# Cardiovascular Event Risk in Rheumatoid Arthritis is Higher than in Type 2 Diabetes: a 15 Year Longitudinal Study

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**Abstract**

**Objective:** Cardiovascular (CV) disease risk is increased in rheumatoid arthritis (RA). However, long-term follow-up studies investigating this risk are scarce.

**Methods:** CARRÉ is a prospective cohort study investigating CV disease and its risk factors in 353 patients with longstanding RA. CV endpoints were assessed at baseline, 3, 10 and 15 years after the start of the study and are compared to a reference cohort(n=2540) including a large number of patients with type 2 diabetes(DM).

**Results:** 95 RA patients developed a CV event during 2973 person-years, resulting in an incidence rate of 3.20 per 100 person-years. 257 CV events were reported in the reference cohort during 18874 person-years, resulting in an incidence rate of 1.36 per 100 person-years. Age and sex adjusted hazard rates(HR) for CV events were increased for RA(HR 2.07, 95%CI 1.57–2.72, *P*<0.01) and DM (HR 1.51, 95%CI 1.02–2.22, *P*=0.04) compared to the non-diabetic participants. HR was still increased in RA (HR 1.82, 95%CI 1.32–2.50, *P*<0.01) after additional adjustment for CV risk factors. Patients with both RA and DM or insulin resistance had the highest HR for developing CV disease (2.21, 95%CI 1.01–4.80, P=0.046 and 2.67, 95%CI 1.30–5.46, P<0.01, respectively).

**Conclusion:** The incidence rate of CV events in established RA was more than double that of the general population. RA patients have an even higher risk of CV disease than patients with DM. This risk remained after adjustment for traditional CV risk factors suggesting that systemic inflammation is an independent contributor to CV risk.

**Keywords**: rheumatoid arthritis, cardiovascular disease, cardiovascular risk, type 2 diabetes mellitus

**Introduction**

Rheumatoid arthritis (RA) is associated with increased cardiovascular (CV) morbidity and premature death of CV origin, when compared to the general population.(1) Several underlying mechanisms are suggested. Traditional CV risk factors, including hypertension, dyslipidaemia, smoking, type 2 diabetes, a sedentary lifestyle and obesity, are associated with the development of CV disease in RA, similar to the general population.(1) RA is characterized by chronic systemic inflammation (i.e., not limited to the joints), which is thought to be another major contributor to CV disease development in these patients.(2-4) Systemic inflammation appears to increase CV risk independently and beyond traditional CV risk factors, while it also potentially alters existing CV risk factors in these patients (3;5;6). A recent meta-analysis of 14 observational cohort studies showed an overall increased CV risk of about 50% in patients with RA, compared to non-RA participants.(7) Other studies report standardized mortality ratios (SMRs) as high as 2.7 compared with the general population, (8;9) SMRs that appear to be constant over 50 years,(10) although this has been challenged by a study reporting decreasing mortality in the last decade.(11) However, study results are heterogeneous, and most studies have a follow up shorter than 10 years. In 2009, our group also reported an increased CV risk in a cohort of RA patients compared with a population-based reference cohort over 3 years of follow up.(4) We now report on the incidence and risk of fatal and non-fatal CV events in this cohort over a maximum follow up period of 15 years, compared with a representative sample cohort of the general population focusing on prevalence and incidence of type 2 diabetes mellitus (DM) and its complications.

## Patients and Methods

To investigate the risk of incident CV disease in participants with RA vs. DM and the general population, the CARRÉ study cohort and the Hoorn study cohort were compared. In both populations data regarding demographics, RA-related variables, risk factors for CV disease, and new or incident CV events after the start of the study, was collected. A brief description of both study cohorts is written below.

### The CARRÉ study

The CARRÉ (CARdiovascular research and RhEumatoid arthritis) study was initiated in 2000 with the purpose of investigating CV disease and its risk factors in patients with longstanding RA. As previously described by van Halm et al.(12), patients were eligible for participation if they were registered at the Jan van Breemen Institute (Reade since 2009) in Amsterdam, the Netherlands, fulfilled the 1987 American College of Rheumatology classification criteria, were diagnosed with RA between 1989 and 2001, and were aged between 50 and 75 years. Patient enrolment was done between January 2001 and January 2002. In total 353 patients with RA were followed prospectively for 15 years. Study assessments were performed at baseline, 3 years (2004 - 2005), and 10 years of follow up (2010 - 2011). Participants were called for a CV disease questionnaire in 2015 (15 years of follow up) to assess the occurrence of CV events during the study period. All reported events since the start of the study were confirmed with medical records.

### The Hoorn study

The Hoorn study is a Dutch cohort study of glucose metabolism and other cardiovascular risk factors that began in 1989 (13). The cohort and its baseline measurements have been described in detail previously (14). Briefly, a random selection of 3,553 men and women 50–75 years old was taken from the population register. A total of 2,540 (71.5%) agreed to participate, and after the exclusion of 56 non-caucasian participants, the Hoorn Study population comprised 2,484 men and women. All Hoorn participants were subject to an extensive and repeated cardiovascular screening program similar to that used in our CARRÉ study. The local Medical Ethics Committee approved both studies (METc VUmc, Amsterdam, The Netherlands, 2001.198) and all participants gave their written informed consent at the baseline visit. An overview of the two cohorts is shown in figure 1.

### Assessment of RA-related values

At baseline, demographic data, medical history, family history, and medication use of all patients with RA were recorded. Additionally, the Health Assessment Questionnaire (HAQ) was performed and a

Disease Activity Score of 28 joints (DAS28) was calculated. IgM-rheumatoid factor (IgM-RF), anti–citrullinated protein antibody (ACPA) were only assessed at baseline. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and the presence of erosions in hands and feet with radiographs were assessed at all visits.

**Assessment of traditional CV risk factors**

CV risk factors were assessed for all subjects according to identical protocols in both studies, as described previously (4). The assessments included smoking status, systolic and diastolic blood pressure (BP), body mass index (BMI, weight/height$^2$ in kg/m$^2$), waist to hip ratio and in fasting blood samples total cholesterol (TC), high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc), triglycerides (TG), TC/HDLc ratio, glucose, HbA1c, and creatinine. Hypertension was defined as a systolic BP above 140 mmHg and/or a diastolic BP above 90 mmHg and/or current use of antihypertensive agents. DM was assessed in both study cohorts according to the 1999 World Health Organization criteria.(15) Patients were grouped according to fasting glucose levels into normal fasting glucose <6.1 mmol/L (<110 mg/dL), impaired fasting glucose (IFG) or insulin resistance ≥6.1 – <7.0 mmol/L (110 – 125 mg/dL) and DM if glucose ≥ 7.0 mmol/L (≥126 mg/dL) or treated with glucose lowering agents.

**Assessment of CV disease**

Prevalent CV disease at baseline and incident fatal and non-fatal CV events at follow up were registered separately according to the International Statistical Classification of Diseases and Related Health Problems 9th revision (ICD-9 codes, 410.0 – 410.9, 435.9, 436, 443.9 and 798). CV disease was defined as a verified medical history of coronary heart disease (i.e. myocardial infarction, percutaneous coronary intervention, coronary angiography with significant stenosis, stent placement or coronary artery bypass graft), cerebral arterial disease (e.g. cerebrovascular accident, transient ischemic attack or carotid endarterectomy) or peripheral arterial disease (e.g. ankle brachial pressure index <0.50, peripheral arterial reconstructive surgery or limb amputation). Sudden deaths were only considered to be CV mortality when this was confirmed by autopsy. After study entry, participants were censored after the first new fatal or non-fatal CV event or death due to other reasons. CV events before baseline (prevalent CV disease) in medical records of study participants were registered separately for additional correction in statistical analyses, but were not used as new incident CV event cases for the primary outcome. The remaining patients were censored at study cessation time: March 1, 2015. Only the first CV event during follow up was recorded. Patients that were lost to follow up were censored at date of their last (event-free) follow up visit. In order to extract data on the

occurrence of CV events of the patients lost to follow up, medical records were searched for the most recent medical status.

**Statistical analysis**

The baseline characteristics of both study cohorts were compared with parametric and nonparametric tests as appropriate. Incidence rates for fatal and non-fatal CV events were calculated per 100 person years. The risk of developing CV events was compared between patients with RA without DM, the non-diabetic general population and patients with DM but without RA by calculating hazard ratios (HR) with Cox proportional hazards models. These hazard models were adjusted for potential confounders identified at baseline and in earlier studies (4). Prevalent CV disease was not excluded from the analyses, except where stated otherwise. Figure 2 was created using the corrected group prognosis method as described by Ghali et al. (31) Several hazard models were made (table 3): the first model corrected adjusted for age and gender; the second model additionally adjusted corrected for systolic blood pressure, use of antihypertensive agents, total cholesterol, high-density lipoprotein cholesterol, statin use, smoking in pack years, body mass index and aspirin use. The HR were first calculated for all patients. In the secondary analysis, patients with prevalent CV disease were excluded. Additionally, the risk of developing CV events in patients with both RA and type 2 DM was compared to the other groups of patients (table 4). All analyses were performed with the software package IBM SPSS statistics (version 19, Armonk, New York). A p-value of less than 0.05 was considered as statistically significant.

## Results

### Baseline characteristics of both study populations

Of the 353 patients with RA at baseline, 326 patients were included in the primary analyses (figure 1). Their baseline characteristics as well as those from the Hoorn study reference cohort are shown in table 1. Of these, 27 were lost to follow up later on in the study due to migration, not wishing to participate due to a high burden or death. The median follow up duration was 11 years, with a minimum of 2 months and a maximum of 15 years. The majority of the RA patients was female (65%) with a mean age of 63 ± 7 years. The median disease duration was 7 (4 – 10) years with a mean DAS28 score of 3.9 ± 1.3. 236 (72%) patients were IgM-RF positive, 168 (52%) were ACPA positive and 263 (81%) had erosions in the hands or feet. Patients with RA were slightly older than the reference cohort and had more often prevalent CV disease (15% vs. 11%), hypertension (61% vs. 32%), a longer cumulative exposure to smoking, and more often used antihypertensive drugs, statins or aspirin.

### New CV events in RA vs. the general population

In the CARRÉ study, 95 patients developed a CV event during a median follow up period of 11 years (range: 2 months to 15 years) and a total follow up time of 2973 patient years, resulting in a CV disease incidence rate of 3.20 per 100 person years (table 2). In the Hoorn study, 257 participants developed a CV event during 12 years of median follow up (range: 1 month to 12 years) and a total follow up time of 18874 patient years, resulting in a CV disease incidence rate of 1.36 per 100 person years (table 2). The occurring CV event subtypes are described in supplementary table 1. Age and sex adjusted Cox regression analyses showed a HR of 1.93 (95%CI 1.51 – 2.45, *P*<0.01) for CV events in RA (table 2). Additional adjustment for CV risk factors resulted in a HR of 1.89 (95%CI 1.40 – 2.46, *P*<0.01) (table 2). Adjustment for prednisone use did not affect the HR significantly (data not shown). Exclusion of patients with prevalent CV disease at baseline resulted in comparable HRs (table 2).

### New CV event in RA and DM vs. the reference population and in RA vs. DM

Before conducting these analyses, RA patients with an impaired fasting glucose (n=26) or already diagnosed with DM (n=22) were excluded from the CARRÉ study and patients with an impaired fasting glucose (n=206) were excluded from the Hoorn study. Cox regression analyses comparing incident CV events were performed with the remaining participants grouped into nondiabetic RA (n=278), DM (n=162) and the nondiabetic reference population (n=1501, table 3). The HR was increased for RA (HR 2.07, 95%CI 1.57 – 2.72, *P*<0.01) and DM (HR 1.51, 95%CI 1.02 – 2.22, *P*=0.04) in the age and sex adjusted model (table 3, figure 2). After adjustment for CV risk factors, the HR (1.82, 95%CI 1.32 – 2.50, *P*<0.01) remained significantly increased in RA while it was not significant in DM (HR 1.28, 95%CI

0.85 – 1.92, *P*=0.25) (table 3, figure 2), with similar results after exclusion of patients with prevalent CV disease (table 3). The adjusted survival curves of the non-diabetic reference population, participants with DM, and nondiabetic participants with RA are shown in figure 2. In addition, a direct comparison between participants with RA (n=278) and participants with DM (n=162) showed a higher HR for CV disease in RA when compared to DM (age and gender adjusted HR 1.64, 95%CI 1.07 – 2.53, P=0.02).

**New CV events in subgroups of RA, insulin resistance and DM vs. the general population**

The risk of developing CV events was compared between the non-diabetic general population (n= 1501), individuals with insulin resistance (IR, n= 206), individuals with DM (n= 162), participants with RA but without IR or DM (n=278 ), study participants with RA and IR (n=26 ), and participants with RA and DM (n=22 ). Compared to the non-diabetic general population, patients with RA and IR resp. DM had the highest risk of developing a CV event when the hazard model was corrected for age and gender followed by the other RA patients. Results were similar after additional correction for systolic blood pressure, antihypertensive agents, total cholesterol, HDLc, statin use, smoking, body mass index, aspirin use and prevalent CV disease (table 4).

**Discussion**

In our second report on this cohort, now with a median follow up of 11 years, the increased risk of CV disease in RA already seen after 3 years of follow up (4) was confirmed, now at a level more than double that of the non-diabetic general population. Traditional CV risk factors, such as hypertension, smoking, older age and previous CV disease partially explained this increased risk. However, the Cox proportional hazard models adjusted for these risk factors still showed an almost twofold increased CV risk in participants with RA. In participants with DM, the increased CV risk was almost fully explained by traditional CV risk factors. In RA, high-grade systemic inflammation most likely amplifies CV risk, as suggested previously.(3-5) Recently, Curtis et al. reported the highest incidence rate of acute myocardial infarction in patients with RA and DM, followed by patients with DM only, RA only and neither RA or DM. (29) We found similar results (highest HR) for participants with RA and IR or DM, but in our study, participants with RA only had a higher CV disease risk than participants with DM only. This might be explained by differences in study design and population and definitions of CV disease outcome. More importantly, both studies underline and establish that RA is a risk factor for the development of CV disease.

Interestingly, although we had a low number of observations, the risk of IR or DM appeared additive to that of RA, suggesting that in such patients risk factors should be approached aggressively. In participants with RA, TC, LDLc and triglycerides were lower than in the non-diabetic general population, while HDLc was higher. In the past, several publications have described this phenomenon as the 'lipid paradox', in which above mentioned observation is not translated into a lower, but paradoxically into a higher CV risk in RA patients.(17-19) However, we identified an increased CV disease risk in RA, regardless of the effect of these lipid changes on this CV risk, as we adjusted for TC, HDLc and statin use in our analyses. Optimal treatment of RA results in a normalization of lipid levels in these patients.(20-23) Unfortunately, this study also demonstrates that, although patients with RA have an increased presence of certain known risk factors for CV disease, only a small proportion of RA patients is receiving appropriate treatment with antihypertensive agents and statins. This finding is also in line with other studies,(24-27) suggesting that appropriate management of lifestyle factors and CV risk factors is lacking in these patients. Possible explanations could be that local CV risk management programs are ineffective or that patients and physicians are unaware of the magnitude of this risk. In addition, current CV risk assessment tools are inaccurate and risk assessment is performed using general population algorithms (e.g. SCORE and Framingham Risk Score). Some risk factors, such as lipids, are influenced by inflammation and are not an appropriate indicator for CV risk during periods of active disease.(19) Therefore, CV risk algorithms that accurately predict CV risk in RA as well as multidisciplinary CV risk assessment and management are certainly of additional value.

Above all, creating awareness of this increased CV risk among patients and clinicians is of great importance.

The major strength of our study is its long follow up duration in which the occurrence of both fatal and non-fatal CV events were recorded in patients with RA and in the general population. Our previous study had a follow up duration of only 3 years, with few events, resulting in limited power, but in the current study the long term observation and the number of events was sufficient to overcome this. However, the present study also has some limitations. The Hoorn study was conducted approximately 10 years before the CARRÉ study. The definition of certain diseases, their assessment, and management may have changed during this period. This may have influenced our results. Additionally, CV disease incidence has declined over the last decades in the Netherlands which could translate into less incident CV disease in the patient with RA (28). However, comparing both groups would in this case only lead to an underestimation of the CV risk in patients with RA. Additionally, the Hoorn study may have included some patients with RA which we could not identify due to insufficient data, but this would also only result in an underestimation of the CV risk in RA. Another important matter is that the prevalence of MTX and biologic treatment at baseline is not representative of the current clinical practice. Treatment guidelines have changed over the last decade and this could have influenced the CV disease incidence in the RA population. However, the effect of antirheumatic treatment on CV disease risk in patients with RA was not the research question of this study.

In conclusion, our study demonstrates a more than twofold higher CV risk in participants with RA when compared with the non-diabetic general population. In this study, this risk is even higher than the CV risk of patients with DM. In accordance with our previous study from 2009 (4), adjustment for CV risk factors still results in a significant residual CV disease risk for patients with RA, indicating that systemic inflammation is likely an independent contributor to CV risk in RA. This underscores that both optimal anti-inflammatory treatment of RA as well as effective CV risk management are likely of major importance to reduce CV risk in these patients.

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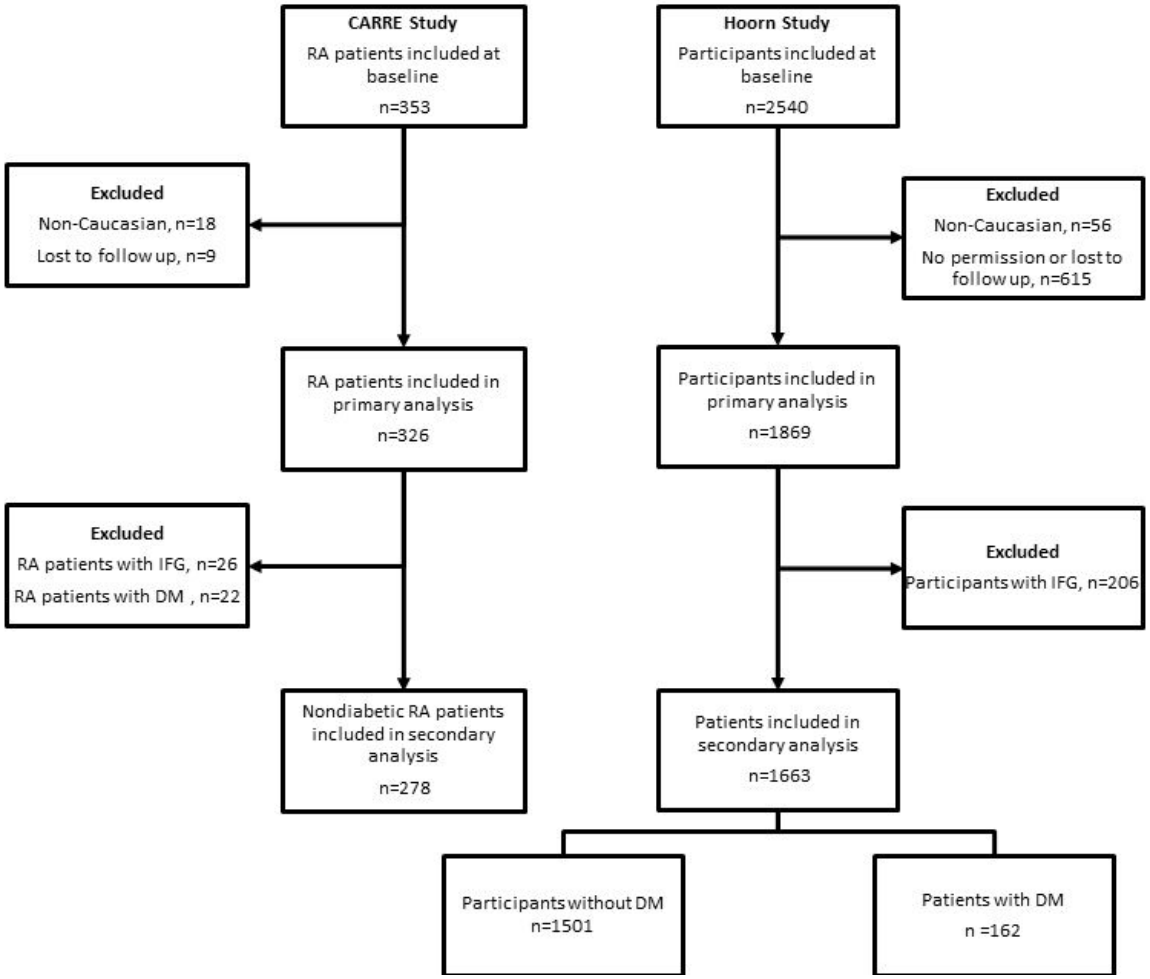
**Figure 1.** Study design of the CARRÉ and Hoorn study cohorts




*CARRÉ= Cardiovascular Research and Rheumatoid Arthritis, IFG= impaired fasting glucose, DM= type 2 diabetes mellitus, RA= rheumatoid arthritis.*

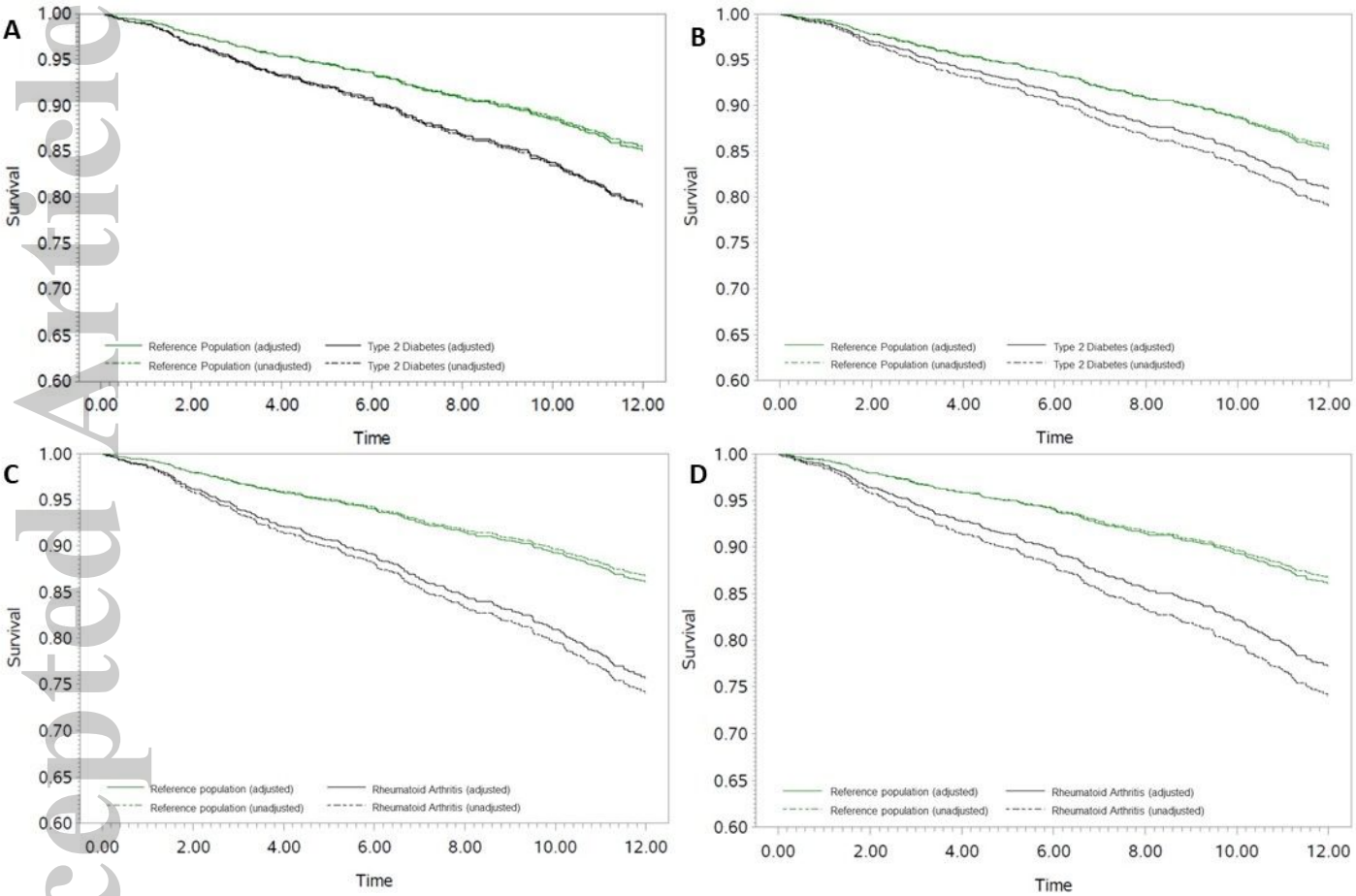



***Figure 2.*** *Survival curves of participants with type 2 diabetes mellitus (black) vs. the non-diabetic reference population (green), adjusted for age, sex (A), and traditional cardiovascular risk factors (B); non-diabetic participants with rheumatoid arthritis (black) vs. the non-diabetic reference population (green), adjusted for age, sex (C) and traditional cardiovascular risk factors (D).*

**Table 1.** Patient characteristics of the RA population and the reference cohort at baseline

| | RA population (n=326) | Reference cohort (n=1869) |
|---|---|---|
| Demographics | | |
| Age, years | 63 ± 7* | 62 ± 7 |
| Women, no. (%) | 212 (65)* | 976 (52) |
| Median inclusion year | 2002 | 1991 |
| Follow up duration, years | 11.2 (6.1 – 12.4) | 12 (9.5 – 12.0) |
| Cardiovascular risk factors | | |
| Previous CVD, no. (%) | 48 (15)* | 123 (7) |
| Hypertension, no. (%) | 200 (61)* | 601 (32) |
| Smoking, no. (%) | | |
| Never | 71 (22)* | 630 (34) |
| Former smoker | 159 (49)* | 666 (36) |
| Current smoker | 96 (29)* | 562 (30) |
| Pack years | 18 (2-38)* | 12 (0-28) |
| Glucose status, no. (%) | | |
| Normal fasting glucose levels | 283 (87) | 1501 (80) |
| IFG levels | 26 (8) | 206 (11) |
| DM | 16 (5) | 162 (9) |
| Known/newly diagnosed DM | 14/8 | 73/89 |
| Systolic BP, mmHg | 142 ± 20* | 135 ± 20 |
| Diastolic BP, mmHg | 81 ± 8* | 82 ± 10 |
| TC, mmol/L | 5.79 ± 1.13* | 6.63 ± 1.16 |
| HDLc, mmol/L | 1.45 ± 0.49* | 1.32 ± 0.37 |
| LDLc, mmol/L | 3.71 ± 1.04* | 4.59 ± 1.06 |
| Triglycerides, mmol/L | 1.32 (0.96 – 1.84) | 1.40 (1.00–1.90) |
| TC/HDLc ratio | 4.38 ± 1.55* | 5.36 ± 1.72 |
| Waist/hip ratio | 0.9 ± 0.1 | 0.9 ± 0.1 |
| Body mass index, kg/m$^2$ | 26.7 ± 4.8 | 26.5 ± 3.4 |
| Medication, no. (%) | | |
| Antihypertensive drugs | 84 (26)* | 373 (20) |
| Statins | 37 (11)* | 29 (2) |
| Aspirin | 54 (17)* | 62 (3) |
| RA-related factors | | |
| Age at RA diagnosis, years | 55 ± 8 | - |
| Disease duration, years | 7 (4 – 10) | - |

| | | |
|---|---|---|
| IgM-RF ≥30 U/ml, no. (%) | 236 (72) | - |
| ACPA ≥50 kU/l, no (%) | 168 (52) | - |
| Erosion on radiographs, no. (%) | 263 (81) | - |
| DAS28, range 0-10 | 3.9 ± 1.3 | - |
| NSAIDs, no (%) | 218 (67) | - |
| Biologic agents, no. (%) | 33 (10) | - |
| Methotrexate, no. (%) | 195 (60) | - |
| Prednisone, no. (%) | 54 (17) | - |
| Sulfasalazine, no. (%) | 53 (16) | - |
| Hydroxychloroquine, no. (%) | 24 (7) | - |
| Leflunomide, no. (%) | 27 (8) | - |
| Other DMARD, no. (%) | 20 (6) | - |

*Continuous variables are presented as mean ± SD or as median (IQR). Categorical and dichotomous variables are presented as numbers and/or percentages. *Significantly different from the general population. CVD= cardiovascular disease, BP= blood pressure, TC= total cholesterol, LDLc= low-density lipoprotein cholesterol, HDLc= high-density lipoprotein cholesterol,* pack years*= (packs smoked per day)*(years as a smoker), IFG= impaired fasting glucose, DM= type 2 diabetes mellitus, RA= rheumatoid arthritis, IgM-RF= immunoglobulin M rheumatoid factor, ACPA= anti–citrullinated protein antibody, DAS28= Disease Activity Score, DMARD= disease-modifying antirheumatic drug*

**Table 2.** Hazard ratios for new CV events in patients with RA vs. the reference population

| | RA population | Reference population | P-value |
|---|---|---|---|
| All patients, no. | 326 | 1869 | |
| Total follow up, years | 2973 | 18874 | |
| Fatal and nonfatal CV events, no. | 95 | 257 | |
| Incidence per 100 person-years | 3.20 | 1.36 | |
| Hazard Ratio RA vs. reference cohort | | | |
| Model 1* | 1.93 (1.51 – 2.45) | 1.00 | <0.01 |
| Model 2# | 1.89 (1.40 – 2.46) | 1.00 | <0.01 |
| Patients with prevalent CVDΔ excluded, no. | 278 | 1746 | |
| Total follow up, years | 2627 | 18008 | |
| Fatal and nonfatal CV event, no. | 69 | 225 | |
| Incidence per 100 person-years | 2.63 | 1.25 | |
| Hazard Ratio RA vs. reference cohort | | | |
| Model 1* | 1.75 (1.31 – 2.32) | 1.00 | <0.01 |
| Model 2# | 1.96 (1.45 – 2.66) | 1.00 | <0.01 |

*Adjusted for age and sex. #Adjusted for age, sex, systolic blood pressure, antihypertensive agents, total cholesterol, high-density lipoprotein cholesterol, statins, smoking in pack years, body mass index, diabetes mellitus, and aspirin

ΔCVD according to the International Classification of Diseases criteria. CV= cardiovascular, RA= rheumatoid arthritis, CVD= cardiovascular disease.

**Table 3.** New CV events in RA and DM vs. the reference population

| | HR | 95% CI | P-value |
|---|---|---|---|
| **All patients** | | | |
| *Model 1* | | | |
| Nondiabetic population | 1.00 | Reference | - |
| DM | 1.51 | 1.02 – 2.22 | 0.04 |
| Nondiabetic patients with RA | 2.07 | 1.57 – 2.72 | <0.01 |
| *Model 2* | | | |
| Nondiabetic population | 1.00 | Reference | - |
| DM | 1.28 | 0.85 – 1.92 | 0.25 |
| Nondiabetic patients with RA | 1.82 | 1.32 – 2.50 | <0.01 |
| **Patients with prevalent CVD excluded** | | | |
| *Model 1* | | | |
| Nondiabetic population | 1.00 | Reference | - |
| DM | 1.42 | 0.92 – 2.21 | 0.12 |
| Nondiabetic patients with RA | 1.82 | 1.32 – 2.50 | <0.01 |
| *Model 2* | | | |
| Nondiabetic population | 1.00 | Reference | - |
| DM | 1.15 | 0.72 – 1.84 | 0.56 |
| Nondiabetic patients with RA | 1.96 | 1.39 – 2.78 | <0.01 |

Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, systolic blood pressure, antihypertensive agents, total cholesterol, high-density lipoprotein cholesterol, statins, pack years, body mass index and aspirin. RA= rheumatoid arthritis, DM= type 2 diabetes mellitus, HR= hazard ratio, 95% CI= 95% confidence interval, CVD= cardiovascular disease.

**Table 4.** New CV events in RA with IR and DM vs. the reference population.

| | *HR* | *95% CI* | *P-value* |
|---|---|---|---|
| **All patients** | | | |
| *Model 1* | | | |
| Reference population, normal glucose tolerance | 1.00 | Reference | - |
| Insulin resistance | 1.46 | 1.04 – 2.07 | 0.03 |
| DM | 1.51 | 1.03 – 2.23 | 0.04 |
| RA | | | |
| + Normal glucose tolerance | 2.08 | 1.58 – 2.74 | <0.01 |
| + Insulin resistance | 2.70 | 1.33 – 5.49 | <0.01 |
| + DM | 2.23 | 1.04 – 4.75 | 0.04 |
| *Model 2* | | | |
| Reference population, normal glucose tolerance | 1.00 | Reference | - |
| Insulin resistance | 1.18 | 0.82 – 1.70 | 0.37 |
| DM | 1.30 | 0.87 – 1.95 | 0.20 |
| RA | | | |
| + Normal glucose tolerance | 1.89 | 1.37 – 2.56 | <0.01 |
| + Insulin resistance | 2.67 | 1.30 – 5.46 | <0.01 |
| + DM | 2.21 | 1.01 – 4.80 | 0.046 |

Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, systolic blood pressure, antihypertensive agents, total cholesterol, high-density lipoprotein cholesterol, statins, smoking in pack years, body mass index, aspirin and prevalent CV disease. RA= rheumatoid arthritis, DM = type 2 diabetes mellitus, HR = hazard ratio;,95% CI = 95% confidence interval, CV= cardiovascular.