Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term outcome

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Aims
Despite a wealth of studies describing an increased incidence of acute coronary syndromes (ACSs) in rheumatoid arthritis (RA), considerably less is known about the clinical characteristics and their association with short-term outcome of such ACS. The aims of this study were therefore to investigate clinical characteristics and case-fatality rates following ACS in patients with RA.

Methods and results
We compared the clinical presentation of incident ACS between 2007 and 2010 and their short-term mortality in a cohort of 1135 subjects with prevalent RA and in a cohort of 3184 matched general population comparators. Rheumatoid arthritis subjects more frequently presented with sudden cardiac death, ST-segment elevation myocardial infarctions, had higher levels of troponin and higher frequencies of in-hospital complications compared with the general population comparators. Furthermore, the short-term mortality was higher among RA-associated ACS (7-day hazard ratio (HR) = 1.65 [95% CI 1.32–2.08]; 30-day HR = 1.57 [95% CI 1.30–1.89]), which were somewhat attenuated but remained statistically significantly increased following adjustment for previous comorbidities, demographics, and educational level (7-day HR = 1.50 [95% CI 1.19–1.90]; 30-day HR = 1.43 [95% CI 1.18–1.72]), and for ACS type (7-day HR = 1.44 [95% CI 1.14–1.82]; 30-day HR = 1.36 [95% CI 1.13–1.64]).

Conclusion
Patients with prevalent RA suffer more severe ACSs compared with the general population and also have poorer outcomes after the events, which can only partly be explained by increased event severity.

Keywords
Rheumatoid arthritis • Acute coronary syndrome • Mortality • Epidemiology

Clinical summary
Rheumatoid arthritis is associated with an increased risk of ACS, but information on clinical characteristics and short-term outcomes is limited. Our results suggest that patients with RA suffer from more severe ACS compared with the general population and also have an increased short-term mortality risk. These findings emphasize the importance of awareness of this group of patients when assessing and identifying high-risk ACS patients in clinical practice.

Introduction
Cardiovascular diseases (CVDs) are the main driver of the excess morbidity and pre-term mortality in patients with rheumatoid arthritis (RA).1–3 Whereas the increased incidence of ACS in RA has been well-researched,4 less is understood about the clinical characteristics and outcomes of acute coronary events in RA, especially since the few available data on phenotype, in-hospital treatment, and short-term outcomes such as case fatality, recurrence, and complications of acute coronary events in RA are contradictory.5–8

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With respect to clinical phenotype of ACS, patients with RA have been reported to describe typical angina symptoms less frequently, more often present with collapse or sudden cardiac death, and display signs of silent myocardial infarction (MI). One study reported that patients with RA and MI received in-hospital treatment with reperfusion therapy less frequently compared with controls, while another study reported no differences.

Reports on outcomes after ACS have described no differences in case fatality, as well as decreased, short-term survival in RA subjects compared with controls. Any decreased survival may be a consequence of an atypical presentation, more severe events, and/or discrepancies in the treatment(s) received.

Despite these indications of phenotypical differences, and of poorer outcomes, few studies have researched clinical ACS characteristics and prognostic outcomes in RA in-depth. In terms of subtypes of ACS, no study have addressed whether patients with RA are more prone to develop specific types of ACS. This is clinically important as ST-segment elevation myocardial infarctions (STEMIs) are more severe than non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). The aims of this study were therefore to investigate (i) clinical characteristics and (ii) case-fatality rates following ACS in a large, contemporary, and population-based cohort of prevalent patients with RA, and (iii) to assess the extent to which differences in clinical characteristics might explain any differences in case fatality.

**Methods**

**Design**

We performed a nationwide population-based cohort study of contemporary patients with prevalent (ongoing) RA with matched general population comparators, based on prospectively recorded register data.

**Setting**

The decentralized and publicly funded Swedish healthcare system enables equal access to all healthcare services, including specialized care for chronic diseases such as RA, for all residents. Beyond an upper annual spending limit of SEK 1100 (~USD 130 (13 July 2015)), all subsequent drug expenditures are provided free of charge. All residents are assigned a unique personal identity number (PIN) that can be used for linkage of different national registers and other data sources.

**Data sources used to identify the study population and outcomes**

With the PIN as key, several nationwide registers were linked to identify a cohort of patients with prevalent RA, matched population comparators, and to obtain all relevant information on exposure, outcomes, and covariates. Data on hospitalizations were collected from the inpatient-part of the national patient register (NPR). National patient register is a nationwide population-based register, and contains information on in-hospital care since 1964 with full coverage since 1987. National patient register also contains one outpatient part, initiated in 2001, including visits in non-primary care. National patient register holds information on admission and discharge dates and diagnoses coded according to the Swedish contemporary version of International Classification of Disease (ICD). Information on mortality was collected from the cause-of-death register (CDR) that holds information on dates and cause of death coded according to ICD. Information on dispensed pharmacotherapies was collected from the prescribed drug register (PDR), including information on all dispensed drugs from Swedish pharmacies since July 2005. Drugs are coded by Anatomical Therapeutic Chemicals (ATC) classifications and reported with dose and dispensed quantity. National patient register and PDR were used to identify pre-existing comorbidities and fulfilled prescriptions of pharmacotherapies to define underlying comorbidities of the cohorts (for ICD and ATC codes used, please be referred to Supplementary material online, Table S1). RIKS-HIA is a national quality of care register for coronary intensive care based on admission to cardiac intensive care units (CICUs). RIKS-HIA includes information on baseline characteristics, symptoms, in-hospital examinations, treatments, interventions, complications, and discharge status and includes over 100 variables with varying degree of coverage for respective variable (full protocol available at the register’s World Wide Web site (www.riks-hia.se)). RIKS-HIA was used to retrieve information on clinical presentation at admission, in-hospital treatments, complications, and status at discharge. The indication for admission to CICUs for elderly varies between regions, which is why the coverage (of all ACS) varies across geographic regions and for patients over the age of 80 is generally lower. Approximately 70% (65.5% of RA cases vs. 69.2% of population cases) of our study subjects who experienced an acute coronary event were included in RIKS-HIA (median age of individuals included was 73 years [interquartile range (IQR) 65–80], and of those not included the median age was 80 years [IQR 73–84]). A total of 49.0% of the RA cases over 80 and 54.3% of the population cases were included in RIKS-HIA. The Total Population Register, provided by Statistics Sweden (SCB), contains demographic information, such as sex, age, civil status, dates of migrations, etc., on all Swedish residents and was used to identify general population comparators for the RA subjects. Data on educational level (categorized as <9, 10–12, and >12 years of schooling), a strong proxy for socioeconomic status was collected from the integrated database for labour and education at SCB. An overview of all included registers is provided in Supplementary material online, Figure S1.

**Study population**

**Prevalent rheumatoid arthritis**

Rheumatoid arthritis is diagnosed based on criteria, including clinical signs, inflammatory parameters, and the presence of autoantibodies, developed by American College of Rheumatology and revised most recently in 2011. In Sweden, patients with RA are treated by rheumatologists. Similar to previous study, the exposed cohort of RA patients was defined as all individuals >18 years of age (no upper age limit) with greater than or equal to two visits at in- or out-patient clinics with a diagnosis of RA, whereof at least one visit should be at an internal medicine or rheumatology department or listed in the Swedish rheumatology quality register. This algorithm to define RA based on diagnosis codes from the NPR has previously been reported to have a predictive value of around 90%. Furthermore, at least one visit should be in the year 2006, 2007, 2008, or 2009 to be defined as having prevalent (actively monitored) RA in that particular year. Between 31 000 and 34 000 subjects were identified with prevalent RA each year (Figure 1).

**General population comparators**

The Swedish population register was used to randomly select up to five individuals, matched on year of birth, sex, educational level, and area of residency, to each RA patient. Individuals with a diagnosis of RA prior to the year of matching were excluded (Figure 1).
Identification of incident first-time acute coronary syndrome

All individuals with a diagnosis of ACS (identified through linkage to the NPR) prior to the start of follow-up were excluded. The RA cohort and the comparison cohort were followed through linkage to NPR during the year following the year of identification (the year an individual was defined and classified as having prevalent RA, i.e. at least one visit with a diagnosis of RA) to identify all individuals with incident ACS (cases). Acute coronary syndrome included diagnoses of MI (transmural MI ICD-10 I21.0 I21.1 I21.2 I21.3; sub-endocardial MI ICD-10 I21.4; unspecified MI ICD-10 I21.9) and UA (ICD-10 I20.0) as identified in the NPR; these ICD codes indicating ACS have a positive predictive value of 95%.

Secondary outcomes

To describe the proportion of subjects suffering out of hospital sudden cardiac death, all individuals not listed with incident ACS in NPR, but with a diagnosis of ACS in CDR, were identified. As an assessment of ischaemic heart disease (IHD), congestive heart failure (CHF), and arrhythmias were performed to identify the proportion of deaths due to these causes (for ICD codes used, please be referred to Supplementary material online, Table S1).

In-hospital cardiac care

Linkage with RIKS-HIA identified all study subjects with incident ACS in NPR who were also registered in RIKS-HIA within a time interval of −10 to 10 days after the ACS diagnosis in NPR. For these individuals, information on ACS characteristics from RIKS-HIA was retrieved. For characterization of the event data on clinical presentation (symptoms, blood pressure, heart rate, Killip class, ECG registration, and biomarkers) at admission, in-hospital treatment (Reperfusion treatment if diagnosed with STEMI and Anticoagulants if diagnosed with NSTEMI), complications, and discharge diagnosis (STEMI or NSTEMI as registered by cardiologist based on ECG changes and laboratory data) were collected, compiled, and analysed.
unrecognized or silent MI, all subjects with a registered diagnosis of ‘old infarction’ (ICD-10 I25.5) prior to the start of follow-up were also identified.

**Statistical analyses**

Descriptive baseline data were summarized and presented as proportions, means, and medians as appropriate. The type of ACS, based on the ICD code used to identify the event in the NPR, was presented along with the descriptive data. The differences between the groups were tested using $\chi^2$ tests for dichotomous and $t$-test for normally distributed continuous and Mann–Whitney U test for ordinal/non-normally distributed continuous variables.

All-cause mortality during follow-up was analysed using the Kaplan–Meier method. All-cause and cause-specific relative risk of death was analysed using Cox regression models adjusted for age and sex. The models were stepwise adjusted for potential confounders using a propensity score (PS), calculated using a multivariate model including demographics (age and sex) and pre-existing comorbidities and pharmacotherapies, and ACS type based on ICD code registered. Pre-existing comorbidities and pharmacotherapies were defined as a diagnosis in the NPR or a dispensed drug in the PDR more than 90 days prior to the ACS to avoid potential influence from the event itself. A list of the pre-existing comorbidities and pharmacotherapies included in the PS are found in the Appendix. As a sensitivity analyses, all individuals with information within RIKS-HIA on type of ACS (as categorized in RIKS-HIA, i.e. STEMI vs. NSTEMI) were analysed in a separate Cox regression model adjusted for age, sex, PS, and ACS type.

All variables used to characterize the event were compiled and presented as percentages, means (if normal distribution), medians (if non-normal distribution), and with the number of individuals with information available for each variable. For differences in dichotomous and normally distributed continuous variables, logistic regression models adjusted for sex and age and with robust standard errors accounting for potential imbalance due to controls potentially occurring multiple times were calculated to obtain a two-tailed $P$-value. For ordinal and non-normal distributed variables, Mann–Whitney $U$ test was used to obtain a two-tailed $P$-value. A $P$-value $< 0.05$ was considered statistically significant.

All analyses were carried out with SAS software package version 9.3 (SAS Institute, Cary, NC, USA).

**Results**

In total, 1135 (0.9%) of the RA patients and 3184 (0.5%) of the comparators were registered with an incident ACS between 1 January 2007 and 31 December 2010 and remained eligible for analyses (Figure 1). During the same period, 248 (0.20%) of the RA patients and 785 (0.13%) of the comparators, not registered with an incident ACS in the NPR, died from ACS or sudden cardiac death out of hospital. For the purpose of this analysis, these individuals were not included in the groups of cases with incident ACS. Of the RA cases, 35 (3.08%) compared with 83 (2.61%) of the population cases had a pre-existing diagnosis of old infarction, interpreted as an unrecognized MI (UMI), prior to the start of follow-up.

Demographic data, pre-existing comorbidities, and pharmacotherapies for RA and population cases with ACS are presented in Table 1. Sex and age distributions remained similar from the original matching for RA cases and comparators. Of the pre-existing CVDS, the prevalence of stable angina pectoris (17% vs. 15%), thrombo-embolic disease (10% vs. 7%), and CHF (15% vs. 10%) was significantly higher among the RA cases. For the other comorbidities, the prevalence of chronic obstructive pulmonary disease (11% vs. 7%) was significantly higher among RA cases compared with population cases. The use of warfarin, $P_{12}$-inhibitors, diuretics, and $\beta$-blockers up to 3 months prior to the ACS event was also significantly more prevalent among RA cases, whereas dispensed lipid-lowering drugs and oral antidiabetics were higher among population cases.

**Acute coronary syndrome characteristics and in-hospital care (data from RIKS-HIA)**

Information on symptoms and clinical signs at admission is presented in Table 2. Rheumatoid arthritis cases did not differ compared with population cases regarding presenting symptoms. Approximately 80% of the RA cases and the population cases reported chest pain as main symptom at admission. Similarly, the median reported time from symptom-onset until admission at ER was 3 h in both groups. The heart rate and was also similar at admission, whereas both systolic and diastolic blood pressure were significantly lower among RA cases compared with population cases. Rheumatoid arthritis cases more often presented with ST elevation (35.3% vs. 30.5%) at admission ECG compared with controls, and had higher maximum levels of troponin compared with controls.

Of the study subjects diagnosed with STEMI, RA patients more often received any primary reperfusion therapy [thrombolysis, primary percutaneous coronary intervention (PCI), coronary artery bypass graft, and acute coronary angiography] compared with population cases (74.1 vs. 66.2%). Out of study subjects receiving primary reperfusion therapy, 62.3% of the RA subjects compared with 54.4% of the comparators received PCI. Treatment with parenteral anticoagulants did not differ between RA cases and population cases diagnosed with NSTEMI (Table 3).

During the hospitalization for the acute coronary event, RA cases more frequently received intravenous diuretics and inotropic agents and were also more often diagnosed with cardiogenic shock compared with population cases. At discharge, a larger proportion of RA cases were diagnosed with STEMI compared with population cases (Table 4).

**Case fatality**

Mortality rates, in all cases with a hospitalization of incident ACS (Figure 2, Table 5), were higher among the RA cases compared with population cases both during the first week and the first month following the ACS. Within the first week following the ACS event, 10.4% of the RA cases vs. 6.7% of the population cases died (age/sex-adjusted HR = 1.65 [95% CI 1.32–2.08]; age/sex- and PS-adjusted HR = 1.50 [95% CI 1.19–1.90]; age/sex-, PS-, and ACS-type adjusted HR = 1.44 [1.14–1.82]). The proportion of deaths within the first month following ACS was 15.7% among RA cases vs. 10.7% of population cases (age/sex-adjusted HR = 1.57 [95% CI 1.30–1.89]; age/sex- and PS-adjusted HR = 1.43 [95% CI 1.18–1.72]; age/sex-, PS-, and ACS-type adjusted HR = 1.36 [1.13–1.63]). The majority of all death (90% among RA cases and 91% among population cases during the first month of follow-up) was related to cardiac mortality (IHD, CHF, and/or arrhythmias). The HR for cause-specific mortality remained similar to...
Table 1  Demographics, year and type of incident acute coronary syndrome, and pre-existing comorbidities and pharmacotherapies occurring in a cohort of Swedish patients with rheumatoid arthritis and among matched general population controls

<table>
<thead>
<tr>
<th>Pre-existing comorbidity</th>
<th>RA cases (n = 1135)</th>
<th>Unexposed cases (n = 3184)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of ACS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmural MI</td>
<td>248 (21.9)</td>
<td>648 (20.4)</td>
</tr>
<tr>
<td>Sub-endocardial MI</td>
<td>414 (36.5)</td>
<td>1158 (36.4)</td>
</tr>
<tr>
<td>Unspecific MI</td>
<td>363 (32.0)</td>
<td>906 (28.5)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>103 (9.1)</td>
<td>468 (14.7)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>7 (0.6)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td><strong>Year of ACS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>333 (29.3)</td>
<td>802 (25.2)</td>
</tr>
<tr>
<td>2008</td>
<td>283 (24.9)</td>
<td>832 (26.1)</td>
</tr>
<tr>
<td>2009</td>
<td>277 (24.4)</td>
<td>808 (25.4)</td>
</tr>
<tr>
<td>2010</td>
<td>242 (21.3)</td>
<td>742 (23.3)</td>
</tr>
<tr>
<td><strong>Educational level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 9 years</td>
<td>602 (53.0)</td>
<td>1739 (54.6)</td>
</tr>
<tr>
<td>10–12 years</td>
<td>390 (34.4)</td>
<td>1057 (33.2)</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>124 (10.9)</td>
<td>344 (10.8)</td>
</tr>
<tr>
<td><strong>RA treatment 6–0 months prior ACS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>687 (60.5)</td>
<td>–</td>
</tr>
<tr>
<td>DMARD, any</td>
<td>648 (57.1)</td>
<td>–</td>
</tr>
<tr>
<td>DMARD, methotrexate</td>
<td>491 (43.3)</td>
<td>–</td>
</tr>
<tr>
<td>Biological drug</td>
<td>105 (9.3)</td>
<td>–</td>
</tr>
<tr>
<td>NSAID</td>
<td>749 (66.0)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Pre-existing CVD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable angina pectoris</td>
<td>197 (17.4)</td>
<td>468 (14.7)**</td>
</tr>
<tr>
<td>Cerebrovascular lesion</td>
<td>150 (13.2)</td>
<td>388 (12.2)</td>
</tr>
<tr>
<td>Venous thrombo-embolic disease</td>
<td>117 (10.3)</td>
<td>211 (6.6)**</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>114 (10.0)</td>
<td>286 (9.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>175 (15.4)</td>
<td>332 (10.4)**</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>10 (0.9)</td>
<td>33 (1.0)</td>
</tr>
<tr>
<td><strong>Pre-existing other comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, Type I</td>
<td>98 (8.6)</td>
<td>283 (8.9)</td>
</tr>
<tr>
<td>Diabetes, Type II</td>
<td>171 (15.1)</td>
<td>504 (15.8)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>124 (10.9)</td>
<td>221 (6.9)**</td>
</tr>
<tr>
<td>Renal failure, chronic</td>
<td>28 (2.5)</td>
<td>53 (1.7)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CVD, cardiovascular disease; DMARD, disease modifying antirheumatic drugs; IQR, interquartile range; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; SD, standard deviation.

*Based on the ICD diagnoses registered in the Swedish Patient Register (UA ICD I200, transmural MI ICD I210-I213, sub-endocardial MI ICD I214, unspecific MI ICD I219, reinfection ICD I22).

All pre-existing comorbidities/dispensed pharmacotherapies are defined as a diagnosis or fulfilled prescription in national patient registry or prescribed drug registry more than 3 months prior to the ACS. International Classification of Disease codes used in Supplementary material online.

**P < 0.001 based on χ² test for dichotomous, t-test for normally distributed continuous, and Mann–Whitney U test for ordinal/non-normally distributed continuous variables.

Discussion

In this large, nationwide population-based study based on prospectively recorded data on RA, ACS, treatments, and outcome, we observed a more severe clinical ACS phenotype among RA subjects compared with controls. We also detected an increased short-term mortality risk, which could only in part be explained by more severe ACS.
Previous studies investigating differences in the clinical phenotype of ACS in RA subjects compared with controls have often failed to demonstrate a difference.\textsuperscript{5–9} These studies have, however, been based on a small number of study subjects and provided limited information on the clinical event itself. McCoy \textit{et al}.\textsuperscript{8} did not find a difference in proportion of STEMI or Killip class in their study including 77 RA patients with MI compared with matched controls. The cohort of RA subjects in their study was however identified within a retrospectively identified MI-cohort and RA-disease characteristics were not described in detail. The RA characteristics seem to differ across studies; only a low proportion (one-fifth) of the RA subjects in their study, compared with two-fifths in our study, used methotrexate at the time of event. In a study by Douglas \textit{et al}.\textsuperscript{6} including 40 RA subjects with matched controls, RA patients more often presented with collapse whereas there was no difference in other included markers of event severity such as Killip class. Except for the small number of study subjects included, the fact that they matched on ACS type precluded assessments of differences in clinical phenotype.

The observed increase in cumulative incidence of sudden cardiac death in combination with more severe clinical features and increased case fatality among the RA patients in our study points...
levels have been associated with an impaired coronary collateral de-
vention. Furthermore, RA patients have an approximately two-fold in-
crease in atherothrombotic events and an associated more unfavourable out-
come of the coagulation system might lead to an increased risk of
sclerotic lesions in combination with inflammation-induced modifi-
ations.27 These subjects had less extensive atherosclerosis and grade of stenosis but
in particular in the context of low coronary collateral circulation
(which may be well developed in cases of long-standing angina),
and lead to a larger infarct size due to insufficient blood supply to
the myocardium during the time of the occlusion.24 Elevated CRP
levels of markers of endothelial damage, and of procoagulatory
factors.28–30 Several of these alterations in haemostatic mediators
benefit from clotting and down-regulation of anticoagulant me-
chanisms, and also affects the composition and stability of ath-
erosclerotic lesions.26 Rheumatoid arthritis patients also have a
documented increased frequency of vulnerable plaques, increased
levels of markers of endothelial damage, and of procoagulatory
factors.28–30 Several of these alterations in haemostatic mediators
in RA subjects have been linked to future atherothrombotic events.28,31 One might thus hypothesize that vulnerable athero-
sclerotic lesions in combination with inflammation-induced modifi-
cations of the coagulation system might lead to an increased risk of
atherothrombotic events and an associated more unfavourable out-
come. Furthermore, RA patients have an approximately two-fold in-
creased risk of venous thromboembolism, although arterial and
venous thrombo-embolic events only partly share risk factors.32
There are few reports on histopathological features of coronary ar-
tery disease in RA subjects, but in one study based on autopsies RA
subjects had less extensive atherosclerosis and grade of stenosis but
independent, possibly in combination with structural alterations of the coron-
ary circulation, in subjects with RA.

A higher proportion of the RA subjects with incident ACS, com-
pared with the comparators with ACS, had a previously registered
diagnosis of ‘old myocardial infarction’ in the NPR. A diagnosis of old
MI in the absence of previous or adjacent ACS diagnosis could indi-
cate an UMI incidentally detected at the ACS event. This is consist-
ent with previously reported increased risks of UMI in RA patients.9
Mechanisms behind UMIs are not well established, but in one MRI-
based study UMs were significantly less associated with overall
prevalence of atherosclerosis and traditional risk factors compared
with recognized MIs.33 Hence, the increased incidence of UMIs
might be yet another manifestation of a different aetiopathology of
ACS in RA patients. In-depth investigation of morphological char-
acteristics of coronary arterial changes during ACS in RA patients
could provide further information to support existing evidence.

While the focus of this study was to assess and quantify ACS pheno-
type and survival in RA vs. the general population, the relative contri-
bution of different driving mechanisms behind our observations of a
different phenotype and impaired survival remains only partly
understood. In addition to the RA-related inflammatory activity, patients
with RA more frequently use drugs that have been linked to adverse
cardiovascular outcomes. Treatment with non-steroidal anti-
flammatory drugs (NSAIDs) has recently been associated, through
several mechanisms, with increased risk of adverse long- and short-
term outcomes in patients receiving antithrombotic therapy after
MI.34 Whether long-term use of glucocorticoids (GCs) alters the
CVD risk in patients with RA is controversial.35 Even though GC treat-
ment is known to enhance the cardiovascular risk profile, by a negative
effect on lipid profile, glucose tolerance, blood pressure, and obesity,36
these negative effects may be compensated by a positive anti-
inflammatory effect on arterial wall inflammation and unstable pla-
quises.37 Hence, the net effect of GC treatment is complex, but could
potentially negatively impact survival after ACS.

With respect to ACS outcomes, a two-fold risk increase in 30-day
mortality after ACS in subjects with RA was detected in an Australian
cohort study,5 whereas investigators focusing on RA subjects in a
Swedish cohort7 and US cohort8 did not observe an increased risk of
short-term mortality. In the present study, the 7- and 30-day mor-
talities for the RA subjects were increased by ~50%, even after ad-
justing for relevant pre-existing comorbidities, demographics, and
educational level, which is consistent with the Australian study.3
Considering the increased cumulative incidence of sudden cardiac death
among the RA subjects in our study, this risk increase is, however,
most likely an underestimation of the true level of increase in case fa-
tality in RA-associated ACS. We have previously reported, in abstract
format and based on incident RA, no difference in case-fatality rates
among RA patients with ACS shortly after RA diagnosis.38 Informal
comparisons suggest that this seeming discrepancy with our current
findings is likely to be explained by longer RA disease duration in our
current study compared with our previously presented incident RA
population, which may affect both ACS severity and mortality. Indeed,
in our study, the increased short-term mortality decreased after ad-
justing for MI type, which supports the hypothesized impact of the
ACS severity on the increased mortality risk, although this explained
but a part of the reduced short-term survival.

**Table 3** In-hospital treatment received as acute coronary syndrome treatment by rheumatoid arthritis cases and population cases

<table>
<thead>
<tr>
<th>Reperfusion treatment</th>
<th>RA cases (n = 743)</th>
<th>Population cases (n = 2203)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>25.9</td>
<td>33.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>5.7</td>
<td>6.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>62.3</td>
<td>54.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute CABG</td>
<td>0.3</td>
<td>0.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Acute coronary angiography</td>
<td>6.0</td>
<td>5.3</td>
<td>0.79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>RA cases (n = 743)</th>
<th>Population cases (n = 2203)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>69.6</td>
<td>72.3</td>
<td>0.17</td>
</tr>
<tr>
<td>During hospitalization</td>
<td>71.5</td>
<td>75.3</td>
<td>0.04</td>
</tr>
<tr>
<td>PCI</td>
<td>53.4</td>
<td>53.3</td>
<td>0.78</td>
</tr>
<tr>
<td>CABG</td>
<td>5.6</td>
<td>1.9</td>
<td>0.24</td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.
*Number reported with respective covariate/total number with information in RIIH-HIA registry.
*Primary reperfusion treatment in individuals with STEMI.
*Acute coronary angiography, but no further intervention.
*Anticoagulants not related to procedures in individuals with NSTEMI.
Strengths and limitations

The use of nationwide patient registers with high reported validity and close to complete coverage enabled adequate identification of RA, ACS, relevant comorbidities, and other covariates. Information on smoking and BMI, both risk factors for CVD, was not available and could not be adjusted for in analyses, which is therefore a limitation to this study. The prognostic importance of smoking on short-term outcomes after ACS is controversial, but smoking is generally not considered an important predictor of short-term outcomes. Smoking is not associated with an increased short-time mortality risk in RIKS-HIA. Furthermore, the reported proportion of smokers among the RA cases and population cases included in this study did not differ. Likewise, BMI is not an important predictor of short-term outcomes. We identified ACS, length of hospitalization, and deaths from linkage to national and virtually complete registers, but used data from RIKS-HIA to assess in-hospital ACS interventions. Some hospitals only register patients at CICUs in the RIKS-HIA registry. Owing to differences in indication of admission to CICUs in patients over 80 years of age, the overall coverage of this age group is lower. As a result approximately one-third of the study population (but, importantly, similarly so for RA and their comparators) were not included in the analysis of ACS treatment. Whereas this restriction will not in itself introduce bias, it may pose a limitation to the generalizability.

Table 4 In-hospital complications and status at discharge after acute coronary syndrome hospitalization among rheumatoid arthritis cases and population cases

<table>
<thead>
<tr>
<th></th>
<th>RA cases (n = 743)</th>
<th>Population cases (n = 2203)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n/tot^a</td>
<td>%</td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV diuretics</td>
<td>25.3</td>
<td>185/732</td>
<td>20.9</td>
</tr>
<tr>
<td>IV inotropic agent</td>
<td>4.6</td>
<td>34/732</td>
<td>2.5</td>
</tr>
<tr>
<td>CPAP</td>
<td>3.6</td>
<td>26/733</td>
<td>5.3</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>3.6</td>
<td>26/719</td>
<td>2.2</td>
</tr>
<tr>
<td>Myocardial reinfarction</td>
<td>1.4</td>
<td>10/731</td>
<td>1.4</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>2.2</td>
<td>16/731</td>
<td>2.1</td>
</tr>
<tr>
<td>CPR in-hospital</td>
<td>4.1</td>
<td>30/731</td>
<td>2.7</td>
</tr>
<tr>
<td>Atrioventricular block II or III</td>
<td>2.2</td>
<td>16/730</td>
<td>2.2</td>
</tr>
<tr>
<td>New fibrillation/flutter</td>
<td>4.0</td>
<td>29/718</td>
<td>4.7</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≥ 50%)</td>
<td>60.3</td>
<td>298/494</td>
<td>59.4</td>
</tr>
<tr>
<td>Slightly depressed (40–40%)</td>
<td>21.5</td>
<td>106/494</td>
<td>21.9</td>
</tr>
<tr>
<td>Moderately depressed (30–39%)</td>
<td>13.0</td>
<td>64/494</td>
<td>12.4</td>
</tr>
<tr>
<td>Severely depressed (&lt;30%)</td>
<td>5.3</td>
<td>26/494</td>
<td>6.3</td>
</tr>
<tr>
<td>Mechanical complicationb</td>
<td>0.4</td>
<td>3/706</td>
<td>0.3</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>6.1</td>
<td>45/740</td>
<td>4.1</td>
</tr>
<tr>
<td>Diagnosis at dischargec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>58.0</td>
<td>382/658</td>
<td>62.6</td>
</tr>
<tr>
<td>STEMI</td>
<td>42.0</td>
<td>276/658</td>
<td>37.4</td>
</tr>
</tbody>
</table>

CPAP, continuous positive airway pressure; CPR, cardiopulmonary resuscitation; IV, intravenous; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

^aNumber reported with respective covariate/total number with information in RIKS-HIA registry.

^bAcute mitral insufficiency, ventricular septal defect, or myocardial rupture.

^cAs diagnosed and registered in RIKS-HIA by a cardiologist.

Figure 2 Kaplan–Meier survival curves of overall survival after acute coronary syndrome among rheumatoid arthritis cases and population cases.
of the reported data on ACS interventions among individuals >80 years of age.

Conclusions

The results of this study suggest that, in addition to the increased incidence of ACS in RA, the nature of these ACS events is more severe, and the outcome is impaired, even after taking ACS type and co-morbidities into account. These findings emphasize the importance of awareness of this group of patients when assessing and identifying high-risk ACS patients in clinical practice. It will now be an important task to further investigate which factors that mediate the observed differences in clinical phenotype as well as the ensuing case fatality.

Supplementary material

Supplementary material is available at European Heart Journal online.

Authors’ contributions

Å.M., M.H., J.A., S.W.J., and T.J.: study concept and design. Å.M. and J.A.: acquisition of data. Å.M.: statistical analysis and drafting of manuscript. Å.M., M.H., T.J., S.W.J., and J.A.: analysis and interpretation of data. Å.M., M.H., T.J., S.W.J., and J.A.: critical revision of manuscript and final approval given. J.A.: obtained funding and study supervision. Å.M. had full access to all of the data used for analyses in this study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. All authors are justifiably credited with authorship, according to the authorship criteria.

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Conflict of interest: none declared.

Table 5 All-cause mortality rates among rheumatoid arthritis cases and population cases hospitalized with incident acute coronary syndrome

<table>
<thead>
<tr>
<th></th>
<th>RA cases, n (%)</th>
<th>IHD specifica</th>
<th>Population cases, n (%)</th>
<th>IHD specifica</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted for age/sex</td>
</tr>
<tr>
<td>7-Day mortality</td>
<td>118 (10.4)</td>
<td>109 (92.4)</td>
<td>212 (6.7)</td>
<td>200 (94.3)</td>
<td>1.65 (1.32–2.08)</td>
</tr>
<tr>
<td>30-Day mortality</td>
<td>178 (15.7)</td>
<td>160 (89.9)</td>
<td>340 (10.7)</td>
<td>309 (90.8)</td>
<td>1.57 (1.30–1.89)</td>
</tr>
</tbody>
</table>

Number (%) of all-cause and cause-specific deaths. Crude and adjusted HRs with 95% CI. PS, propensity score.

aSpecific causes of deaths include a registered underlying and/or contributory cause of IHD (ICD-10 I20-I25), CHF (ICD-10 I50), and cardiac arrhythmias (I48-I49). Presented as number (% of total deaths)

bInfarct type based on registered ICD code.

References
