

# Heart Failure in Rheumatoid Arthritis: Rates, Predictors, and the Effect of Anti-Tumor Necrosis Factor Therapy

Frederick Wolfe, MD, Kaleb Michaud, MS

**PURPOSE:** We sought to determine the frequency of heart failure in patients with rheumatoid arthritis, and to determine its predictors, particularly the use of anti-tumor necrosis factor (TNF) therapy.

**METHODS:** Rheumatoid arthritis (n = 13,171) and osteoarthritis (n = 2568) patients were studied during a 2-year period ending in June 2002. The diagnosis of heart failure was based on self-report or review of medical records. Propensity scores were used to adjust for the risk of anti-TNF (infliximab and etanercept) prescription.

**RESULTS:** Heart failure was more common among patients with rheumatoid arthritis (3.9% [n = 461]) than in those with osteoarthritis (2.3% [n = 87]), after adjusting for differences in

demographic characteristics. Patients with rheumatoid arthritis had similar risk factors for heart failure (e.g., hypertension, prior myocardial infarction, diabetes, advanced age) as persons in population-based studies. Heart failure was significantly ( $P < 0.05$ ) less common in anti-TNF-treated patients (3.1% [180/5832]) than in the remaining patients (3.8% [281/7339]), even after adjusting for baseline differences. In the absence of pre-existing cardiovascular disease, the risk of heart failure was low (0.4% [24/6251]) and was not related to anti-TNF therapy.

**CONCLUSION:** Our results suggest that rheumatoid arthritis increases the risk of heart failure, which may be ameliorated by anti-TNF therapies. *Am J Med.* 2004;116:305-311. ©2004 by Excerpta Medica Inc.

There is now substantial evidence that rheumatoid arthritis is associated with increased cardiovascular morbidity and mortality (1-12). Cardiovascular manifestations of rheumatoid arthritis include pericarditis, myocardial infarction, and heart failure (13), perhaps including diastolic dysfunction (14). Although the risk of myocardial infarction appears to be increased, little is known about the risk of heart failure in rheumatoid arthritis. Heart failure is of special interest because the failing heart produces tumor necrosis factor (TNF), but the normal heart does not (15). Although the effects of circulating TNF- $\alpha$  on cardiovascular function are uncertain (15-18), data from murine heart failure models support the theory that blockade of circulating TNF may ameliorate ventricular dysfunction (19,20). However, clinical trials of TNF blockade in patients with advanced heart failure have shown little benefit or even harm (17,21,22). It is not known whether anti-TNF therapy, which is being used increasingly in the treatment of rheumatoid arthritis, affects the risk of heart failure in these patients.

The purpose of this report was to determine the prevalence of heart failure in patients with rheumatoid arthritis,

in comparison with patients with osteoarthritis; to determine the factors associated with heart failure; and to study the effects of anti-TNF therapy on the risk of heart failure.

## METHODS

Subjects were participants in the National Data Bank for Rheumatic Diseases study of the outcomes of arthritis. Patients are recruited for this ongoing study from the practices of U.S. rheumatologists (23-25), and are followed with semiannual questionnaires. Approximately 8% of patients decline to participate per year. This report includes 13,171 rheumatoid arthritis patients (including 3862 who were enrolled as part of an infliximab safety registry) who completed 35,064 biannual questionnaires during consecutive 6-month assessment periods ending in June 2002. In addition, data from 2568 patients with osteoarthritis of the hip or knee who were enrolled similarly were also analyzed for comparison.

At each assessment, demographic and clinic variables are obtained (26-35). Patients report all comorbid conditions, medications, and side effects of treatment. We obtained a history of pre-existing cardiovascular illness, current and previous hypertension, myocardial infarction, and other cardiovascular conditions. We asked specifically, "During the last 6 months were you diagnosed or treated for heart failure?" We also requested and reviewed records for all hospitalizations. Patients reporting heart failure were interviewed by the research staff using a standardized, written protocol. A diagnosis of heart failure was considered valid if the patient provided data indicat-

From the Arthritis Research Center Foundation (FW, KM) and the University of Kansas School of Medicine (FW), Wichita, Kansas.

The infliximab registry is supported by a grant from Centocor, Inc., Malvern, Pennsylvania.

Requests for reprints should be addressed to Frederick Wolfe, MD, National Data Bank for Rheumatic Diseases, Arthritis Research Center Foundation, 1035 N. Emporia, Suite 230, Wichita, Kansas 67214, or fwolfe@arthritis-research.org.

Manuscript submitted January 14, 2003, and accepted in revised form September 9, 2003.

**Table 1.** Characteristics of the Patients with Rheumatoid Arthritis (N = 13,171)

Characteristic	Number (%) or Mean $\pm$ SD
Age (years)	61 $\pm$ 13
Male sex	3015 (23)
Married	9039 (69)
Nonhispanic white	12,308 (94)
At least high school graduate	11,712 (89)
Income (\$)	46,000 $\pm$ 28,800
Disease duration (years)	14.9 $\pm$ 11.1
Lifetime comorbidity score (scale, 0 to 11)	2.4 $\pm$ 1.7
Body mass index (kg/m <sup>2</sup> )	27.5 $\pm$ 6.3
Use of cardiovascular medication(s)	6797 (52)
History of hypertension	6190 (47)
Any cardiovascular history	6849 (52)
Treatment	
Methotrexate	7386 (56)
Prednisone	5160 (39)
Infliximab	4307 (33)
Hydroxychloroquine	2590 (20)
Leflunomide	2316 (18)
Etanercept	1680 (13)
Sulfasalazine	761 (6)
No DMARD or anti-TNF agent*	4307 (14)
Severity and status (scale)	
Health Assessment Questionnaire disability index (0–3)	1.1 $\pm$ 0.7
Rheumatoid Arthritis Disease Activity Index (0–10)	3.6 $\pm$ 2.1
Pain (0–10)	3.9 $\pm$ 2.8
Global severity (0–10)	3.6 $\pm$ 2.5
Fatigue (0–10)	4.5 $\pm$ 2.9
Depression (0–10)	2.5 $\pm$ 1.8
SF-36 physical component score (0–100)	32.1 $\pm$ 10.3
SF-6 utility index (0–1)	0.62 $\pm$ 0.1
EuroQol-5D utility (0–1)	0.63 $\pm$ 0.2

\* DMARDs include methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, oral and injectable gold, azathioprine, and cyclosporine.

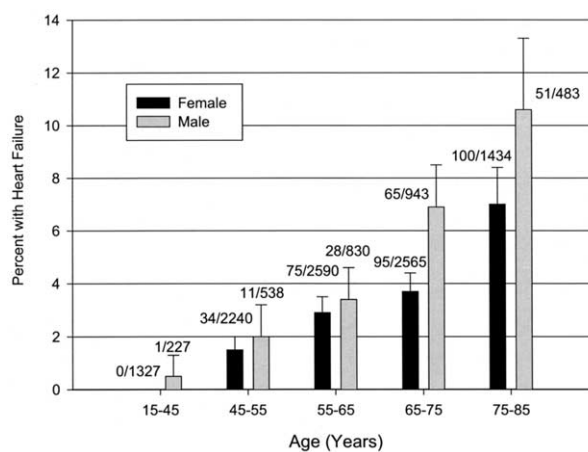
DMARD = disease-modifying antirheumatic drug; SF = short form; TNF = tumor necrosis factor.

ing that a physician diagnosed heart failure, or if the diagnosis was supported by medical records or physician contact. Reports of heart failure were found to be valid in more than 90% of cases. Incident cases of heart failure were defined as those occurring in persons without a history of cardiovascular disease, including the use of cardiovascular medications.

### Statistical Analyses

Each study observation relates to events that occurred in the previous 6-month period; patients had between one and four such observations. Of these, one observation was chosen for study. For patients with heart failure, we selected the first observation when heart failure was present. For patients without heart failure, a random observation was chosen.

Propensity scores were used to adjust for nonrandom assignment to treatment (36–38). Variables used in constructing the propensity score were Health Assessment



**Figure.** Frequency of heart failure in 13,171 rheumatoid arthritis patients stratified by age and sex. Bars represent 95% confidence intervals. Numbers for each age group represent the numerator/denominator by sex. Rates increase with age ( $P < 0.001$ ) and are always greater in men than in women ( $P < 0.001$ ).

**Table 2.** Univariate Correlates of Heart Failure in Rheumatoid Arthritis Patients

Variable	All Heart Failure (n = 461 Cases)	Incident Cases of Heart Failure Only (n = 42 Cases)
	Odds Ratio (95% Confidence Interval)	
Hypertension (ever)	2.6 (2.1–3.2)	
Myocardial infarction (last 6 months)	16.1 (11.0–23.7)	
Myocardial infarction (ever)	6.6 (5.4–8.0)	
Diabetes	3.4 (2.7–4.3)	2.1 (0.9–5.1)
Body mass index per 10-unit increase	1.3 (1.1–1.5)	1.6 (1.0–2.7)
Body mass index $\geq 25$ kg/m <sup>2</sup>	1.2 (1.0–1.5)	1.4 (0.6–3.2)
Male sex	1.8 (1.4–2.1)	1.7 (0.9–3.3)
Current or past smoker	1.6 (1.3–1.9)	1.8 (1.0–3.5)
Disability index per unit increase (lagged)	2.1 (1.8–2.5)	2.8 (1.5–5.2)
Disability index >0 (lagged)	4.2 (2.2–8.2)	NA*
Age (per 10-year increase)	1.8 (1.7–2.0)	1.6 (1.2–2.1)
Education		
High school graduate	Reference	Reference
0–8 years	1.7 (1.1–2.7)	1.5 (0.3–6.3)
8–11 years	1.6 (1.2–2.1)	1.5 (0.6–3.7)
13–15 years	0.7 (0.5–0.9)	0.4 (0.1–1.0)
$\geq 16$ years	0.7 (0.5–0.9)	0.5 (0.2–1.1)

\* All incident cases of heart failure had a disability index >0 at previous observation.

Questionnaire disability index, pain, global severity, prednisone use, age, age squared, and sex.

Two sets of potential covariates were used. In one analytic model, variables were ‘lagged’ from data of the previous observation for each patient; thus, the covariates were measured ‘before’ the heart failure outcome (or the random observation in those without heart failure). For approximately one third of patients, lagged variables were not available, and variables from the current observation were used based on the assumption that disability index, pain, and global severity had similar effects regardless of whether they came before or after the event. However, to assess the validity of this assumption, analyses were also conducted after excluding patients without lagged variables. Because results were very similar regardless of method, we report results from the first model including all participants.

Adjustment to the demographic characteristics of the general population was made using Monte Carlo simulations with 1000 repetitions (39). This method was also used to adjust the frequency of heart failure in osteoarthritis patients. All statistical analyses were performed using Stata (College Station, Texas), version 7.0 (40). This study was approved by the Via Christi Regional Medical Center Institutional Review Board, Wichita, Kansas.

## RESULTS

The majority of the patients with rheumatoid arthritis were white women (Table 1); about half had a history of

cardiovascular disease. About one third were treated with infliximab, reflecting the inclusion of patients in the infliximab safety registry. By comparison, patients with osteoarthritis were older (mean [ $\pm$  SD] age,  $67 \pm 12$  years), less likely to be male (18% [ $n = 482$ ]), and slightly more likely to have graduated from high school (92% [ $n = 2350$ ]) than were those with rheumatoid arthritis.

There were 461 cases of heart failure among the 13,171 patients with rheumatoid arthritis, including 42 incident cases of which 24 occurred in patients without previous cardiovascular disease history. The frequency of heart failure in the rheumatoid arthritis cohort was 5.2% in men and 3.0% in women, for an overall risk of 3.5%. Increased age was associated with a greater frequency of heart failure (Figure). Of the 2568 patients with osteoarthritis, 87 (3.4%) had heart failure. After adjusting for demographic characteristics, the risk of heart failure was 3.9% (95% confidence interval [CI]: 3.4% to 4.3%) in patients with rheumatoid arthritis compared with 2.3% (95% CI: 1.6% to 3.3%) in those with osteoarthritis.

In general, the factors associated with the presence of heart failure among patients with rheumatoid arthritis were similar to those in the general population (Table 2). Several measures of disease, including the disability index, pain, and global severity, were also associated with the prevalence and incidence of heart failure (Table 2).

### *Effects of Anti-TNF Therapy*

There were significant differences between nearly all of the characteristics of patients who were and were not

**Table 3.** Characteristics of Patients by Type of Treatment

Variable	Anti-TNF* (N = 5832)	Infliximab (N = 4152)	Etanercept (N = 1525)	No Anti-TNF (N = 7339)	P Value†
	Number (%) or Mean ± SD				
Age (years)	60 ± 12	61.5 ± 13.0	56.7 ± 12.1	61.5 ± 13.0	<0.001
Male sex	1283 (22)	955 (23)	310 (20)	1725 (24)	0.06
Nonhispanic white	5540 (95)	3998 (96)	1408 (92)	6759 (92)	<0.001
Married	3966 (68)	2703 (65)	1127 (74)	5101 (70)	0.01
High school graduate	5097 (87)	3558 (85)	1400 (92)	6605 (90)	<0.001
Total income (\$)	46,800 ± 29,100	43,300 ± 28,100	53,000 ± 29,800	45,500 ± 28,700	0.02
Disease duration (years)	14.2 ± 10.7	13.8 ± 10.7	15.2 ± 10.5	15.5 ± 11.4	<0.001
Lifetime comorbidity score (0–11)	2.2 ± 1.6	2.1 ± 1.5	2.5 ± 1.8	2.5 ± 1.8	<0.001
Health Assessment Questionnaire disability index (0–3)	1.2 ± 0.7	1.2 ± 0.7	1.1 ± 0.7	1.0 ± 0.7	<0.001
Rheumatoid Arthritis Disease Activity Index (0–10)	3.7 ± 2.1	3.7 ± 2.1	3.6 ± 2.1	3.5 ± 2.2	<0.001
Pain (0–10)	4.2 ± 2.8	4.2 ± 2.8	3.9 ± 2.7	3.8 ± 2.8	<0.001
Global severity (0–10)	3.8 ± 2.5	3.8 ± 2.5	3.5 ± 2.5	3.4 ± 2.5	<0.001
Fatigue (0–10)	4.7 ± 2.8	4.8 ± 2.8	4.6 ± 2.9	4.3 ± 2.9	<0.001
Depression (0–10)	2.6 ± 1.8	2.6 ± 1.8	2.5 ± 1.8	2.4 ± 1.8	<0.001
Physical component score (SF-36)	31.0 ± 9.9	30.7 ± 9.9	31.6 ± 10.1	32.8 ± 10.4	<0.001
SF-6 utility index (0–1)	0.61 ± 0.09	0.61 ± 0.09	0.61 ± 0.0	0.63 ± 0.1	<0.001
EuroQol-5D utility index (0–1)	0.60 ± 0.21	0.60 ± 0.21	0.61 ± 0.2	0.64 ± 0.2	<0.001
Treatment					
Methotrexate	3907 (67)	3135 (76)	669 (44)	3479 (47)	<0.001
Prednisone	2729 (47)	2151 (49)	593 (39)	2429 (33)	<0.001
Hydroxychloroquine	816 (14)	561 (14)	239 (16)	1769 (24)	<0.001
Leflunomide	793 (14)	544 (13)	223 (15)	1519 (21)	<0.001
Sulfasalazine	280 (5)	195 (5)	79 (5)	84 (7)	<0.001
Etanercept	1680 (29)	0	1525 (100)	0	
Azathioprine	152 (3)	112 (3)	29 (2)	132 (2)	0.003
Injectable gold	58 (1)	42 (1)	15 (1)	161 (2)	<0.001
Minocycline	58 (1)	33 (1)	23 (2)	139 (2)	<0.001
Anakinra	41 (1)	25 (1)	11 (1)	44 (1)	0.52
Cyclosporine	17 (0)	17 (0)	0	29 (0)	0.22
Auranofin	6 (0)	4 (0)	3 (0)	15 (0)	0.002
Penicillamine	6 (0)	8 (0)	0	37 (1)	0.27
Cyclophosphamide	0	0	0	7 (0)	0.20

\* Patients that received both etanercept and infliximab are included here.

† Comparing anti-TNF with no anti-TNF.

SF = Short Form; TNF = tumor necrosis factor.

treated with anti-TNF therapy (Table 3). There were also differences between patients treated with infliximab versus etanercept (Table 3), suggesting that infliximab-treated patients had worse clinical status and slightly lower socioeconomic status.

Among all cases of heart failure (both prevalent and incident), patients receiving anti-TNF therapy were less likely to have heart failure than were those not receiving anti-TNF treatment. These differences became even greater after covariate adjustment: the frequency of heart failure was 1.2% lower in anti-TNF-treated patients in adjusted analyses.

There were no significant differences in the risk of in-

cident heart failure by use of anti-TNF therapy, although the numbers of cases were small (Table 4).

Of patients receiving infliximab, 47.8% (2057/4307) had a history of cardiovascular disease compared with 54.4% (4820/8864) of those not receiving infliximab. We therefore performed sensitivity analyses by adding prior cardiovascular history to the models. For all cases of heart failure, the adjusted frequency of heart failure was 2.8% in those treated with anti-TNF therapies, versus 3.9% in the remaining patients ( $P = 0.03$ ). Among incident cases of heart failure, the risks were 0.2% in both groups ( $P = 0.68$ ). When limited to observations prior to the U.S. Food and Drug Administration's warning of increased

**Table 4.** Adjusted and Unadjusted Rates of Heart Failure by Treatment\*

Outcome	All Anti-TNF <sup>†</sup> (n = 5832)	Infliximab (n = 4152) Percentage (N)	Etanercept (n = 1525)	No Anti-TNF (n = 7339)
All heart failure				
Unadjusted	3.1 (180)	3.2 (134)	2.6 (40)	3.8 (281)
Adjusted	2.8	2.6	2.9	3.4 to 3.9 <sup>‡</sup>
Difference from no anti-TNF (95% confidence interval)	-1.2% (-1.9% to -0.5%)	-1.4% (-2.2% to -0.6%)	-0.5% (-1.5% to 0.4%)	
Incident heart failure	(n = 3003)	(n = 2162)	(n = 768)	(n = 3248)
Unadjusted	0.4 (12)	0.5 (10)	0.3 (2)	0.4 (12)
Adjusted	0.2	0.2	0.3	0.2 to 0.3 <sup>‡</sup>
Difference from no anti-TNF (95% confidence interval)	-0.1% (-0.1% to 0%)	-0.1% (-0.1% to 0%)	0% (0% to 0.1%)	

\* All heart failure refers to heart failure occurring in patients with or without a history of previous cardiovascular disease, including use of cardiovascular medications. Incident heart failure refers to heart failure occurring in persons without any history of cardiovascular disease, including use of cardiovascular medications. Adjusted rates were based on use of a propensity score.

<sup>†</sup> Includes patients that took both infliximab and etanercept

<sup>‡</sup> Adjusted rates vary because propensity scores varied in the three comparison groups.

TNF = tumor necrosis factor.

heart failure with anti-TNF use, the adjusted frequency of heart failure was 3.6% (n = 1555) in those treated with anti-TNF therapies versus 4.3% (n = 4034) in the remaining patients ( $P = 0.16$ ).

We also examined incident cases of heart failure occurring in patients under the age of 50 years. No increase was found (0/1569 patients using anti-TNF therapy vs. 3/1401 not using anti-TNF therapy).

## DISCUSSION

Our results suggest that—at least as compared with patients who had osteoarthritis—the prevalence of heart failure is increased among patients with rheumatoid arthritis. However, we found no increase in heart failure among patients receiving anti-TNF therapy. Because of recent concerns about the risk of anti-TNF therapy among patients without a history of cardiovascular disease (41), we also looked at patients <50 years of age and found no evidence of harmful effects.

The overall increase in heart failure among rheumatoid arthritis patients may be related to increased inflammatory activity, perhaps leading to premature arteriosclerosis. Potential explanations include endothelial dysfunction and injury (42–44), lipid abnormalities and atherogenic lipoprotein factors (45–47), adhesion molecules (48), and proinflammatory cytokines, including interleukin 1 and TNF (17,18,49). Indeed, clinical markers of inflammation have been associated with cardiovascular mortality and morbidity in these patients (50).

There is growing recognition that TNF- $\alpha$  is involved in the inflammatory process in rheumatoid arthritis and

cardiac disease, and that anti-TNF therapy may be effective (15,16,18,42). Several trials have evaluated the effects of anti-TNF therapy in patients with severe heart failure. However, the Research Into Etanercept: Cytokine Antagonism in Ventricular Dysfunction (RECOVER) (N=900), Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) (N = 900), and Randomized Etanercept World Wide Evaluation (RENEWAL) (N = 1500) trials of etanercept as treatment for heart failure were stopped due to the lack of efficacy (21,22,51). In addition, there was a nonstatistically significant increase in mortality among patients with heart failure in the Anti-TNF Alpha Therapy Against CHF (ATTACH) (N = 150) trial who received infliximab therapy (10 mg/kg) when compared with placebo (21,51). These data raise concerns about the use of infliximab or etanercept in patients with symptomatic heart failure (17).

Because most of our results were based on prevalent cases of heart failure, it is possible that infliximab was less likely to be given to patients with known heart failure, particularly in view of the U.S. Food and Drug Administration's warning. Indeed, fewer patients receiving infliximab had a history of cardiovascular disease than those not receiving infliximab. When we adjusted for previous history, however, we continued to find no increase in heart failure in patients treated with anti-TNF agents.

In summary, heart failure is more common in rheumatoid arthritis patients than in those with osteoarthritis. Rheumatoid arthritis activity and severity measures were associated with heart failure, whereas patients receiving anti-TNF therapy were less likely to have heart failure.

## REFERENCES

- Monson RR, Hall AP. Mortality among arthritics. *J Chronic Dis*. 1976;29:459–467.
- Mutru O, Koota K, Isomäki HA. Causes of death in autopsied RA patients. *Scand J Rheumatol*. 1976;5:239–240.
- Koota K, Isomäki HA, Mutru O. Death rate and causes of death in RA patients during a period of five years. *Scand J Rheumatol*. 1977;6:241–244.
- Lewis P, Hazleman BL, Hanka R, Roberts S. Cause of death in patients with rheumatoid arthritis with particular reference to azathioprine. *Ann Rheum Dis*. 1980;39:457–461.
- Pincus T. Is mortality increased in rheumatoid arthritis? *J Musculo Med*. 1988;5:27–46.
- Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum*. 1994;37:481–494.
- Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol*. 1997;24:445–451.
- Goodson NJ, Wiles NJ, Lunt M, et al. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. *Arthritis Rheum*. 2002;46:2010–2019.
- Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol*. 2003;30:36–40.
- DeMaria AN. Relative risk of cardiovascular events in patients with rheumatoid arthritis. *Am J Cardiol*. 2002;89:33D–38D.
- Goodson N. Coronary artery disease and rheumatoid arthritis. *Curr Opin Rheumatol*. 2002;14:115–120.
- del Rincon ID, Williams K, Stern MP, et al. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum*. 2001;44:2737–2745.
- Khan AH, Spodick DH. Rheumatoid heart disease. *Semin Arthritis Rheum*. 1972;1:327–337.
- Mustonen J, Laakso M, Hirvonen T, et al. Abnormalities in left ventricular diastolic function in male patients with rheumatoid arthritis without clinically evident cardiovascular disease. *Eur J Clin Invest*. 1993;23:246–253.
- Feldman AM, Combes A, Wagner D, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. *J Am Coll Cardiol*. 2000;35:537–544.
- Hurlimann D, Forster A, Noll G, et al. Anti-tumor necrosis factor- $\alpha$  treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation*. 2002;106:2184–2187.
- Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res*. 2002;91:988–998.
- Dinarello CA, Pomerantz BJ. Proinflammatory cytokines in heart disease. *Blood Purif*. 2001;19:314–321.
- Kubota T, Bounoutas GS, Miyagishima M, et al. Soluble tumor necrosis factor receptor abrogates myocardial inflammation but not hypertrophy in cytokine-induced cardiomyopathy. *Circulation*. 2000;101:2518–2525.
- Kadokami T, Frye C, Lemster B, et al. Anti-tumor necrosis factor- $\alpha$  antibody limits heart failure in a transgenic model. *Circulation*. 2001;104:1094–1097.
- Hughes S. Infliximab harmful in CHF—final results of ATTACH. *Heartwire*. June 12, 2002. Available at: <http://www.theHeart.org>. Accessed January 1, 2003.
- Wood S. RENEWAL trial: no improvement in CHF with etanercept. *Heartwire*. June 11, 2002. Available at: <http://www.theHeart.org>. Accessed January 1, 2003.
- Wolfe F, Anderson J, Burke TA, et al. Gastroprotective therapy and risk of gastrointestinal ulcers: risk reduction by COX-2 therapy. *J Rheumatol*. 2002;29:467–473.
- Wolfe F, Flowers N, Burke TA, et al. Increase in lifetime adverse drug reactions, service utilization, and disease severity among patients who will start COX-2 specific inhibitors: quantitative assessment of channeling bias and confounding by indication in 6689 patients with rheumatoid arthritis and osteoarthritis. *J Rheumatol*. 2002;29:1015–1022.
- Michaud K, Messer J, Choi HK, Wolfe F. Direct medical costs and their predictors in persons with rheumatoid arthritis: a 3 year study of 7,527 patients. *Arthritis Rheum*. 2003;48:2750–2762.
- Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol*. 1982;9:789–793.
- Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum*. 1980;23:137–145.
- Hawley DJ, Wolfe F. Depression is not more common in rheumatoid arthritis: a 10 year longitudinal study of 6,608 rheumatic disease patients. *J Rheumatol*. 1993;20:2025–2031.
- Hawley DJ, Wolfe F. Anxiety and depression in patients with rheumatoid arthritis: a prospective study of 400 patients. *J Rheumatol*. 1988;15:932–941.
- Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). 1. Conceptual framework and item selection. *Med Care*. 1992;30:473–483.
- Hurst NP, Kind P, Ruta D, et al. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *Br J Rheumatol*. 1997;36:551–559.
- Wolfe F, Hawley DJ. Measurement of the quality of life in rheumatic disorders using the EuroQol. *Br J Rheumatol*. 1997;36:786–793.
- Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ*. 2002;21:271–292.
- Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. *J Clin Epidemiol*. 1998;51:1115–1128.
- Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol*. 1996;23:1407–1417.
- Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127:757–763.
- Rubin DB. Estimation of nonrandomized treatment comparisons using subclassification on propensity scores. In: Abel U, Koch A, eds. *Nonrandomized Comparative Clinical Studies: Proceedings of the International Conference on Nonrandomized Comparative Clinical Studies in Heidelberg*. Heidelberg, Germany: Symposium Publishing; 1997.
- Becker SO, Ichino A. Estimation of average treatment effects based on propensity scores. *Stata J*. 2002;2:358–377.
- CLARIFY: *Software for Interpreting and Presenting Statistical Results*. Version 2.0. Cambridge, Massachusetts: Harvard University; 2001.
- Stata Statistical Software: Release 7.0*. College Station, Texas: Stata Corporation; 2001.
- Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med*. 2003;138:807–811.
- Bacon PA, Raza K, Banks MJ, et al. The role of endothelial cell dysfunction in the cardiovascular mortality of RA. *Int Rev Immunol*. 2002;21:1–17.
- Bergholm R, Leirisalo-Repo M, Vehkavaara S, et al. Impaired responsiveness to NO in newly diagnosed patients with rheumatoid arthritis. *Arterioscler Thromb Vasc Biol*. 2002;22:1637–1641.
- Park YB, Ahn CW, Choi HK, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. *Arthritis Rheum*. 2002;46:1714–1719.
- Park YB, Lee SK, Lee WK, et al. Lipid profiles in untreated patients with rheumatoid arthritis. *J Rheumatol*. 1999;26:1701–1704.

46. Kavanaugh A. Lipid profiles in patients with rheumatoid arthritis. *Ann Rheum Dis.* 1998;57:175.
47. Hurt-Camejo E, Paredes S, Masana L, et al. Elevated levels of small, low-density lipoprotein with high affinity for arterial matrix components in patients with rheumatoid arthritis: possible contribution of phospholipase A2 to this atherogenic profile. *Arthritis Rheum.* 2001;44:2761–2767.
48. Wallberg-Jonsson S, Cvetkovic JT, Sundqvist KG, et al. Activation of the immune system and inflammatory activity in relation to markers of atherothrombotic disease and atherosclerosis in rheumatoid arthritis. *J Rheumatol.* 2002;29:875–882.
49. Bacon PA, Townend JN. Nails in the coffin: increasing evidence for the role of rheumatic disease in the cardiovascular mortality of rheumatoid arthritis. *Arthritis Rheum.* 2001;44:2707–2710.
50. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol.* 1999;26:2562–2571.
51. Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int J Cardiol.* 2002;86:123–130.