Official Positions for FRAX® Clinical Regarding Rheumatoid Arthritis

From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®

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on behalf of the FRAX® Position Development Conference Members

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Abstract

Rheumatoid arthritis is the only secondary cause of osteoporosis that is considered independent of bone density in the FRAX® algorithm. Although input for rheumatoid arthritis in FRAX® is a dichotomous variable, intuitively, one would expect that more severe or active disease would be associated with a greater risk for fracture. We reviewed the literature to determine if specific disease parameters or medication use could be used to better characterize fracture risk in individuals with rheumatoid arthritis. Although many studies document a correlation between various parameters of disease activity or severity and decreased bone density, fewer have associated these variables with fracture risk. We reviewed these studies in detail and concluded that disability measures such as HAQ (Health Assessment Questionnaire) and functional class do correlate with clinical fractures but not morphometric vertebral fractures. One large study found a strong correlation with duration of disease and fracture risk but additional studies are needed to confirm this. There was little evidence to correlate other measures of disease such as DAS (disease activity score), VAS (visual analogue scale), acute phase reactants, use of non-glucocorticoid medications and increased fracture risk. We concluded that FRAX® calculations may underestimate fracture probability in patients with impaired functional status from rheumatoid arthritis but that this could not be quantified at this time. At this time, other disease measures cannot be used for fracture prediction. However only a few, mostly small studies addressed other disease parameters and further research is needed. Additional questions for future research are suggested.

Key Words: Rheumatoid arthritis; osteoporosis; osteoporotic fracture; vertebral fracture; fracture risk; FRAX.

Introduction

Rheumatoid arthritis is a systemic inflammatory disease that is commonly associated with both local (peri-articular) and systemic osteoporosis. Multiple studies have documented decreased bone density in patients with rheumatoid arthritis (1–6) as well as increased hip (1,7–10), clinical spine (1) and morphometric spine (11–14) fractures compared to control populations. Although there are many other causes for secondary osteoporosis, their effect can usually be explained by the effect of the disease on decreasing bone density. Rheumatoid arthritis is the only secondary cause of osteoporosis that is considered independent of bone density in the FRAX® algorithm (15).

Etiology of systemic osteoporosis and fragility fracture in rheumatoid arthritis is multifactorial and includes use of
glucocorticoids, chronic inflammation with associated cyto-
kine production, inactivity and increased risk of falling
\((16,17)\). The relative contribution of these factors to the
development of osteoporosis and osteoporotic fractures in
these patients is not well understood. Although input for
rheumatoid arthritis in the FRAX algorithm is a dichotomous
variable, intuitively, one would expect that more severe or
active disease would be associated with more severe osteo-
porosis. There are multiple methods to characterize disease
severity/activity in rheumatoid arthritis. These can be
divided into

1. Severity measures
   a. Functional measures — includes disability scores such
      as HAQ (health assessment questionnaire), and func-
      tional class.
   b. Structural measures — reflects amount of end-stage
disease and includes number of deformed joints and
      erosion scores.
2. Activity measures — includes standard measures of dis-
   ease activity such as VAS (visual analog scale of disease
   activity by both physician and patient: pain or global
   activity of disease), acute phase reactants (e.g. ESR
   and/or CRP) and DAS (disease activity score - includes
   number of tender/swollen joints as well as VAS).

Several studies have associated various disease param-
ters seen in rheumatoid arthritis patients with decreased
bone density including HAQ measures \((2,4,5,18)\), functional
class \((6)\), disease duration \((1,2,4,23)\), DAS \((2,4,18)\), acute
phase reactants \((2,19,20)\). Other studies have associated
specific rheumatoid arthritis medications with decreased
bone density. However, few studies have correlated disease
parameters or medication use with fracture risk in these
patients.

We reviewed the available literature to determine if spe-
cific disease parameters or medications used in rheumatoid
arthritis could be used to better characterize fracture risk in
patients with rheumatoid arthritis. We included all studies
that evaluated either clinical fractures (nonvertebral and ver-
tebral) or morphometric spine fractures. Although morpho-
metric vertebral fractures were not evaluated in the FRAX
cohorts that included rheumatoid arthritis, these fractures rep-
resent the majority of vertebral fractures and are clearly asso-
ciated with future fractures \((21,22)\).

Methodology & Data sources

To determine the effect of various disease parameters and
medication use on fracture risk in rheumatoid arthritis
patients, a Medline search limited to English language
publications was completed September 1, 2010. Items searched
were: rheumatoid arthritis and fracture, rheumatoid arthritis
and osteoporotic fracture, rheumatoid arthritis and vertebral
fracture, medication and rheumatoid arthritis and fracture.
Abstracts were reviewed and complete articles that correlated dis-
ease activity/severity or medication use to fracture prevalence
or incidence were further evaluated. Studies looking at clinical
fractures were distinct from studies looking at morphometric
vertebral fractures so these were analyzed separately.

Statements

**Question:** Can parameters of disease activity or severity be
used to assess fracture risk in rheumatoid arthritis patients in
a modified FRAX calculation?

**Official Position:** Impaired functional status in patients
with rheumatoid arthritis may be a risk factor for clinical frac-
tures. FRAX may underestimate fracture probability in these
patients.

**Grade:** Good, A, W

**Rationale**

**Clinical Fractures**

We found 8 studies that examined the effect of disease
activity or severity on clinical fractures \((1,10,23,24,25,26,
27,28)\) - see Table 1. Six of the eight studies documented a signif-
ificant correlation between disability measures (HAQ, JHAQ for
the Japanese studies or functional class) and fracture risk. Risk
was particularly significant for clinical vertebral fractures.

In the three studies where vertebral fractures were considered
separately, risk ranged from a RR 2.42 (25), OR 4.99 (28)
and OR 7.74 (26). One small study (23) found no association
and the final study (1) did not include a disability measure.

The effect of duration of disease was mixed: three Japa-
nese observational cohort studies showed no association
(25,26,28), two did not evaluate disease duration (10,24)
and two showed a marginal association (20,23). However,
the largest study, the British General Practice Research Data-
base (GPRD) of 30,262 men and women over age 40 with
rheumatoid arthritis, median follow-up 7.6 years, documented
a significant association of incident fractures with duration of
disease (1). In fact, disease duration was the strongest predic-
tor of future fractures in this study with a RR 3.4 with disease
duration > 10 years.

There was little evidence to associate other disease param-
eters and fracture risk. Only two studies (25,26) looked at
acute phase reactants and surprisingly found a decreased
risk of nonvertebral fractures with increased CRP with a
RR 0.46 (0.17—1.28) in one study (25) and a HR of 0.60
(0.38—0.95) in the other (26). However, neither study looked
at gradient of risk; risk was based on less than or greater than
a CRP of 0.7. In addition, one of these studies (25) found an
increased risk of clinical vertebral fractures with increased
CRP: RR 1.31 (0.43—4.00). No association of fracture with
VAS scores were seen in three studies (24,25,26) or DAS in
one study (23). Only two studies looked at structural mea-
sures of disease severity. One showed a correlation with num-
ber of deformed joints (23), the other showed no association
with erosion scores (24).

**Morphometric Vertebral Fractures**

Seven studies evaluated the correlation between
morphometric vertebral fractures and disease parameters
\((11,12,29—33)\) - see Table 2. However, these were much smaller
Only three looked at HAQ scores: two showed no association (32,33), one suggested an association (31) with an MHAQ (modified HAQ score, range 1 to 3) of 1.87 in patients with an incident deformity vs. 1.53 in those without an incident deformity (p<0.008). Of interest, both studies that looked at erosion scores and fracture risk (29,30) found a positive association with a p value <0.0001 in one study (29). The other study reported that only age and Larsen erosion scores were independent determinants of vertebral deformities in multiple regression analyses. Although these studies did not look at measures of disability, it is likely that patients with greater erosion scores would have greater disability. Of interest, other studies suggest that erosion scores correlate with decreased bone density (34,35) with one (34) documenting a linear correlation between disability measured by Steinbrocker’s functional stage and frequency of osteoporosis (p = 0.0001). This observation deserves further evaluation to determine if this translates into an increased risk of fracture. At this time, there is no evidence that disease parameters can be used to predict risk for morphometric vertebral fractures in patients with rheumatoid arthritis.

**Question:** Does medication use in rheumatoid arthritis alter the calculated fracture risk?

**Official Position:** There is no consistent evidence that non-glucocorticoid medications for rheumatoid arthritis alter fracture risk

**Grade:** Fair, B, W

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### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Study size</th>
<th>f/u</th>
<th>Disability (HAQ or equiv)</th>
<th>Disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Britain (GPRD)</td>
<td>30,262 men and women</td>
<td>7.6 years median</td>
<td>NR</td>
<td>RR 3.4 &gt; 10 years (3.0–3.9)</td>
</tr>
<tr>
<td>(23) Norway (county register)</td>
<td>249 women</td>
<td>NR</td>
<td>No assoc</td>
<td>OR 1.04/year (1.01–1.07)</td>
</tr>
<tr>
<td>(24) USA (CORRONA)</td>
<td>8,419 women</td>
<td>18 mos</td>
<td>IRR&lt;sup&gt;a&lt;/sup&gt; 1.5</td>
<td></td>
</tr>
<tr>
<td>(25) Japan</td>
<td>1,733 women</td>
<td>54 mos</td>
<td>RR 1.76 non-vert (1.07–2.89)</td>
<td></td>
</tr>
<tr>
<td>(26) Japan</td>
<td>1,050 men</td>
<td>6–66 mos (median 49)</td>
<td>HR 1.33 non-vert (0.60–2.98) 7.74 vert (2.10–28.48)</td>
<td></td>
</tr>
<tr>
<td>(27) Canada and USA (ARAMIS)</td>
<td>1,110 men and women</td>
<td>8.4 years</td>
<td>OR 1.28/1unit (1.05–1.57)</td>
<td></td>
</tr>
<tr>
<td>(28) Japan</td>
<td>209 men and women</td>
<td>1 year</td>
<td>OR 2.96/class&lt;sup&gt;b&lt;/sup&gt; nonvert (1.60–4.50) 4.99/class&lt;sup&gt;b&lt;/sup&gt; vert (2.03–12.24)</td>
<td></td>
</tr>
<tr>
<td>(10) USA (MAYO clinic)</td>
<td>388 women</td>
<td>25 years</td>
<td>RR 4.21 hip (1.82–8.30) functional classes III and IV&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*Abbr:* NR, not reported.
*a*Adjusted incidence rate ratio.
*b*Disability assessed by Steinbrocker’s functional class I-IV.

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### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Study size</th>
<th>HAQ</th>
<th>Disease duration</th>
<th>ESR/CRP</th>
<th>Erosion score</th>
<th>Deformed joints</th>
<th>Glucocorticoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>(29) Morocco VFA</td>
<td>172 women</td>
<td>+</td>
<td></td>
<td></td>
<td>+ (Sharp Score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(11) UK x-ray</td>
<td>191 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neg assoc</td>
<td></td>
</tr>
<tr>
<td>(31) Norway VFA</td>
<td>255 women</td>
<td>No assoc</td>
<td></td>
<td></td>
<td></td>
<td>No assoc</td>
<td></td>
</tr>
<tr>
<td>(32) Norway x-ray</td>
<td>229 women</td>
<td>No assoc</td>
<td></td>
<td></td>
<td></td>
<td>No assoc</td>
<td></td>
</tr>
<tr>
<td>(33) Netherlands x-ray</td>
<td>98 men and women</td>
<td>No assoc</td>
<td></td>
<td></td>
<td></td>
<td>No assoc</td>
<td></td>
</tr>
<tr>
<td>(12) Turkey x-ray</td>
<td>100 women</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(30) Norway, UK, Netherlands x-ray</td>
<td>150 women</td>
<td></td>
<td></td>
<td></td>
<td>+ (Larsen score)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Multiple studies have documented increased fracture risk in patients on glucocorticoids. However, it has been difficult to separate the effect of the disease from the effect of glucocorticoid use. Of interest, all of the studies in Table 1 except a small Norwegian study (23) documented a significant association between use of glucocorticoids and clinical fracture in patients with rheumatoid arthritis. However, dose and duration were poorly characterized. In addition, effect of glucocorticoids on morphometric vertebral fractures in patients with rheumatoid arthritis is mixed with two studies showing no association (31,33) and two studies showing a positive association (29,32) and one suggesting a negative association (11) in Table 2. Since another task force is evaluating the dose-effect of glucocorticoid use, we limited our evaluation to nonglucocorticoid medications used in rheumatoid arthritis and fracture risk.

We found five relevant studies (1,14,24,35,36) evaluating the correlation between use of nonglucocorticoid medications in rheumatoid arthritis and fractures — Table 3. The large GPRD study found a significant correlation with all DMARD’s and fracture, especially in the spine with a RR 2.4 (2.0–2.8), but individual medications were not evaluated separately (1). Three studies looked at methotrexate: increased risk was seen only in one Japanese study (37), not in another Japanese study (14) or a much larger Danish study (36). In the same large Danish study of three registries, azathioprine was associated with an increase in overall fracture risk but the increase did not come from the traditional osteoporotic skeletal sites such as hip, spine and forearm (36). In addition, the increased risk was only seen at low doses suggesting a chance finding. Interestingly, the use of anti-TNF agents were shown to be protective of fractures in the CORRONA data base (24). Other classes of biologic agents have not been analyzed.

### Table 3

<table>
<thead>
<tr>
<th>Medication and reference</th>
<th>Study design</th>
<th>Study size</th>
<th>Data bank</th>
<th>Risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>“DMARD”</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Case-control</td>
<td>30,362 men and women</td>
<td>GPRD</td>
<td>RR 1.5 (1.3–1.8)</td>
<td>RR hip 2.0 (1.8–2.3) spine 2.4 (2.0–2.8)</td>
</tr>
<tr>
<td>(1) UK</td>
<td>median 7.6 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Methotrexate</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Case-control</td>
<td>124,655 men and women</td>
<td>National Danish Registers</td>
<td>none</td>
<td>Trend of decreased risk forearm fracture</td>
</tr>
<tr>
<td>(36) Denmark</td>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(14) Japan</td>
<td>Cross-sectional</td>
<td>117 post-menopausal</td>
<td>Spine x-rays</td>
<td>none</td>
<td>Increased risk steroids only</td>
</tr>
<tr>
<td>(37) Japan</td>
<td>Prospective observational</td>
<td>795 women &gt; 50</td>
<td>IORRA</td>
<td>HR 1.88 (1.12–3.15)</td>
<td>Increased non-vertebral fracture risk</td>
</tr>
<tr>
<td><strong>Cyclosporine</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Case-control</td>
<td>124,655 men and women</td>
<td>National Danish Registers</td>
<td>none</td>
<td>Cases more “frail”</td>
</tr>
<tr>
<td>(36) Denmark</td>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Azathioprine</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Case-control</td>
<td>124,655 men and women</td>
<td>National Danish Registers</td>
<td>OR 1.17 (1.03–1.33)</td>
<td>Increased overall fracture risk only at low dose. No increase in hip, spine or forearm risk</td>
</tr>
<tr>
<td>(36) Denmark</td>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-TNF</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Linear regression models</td>
<td>11,429 men and women</td>
<td>CORRONA</td>
<td>IRR&lt;sup&gt;c&lt;/sup&gt; 0.568</td>
<td>Decreased overall fracture risk</td>
</tr>
<tr>
<td>(24) USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes any of the following in the previous 6 months: sulfasalazine, gold, penicillamine, hydroxychloroquine, azathioprine, leflunomide, methotrexate, cyclosporine, etanercept, anakinra, cyclophosphamide.

<sup>b</sup>National hospital discharge register, psychiatric central register, Danish medicines agency.

<sup>c</sup>Adjusted incidence rate ratio.

### Rationale

Multiple studies have documented increased fracture risk in patients on glucocorticoids. However, it has been difficult to separate the effect of the disease from the effect of glucocorticoid use. Of interest, all of the studies in Table 1 except a small Norwegian study (23) documented a significant association between use of glucocorticoids and clinical fracture in patients with rheumatoid arthritis. However, dose and duration were poorly characterized. In addition, effect of glucocorticoids on morphometric vertebral fractures in patients with rheumatoid arthritis is mixed with two studies showing no association (31,33), two studies showing a positive association (29,32) and one suggesting a negative association (11) in Table 2. Since another task force is evaluating the dose-effect of glucocorticoid use, we limited our evaluation to nonglucocorticoid medications used in rheumatoid arthritis and fracture risk.

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### In summary

Rheumatoid arthritis is a systemic inflammatory disease that varies in severity from a mild, well controlled disease to a severe, crippling and life-threatening disease. Although it is logical to assume that more severe disease would be associated with a greater risk for fractures, evidence for this is limited.
Disability measures such as HAQ and functional class do show a correlation with clinical fracture risk in several studies and could be used to improve risk prediction for clinical fractures but not morphometric vertebral fractures. There is no current evidence that other parameters of disease activity can predict fractures. One large study found a strong correlation with duration of disease and fracture risk (1) but additional studies are needed to confirm this. There is not enough evidence to associate specific rheumatoid arthritis medications and fracture risk.

Additional Questions for Future Research:

1. Does FRAX overestimate fracture risk in rheumatoid arthritis because input for rheumatoid arthritis in the FRAX algorithm was based on self-report?

Of note, Pluijm et al. reviewed data from two prospective cohort studies (Rotterdam n = 4157 and Longitudinal Aging Study Amsterdam n = 762) and found that 14% of patients reported a diagnosis of rheumatoid arthritis, yet only 4% were diagnosed by a physician (38).

2. Does FRAX overestimate fracture risk in patients with rheumatoid arthritis and glucocorticoids?

The effect of glucocorticoids on bone health in rheumatoid arthritis patients is complex. FRAX does not consider dose and duration of glucocorticoid use, yet many rheumatoids are on a very low maintenance dose of ≤5mg which may be protective by controlling the inflammatory process. Some studies do suggest that fracture risk is no greater in patients with rheumatoid arthritis taking glucocorticoids compared to patients with rheumatoid arthritis who are not on glucocorticoids (8,23,31,33). One small study (n = 191 postmenopausal women) even suggested a greater fracture risk in rheumatoid patients who were not taking glucocorticoids (11). Further study is needed.

3. Does FRAX overestimate fracture risk because patients with rheumatoid arthritis have a higher mortality rate than population controls?

Management of rheumatoid arthritis has improved dramatically over the past 10 years and it was thought that mortality was also improving. However, the large British General Practice Research Database reported 17.5% 5-year mortality in rheumatoid arthritis patients compared to 11.8% in population controls (1). In addition, a recent review concluded that “patients have about a 50% increased risk of premature mortality, and their life expectancy is decreased by 3 to 10 years compared with the general population” (39). If mortality in rheumatoid arthritis patients is much greater than the mortality data used in FRAX, fracture risk would be overestimated.

References


Appendix 1. Position Conference Members

Organizers: Didier B. Hans (Chair), Cyrus Cooper (Co-chair), Sanford Baim, Bess Dawson-Hughes, John A. Kanis, William D. Leslie, Marjorie M. Luckey, Rene Rizzoli, Catalina Poiana, John P. Bilezekian (Moderator), Socrates E. Papapoulos (Co-moderator).


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