



# Is Fragility Fracture a Strong Risk Factor for a Cardiovascular Event in Rheumatoid Arthritis? The Challenge of Dealing with Multiple Comorbidities

Multiple comorbidities are among the most important challenges today because comorbidity is age-related and the population is aging<sup>1</sup>. In patients with rheumatoid arthritis (RA), the risk of both fragility fractures (FF) and cardiovascular (CV) manifestations is elevated<sup>2,3,4,5</sup>, but are these comorbidities separate processes, or are they interrelated? If these events (partly) share a common pathogenesis, an FF is not only a strong risk factor for a subsequent fracture<sup>6</sup>, but also for a CV event. As a consequence, it might be useful to determine the CV risk after a recent fracture.

The study by Ni Mhuirheartaigh, *et al*<sup>7</sup> brings up exciting data that show that CV risk, both of myocardial infarction (MI) and heart failure, is elevated after an FF in patients with RA. In an observational study in Olmsted County (USA) from 1995 to 2007, 1171 patients with incident RA and 1171 controls were included. At baseline, the patients had hypertension, obesity, and dyslipidemia more often, but RA patients with a previous event were excluded. During followup, 406 and 346 FF were observed, and 286 and 225 CV events, respectively. After adjustments, the overall CV risk was increased for patients with RA following any FF (HR 1.81, 95% CI 1.38–2.37), and also after a major fracture (HR 1.80, 95% CI 1.35–2.40). Because FF predominantly occur in the elderly, the 80% increase in relative risk indicates a substantial increase in absolute risk of CV events. In the RA patients without an FF fracture, no statistically significant difference was found (HR 1.18, 95% CI 0.85–1.63).

What is the explanation for the elevated CV risk in patients with RA after a recent FF? Some traditional risk factors are relevant for both osteoporotic fractures and CV events: aging, postmenopausal status, and smoking. Recently it has been shown that diabetes mellitus is not only a risk factor for CV events, but it also impairs bone strength and increases the incidence of fractures<sup>8</sup>. Systemic inflammation, a sedentary lifestyle, and frailty are probably among the most important risk factors for both osteoporotic fractures and CV events. Earlier, it was shown that elevated C-reactive protein levels are associated with an increase in both types of

events<sup>9,10</sup>, probably related to increased levels of inflammatory cytokines as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 1 (IL-1), and IL-6.

Theoretically, smoking, diabetes, and systemic inflammation are among the modifiable risk factors for both FF and CV events. This opens up the possibility that with modern antirheumatic treatment in a treat-to-target design aiming at remission, systemic inflammation is more under control, with subsequent lowering in event rate. Indeed, we have shown that with effective treatment of RA with infliximab or adalimumab, the usually occurring generalized bone loss, measured by bone mineral density (BMD) at the spine and hips, can be arrested<sup>11,12</sup>. Very recent data suggest that the use of TNF inhibitors reduces CV risk in RA<sup>13</sup>.

A striking point is that in the control group of RA patients without a recent FF, no statistically significant increase in CV events was found, which could be related to a type 2 error that masks an only slightly elevated CV event rate in RA patients with mild disease, while it could probably be documented in a study with a larger number of patients. In line with that, in a recent metaanalysis, it was shown in the general population that in individuals with BMD in the osteoporotic range, the risk of atherosclerotic vascular abnormalities was 2 to 3 times higher<sup>14</sup>.

Another question is whether fracture risk is elevated after a recent CV event. In an earlier systematic review, that question could not be answered properly, because of the heterogeneity of CV events that were enrolled: patients with MI, stroke, and aortic calcification<sup>15</sup>. However, hip fracture risk was elevated after heart failure and stroke<sup>16</sup>, and in postmenopausal women with a recent MI<sup>17</sup>.

One of the limitations of the study is that it was conducted in white women (93%). Thus, extrapolation to men and women from other continents or another genetic background or race is not possible<sup>18</sup>. The authors mention that the use of calcium supplementation might be a bias, because calcium (and vitamin D) is often prescribed after an FF and because calcium supplementation and increased CV risk might be

See Fragility fractures and CV events in RA, page 558

associated, but that is still a matter of debate. Another issue is whether the relationship can also be found in recent cohorts of RA, with modern treatment aiming at remission. Probably the most important limitation is that no data are presented that show the relationship with (cumulative) disease activity, functional capacity, and/or radiological damage, and the risk of CV events. On average, the risk of a CV event is 80% higher in patients with RA, but likely even higher in RA patients with severe or less controllable disease, and lower in patients in clinical remission.

What is the next step on the research agenda? First, the data from Olmsted should be confirmed in other RA cohorts, preferably from other continents and including also non-white patients. If confirmed, we will have better insight into the additional risk for RA patients for CV events after an FF, preferably with data for subcategories of RA patients with severe or mild RA. Interestingly, it was recently mentioned by the European League Against Rheumatism that comorbidities are often suboptimally prevented, screened, and managed<sup>19</sup>. Nevertheless, in an aging population, our patients expect from us as rheumatologists: optimal care and treatment not only for their rheumatic disease, but also for their comorbidities.

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