

Trends in Incidence of Chronic Heart Failure in Patients With Rheumatoid Arthritis: A Population-Based Study Validating Different Heart Failure Definitions

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ABSTRACT. *Objective.* To assess trends in the incidence of heart failure (HF) in patients with incident rheumatoid arthritis (RA) from 1980 to 2009 and to compare different HF definitions in RA.

Methods. The study population comprised Olmsted County, Minnesota residents with incident RA (age \geq 18 yrs, 1987 American College of Rheumatology criteria met in 1980-2009). All subjects were followed until death, migration, or April 30, 2019. Incident HF events were defined as follows: (1) meeting the Framingham criteria for HF, (2) diagnosis of HF (outpatient or inpatient) by a physician, or (3) International Classification of Diseases, 9th revision (ICD-9), or ICD, 10th revision (ICD-10), codes for HF. Patients with HF prior to the RA incidence/index date were excluded. Cox proportional hazards models were used to compare incident HF events by decade, adjusting for age, sex, and cardiovascular risk factors. HF definitions 2 and 3 were compared to the Framingham criteria.

Results. The study included 905 patients with RA (mean age 55.9 years; 68.6% female; median follow-up 13.4 years). The 10-year cumulative incidence of HF events by any chart-reviewed method in the RA cohort in the 1980s was 11.66% (95% CI 7.86-17.29), in the 1990s it was 12.64% (95% CI 9.31-17.17), and in the 2000s it was 7.67% (95% CI 5.36-10.97). The incidence of HF did not change across the decades of RA incidence using any of the HF definitions. Physician diagnosis of HF and ICD-9/10 code-based definitions of HF performed well compared to the Framingham criteria, showing moderate to high sensitivity and specificity.

Conclusion. The incidence of HF in patients with incident RA in the 2000s vs the 1980s was not statistically significantly different. Physician diagnosis of HF and ICD-9/10 codes for HF performed well against the Framingham criteria.

Key Indexing Terms: epidemiology, heart failure, rheumatoid arthritis

Heart failure (HF) is among the most common cardiovascular comorbidities in patients with rheumatoid arthritis (RA). The incidence of HF in RA is 2-fold higher than in the general population.¹⁻³ HF is associated with high risk for hospitalization and mortality in RA and is a major contributor to the excess mortality in RA.^{1,2,4} Recent analysis of the Medicare Expenditure Panel Survey showed that HF results in the highest incremental

healthcare expenditure and the lowest likelihood of being employed compared to other common comorbidities in RA.⁵ This underscores the tremendous clinical and economic effects of HF in RA and the need for developing prevention and management strategies for HF in this high-risk patient population.

Whereas studies from the US general population report a declining incidence of HF, particularly HF with reduced left

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ventricular ejection fraction (LVEF) after 2000, the epidemiology of HF overall and stratified by LVEF in RA is not well understood.⁶ In clinical practice, HF is diagnosed based on the clinical history and physical examination, with further testing to support the diagnosis and determine the underlying etiology, according to the American College of Cardiology (ACC) guidelines.⁷ Research studies in RA populations use variable definitions of HF (ie, Framingham criteria; International Classification of Diseases, 9th revision [ICD-9] codes; ICD, 10th revision [ICD-10] codes; physician diagnosis; and hospitalization for HF), which complicates the comparison of the results and understanding of HF epidemiology.^{4,8,9} The Framingham criteria are the most common gold standard for the validation of HF cases using administrative data in the general population.^{10,11} They capture the cardinal signs and symptoms of HF as outlined in the ACC guidelines and can be applied to retrospective data. However, performance of different HF definitions in patients with RA has not been systematically compared, and a standardized approach to identifying patients with HF from the medical records is lacking.

To address these scientific knowledge gaps, we aimed to (1) assess trends in the incidence of HF using 3 different HF definitions in patients with incident RA from 1980 to 2009 and (2) test the performance of HF definitions based on physicians' diagnoses and ICD-9/10 codes for HF against the Framingham criteria for HF in our population-based RA cohort. We hypothesized that, like other cardiovascular outcomes in RA, the incidence of HF is improving in recent years and that HF in RA can be reliably identified using different prespecified definitions.

METHODS

A retrospectively identified population-based cohort of patients with incident RA from 1980 to 2009 (age \geq 18 yrs, 1987 American College of Rheumatology [ACR] criteria) at risk of HF was assembled using the resources of the Rochester Epidemiology Project (REP). The REP is a unique population-based medical records linkage system that ensures ready access to the complete inpatient and outpatient medical records from all community medical providers in Olmsted County, Minnesota.¹² For each patient, the earliest date of fulfillment of \geq 4 1987 ACR criteria for RA was considered the RA incidence date. HF was defined using the definitions in the following sections.

Framingham criteria. For each patient, the entire length of their medical record was reviewed for possible HF. HF diagnosis requires \geq 2 major criteria (ie, paroxysmal nocturnal dyspnea or orthopnea; neck vein distention; rales; radiographic cardiomegaly, such as increasing heart size on chest radiograph; acute pulmonary edema; S3 gallop; increased central venous pressure of \geq 16 cm of water at the right atrium; circulation time of \geq 25 seconds; hepatojugular reflux; or weight loss of $>$ 4.5 kg in 5 days in response to treatment of congestive HF) or the presence of 1 major criterion and \geq 2 minor criteria (ie, bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by 33% from maximal value recorded, or tachycardia rate of \geq 120 beats/min). Minor criteria were counted only if not attributable to another medical condition. The Framingham criteria^{13,14} were required to be met in a single episode. Data on LVEF measured by transthoracic echo were electronically retrieved and included where available to classify HF with preserved LVEF (HFpEF; LVEF \geq 50%) and HF with reduced LVEF (HFrEF; LVEF $<$ 50%).

First-ever physician diagnosis of HF based on the medical records review. Diagnoses were as follows: (1) any diagnosis (outpatient or inpatient) and (2) inpatient diagnosis. For both outpatient and inpatient diagnoses, HF was included if it was on the list of diagnoses and not just limited to the principal diagnosis.

ICD-9 and ICD-10 codes for HF (ICD-9 code 428 and ICD-10 code I50). We evaluated definitions with 1 and 2 ICD-9/10¹⁵ codes 30 days apart.

All subjects were followed until death, migration, or April 30, 2019. HF events prior to RA incidence based on each of the definitions were excluded from the respective analyses. Information on the following sociodemographic and clinical characteristics was collected by retrospective medical records review for all patients by trained nurse abstractors who were blinded to the study hypotheses. Cardiovascular risk factors—age, smoking (current or former), BMI (obesity defined as BMI $>$ 30; calculated as weight in kilograms divided by height in meters squared), hypertension (HTN), diabetes mellitus (DM), and dyslipidemia—were ascertained using standardized criteria as described previously.⁹ Coronary heart disease (CHD) was defined as the presence of 1 of the following: angina pectoris, coronary artery disease, myocardial infarction (MI; including silent events), and coronary revascularization procedures (ie, percutaneous coronary intervention and coronary artery bypass grafting). Cases of MI were identified from the medical records according to standardized criteria.¹⁶ Information on RA disease characteristics (ie, RA duration, erythrocyte sedimentation rate [ESR], erosions/destructive changes on radiographs, rheumatoid factor [RF], and/or anticitrullinated protein antibody [ACPA] positivity), use of conventional synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), and use of glucocorticoids (GCs; ie, oral, intravenous, or intramuscular use) were also gathered from the medical records.

Ethical considerations. This study was approved by the Institutional Review Boards (IRBs) of the Mayo Clinic (IRB No. 17-002593) and the Olmsted Medical Center (IRB No. 017-OMC-17). The need for informed consent was waived. Patients who declined the use of their medical records for research purposes were not included in the study, per Minnesota law. This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for observational studies.

Statistical analysis. Kruskal-Wallis and chi-square tests were used to compare characteristics between patients with RA incidence in different decades. Cox proportional hazards models were used to compare incident HF events by decade, adjusting for age, sex, and cardiovascular risk factors (ie, smoking, obesity, DM, HTN, and dyslipidemia), as well as RA treatment. The cumulative incidence of HF adjusted for death was computed. For the purposes of validation, different definitions of HF were compared to the Framingham criteria for HF. In a subset of patients with available LVEF measures within 6 months of meeting the respective definition for incident HF, we compared each definition of HF with the Framingham criteria for HF within the categories of patients with HFpEF and HFrEF. Patients who developed HFpEF were censored for analyses on HFrEF and vice versa. Patients with HF and missing LVEF were censored for both analyses (ie, HFpEF and HFrEF). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value were calculated for each HF definition. Exact binomial 95% CIs were summarized. Analyses were performed using SAS, version 9.4 (SAS Institute Inc.), and R 3.4.2 (R Foundation for Statistical Computing).

RESULTS

The study included 905 patients with RA. The 10-year cumulative incidence of HF events by any chart-reviewed method (ie, the Framingham criteria and/or a physician diagnosis of HF) in the RA cohort in the 1980s was 11.66% (95% CI 7.86-17.29), in the 1990s it was 12.64% (95% CI 9.31-17.17), and in the 2000s it was 7.67% (95% CI 5.36-10.97). The 10-year cumulative incidence estimates for HF by definition (ie, Framingham criteria,

ICD-9/10 codes, and physician diagnosis) and by decade of RA incidence are presented in Supplementary Table S1 (available with the online version of this article).

Among patients who met the Framingham criteria for HF, the proportion of patients with available echocardiograms did not change significantly across the decades of RA incidence, as follows: 1980s, 79.4%; 1990s, 76.5%; and 2000s, 85.4% ($P = 0.53$). Of 172 patients with HF based on the Framingham criteria, LVEF measures within 6 months before or after the HF date were lacking in 20.3% of the patients ($n = 35$). In patients with available LVEF measures ($n = 137$), the absolute difference between the HF date by Framingham criteria and available LVEF was a median of 2 (IQR 1-17) days.

The cumulative incidence of HF defined by the Framingham criteria in the overall cohort and in a subset of patients with available LVEF by decade of RA incidence is shown in Figure 1. No differences were found in age, sex, RF positivity, ACPA positivity, radiographic erosions during the first year of RA, presence of HF before diagnosis by each of the definitions, or prevalence of CHD (Table 1). Among patients with erosions, the median number of days from meeting criteria for RA to the date of the earliest erosions/destructive changes was 0 (IQR -125 to 26; ie, erosions near RA onset). Smoking rates, ESR measures, and use of conventional DMARDs other than methotrexate (MTX) and hydroxychloroquine (HCQ) were lower. In contrast, BMI; rates of obesity, HTN, and dyslipidemia; and use of MTX, HCQ, tumor necrosis factor inhibitors (TNFi), and GCs were higher among patients with an RA incidence in more recent decades (Table 1).

Table 2 shows the risk of HF by decade of incidence using different HF definitions. There were no differences in risk of HF among patients with RA in the 1990s and the 2000s vs those with RA in the 1980s using all studied definitions, adjusting for age and sex. The results were similar after adjusting for cardiovascular risk factors (ie, smoking, obesity, DM, HTN, and dyslipidemia), DMARD use, and GC use. No statistically significant differences were detected when examining risk of HF by decade of RA incidence, stratifying by RF/ACPA status with the use of any of the HF definitions, and adjusting for age,

sex, cardiovascular risk factors, and the use of conventional and biologic DMARDs (Supplementary Tables S2-4, available with the online version of this article).

All definitions of HF performed well compared to the Framingham criteria, showing moderate to high sensitivity and specificity (Table 3). Sensitivity was highest for any physician diagnosis of HF (sensitivity: 98.22%; specificity: 96.32%); however, sensitivity was lower for the inpatient diagnosis of HF (66.67%), whereas specificity remained high (98.16%). PPVs were highest with any physician diagnosis of HF, particularly inpatient diagnosis of HF, and with the use of 2 ICD-9/10 codes. In the subset of patients with available LVEF, all definitions performed well against the Framingham criteria within the HFpEF and HFrEF categories (Table 3).

DISCUSSION

Increasingly high prevalence, morbidity, mortality, healthcare utilization, and associated economic costs position HF as a major public health problem, with amplified effects in patients with RA, who have double the risk of HF as compared to the general population.^{3,6,17} Our first and key finding is that the incidence of HF in patients with incident RA in the 2000s vs the 1980s was not statistically significantly different.

These results should be considered in the context of findings from the general US population. In a study combining several community-based samples, the incidence of HF overall remained stable from 1990 to 2009, whereas the incidence of HFrEF has declined and the incidence of HFpEF has increased.¹⁸ In contrast, in the general population of Olmsted County, Minnesota, the incidence of HF overall, particularly HFrEF, has declined from 2000 to 2010, potentially because of a decline in the incidence of MI and improved cardiovascular disease (CVD) management.⁶ The reasons for more pronounced improvements in Olmsted County vs other US general population cohorts are not entirely clear.

In our study, the effect estimates for HFpEF in the 1990s and the 2000s were about 20% to 30% higher, and those for HFrEF were about 30% lower than the reference (ie, the 1980s). This

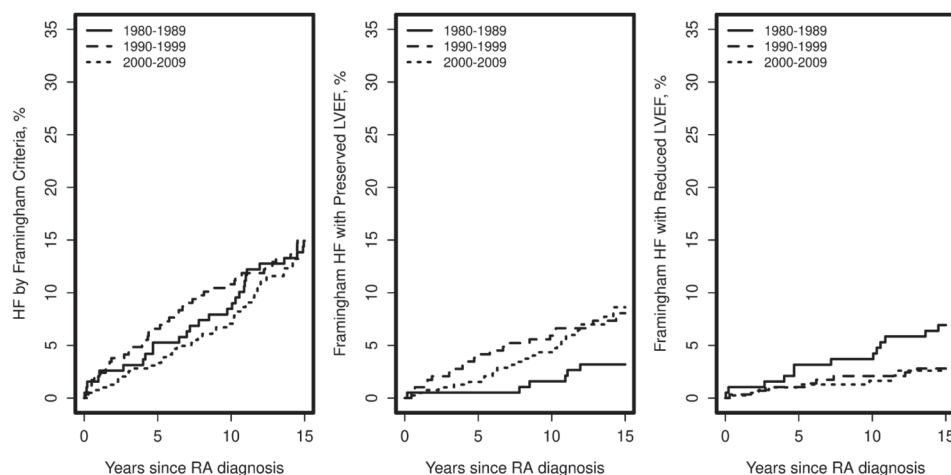


Figure 1. Cumulative incidence of HF defined by Framingham criteria in patients with RA by decade of RA incidence. LVEF: left ventricular ejection fraction; HF: heart failure; RA: rheumatoid arthritis.

Table 1. Characteristics of patients with RA by decade of incidence.

	Decade of RA Incidence				P
	1980-1989, n = 200	1990-1999, n = 299	2000-2009, n = 406	Total, N = 905	
Age at index date, yrs, mean (SD)	57.4 (15.6)	56.2 (15.9)	55.0 (15.4)	55.9 (15.6)	0.16
Sex, female	136 (68)	197 (65.9)	288 (70.9)	621 (68.6)	0.35
RF/ACPA positivity	134 (67.7)	209 (69.9)	282 (69.6)	625 (69.3)	0.85
Erosion/destructive changes on radiographs in the first year of RA	51 (25.5)	75 (25.1)	116 (28.6)	242 (26.7)	0.53
Highest ESR during first year of RA, mean (SD)	39.0 (27.7)	31.5 (25.1)	30.1 (24.7)	32.5 (25.7)	< 0.001
Smoking status					< 0.001
Never	79 (39.5)	124 (41.5)	211 (52)	414 (45.7)	
Former	55 (27.5)	115 (38.5)	133 (32.8)	303 (33.5)	
Current	66 (33)	60 (20.1)	62 (15.3)	188 (20.8)	
BMI at index date ^a , mean (SD)	26.1 (5.1)	27.5 (5.5)	29.2 (6.7)	28.0 (6.1)	< 0.001
Obesity (BMI ≥ 30)	33 (16.5)	83 (27.8)	168 (41.4)	284 (31.4)	< 0.001
Physician diagnosis of HTN	77 (38.5)	105 (35.1)	184 (45.3)	366 (40.4)	0.02
DM	22 (11)	24 (8)	51 (12.6)	97 (10.7)	0.16
Dyslipidemia	81 (40.5)	172 (57.5)	258 (63.5)	511 (56.5)	< 0.001
CHD ^b	22 (11)	36 (12)	43 (10.6)	101 (11.2)	0.83
Treatments in first year of RA incidence					
MTX	4 (2)	83 (27.8)	237 (58.4)	324 (35.8)	< 0.001
HCQ	50 (25)	134 (44.8)	226 (55.7)	410 (45.3)	< 0.001
Conventional synthetic DMARD	55 (27.5)	44 (14.7)	37 (9.1)	136 (15)	< 0.001
Biologics					
Total	0 (0)	1 (0.3)	45 (11.1)	46 (5.1)	< 0.001
TNFi	0 (0)	1 (0.3)	45 (11.1)	46 (5.1)	< 0.001
Non-TNFi biologics	0 (0)	0 (0)	1 (0.2)	1 (0.1)	0.54
JAKi	0 (0)	0 (0)	0 (0)	0 (0)	–
GCs (oral, IV, or intramuscular)	50 (25)	179 (59.9)	281 (69.2)	510 (56.4)	< 0.001
Any HF by chart review (ie, Framingham or physician diagnosis) prior to or on index date	7 (3.5)	10 (3.3)	13 (3.2)	30 (3.3)	0.98
Physician diagnosis of HF prior to or on incidence date	7 (3.5)	10 (3.3)	12 (3.0)	29 (3.2)	0.92
Physician diagnosis of inpatient with HF prior to or on incidence date	4 (2)	6 (2)	5 (1.2)	15 (1.7)	0.66
Framingham criteria for HF met prior to or on incidence date	7 (3.5)	8 (2.7)	10 (2.5)	25 (2.8)	0.76
ICD-9/10 (1 code) for HF prior to or on incidence date	10 (5)	15 (5)	20 (4.9)	45 (5)	0.99
ICD-9/10 (2 codes) for HF prior to or on incidence date	5 (2.5)	6 (2)	8 (2)	19 (2.1)	0.90
Duration from RA incidence to last follow-up, yrs, mean (SD)	19.0 (11.2)	16.8 (7.2)	10.7 (3.9)	14.5 (8.1)	–

Data are in n (%) unless otherwise indicated. ^a BMI is calculated as weight in kilograms divided by height in meters squared. ^b CHD was defined as the presence of one of the following: angina pectoris, coronary artery disease, myocardial infarction (including silent events), and coronary revascularization procedures (ie, percutaneous coronary intervention and coronary artery bypass grafting). ACPA: anticitrullinated protein antibody; CHD: coronary heart disease; DM: diabetes mellitus; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; GC: glucocorticoid; HCQ: hydroxychloroquine; HF: heart failure; HTN: hypertension; ICD-10: International Classification of Diseases, 10th revision; ICD-9: ICD, 9th revision; IV: intravenous; JAKi: Janus kinase inhibitors; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; TNFi: tumor necrosis factor inhibitors.

could reflect a possible evolving trend that reflects the general population of the USA, including Olmsted County, Minnesota, and globally, with an increasing proportion of patients with HFpEF in the case mix.^{6,17,18} This phenotype of HF has limited specific treatment and has been associated with a higher burden of comorbidities and a greater effect on hospitalization-related costs than HFrEF.^{19,20} Greater awareness and recognition of

HFpEF in recent years and increasing HFpEF risk factor burden (eg, obesity and multimorbidity) may, in part, explain the increasing prevalence of HFpEF in the general population, and similar dynamics, although not reaching statistical significance, may be emerging in RA.²¹⁻²³

Chronic systemic inflammation early in the RA disease course has been associated with increased risk of incident HF,

Table 2. Decade of index date as a risk factor to predict HF using different definitions of HF.

Event Type	Decade	Patients, n	Events, n	Model 1 ^a , HR (95% CI)	Model 2 ^b , HR (95% CI)	Model 3 ^c , HR (95% CI)
Framingham criteria for HF	1980-1989	193	63	Ref	Ref	Ref
	1990-1999	291	68	0.90 (0.62-1.31)	0.91 (0.62-1.35)	0.85 (0.55-1.31)
	2000-2009	396	41	0.81 (0.52-1.27)	0.73 (0.46-1.18)	0.68 (0.39-1.17)
Framingham HF with preserved LVEF	1980-1989	193	25	Ref	Ref	Ref
	1990-1999	291	33	1.23 (0.69-2.19)	1.14 (0.62-2.08)	1.17 (0.60-2.30)
	2000-2009	396	24	1.32 (0.68-2.54)	1.01 (0.50-2.04)	0.99 (0.44-2.26)
Framingham HF with reduced LVEF	1980-1989	193	25	Ref	Ref	Ref
	1990-1999	291	19	0.64 (0.34-1.22)	0.67 (0.34-1.32)	0.48 (0.23-1.03)
	2000-2009	396	11	0.67 (0.30-1.49)	0.70 (0.30-1.64)	0.47 (0.17-1.27)
Physician diagnosis of HF	1980-1989	193	67	Ref	Ref	Ref
	1990-1999	289	80	0.98 (0.69-1.39)	1.00 (0.70-1.44)	0.96 (0.64-1.44)
	2000-2009	394	46	0.85 (0.56-1.29)	0.76 (0.48-1.19)	0.72 (0.43-1.20)
Physician diagnosis of HF, inpatient only	1980-1989	196	49	Ref	Ref	Ref
	1990-1999	293	49	0.79 (0.51-1.20)	0.76 (0.49-1.18)	0.63 (0.39-1.04)
	2000-2009	401	30	0.74 (0.45-1.23)	0.64 (0.38-1.10)	0.52 (0.28-0.98)
ICD-9/10 (1 code) for HF	1980-1989	190	75	Ref	Ref	Ref
	1990-1999	283	75	0.81 (0.58-1.15)	0.83 (0.58-1.19)	0.72 (0.49-1.08)
	2000-2009	386	54	0.96 (0.65-1.42)	0.88 (0.58-1.34)	0.78 (0.48-1.28)
ICD-9/10 (2 codes) for HF	1980-1989	195	61	Ref	Ref	Ref
	1990-1999	292	59	0.80 (0.55-1.18)	0.85 (0.57-1.27)	0.82 (0.53-1.28)
	2000-2009	398	48	1.04 (0.68-1.61)	0.95 (0.60-1.52)	0.96 (0.55-1.65)

^a Model 1 was adjusted for age and sex. ^b Model 2 was adjusted for age, sex, smoking, obesity, diabetes, hypertension, and dyslipidemia. ^c Model 3 was adjusted for age, sex, smoking, obesity, diabetes, hypertension, dyslipidemia, use of methotrexate, hydroxychloroquine, other disease-modifying antirheumatic drugs, biologics, and glucocorticoids. HF: heart failure; HR: hazard ratio; ICD-10: International Classification of Diseases, 10th revision, ICD-9: ICD, 9th revision; LVEF: left ventricular ejection fraction.

particularly HFpEF in RA, independent of traditional HF risk factors and ischemic heart disease, whereas the use of DMARDs, such as MTX, has been linked to lower risk of HF.^{9,24-27} In a Swedish nationwide patient registry, high RA disease activity and the use of oral GCs were each associated with a 3-fold increase in the incidence of nonischemic HF (ie, HF without antedating ischemic heart disease) in individuals with RA.²⁷ An increase in the proportion of GC users from the 1980s to the 2000s was found in our study, but including it as an adjustor did not change the results. Literature regarding the association between GC use and CVD outcomes in RA is heterogenous, and confounding by indication (ie, high disease activity) cannot be excluded.²⁸ Nevertheless, minimizing unnecessary and excessive use of systemic GCs for improved CVD safety in RA is in accordance with the recent European Alliance of Associations for Rheumatology recommendations.²⁸ Early control of inflammation in RA with conventional or biologic DMARDs can be helpful in reducing the risk of HFpEF in RA.

Concordantly, we found that the use of MTX and TNFi was more prevalent in more recent RA cohorts, and time to first DMARD initiation—most frequently, MTX—has reduced in the 2000s (median 0.3 months) vs the 1980s (median 4.5

months), as previously reported.²⁹ However, these improvements have not yet translated into improved HF incidence in RA on the population level. The reasons for this lack of significant improvement are unclear, but the following RA-related factors can be considered: (1) lack of improvement in RA severity at the time of RA onset and preexisting cumulative burden of systemic inflammation, as demonstrated by similar rates of early erosions by decade of RA incidence in our study; (2) inadequate response to DMARDs resulting in uncontrolled inflammation in up to 50% patients at 1 year despite the use of conventional and biologic DMARDs, as reported in the Norwegian RA registry.³⁰ Indeed, an increased risk of CVD, specifically HF, may precede RA diagnosis^{31,32} or may increase shortly after the diagnosis along with increasing systemic inflammatory burden.²⁷

Amplifying the effects of systemic inflammation, traditional risk factors that overlap between RA and the general population also contribute to the risk of HF in RA.³³ Increased prevalence of obesity, HTN, and dyslipidemia and a lack of improvement in the prevalence of DM over time was found in our study, and can be considered among potentially modifiable metabolic targets for improvement of HF risk.^{33,34} The clinical implications of the

Table 3. Performance of different HF definitions in RA against Framingham criteria for HF.

Definition	Sensitivity, rate (95% CI)	Specificity, rate (95% CI)	PPV, rate (95% CI)	NPV, rate (95% CI)	Accuracy, rate (95% CI)	True Positive, n	True Negative, n	False Positive, n	False Negative, n
All HF, regardless of LVEF									
Physician diagnosis of HF	98.22 (94.90-99.63)	96.32 (94.65-97.58)	86.46 (80.79-90.96)	99.56 (98.72-99.91)	96.69 (95.27-97.77)	166	680	26	3
Physician diagnosis of HF, inpatient only	66.67 (59.07-73.68)	98.16 (96.88-99.02)	89.76 (83.13-94.44)	92.42 (90.29-94.21)	92.04 (90.05-93.74)	114	695	13	57
1 ICD-9/10 code for HF	89.94 (84.17-94.14)	91.79 (89.49-93.72)	71.50 (64.71-77.64)	97.55 (96.05-98.59)	91.44 (89.36-93.23)	143	637	57	16
2 ICD-9/10 codes for HF	78.24 (71.27-84.19)	95.62 (93.83-97.00)	81.10 (74.26-86.78)	94.81 (92.92-96.32)	92.25 (90.27-93.93)	133	676	31	37
LVEF ≥ 50% (HFpEF)									
Physician diagnosis of HF	98.65 (92.70-99.97)	98.53 (97.38-99.26)	86.90 (77.78-93.28)	99.86 (99.25-99.99)	98.54 (97.46-99.24)	73	735	11	1
Physician diagnosis of HF, inpatient only	62.50 (50.96-73.08)	99.34 (98.46-99.78)	90.91 (80.05-96.98)	96.15 (94.55-97.39)	95.81 (94.22-97.06)	50	750	5	30
1 ICD-9/10 code for HF	87.88 (77.51-94.62)	96.60 (94.98-97.81)	70.73 (59.65-80.26)	98.84 (97.73-99.50)	95.85 (94.19-97.14)	58	681	24	8
2 ICD-9/10 codes for HF	77.27 (65.30-86.69)	99.04 (98.03-99.61)	87.93 (76.70-95.01)	97.97 (96.67-98.86)	97.24 (95.85-98.26)	51	723	7	15
LVEF < 50% (HFrEF)									
Physician diagnosis of HF	92.59 (82.11-97.95)	99.61 (98.86-99.92)	94.34 (84.34-98.82)	99.48 (98.67-99.86)	99.15 (98.25-99.66)	50	763	3	4
Physician diagnosis of HF, inpatient only	70.37 (56.39-82.02)	99.74 (99.08-99.97)	95.00 (83.08-99.39)	97.99 (96.75-98.85)	97.84 (96.61-98.72)	38	779	2	16
1 ICD-9/10 code for HF	80.43 (66.09-90.64)	99.45 (98.59-99.85)	90.24 (76.87-97.28)	98.77 (97.67-99.43)	98.31 (97.13-99.10)	37	721	4	9
2 ICD-9/10 codes for HF	70.21 (55.11-82.66)	99.60 (98.83-99.92)	91.67 (77.53-98.25)	98.16 (96.93-98.99)	97.86 (96.60-98.75)	33	746	3	14

HF: heart failure; HFpEF: HF with preserved LVEF; HFrEF: HF with reduced LVEF; ICD-10: International Classification of Diseases, 10th revision; ICD-9: ICD, 9th revision; LVEF: left ventricular EF; NPV: negative predictive value; PPV: positive predictive value; RA: rheumatoid arthritis.

lack of improvement in the incidence of HF in RA build on the substantial effect of HF on the healthcare system and the associated complexity and cost of medical care; this requires healthcare utilization planning and continuing research efforts for identifying effective ways to prevent HF.

Our second major finding is that physician diagnosis of HF and ICD-9/10 codes for HF performed well against the Framingham criteria overall and in the categories of HFpEF and HFrEF. The Framingham criteria for HF that include the most common signs and symptoms of HF are well documented by primary care physicians; thus, they can be reliably detected in the medical records.^{35,36} However, manual data abstraction is costly and laborious. ICD-9/10 codes for HF were validated against the Framingham criteria in the general population, with PPVs of 63% to 97% for outpatient diagnosis of HF and 84% to 100% for inpatient HF cases.¹¹ In the Olmsted County, Minnesota, cohort for the years 2010 to 2012, the PPV for more than 2 ICD-9 codes for HF was 79.3%, which is quite similar to the PPV of 81.1% in our study.³⁷ A combination of more than 2 ICD-9 HF codes, any HF medication, and elevated N-terminal pro-brain natriuretic peptide provided the highest PPV (86.5%) in that study, while reducing sensitivity. Consistent with findings from the general population, in our study sensitivity of inpatient diagnosis of HF was lower and PPV was higher than for other

definitions; this is not surprising, considering the likelihood of ascertainment bias because of the hospitalization of more severe HF cases and the likelihood of them being “true” cases.¹¹

These results suggest that physician diagnosis and ICD codes can be used for initial HF case identification, which can be further improved by the addition of data on HF medications and N-terminal pro-brain natriuretic peptide. Subsequent case review by a cardiologist can be sought for verification of unclear HF diagnosis. Results of this validation analysis can be helpful in guiding future studies on optimizing HF case identification (ie, inpatient and outpatient HF) in retrospective RA cohorts.

Strengths of our study include the use of a large, longitudinal, population-based cohort of patients with incident RA with long-term and complete follow-up and the availability of complete inpatient and outpatient medical records from all medical care providers in the community, providing comprehensive data and allowing for manual verification of the records for fulfillment of the Framingham criteria for HF.

Our study has several potential limitations. The population of Olmsted County, Minnesota, is predominantly White; thus, the generalizability of our findings to more ethnically diverse populations may be limited. The retrospective study design required that only information available from medical records could be used to ascertain HF outcomes. Overall, the

use of the comprehensive population-based resources of the REP and standardized case ascertainment likely minimized this bias. However, we were not able to account for the use of nonsteroidal analgesics, as these are over-the-counter medications and information on their use is inconsistently documented in the medical charts. Another limitation inherent to the use of medical records is the lack of the LVEF measures within 6 months before or after the HF date in 20.3% of patients with HF based on the Framingham criteria. Thus, results of analyses of HF incidence by the Framingham criteria in subgroups of patients with available LVEF should be interpreted with caution. Reassuringly, the proportion of patients with missing LVEF who met the Framingham criteria for HF was not significantly different across the decades of RA incidence: 1980s, 20.6%; 1990s, 23.5%; and 2000s, 14.6%. Further, in the validation analyses, all definitions performed well against the Framingham criteria within the HFpEF and HFrEF categories. In this study, HF was divided into HFpEF (LVEF \geq 50%) and HFrEF (LVEF < 50%) categories. The most recent guideline for the management of HF separates HFrEF (LVEF \leq 40%) from HF with mildly reduced LVEF (LVEF 41-49%). We did not study HF with mildly reduced LVEF as a separate category in this study.³⁸ Although the HF category can change if LVEF changes over time, in our study, the absolute difference between the HF date by the Framingham criteria and the date by available LVEF was a median of only 2 days; thus, misclassification of HFpEF and HFrEF categories was unlikely. We did not classify HF phenotype as ischemic vs nonischemic, as done in some prior studies.²⁷ The prevalence of patients with CHD by decade of RA incidence was similar in patients with RA onset in the 1990s and the 2000s vs the 1980s; thus, it is unlikely to affect the comparisons between the decades for HF overall.

Determining etiologies of different HF subtypes was beyond the scope of this study and would be of interest for future studies. Although minor Framingham criteria may overlap between HF and RA-associated interstitial lung disease (RA-ILD), these criteria were counted only if they could not be attributed to another medical condition (eg, ILD). Further, there were only 5 patients with RA-ILD and HF within 1 year of RA incidence, which is unlikely to bias the results.

The approach to diagnosis and guideline-directed treatment of RA and HF has changed over the decades, which may have affected the study results. We did not collect information on medical therapies for HF or on natriuretic peptide measurements. Although measurement of natriuretic peptides is currently a standard of care for HF, its availability and use in clinical practice changed markedly over the course of the study period and was not routinely performed until the early 2000s.^{7,39} We believe that the use of longitudinal data and uniformly collected standardized criteria (ie, Framingham criteria) ensured reliable HF case ascertainment, whereas physician diagnosis of HF and code-based definitions of HF performed well against the Framingham criteria as a gold standard definition. In addition, there was a lack of significant change in the incidence of HF across the decades, and the results were similar when adjusting for the use of conventional and biologic DMARDs. Thus, it is

unlikely that clinical practice changes in RA had a major effect on the study results. Finally, in this study, we did not compare trends in HF incidence in patients with or without RA. We reference previous studies that reported on trends in the incidence of HF in Olmsted County, Minnesota.⁶

In summary, we found that the incidence of HF in patients with incident RA in the 2000s vs the 1980s was not statistically significantly different, which is important for healthcare planning and identifying research avenues for studying effective preventive strategies of HF in RA. The results of our study demonstrate that in patients with RA, physician diagnosis and code-based definitions can be used for initial identification of patients with HF.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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