Fragility Fractures Are Associated with an Increased Risk for Cardiovascular Events in Women and Men with Rheumatoid Arthritis: A Population-based Study

Orla Ni Mhuircheartaigh, Cynthia S. Crowson, Sherine E. Gabriel, Veronique L. Roger, L. Joseph Melton III, and Shreyasee Amin

ABSTRACT. ***Objective.*** Women and men with rheumatoid arthritis (RA) have an increased risk for fragility fractures and cardiovascular disease (CVD), each of which has been reported to contribute to excess morbidity and mortality in these patients. Fragility fractures share similar risk factors for CVD but may occur at relatively younger ages in patients with RA. We aimed to determine whether a fragility fracture predicts the development of CVD in women and men with RA.

Methods. We studied a population-based cohort with incident RA from 1955 to 2007 and compared it with age- and sex-matched non-RA subjects. We identified fragility fractures and CVD events following the RA incidence/index date, along with relevant risk factors. We used Cox models to examine the association between fractures and the development of CVD, in which fractures and CVD risk factors were modeled as time-dependent covariates.

Results. There were 1171 subjects (822 women; 349 men) in each of the RA and non-RA cohorts. Over followup, there were 406 and 346 fragility fractures and 286 and 225 CVD events, respectively. The overall CVD risk was increased significantly for RA subjects following a fragility fracture (HR 1.81, 95% CI 1.38–2.37) but not for non-RA subjects (HR 1.18, 95% CI 0.85–1.63). Results were similar for women and men with RA.

Conclusion. Fragility fractures in both women and men with RA are associated with an increased risk for CVD events and should raise an alert to clinicians to target these individuals for further screening and preventive strategies for CVD. (J Rheumatol First Release January 15 2017; doi:10.3899/jrheum.160651)

Key Indexing Terms:
RHEUMATOID ARTHRITIS FRACTURE CARDIOVASCULAR DISEASE
ISCHEMIC HEART DISEASE HEART FAILURE

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in women and men with rheumatoid arthritis (RA)[1]. Patients with RA have an increased risk of CVD, including both ischemic heart disease (IHD) and heart failure (HF), independent of traditional CV risk factors[2]. Improved identification of patients with RA at greatest CV risk would help better target these individuals for additional screening and preventive strategies.

It is well recognized that both women and men with RA are also at increased risk for fragility fractures[3,4,5,6], including those diagnosed with RA in young adulthood[5,6]. Indeed, we have reported that women with RA are at increased risk for fragility fractures even before they reach age 50[6]. Interestingly, there is emerging evidence suggesting that fragility fractures may be a sentinel event that could prove valuable in recognizing patients with RA at increased risk for CVD. Bone loss and CVD share common risk factors, including cigarette smoking, sedentary lifestyle, and glucocorticoid (GC) use[7,8]. In RA, ongoing chronic inflammation may be another prominent factor contributing to both outcomes. In the general population, elevated levels of pro-

inflammatory molecules such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) are increasingly recognized as key factors in the pathogenesis of both bone loss[9,10] and CVD[11,12,13]. Collectively, these findings suggest that common pathological mechanisms may link fragility fractures and CVD among those with RA[14,15,16].

Given the relatively younger age at which fragility fractures can occur in RA, we hypothesized that the presence of a fragility fracture following diagnosis of RA could be a predictor of future CV events. We therefore studied a population-based cohort of women and men with an incident diagnosis of RA, in whom all fractures and CV outcomes have been identified over followup. We sought to determine whether a fragility fracture in women and men with RA predicts the subsequent risk of CVD, specifically IHD and HF, independent of traditional CV risk factors.

MATERIALS AND METHODS

Study subjects. We studied a well-characterized population-based cohort of Olmsted County, Minnesota, USA, women and men who had an incident diagnosis of RA made in 1955 to 2007[17]. The study population was assembled using the Rochester Epidemiology Project (REP), a unique medical records linkage system that makes population-based epidemiologic research possible in Olmsted County[18]. Through the resources of the REP, the comprehensive (inpatient and outpatient) medical records for all Olmsted County residents, at any local provider, are available for review.

Following approval by the institutional review boards (IRB) of the Mayo Clinic (09-001066) and the Olmsted Medical Center (013-OMC-09), REP resources were used to identify all Rochester residents (the central city of Olmsted County) who were ≥ 18 years of age when they fulfilled American College of Rheumatology (ACR) 1987 criteria for RA between January 1, 1955, and December 31, 1994[19]. The cohort was subsequently expanded, using the same methodology, to include all Olmsted County residents fulfilling ACR criteria for RA from January 1, 1980, to December 31, 2007[17]. Potential RA subjects were identified by searching the computerized diagnostic index for any diagnosis of arthritis (excluding degenerative arthritis or osteoarthritis) made for residents during these time frames. The complete medical record for each potential RA subject was then reviewed by trained nurse abstractors using a pretested data collection form to confirm or reject the diagnosis, with RA incidence defined as the date of first fulfillment of 4 of the 7 ACR classification criteria. For each subject identified with incident RA, an individual without RA from the same population was randomly selected and matched for sex and birth year (± 3 yrs). Subjects in the non-RA cohort were assigned an index date corresponding to the RA incidence date of their matched pair.

Ascertainment of fractures. After additional approval by the respective IRB, these subjects were followed from the date of RA incidence (or corresponding index date for non-RA subjects) until death or last clinical contact through their linked medical records in the community (historical cohort study), and their records were searched by trained nurse abstractors for the occurrence of any fracture[6]. Collecting of all clinically evident fractures is believed to be complete[6]. Records at Mayo Clinic, for example, contain the details of every hospitalization and outpatient visit, all emergency room and nursing home care, as well as all radiographic and pathology reports, including autopsies, and all correspondence with each patient[18]. By convention, fractures occurring during daily activities and falls from standing height or less were considered to have resulted from no more than moderate trauma, whereas fractures resulting from motor vehicle accidents and falls from a greater height were deemed from severe trauma. In addition, we are able to distinguish fractures that were due to a specific bone lesion, such as metastatic disease (pathologic fractures), as well as fractures only discovered because of radiographic tests performed in the clinical setting for unrelated indications (incidental fractures). From all fractures identified, we defined a subset of fragility fractures (i.e., all nonpathologic fractures occurring as a result of no more than moderate trauma or identified incidentally), as well as a subset of traditional major osteoporotic fractures [i.e., fragility fractures of the proximal femur (hip), thoracic/lumbar vertebrae (spine), distal forearm (wrist), or proximal humerus (shoulder)].

Ascertainment of CV outcomes. CV outcomes were defined as the earliest of IHD or HF. IHD included documentation of angina, myocardial infarction (MI; including silent events), and coronary revascularization procedures (i.e., coronary artery bypass graft, percutaneous angioplasty, insertion of stents, and atherectomy). MI was defined using standardized epidemiologic criteria[20]. Silent MI was considered present as of the date of the first documentation of a characteristic electrocardiogram or a recorded physician's diagnosis in a patient with no documented history of MI. HF was defined according to Framingham criteria and could be of any etiology[21].

Risk factors for CVD. CV risk factors were defined according to standard epidemiological criteria. Smoking history was collected as never, current, or former. Hypertension (HTN) was defined as 2 or more ambulatory blood pressure readings ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic obtained during a 1-year period, or a physician's diagnosis or documented use of antihypertensive medications[22]. Body mass index (BMI) was documented at baseline; obesity was defined as BMI ≥ 30 kg/m^2. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl, a physician's diagnosis, or documented use of insulin and/or oral hypoglycemic agents[23]. Dyslipidemia was defined as a low-density lipoprotein cholesterol ≥ 160 mg/dl, a total cholesterol ≥ 240 mg/dl, a high-density lipoprotein cholesterol of < 40 mg/dl or triglycerides ≥ 150 mg/dl, a physician's documentation of dyslipidemia, or treatment with a lipid-lowering medication[24].

RA disease characteristics. For the RA cohort, information on RA disease severity had been collected previously through medical record review[25]. Disease severity measures included rheumatoid factor (RF) positivity, as well as the presence of joint erosions/destructive changes and rheumatoid nodules during the first year following RA diagnosis. Information on GC use and hormone replacement therapy was also collected.

Statistical analysis. Descriptive statistics were used to summarize subject characteristics. Subjects with CVD events before the index date were excluded from analyses as they were not at risk of a first CVD event. Cox models, adjusted for traditional CV risk factors (age, sex, calendar year of RA incidence/index date, current smoking, HTN, obesity, diabetes mellitus, and dyslipidemia), were used to examine the association between either a fragility fracture or major osteoporotic fracture and the development of CVD in each cohort. In addition to the combined CVD outcome, the outcomes of IHD and HF were also examined separately. Time-dependent covariates were used to represent fractures and CVD risk factors in these analyses, which allowed subjects to be modeled as unexposed over followup, then changed to exposed following development of a risk factor. Interactions between sex and fractures were used to determine whether the association between fractures and CVD differed in women compared to men. Interactions between calendar year of RA incidence/index date and fracture were used to examine potential time trends in the association between fractures and CVD.

RESULTS

The RA and non-RA cohorts each contained 1171 subjects (822 women, 349 men) with a mean (± SD) age that was identical for each cohort as of the RA incidence/index date at 57 ± 16 years. Both cohorts were predominately white (93% in RA vs 94% in non-RA). The median duration (range) of followup was 10.0 years (0.02-45.7) for RA subjects and 11.8 years (0.01-47.3) in the non-RA subjects. RA subjects were more likely to be current smokers at index date than

non-RA subjects. At the index date, RA subjects were more likely than non-RA subjects to have HTN, obesity, and dyslipidemia but not diabetes mellitus. Among RA subjects, 67% were RF-seropositive, while 26% had erosions and 16% had nodules within the first year after RA diagnosis. The majority of RA subjects (68%) were exposed to GC over the course of their followup, while 31% of the women had been administered hormone replacement therapy at some point.

Risk for any CVD events following fracture. There were 137 RA subjects with CVD prior to their diagnosis compared to 139 non-RA subjects who had CVD prior to their index date. These subjects were excluded from analyses examining the risk of CVD following a fracture. Characteristics of the remaining 1034 RA and 1032 non-RA subjects are reported in Table 1. The excluded subjects in both groups were older, more likely to be male, and had higher frequencies of CVD risk factors than subjects who were not excluded. Among the included subjects, the differences in characteristics between the RA and non-RA subjects remained similar to the original cohort. Loss to followup was similar in both groups (20% in RA vs 22% in non-RA).

Over 14,125 person-years (p-y) of followup following the RA incidence date, there were 406 RA subjects (301 women, 105 men) who had a fragility fracture, and 318 RA subjects (234 women, 84 men) who had a major osteoporotic fracture. There were 286 RA subjects (183 women, 103 men) who developed CVD over followup. The rates of CVD among RA subjects after and before/without fractures are presented in Table 2. The median (interquartile range) time to CVD among RA subjects who fractured was 4.7 years (1.8–9.3) after a fragility fracture and 4.4 years (1.6–7.7) after a major osteoporotic fracture.

Compared to RA subjects who did not experience a fracture, RA subjects who sustained a fragility fracture had a significantly increased risk for any CVD (HR 1.81, 95% CI 1.38–2.37). Similar findings were noted following major osteoporotic fractures (Table 3). Further, when adjusted for GC use and hormone replacement therapy, the association between fractures and CVD in RA subjects showed little difference (data not shown).

No significant differences were observed between women and men with RA for the development of CVD following either a fragility fracture (HR 1.68, 95% CI 1.12–2.34 for women; HR 2.28, 95% CI 1.43–3.65 for men; interaction $p = 0.26$) or for major osteoporotic fractures (HR 1.69, 95% CI 1.20–2.38 for women; HR 2.38, 95% CI 1.43–3.97 for men; interaction $p = 0.35$). Similarly, the age at RA diagnosis ($\geq$ or $<$ 50 years) did not appear to have any significant influence on the association between fractures and CVD (interaction $p > 0.4$ for both fracture definitions). There were no apparent time trends in the association between fractures and CVD (interaction $p > 0.8$ for both fracture definitions).

Table 1. Descriptive characteristics of 1034 Olmsted County women and men age ≥ 18 years with incident rheumatoid arthritis (RA) from 1955 to 2007 and 1032 age- and sex-matched non-RA subjects. Data are n (%) unless otherwise indicated.

Characteristics	RA, n = 1034	Non-RA, n = 1032	p
Age at index date, yrs, mean ± SD	54.6 ± 15.0	54.5 ± 14.9	0.84
Length of followup, yrs, median (range)	10.5 (0.02–45.7)	12.5 (0.01–47.3)	—
Female sex	739 (71)	744 (72)	0.75
White race	959 (93)	967 (94)	0.39
Current smoker at incidence/index date	261 (25)	221 (21)	0.04
Diabetes mellitus			
At incidence/index date	81 (8)	60 (6)	0.07
Ever[a]	193 (25)	198 (28)	0.99
Hypertension			
At incidence/index date	586 (57)	476 (46)	< 0.001
Ever[a]	877 (92)	777 (89)	< 0.001
Dyslipidemia			
At incidence/index date	410 (40)	354 (34)	0.012
Ever[a]	654 (69)	687 (78)	0.054
Obesity			
At incidence/index date	319 (31)	265 (26)	0.009
Ever[a]	398 (41)	389 (42)	0.70
Prior major osteoporotic fracture	89 (9)	99 (10)	0.44
RF positivity	675 (67)	—	
Erosions[b]	269 (26)	—	
Nodules[b]	163 (16)	—	
Ever[a] glucocorticoids	706 (68)	—	
Ever[a] hormone replacement therapy	284 (27)	—	

[a] Ever percentages represent the cumulative incidence at 30 years after incidence/index date, adjusted for the competing risk of death. [b] In the first year after incidence date. RF: rheumatoid factor.

Table 2. Incidence of cardiovascular disease (CVD) outcomes among subjects with and without rheumatoid arthritis (RA) during followup time before/without and after fractures [any fragility or major osteoporotic (OP)[a] fracture].

Outcome	Fracture Definition	CVD Rate per 100 Person-years			
		RA Cohort		Non-RA Cohort	
		No Fracture[b]	After Fracture	No Fracture[b]	After Fracture
Any CVD	Fragility	1.99	4.84	1.42	3.21
	Major OP	2.04	5.79	1.50	3.36
IHD	Fragility	1.36	3.22	1.20	2.16
	Major OP	1.44	3.50	1.24	2.25
HF	Fragility	1.28	3.37	0.82	2.06
	Major OP	1.32	4.03	0.87	2.24

[a] Major OP fracture defined as a fragility fracture at the hip, thoracic or lumbar spine, wrist, or shoulder. [b] Person-years of followup and CVD events occurring before fracture are included in the "no fracture" computations. IHD: ischemic heart disease; HF: heart failure.

Table 3. Risk (HR) for cardiovascular disease (CVD) following either any fragility fracture or major osteoporotic (OP)[a] fracture among subjects with and without rheumatoid arthritis (RA). In each cohort, subjects without the defined fracture served as the referent group.

Outcome	Fracture Definition	HR (95% CI)[b]	
		RA Cohort	Non-RA Cohort
Any CVD (n = 286 RA; n = 225 non-RA)	Fragility	1.81 (1.38–2.37)	1.18 (0.85–1.63)
	Major OP	1.80 (1.35–2.40)	1.12 (0.77–1.62)
IHD (n = 202 RA; n = 182 non-RA)	Fragility	1.72 (1.24–2.36)	1.10 (0.75–1.60)
	Major OP	1.56 (1.10–2.20)	1.09 (0.71–1.68)
HF (n = 220 RA; n = 156 non-RA)	Fragility	1.83 (1.35–2.49)	1.12 (0.76–1.63)
	Major OP	1.81 (1.32–2.47)	1.07 (0.70–1.63)

[a] Major OP fracture defined as a fragility fracture at the hip, thoracic or lumbar spine, wrist, or shoulder. [b] Adjusted for age, sex, calendar year of RA incidence/index date, current smoking at incidence/index date, diabetes mellitus, hypertension, dyslipidemia, and obesity. IHD: ischemic heart disease; HF: heart failure.

Markers for RA severity including RF positivity, presence of erosions in the first year, and presence of nodules in the first year also did not appear to have any significant influence on the associations between fractures and CVD (interaction p ranged from 0.18 to 0.96).

In comparison, over 16,151 p-y of followup following the index date, there were 346 non-RA subjects (260 women, 86 men) who had a fragility fracture and 245 non-RA subjects (186 women, 59 men) with a major osteoporotic fracture, while 225 non-RA subjects (151 women, 74 men) had CVD events over followup. CVD event rates in patients with RA were significantly higher than in non-RA subjects, both before/without and after fracture (Table 2). When compared with non-RA subjects who did not have a fracture, those with a fragility fracture did not have any significant increase in subsequent risk for CVD (HR 1.18, 95% CI 0.85–1.63; Table 3). Again, similar findings were noted when considering major osteoporotic fractures.

Risk of IHD and HF following fracture. In addition to analyzing the first CVD event of any type, we also analyzed IHD events and HF events separately. There were 123 RA subjects who had IHD prior to their diagnosis, while 131 non-RA subjects had IHD prior to their matched index date. When these subjects were excluded from analyses, there were 202 RA subjects (125 women, 77 men) and 182 non-RA subjects (118 women, 64 men) who developed IHD over followup. Similarly, there were 38 RA and 34 non-RA subjects who had HF prior to RA incidence/index date; these subjects were excluded from analyses of HF. There were 220 RA subjects (146 women, 74 men) and 156 non-RA subjects (100 women, 56 men) who developed HF over followup. Rates of IHD and HF outcomes in each of these groups are presented in Table 2.

RA subjects who sustained a fragility fracture had a significantly increased risk for subsequent IHD (HR 1.72, 95% CI 1.24–2.36) as well as HF (HR 1.83, 95% CI 1.35–2.49) when compared with RA subjects who did not fracture (Table 3). In contrast, non-RA subjects with a fragility fracture were not at any significantly increased subsequent risk for IHD (HR 1.10, 95% CI 0.75–1.60) or HF (HR 1.12, 95% CI 0.76–1.63) when compared with those who did not fracture. Similar findings were noted following major osteoporotic fractures in each of the RA and non-RA cohorts (Table 3).

DISCUSSION

While RA is an established risk factor for both fragility fractures and CVD, the association between the development

of CVD in patients with RA following any fragility fracture has not previously been established, to our knowledge. Our findings support our hypothesis that women and men with RA who develop a fragility fracture have a higher risk of subsequently developing CV events. This was observed for both IHD and HF outcomes. This increased risk of CVD following fragility fractures also appeared to be independent of many of the established CV risk factors, as well as GC use and hormone replacement therapy. In contrast, in non-RA subjects, we observed no association between fractures and CVD following adjustment for CVD risk factors. As we have previously reported, the Framingham risk score underestimates CVD risk among patients with RA, suggesting that other mechanisms, such as RA disease activity, may contribute to the excess risk of CVD in RA[26]. Fractures may be a surrogate marker for these other mechanisms.

There is growing recognition of the importance of establishing recommendations for CV risk assessment and prevention in patients with RA. However, fragility fractures are not considered in current risk assessment guidelines for CVD in RA[27,28]. Our findings suggest that a fragility fracture in a patient with RA may signal an individual at heightened risk for CVD events, who should receive more aggressive management of any modifiable risk factors and for primary preventive strategies to help lower their CVD risk.

That the risk of new CVD events, both IHD and HF, increases following a fragility fracture in RA is a novel finding. While shared risk factors likely account for this observed association, additional work is necessary to understand the potential pathogenic link between fragility fractures in RA and subsequent risk for CVD, both IHD and HF. That understanding may help identify novel methods for decreasing CVD events in patients with RA. Such work may also have implications for CVD management generally. While a number of studies have demonstrated that CVD is associated with future fractures in the general population[16,29,30,31], 1 study did report that patients with HF were also more likely to have a history of fractures prior to their HF diagnosis[31], again suggesting the role of shared chronic risk factors. That said, we did not observe an increased risk for CVD following a fragility fracture in our non-RA cohort, which would indicate unique shared risk factors for CVD in RA.

Among the leading potential explanations for our study observations is ongoing chronic inflammation as a shared risk factor. Chronic inflammation appears to have a strong effect on the quality and quantity of bone. The induction of proinflammatory cytokines influences bone remodeling and structure, stimulating bone homeostasis in the direction of net bone loss and increasing the likelihood of fracture[32,33]. It is primarily because of T-cell mediated stimulation of osteoclastogenesis by receptor activator of nuclear factor-κB ligand, although elevated TNF-α, IL-6, and IL-1 (all key inflammatory markers in RA) also adversely affect bone homeostasis through stimulation of bone resorption and inhibition of bone formation[32,33,34,35]. Chronic inflammation is also a well-recognized cause of atherosclerosis; it is responsible for the development and destabilization of arterial plaques, the cornerstone of IHD[36]. Proinflammatory cytokines that are attributed to the development of atherosclerosis are also those seen in RA-driven inflammation. Thus, TNF-α is responsible for a decrease in vascular adhesion molecules[37], IL-1 is responsible for upregulation of endothelial adhesion molecules and activation of macrophages and vascular cells[38,39], and IL-6 has been shown to enhance fatty lesion development[38,39]. Proinflammatory cytokines, including TNF-α and IL-6, are also associated with an increased risk for HF[13], although the pathogenesis is not yet as well understood. Of note, the associations we identified between fragility fractures and subsequent CVD events were independent of potential markers of RA disease severity, but they were only considered at baseline. Cumulative RA disease activity over followup may therefore be more relevant.

There are other possible factors that might account for CVD following fragility fractures in patients with RA. Frailty, which is a potentially modifiable risk factor[40], is a predictor for both fractures and CVD[41,42,43]. Interestingly, chronic inflammation is also implicated as a risk factor for frailty[44]. Patients with RA are often given calcium and vitamin D supplementation for osteoporosis management. Although somewhat controversial, reports have linked calcium supplementation, with or without vitamin D, to the development of CVD[45]. Other studies have not observed that effect[46], while vitamin D supplementation may even be protective for HF[47]. In addition, nonsteroidal antiinflammatory drugs (NSAID) may increase the risk for CVD[48], and owing to their effect on the release of prostaglandins, may reduce bone quality[49,50]. Neither calcium and vitamin D supplementation nor NSAID use could be accounted for in our analyses, because these are often available over the counter and are not well documented in the medical record.

Our study has a number of strengths. First, the population-based design of the study with extensive followup and the use of complete (inpatient and outpatient) contemporary medical record documentation strengthens our work by providing complete ascertainment of study outcomes. Second, inclusion of data about the non-RA comparison cohort, taken from the same population with identical data collection methods, enables us to compare risks. As with all studies, our results also need to be interpreted in light of potential limitations. The Olmsted County population is predominately white, therefore our results may not be generalizable to other racial groups. Changes in management have occurred over the time period studied; however, we found no significant time trends in our results. Also, RA disease activity over followup was not consistently available for all subjects to be considered in analyses. Data on inflammatory cytokines were not available, so we could not specifically

address whether they played a role in our study findings. If chronic inflammation is a key factor in the observations identified, newer biologic therapies for RA may better control the inflammatory state and thereby lower the risk for both fractures and CVD. However, the majority of our RA subjects were diagnosed and treated in the prebiologic era, so we were unable to address this possibility. Even with larger numbers of subjects in the post-biologic era, longer followup than is currently available would be needed to address this question, at least at this time. Nevertheless, it is an important question to address. Given that cumulative shared risk factors may be the key explanation for how fragility fractures predict future CVD, a fragility fracture in a patient with RA, regardless of current management or disease control, may still signal a particularly high risk for CVD.

Fragility fractures in patients with RA are associated with an increased risk for the development of future CVD events (including both IHD and HF), independent of traditional CV risk factors. While shared risk factors likely account for this association, inflammation is a key pathogenic mechanism that is associated with both fragility fractures and CVD and could be an especially important explanation for our findings. Further studies are required to better address this hypothesis. Based on our results, patients with RA who have experienced a fragility fracture should be particularly screened for CVD and may warrant more aggressive preventive therapy.

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