Title page

Short running head: Heart failure in rheumatoid arthritis

Full title of manuscript: Trends in incidence of chronic heart failure (HF) in patients with rheumatoid arthritis: a population-based study validating different HF definitions

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Abstract

Background/Purpose. To assess trends in incidence of heart failure (HF) in patients with incident rheumatoid arthritis (RA) in 1980-2009 and to compare different HF definitions in RA.

Methods. The study population comprised Olmsted County, Minnesota residents with incident RA (age ≥ 18 years, 1987 ACR criteria met in 1980-2009). All subjects were followed until death, migration, or 04/30/2019. Incident HF events were defined as: 1) Framingham criteria for HF; 2) Diagnosis of HF (outpatient or inpatient) by a physician; 3) ICD-9/10 codes for HF. Patients with HF prior to 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 event by any chart-reviewed method in RA cohort in the 1980s was 11.66% (95%CI 7.86-17.29%), 1990s was 12.64% (95%CI 9.31-17.17%), and 2000s was 7.67% (95%CI 5.36-10.97%). 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 Framingham criteria, showing moderate-to-high sensitivity and specificity.

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

Introduction

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 impact of HF in RA and the need for developing prevention and management strategies for HF in this high-risk patient population.

While studies from the US general population report declining incidence of HF, particularly HF with reduced ejection fraction after 2000, the epidemiology of HF overall and stratified by ejection fraction 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 (i.e., Framingham criteria, International Classification of Disease [ICD] 9/10 codes, physician diagnosis, 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 billing 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 incidence of HF using three different HF definitions in patients with incident RA in 1980-2009 and 2) test the performance of HF definitions based on physician's diagnosis 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 in 1980-2009 (age ≥ 18 years, 1987 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 (in-patient and out-patient) medical records from all community medical providers in Olmsted County, MN (12). For each patient, the earliest date of fulfillment of ≥4 1987 ACR criteria for RA was considered the RA incidence date. HF was defined using the following definitions.

1) Framingham criteria (13, 14). For all patients, the entire length of medical records was reviewed for possible HF. HF diagnosis requires ≥2 major criteria (i.e., paroxysmal nocturnal dyspnea or orthopnea, neck vein distention, rales, radiographic cardiomegaly (i.e., increasing heart size on chest radiograph), acute pulmonary edema, S3 gallop, increased central venous pressure ≥ 16 cm of water at the right

atrium, circulation time ≥25 seconds, hepatojugular reflux, weight loss >4.5 kg in 5 days in response to treatment of congestive HF), or the presence of 1 major criterion and ≥2 minor criteria (i.e., bilateral ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by 33% from maximal value recorded, and tachycardia rate ≥120 beats/min). Minor criteria were counted only if not attributable to another medical condition. The Framingham criteria were required to be met in a single episode. Data on left ventricular ejection fraction (EF) measured by transthoracic echo were electronically retrieved and included where available to classify HF with preserved EF (EF ≥50%, HFpEF) and HF with reduced EF (EF<50%, HFrEF).

2) First ever physician diagnosis of HF based on the medical records review: a) any diagnosis (outpatient or inpatient) and b) inpatient diagnosis. For both outpatient and inpatient diagnoses, HF was included if it was on the list of diagnoses, not limited to the principal diagnosis.
3) ICD codes 9 and 10 for HF (ICD-9 code 428 and ICD-10 code I50) (15). We evaluated definitions with one and two ICD9/10 codes 30 days apart.

All subjects were followed until death, migration, or 04/30/2019. HF events prior to RA incidence based on each of the definitions were excluded from the respective analyses. Information on the following sociodemographics and clinical characteristics was collected by retrospective medical records review in all patients by trained nurse abstractors who were blinded to the study hypotheses. Cardiovascular risk factors: age, smoking (current or former), body mass index (BMI; obesity defined as BMI ≥30 kg/m^2), hypertension, diabetes mellitus, and dyslipidemia were ascertained using standardized

criteria as described previously (9). Coronary heart disease (CHD) was defined as the presence of one of the following: angina pectoris, coronary artery disease, myocardial infarction (MI; including silent events), and coronary revascularization procedures (i.e., 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, i.e., RA duration, erythrocyte sedimentation rate, erosions/ destructive changes on radiographs, rheumatoid factor [RF] and/ or anti-citrullinated protein antibody [ACPA] positivity, use of conventional and biologic disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids (oral, intravenous or intramuscular use) was also gathered from the medical records. This study was approved by the institutional review boards of Mayo Clinic (IRB #17-002593) and Olmsted Medical Center (IRB #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 [15].

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 (smoking, obesity, diabetes mellitus, hypertension, dyslipidemia) as well as RA treatment. 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 EF 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 EF were censored for both analyses, i.e. HFpEF and HFrEF. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each HF definition. Exact binomial confidence intervals were summarized. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria.

Results

The study included 905 patients with RA. The 10-year cumulative incidence of HF event by any chart reviewed method (i.e., the Framingham criteria and/ or a physician diagnosis of HF) in RA cohort in the 1980s: 11.66% (95%CI 7.86-17.29%), 1990s: 12.64% (95%CI 9.31-17.17%), and 2000s: 7.67% (95%CI 5.36-10.97%). The 10-year cumulative incidence estimates for HF by definition (i.e., Framingham criteria, ICD-9/10 codes and physician diagnosis) and decade of RA incidence are presented in Supplemental Table 1.

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%; 2000s – 85.4% (p=0.53). Of 172 patients with HF based on Framingham criteria, EF measures within ± 6 months of HF date were lacking in 20.3% (n=35). In patients with available EF measures (n=137), the

absolute difference between HF date by Framingham criteria and available EF was a median of 2 days (Interquartile range [IQR] 1 to 17 days).

Cumulative incidence of HF defined by Framingham criteria in the overall cohort and in subset of patients with available EF, by decade of RA incidence is shown on Figure 1. No differences were found in age, sex, RF-positivity or 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 date of earliest erosions/destructive changes was 0 (IQR -125 to 26), i.e., erosions near RA onset. Smoking rates and ESR measures, as well as use of conventional DMARDs other than methotrexate and hydroxychloroquine were lower, while BMI, rates of obesity, hypertension, and dyslipidemia, and use of methotrexate, hydroxychloroquine, tumor necrosis factor-alpha (TNF-α) inhibitors and glucocorticoids were higher among patients with 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 1990s and 2000s versus those with RA in 1980s using all studied definitions, adjusting for age and sex. The results were similar after adjusting for cardiovascular risk factors (smoking, obesity, diabetes, hypertension, dyslipidemia), DMARD use and glucocorticoids. 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, adjusting for age and sex, cardiovascular risk factors and the use of conventional and biologic DMARDs (Supplemental Tables 2-4).

All definitions of HF performed well compared to 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%) and lower for the inpatient diagnosis of HF (66.67%, while specificity remained high, 98.16%). PPVs were highest with any physician diagnosis of HF, particularly, inpatient diagnosis of HF, and with the use of two ICD-9/10 codes. In the subset of patients with available EF, 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 impact 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 2000s versus 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 in 1990-2009, while the incidence of HFrEF has declined and the incidence of HFpEF has increased (18). In contrast, in the general population of Olmsted County, MN the incidence of HF overall and particularly HFrEF has declined in 2000-2010, potentially due to decline in incidence of MI and improved CVD management (6). The reasons for more pronounced improvements in Olmsted County versus other US general population cohorts are not entirely clear.

In our study, the effect estimates for HFpEF in the 1990s and 2000s were about 20-30% higher and those for HFrEF were about 30% lower than the reference (1980s), a possible evolving trend that reflects the general population of the US, including Olmsted County, MN, and globally, with 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 impact on hospitalization-related costs than HFrEF (19, 20). Greater awareness and recognition of HFpEF in recent years and increasing HFpEF risk factor burden (e.g., obesity, multimorbidity) may in part explain 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, particularly HFpEF in RA, independent of traditional HF risk factors and ischemic heart disease, while use of DMARDs such as methotrexate has been linked to lower risk of HF (9, 24-27). In Swedish nationwide patient registry, high RA disease activity and use of oral glucocorticoids were each associated with a 3-fold increase in incidence of non-ischemic HF (i.e., HF without antedating ischemic heart disease) in individuals with RA (27). Increase in proportion of glucocorticoid users from 1980s to 2000s was found in our study but including it as an adjustor did not change the results. Literature regarding the association between the glucocorticoids and CVD outcomes in RA is heterogenous and confounding by indication (i.e. high disease activity) cannot be excluded (28). Nevertheless, minimizing unnecessary and excessive use of systemic glucocorticoids for improved CVD safety in RA is in accordance with the recent

EULAR 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 methotrexate and TNF-α inhibitors was more prevalent in more recent RA cohorts, and time to first DMARD initiation (most frequently, methotrexate) has reduced in 2000s (median 0.3 months) versus 1980s (median 4.5 months), as previously reported (29). However, these improvements have not yet translated in 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: a) 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; b) 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, increased risk of CVD and specifically HF may precede RA diagnosis (31, 32), or 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, hypertension and dyslipidemia and lack of improvement in prevalence of diabetes 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 lack of improvement in incidence of HF in RA build on the substantial impact of HF on healthcare system and associated complexity and cost of medical care,

requiring healthcare utilization planning and continuing research efforts for identifying effective ways for HF prevention.

Our second major finding is that physician diagnosis of HF and ICD-9/10 codes for HF performed well against 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 the primary care physicians, and thus can be reliably detected in the medical records (35, 36). However, manual data abstraction is costly and effort-consuming. ICD-9/10 codes for HF were validated against the Framingham criteria in the general population with PPV 63-97% for outpatient diagnosis of HF and 84-100% for inpatient HF cases (11). In Olmsted County, MN cohort 2010-2012 PPV for ≥2 ICD-9 codes for HF was 79.3% which is quite similar to PPV 81.1% in our study (37). A combination of ≥2 ICD-9 HF codes, any HF medication, and elevated N-terminal B-type natriuretic peptide provided the highest PPV (86.5%) in that study, while reducing sensitivity. Consistent with the findings from the general population, in our study sensitivity of inpatient diagnosis of HF was lower and PPV was higher than for other definitions which is not surprising, considering the likelihood of ascertainment bias due to 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 addition of data on HF medications and N-terminal-B-type 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 (i.e., inpatient and outpatient HF) in retrospective RA cohorts.

Strengths of our study include the use of a large, longitudinal population-based cohort of incident RA patients with long and complete follow-up; 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 non-steroidal 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 EF measures within ± 6 months of HF date in 20.3% of patients with HF based on Framingham criteria. Thus, results of analyses of HF incidence by Framingham criteria in subgroups of patients with available EF should be interpreted with caution. Reassuringly, the proportion of patients with missing EF who met the Framingham criteria for HF was not significantly different across the decades of RA incidence: 1980s – 20.6%; 1990s – 23.5%; 2000s – 14.6%. Furthermore, in the validation analyses, all definitions performed

well against the Framingham criteria within the HFpEF and HFrEF categories. In this study, HF was divided in HFpEF (EF≥50%) and HFrEF (EF<50%). The most recent guideline for the management of HF separates HFrEF (EF<=40%) and HF with mildly reduced EF (EF 41-49%). We did not study HF with mildly reduced EF as a separate category in this study (38). While HF category can change if EF changes over time, in our study the absolute difference between HF date by Framingham criteria and available EF was a median of only 2 days, thus misclassification of HFpEF and HFrEF categories is unlikely. We did not classify HF phenotype as ischemic vs non-ischemic, as done in some prior studies (27). Prevalence of patients with CHD by decade of RA incidence was similar in patients with RA onset in 1990s and 2000s versus 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. While 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 (e.g. ILD). Furthermore, 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 and natriuretic peptide measurements. While measurement of natriuretic peptide 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 obtained until early 2000s (7, 39). We believe that the use of longitudinal

data and uniformly collected standardized criteria (i.e. Framingham criteria) ensured reliable HF case ascertainment, while 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 lack of significant change in the incidence of HF across the decades and the results were similar adjusting for the use of conventional and biologic DMARDs. Thus, it is unlikely that clinical practice changes in RA had a major impact on the study results. Finally, in this study we did not compare trends in HF incidence in patients with and without RA. We reference previous studies that reported on trends in the incidence of HF in Olmsted County, MN (6).

In summary, we found that the incidence of HF in patients with incident RA in 2000s versus 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 utilized for initial identification of patients with HF.

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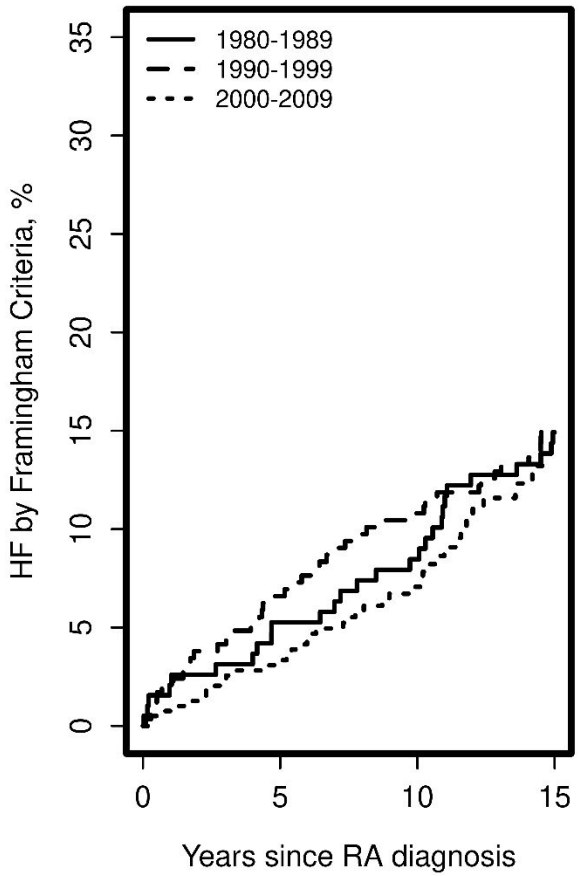
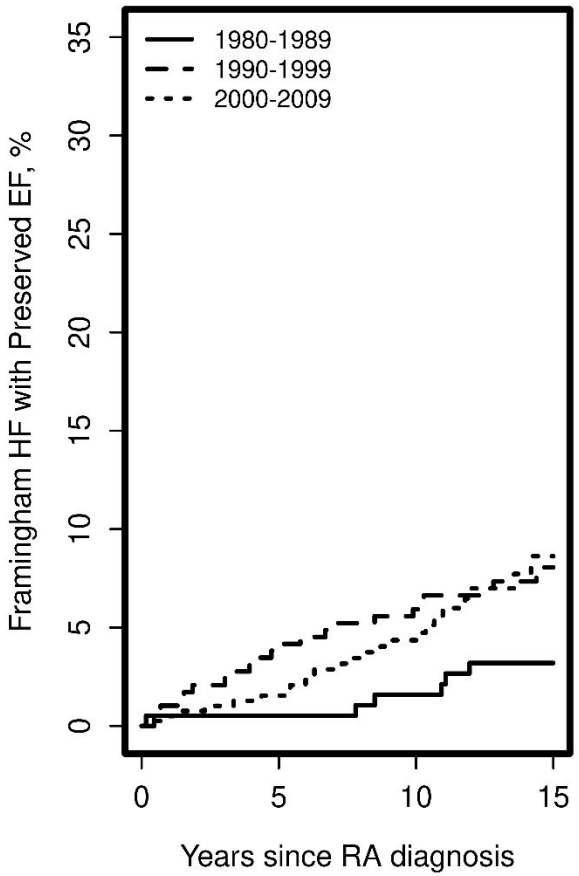
Figure Legend:

Figure 1. Cumulative incidence of heart failure defined by Framingham criteria in patients with rheumatoid arthritis by decade of RA incidence





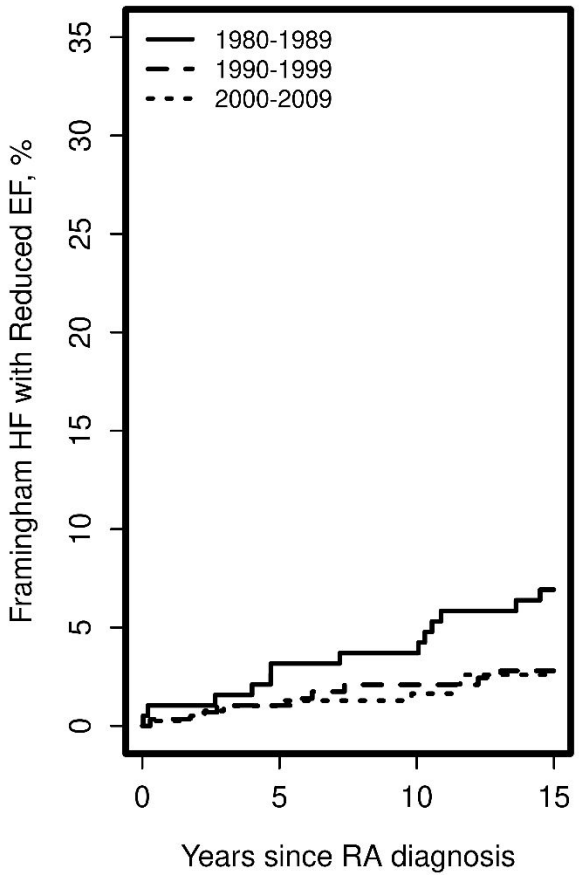


Table 1. Characteristics of patients with rheumatoid arthritis by decade of incidence

Decade of RA incidence	1) 1980-1989 (N=200)	2) 1990-1999 (N=299)	3) 2000-2009 (N=406)	Total (N=905)	p-value
Age (years) at index date	57.4 (15.6)	56.2 (15.9)	55.0 (15.4)	55.9 (15.6)	0.16
Sex, female	136 (68.0)	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 erythrocyte sedimentation rate during first year of RA	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 (52.0)	414 (45.7)	
Former	55 (27.5)	115 (38.5)	133 (32.8)	303 (33.5)	
Current	66 (33.0)	60 (20.1)	62 (15.3)	188 (20.8)	
BMI at index date (kg/m^2)	26.1 (5.1)	27.5 (5.5)	29.2 (6.7)	28.0 (6.1)	<0.001
Obesity (BMI≥30 kg/m^2)	33 (16.5)	83 (27.8)	168 (41.4)	284 (31.4)	<0.001
Physician diagnosis of Hypertension	77 (38.5)	105 (35.1)	184 (45.3)	366 (40.4)	0.020
Diabetes Mellitus	22 (11.0)	24 (8.0)	51 (12.6)	97 (10.7)	0.16
Dyslipidemia	81 (40.5)	172 (57.5)	258 (63.5)	511 (56.5)	<0.001
CHD *	22 (11.0)	36 (12.0)	43 (10.6)	101 (11.2)	0.83
Treatments in first year of RA incidence					
Methotrexate	4 (2.0)	83 (27.8)	237 (58.4)	324 (35.8)	<0.001
Hydroxychloroquine	50 (25.0)	134 (44.8)	226 (55.7)	410 (45.3)	<0.001
Other conventional DMARD	55 (27.5)	44 (14.7)	37 (9.1)	136 (15.0)	<0.001
Biologics	0 (0.0)	1 (0.3)	45 (11.1)	46 (5.1)	<0.001
TNFi	0 (0.0)	1 (0.3)	45 (11.1)	46 (5.1)	<0.001
Non-TNFi biologics	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	0.54
Janus Kinase inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	--
Glucocorticoids (oral, intravenous or intramuscular)	50 (25.0)	179 (59.9)	281 (69.2)	510 (56.4)	<0.001

Any HF by chart review (i.e. Framingham or physician diagnosis) prior to or on index	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 HF inpatient prior to or on incidence date	4 (2.0)	6 (2.0)	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 (5.0)	15 (5.0)	20 (4.9)	45 (5.0)	0.99
ICD 9/10 (2 codes) for HF prior to or on incidence date	5 (2.5)	6 (2.0)	8 (2.0)	19 (2.1)	0.90
Years from RA incidence to last follow up	19.0 (11.2)	16.8 (7.2)	10.7 (3.9)	14.5 (8.1)	

Abbreviations: RF=rheumatoid factor; ACPA=Anti-citrullinated Peptide Antibody; RA=rheumatoid arthritis; BMI=body mass index; CHD = coronary heart disease; DMARD = disease-modifying antirheumatic drug; TNFi=Tumor necrosis Factor-alpha inhibitors; ICD= international classification of diseases; HF= heart failure.

Values in the table are mean (±standard deviation) or N (%), as indicated.

* CHD was defined as the presence of one of the following: angina pectoris, coronary artery disease, myocardial infarction (MI; including silent events), and coronary revascularization procedures (i.e., percutaneous coronary intervention and coronary artery bypass grafting).

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

Event Type	Decade	Total (Event)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Framingham criteria for HF	1980-1989	193 (63)	Reference	Reference	Reference
	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 EF	1980-1989	193 (25)	Reference	Reference	Reference
	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 EF	1980-1989	193 (25)	Reference	Reference	Reference
	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)	Reference	Reference	Reference
	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	1980-1989	196 (49)	Reference	Reference	Reference
	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)	Reference	Reference	Reference
	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)	Reference	Reference	Reference
	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)

Abbreviations: HR = Hazard Ratio; 95% CI = 95% confidence interval; HF = heart failure; EF = left ventricular ejection fraction; ICD = international classification of diseases

Model 1: Adjusted for Age and Sex

Model 2: Adjusted for Age, Sex, smoking, Obesity, Diabetes, Hypertension, Dyslipidemia

Model 3: Adjusted for Age, Sex, smoking, Obesity, Diabetes, Hypertension, Dyslipidemia, use of methotrexate, hydroxychloroquine, other disease-modifying antirheumatic drugs, biologics, glucocorticoids

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

Definition	Sensitivity, rate (CI)	Specificity, rate (CI)	PPV, rate (CI)	NPV, rate (CI)	Accuracy, rate (CI)	True Positive	True Negative	False Positive	False Negative
All HF, regardless of EF									
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	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
One ICD9/ICD10 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
Two ICD9/ICD10 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
EF ≥ 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	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
One ICD9/ICD10 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
Two ICD9/ICD10 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
EF < 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	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
One ICD9/ICD10 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
Two ICD9/ICD10 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

Abbreviations: PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval; HF = heart failure; EF = left ventricular ejection fraction; HFrEF = HF with reduced EF; HFpEF = HF with preserved EF; ICD= international classification of diseases.