investigator global assessment modified 2011 0/1; OMERACT, outcome measures in rheumatology; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; PsO, plaque psoriasis.

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NOVARTIS

Prescribing information, adverse event reporting and full indication can be found on the next page.

UK | May 2024 | 425034

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. 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Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. 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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com