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Is rheumatoid arthritis a risk factor for acute coronary syndrome also among individuals at elevated risk, such as individuals presenting with acute chest pain?

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ABSTRACT

Background Patients with rheumatoid arthritis (RA) are, on average, at increased risk of acute coronary syndrome (ACS) compared to the general population, but it remains unknown whether RA remains an ACS risk factor also in settings where the ACS risk is already high elevated, such as among individuals presenting to the emergency department (ED) with chest pain.

Methods and results We included 49 283 individuals (514 (1.0%) had RA) presenting with chest pain at the four hospital EDs in Stockholm, Sweden, 2013–2016 in a cohort study. Information on exposure (RA), outcome (ACS) and comorbidities was provided through national registers. The association between RA and ACS was assessed, overall and by levels of high-sensitivity cardiac troponin T (hs-cTnT) and number of ACS risk factors, using logistic regression models adjusted for age, sex, hospital, calendar year and cardiovascular risk factors. ACS was more common in patients with (8.2%) than without (4.6%) RA, adjusted OR =1.4, 95% CI 1.0 to 2.0. This association was particularly strong in individuals with initial hs-cTnT levels between 5 and 14 ng/L, or no additional ACS risk factors (adjusted ORs above 2), but no longer detectable in those with hs-cTnT >14 ng/L or with three or more additional ACS risk factors.

Conclusion RA is a risk factor for ACS also among patients at the ED with chest pain. This association is not explained by traditional ACS risk factors, and most pronounced in patients with normal hs-cTnT and few other ACS risk factors, prompting particular ACS vigilance in this RA patient group.

Key messages

What is already known about this subject?

- Compared to individuals without RA, individuals with rheumatoid arthritis are at well-documented, on average 50–100% increased, risk for acute coronary syndrome. What remains less well understood is whether RA is marker of increased risk, of the same magnitude, also among individuals and in settings where the underlying risk of an acute coronary syndrome is already elevated, such as among individuals with or without additional traditional cardiovascular risk factors, and who have signs or symptoms that may indicate an acute coronary syndrome.

What does this study add?

- Rheumatoid arthritis remains a risk factor for acute coronary syndrome, also in a high-risk setting such as among individuals seeking emergency care due to chest pain; this risk increase is not simply explained by traditional cardiovascular risk factors.
- In this setting, RA adds to the probability of a diagnosis of acute coronary syndrome in paricular among those with other few cardiovascular risk factors and low initial troponin T values. By contrast, among those with several additional cardiovascular risk factors and highly elevated troponin-T values, the presence of an RA diagnosis adds little additional information on the risk that their chest pain would represent an acute coronary syndrome.

How might this impact on clinical practice or future developments?

- Clinicians should be aware that RA patients with chest pain in the emergency department face a higher risk of acute coronary syndrome compared to patients without RA, especially in those individuals where this risk may otherwise have been categorised as low.

INTRODUCTION

It is well established that the average risk of myocardial infarction (MI) in patients with rheumatoid arthritis (RA) is higher than in the general population.[1–3] This risk increase is not readily explained by an increased prevalence of traditional cardiovascular risk factors,[4 5] pointing to a role of RA inflammation or its treatments, but it remains unknown exactly how this risk increase is mediated; via 'more' of 'ordinary' acute coronary syndromes (ACS) or through pathways specific

to RA. In the former case, the predictive role of RA as an ACS risk factor would decrease and disappear in settings where the underlying ACS risk is already elevated, such as among individuals presenting to the emergency department (ED) with chest pain. In the latter case, it should have important clinical implications for the evaluation of chest pain in such settings. For instance, current guidelines for the evaluation of patients with chest pain in the ED do not consider RA.[6]

Our aim with this study was therefore to investigate whether RA is associated with ACS in a large sample of individuals presenting at the ED with acute chest pain. Secondly, we aimed at assessing the importance of RA, in this setting, in relation to age, gender, traditional ACS risk factors. In addition, we assessed the importance of RA in relation to the initial level of cardiac troponin T as measured with a high-sensitivity assay (hs-cTnT). The first sample drawn in the ED was considered the most relevant for the study setting because it is the clinical test used in the initial evaluation of acute chest pain.[6]

SUBJECTS AND METHODS

Study population and setting

We used prospectively recorded data on all individuals presenting with chest pain, aged 18 years or older and with a valid Swedish Personal Identification Number, at or admitted to either of the four EDs in the capital Stockholm area, Sweden, between 1st January, 2013 and 31st December, 2016, as outlined in online supplemental figure S1.[7] All sites had constant access to catheterisation laboratories on site or nearby with direct admission for patients with ST-elevation myocardial infarction. We only included the first visit of each individual during the study period. Data on the study population were linked to the following national and virtually complete population-based health registers by means of each individual's unique Personal Identification Number. The National Board of Health and Welfare provided data from the National Patient Register (NPR) that contains data on hospital admissions and outpatients visits in secondary care coded according to the International Classification of Diseases (ICD) version 10. The Cause of Death Register contains data on causes of death coded according to ICD. The Prescribed Drugs Register contains information on all dispensed drugs according to the Anatomical Therapeutic Chemical Classification (ATC). Through these registers (described in more detail in online appendix 1), we extracted data on all diagnoses (ICD codes) assigned in- and outpatient care within the 10 years preceding the ED visit, and all dispensed drugs (ATC codes) prescribed within 1 year before the ED.

Exposure

The exposure, RA, was defined as at least two registrations with the ICD-codes M05 and M06 as main or secondary visit diagnosis in the NPR, predating the ED visit. The PPV of this definition is close to 90%,[8] see online supplemental appendix for codes.

Covariates

In the study population, we identified all registrations with the following co-morbid conditions (ACS risk factors) predating the ED visit: hypertension, hyperlipidaemia, diabetes mellitus, obesity, stroke, MI, atrial fibrillation and peripheral vascular disease. Patients with a history of stroke, MI or peripheral arterial disease were considered as having prior cardiovascular disease. Additionally, patients with a record of prescribed antihypertensive drugs, lipid-lowering drugs or anti-diabetic agents were considered as having hypertension, hyperlipidaemia, and diabetes mellitus, respectively. This classification has been described previously.[9]

Initial values of hs-cTnT obtained in the ED, defined as the first value obtained after the patients arrival, were identified via the clinical laboratory databases at all included hospitals. Analyses of cardiac troponin T were all performed using a high-sensitivity assay (Elecsys, Roche Diagnostics, Switzerland) with a detection limit of 5 ng/L, the 99th percentile of the upper limit of the reference interval being 14 ng/L, and a coefficient of variation of less than 10% below the 99th percentile. We similarly collected information on eGFR at the ED visit.

Outcome

For patients admitted to hospital, the outcome was incident ACS, defined as fatal and non-fatal events of MI or unstable angina requiring acute revascularization. To avoid excluding true ACS events in individuals discharged from the ED without such a diagnosis, our outcome-definition also included any new admission with ACS, or death within 30 days of the ED visit.

Statistical methods

We calculated ORs (OR) and 95% CIs (CI) for the association between RA and the ACS using logistic regression. Models included age, sex, hospital, and calendar year of ED visit ('model 1'). As age was non-linearly associated with the log odds of the outcome, we used a restricted cubic spline function with 4 knots.[10] Additionally, we adjusted also for hypertension, hyperlipidaemia, diabetes mellitus, obesity and prior cardiovascular disease ('model 2'). We performed fully adjusted analyses overall and stratified by initial hs-cTnT levels (categorised as <5 ng/L, 5-≤14 ng/L and >14 ng/L), number of cardiovascular risk factors (0, 1–2, 3+), sex, and age (<65 vs ≥65 years of age). We investigated effect modification by each stratification variable by testing the product term between RA and the stratifying variable in the fully adjusted model. Statistical analyses were made with Stata Statistical Software: Release 15.1.

Ethical considerations

Ethical permit for the study was granted by the Regional Ethical Review Board in Stockholm, Sweden. Dnr 2016/

744-31/4 and 2017/274-32. The study analysed routinely collected clinical data and data from mandatory national registers. All data were pseudonymized for the researchers.

RESULTS

Overall, we included 49 283 unique visits and individuals. Of these, 514 (1.0%) had RA, and 2300 (4.7%) developed ACS, table 1. The components of the combined outcome ACS are presented in online supplemental etable 3. Patients with RA were older (median age 70 vs 53 years) and more often female (75% vs 49%). All assessed comorbidities were more prevalent among patients with RA, but taking age and sex into account only hypertension and obesity remained overrepresented in RA. Patients with RA also had lower eGFR (median 72 vs 81 mL/min/1.73 m^2), and more often presented with an initial elevated hs-cTnT (>14 ng/L, 32% vs 16%, age- and gender-adjusted p-value<0.001).

RA was more common in individuals whose ED presentation led to a diagnosis of ACS, table 1; in model 1 (adjustment for age, sex, hospital, inclusion year) the OR was 1.4 (95% CI 1.0 to 2.0). The increased risk was not explained by the increased burden of co-morbidities in RA, as in model 2 (additionally adjusted for the co-morbidities in table 1) the OR was similar, 1.4 (95% CI 1.0 to 2.0).

When stratified by the initial hs-cTnT level (table 2), the association between RA and ACS was the most pronounced among individuals with a hs-cTnT between 5 and 14 ng/L (figure 1), among whom the absolute risk of ACS was in the order of 3–5%; the corresponding OR from model 2 was 2.1 (95% CI 1.1 to 4.2). By contrast, in patients with hs-cTnT levels above the upper reference limit of 14 ng/L, among whom the absolute risk of ACS was as high as 20%, we no longer observed any association between RA and ACS (model 2 OR=0.9, 95% CI 0.6 to 1.4). The small number of ACS events in the strata of hs-cTnT below 5 ng/L precluded analyses within this stratum.

When stratified by the number of ACS risk factors, we noted evidence of effect modification of the strength of the association between RA and ACS by the number of pre-existing ACS risk factors (figure 1 and table 3). The strong association (ORs around 2) among individuals with no other ACS risk factors was no longer evident among individuals with three or more other ACS risk factors (ORs around 1).

The associations between RA and ACS for strata defined by age and gender are presented in table 4. We noted no evidence of any interaction between RA and age (p=0.77) or sex (p=0.88) on the association between RA and ACS.

Table 1 Baseline characteristics of the study population. Characteristics of individuals presenting to the ED with chest pain as chief complaint, in relation to pre-existing RA-diagnosis

	Individuals without RA n=48 769 (99% of entire study population)	Individuals with RA n=514 (1% of entire study population)
Age		
Median years, (IQR)	52.6 (30)	69.6 (20)
<65 years	34434 (71)	189 (37)
≥65 years	14335 (29)	325 (63)
Sex		
Female	23741(49)	383 (74)
Medical history		
Hypertension	16146 (33)	300 (58)
Hyperlipidaemia	7912 (16)	121 (24)
Diabetes mellitus	4698 (10)	67 (13)
Obesity	2056 (4)	36 (7)
Atrial fibrillation	3441(7)	65 (13)
Stroke	1289 (3)	32 (6)
Previous MI	2415 (5)	44 (9)
Heart failure	2398 (5)	57(11)
Any cardiovascular disease	3980 (8)	80 (16)
Year of ED-visit		
2013	11156 (23)	123 (24)
2014	10090 (21)	103 (20)
2015	11588 (24)	134 (26)
2016	15935 (33)	154 (30)
Initial hs-cTnT(ng/L)		
<5	22518 (52)	144 (30)
5–14	14100 (32)	182 (38)
>14	6850 (16)	151 (32)
eGFR (mL/min/1.73 m^2)		
Missing	3830	21
>90	13750 (31)	80 (16)
60–90	24505 (54)	264 (54)
30–60	5851 (13)	132 (27)
15–30	675 (2)	13 (3)
0–15	158 (0.4)	4 (1)
CRP (mg/L)	2(<1–5)	5 (2–13)
Fulfilled definition of incident ACS	2258 (5)	42 (8)

ACS, Acute coronary syndrome; ED, Emergency department; eGFR, Estimated glomerular filtration rate; Hs-cTnT, High-sensitivity assay for cardiac troponin T; IQR, IQR; MI, Myocardial infarction; RA, Rheumatoid arthritis; SD, SD.

DISCUSSION

In our study, to our knowledge the first investigating the role of RA on ACS in a high-risk setting such as the ED, we made a series of important observations: In this ACS high-risk setting, RA remained an overall risk factor for ACS, of similar magnitude as the association between RA and ACS

Table 2 ORs for the association between RA and ACS among Swedish patients seeking emergency department because of chest pain, overall and by initial hs-cTnT levels (ng/L)

hs-cTnT	Overall (n=49 283)	<5 ng/L (n=22 662)	5–14 ng/L (n=14 282)	>14 ng/L (n=7001)
Number and proportion with ACS, n, (%)				
RA	42 (8.0)	0 (0)	9 (5.0)	33 (22)
No RA	2258 (4.6)	51 (0.2)	421 (3.0)	1773 (26)
OR model 1*	1.4 (1.0–2.0)	n.a§	2.1 (1.1–4.2)	0.9 (0.6–1.4)
OR model 2*	1.4 (1.0–2.0)	n.a§	2.1 (1.1–4.2)	1.0 (0.7–1.5)

*ORs using no RA, within in each strata of trop T, as reference category.
†Logistic regression models: Model 1, adjusted for age, sex, hospital, inclusion year. Model 2 additionally adjusted for hypertension, hyperlipidaemia, diabetes mellitus, obesity and prior cardiovascular disease.
‡ACS, Acute coronary syndrome; RA, Rheumatoid arthritis; Hs-cTnT, High-sensitivity assay for cardiac troponin T.
§n.a., Not analysed (because of small numbers).

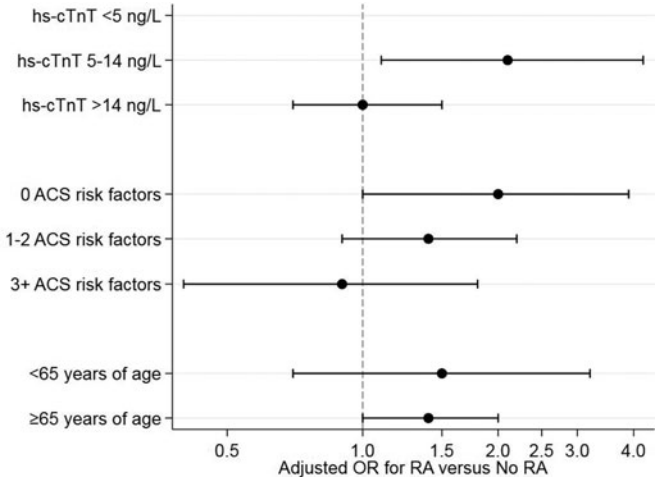

Figure 1 ORs for ACS with RA by age group, initial hs-cTnT value and risk factors. All ORs are adjusted for age, sex, hospital, inclusion year and comorbidities. hs-cTnT, High-sensitivity assay for cardiac troponin T.

reported in the general population on a whole.[3] This association further remained largely unchanged after adjustment for traditional ACS risk factors, suggesting that it was not explained simply by RA having more other ACS risk factors than individuals without RA.

Interestingly, the association between RA and ACS was twofold among individuals with chest pain, a non-elevated hs-cTnT, and few other ACS risk factors, but no longer detectable among individuals who presented with chest pain and had a hs-cTnT above 14 (among whom the absolute risk for ACS was above 20%), nor among those with three or more other established ACS risk factors, among whom the risk of ACS was around 10%. From a pathogenesis point of view, these results suggest that, in contexts where the ACS risk is very high the direct impact of RA-specific pathways on ACS risk are lower and that the effect of RA on ACS is rather mediated via ACS risk factors that arise as a consequence of the RA disease (and therefore, when conditioning on the presence of several ACS risk factors, the association between RA and ACS is no longer visible). From a clinical point of view, our findings indicate that history of RA serves as useful information in chest pain diagnostics, in particular among those presenting without highly elevated hs-cTnT, which comprise approximately one-quarter of all ACS in the RA group.

Individuals seeking ED care due to chest pain are not as healthy as the general population, and naturally, the MI risk is much higher among cases of suspected MI in the ED than in the general population. Our results demonstrate how the relative contribution of RA on ACS risk remains important in this high-risk setting, but also how the importance of RA decline and is lost in those subsets with the highest underlying risk of ACS.

With the introduction of high-sensitivity assays for troponin I and T the prognosis of discharged chest pain patients have been improved[11], accelerated diagnostic protocols for early discharge of patients with non-elevated or undetectable troponin levels at presentation have been developed and implemented in clinical routine.[6 12 13] Chapman *et al*[14] showed that the diagnostic accuracy of a protocol for early discharge of patients with a non-ischaemic ECG and an initial undetectable troponin I level with a high-sensitivity assay was not improved by the addition of common risk assessment scores for ACS. These scores do not include RA as a risk factor. Our findings, however, indicate that RA, in contrast to what is stated in current guidelines[6], should be considered as a risk factor in the evaluation of acute chest pain in the ED. Our findings underscore the importance of serial troponin testing in the ED and that a second sample, preferably 1 or 2 hours after the first sample according to current guidelines[6], may be especially important in RA-patients before ruling out ACS. Since we lack information on symptom onset we cannot draw any conclusions on when ACS can be safely ruled out with a single test in relation to the chest pain duration in RA-patients.

The overall absolute risk of ACS in our population was similar to other ED cohorts[15], but lower compared to some cohorts in which patients were selected based on a higher suspicion of ACS.[13 16] As patients with ST-elevation myocardial infarction (STEMI) often are

Table 3 ORs for the association between RA and ACS among Swedish patients seeking emergency department because of chest pain, overall and by number of pre-existing ACS risk factors

Number of ACS risk factors	Overall (n=49 263)	0 ACS risk factors (n=27 601)	1–2 ACS risk factors (n=15 467)	3 or more ACS risk factors (n=6215)
Number and proportion with ACS, n (%)				
RA	42 (8.0)	11 (6.8)	22 (9.1)	9 (8.1)
No RA	2258 (4.6)	655 (2.4)	973 (6.4)	630 (10)
OR model 1*	1.4 (1.0–2.0)	2.0 (1.1–3.9)	1.5 (1.0–2.4)	0.9 (0.4–1.7)
OR model 2*	1.4 (1.0–1.9)	2.0 (1.0–3.9)	1.4 (0.9–2.2)	0.9 (0.4–1.8)

*ORs using no RA, within in each subgroup of risk factors as reference category.
†Logistic regression model: Model 1, adjusted for age, sex, hospital, inclusion year. Model 2, adjusted for age, sex, hospital, inclusion year, eGFR.
‡ACS, Acute coronary syndrome; CVD, Cardiovascular disease; RA, Rheumatoid arthritis.
Risk factors were hypertension, hyperlipidaemia, diabetes, obesity, and family history of ACS.

Table 4 ORs for the association between RA and ACS among Swedish patients seeking emergency department because of chest pain, by age and sex

	Male (n=25 159)	Female (n=24 124)	Age<65 (n=34 623)	Age>-65 (n=14 660)
Number and proportion with ACS, n (%)				
RA	23 (17.6)	19 (5.0)	8 (4.2)	34 (10.5)
No RA	1696 (6.8)	562 (2.4)	908 (2.6)	1350 (9.4)
OR model 1*	1.6 (1.0–2.5)	1.3 (0.8–2.1)	1.5 (0.7–3.2))	1.4 (1.0–2.0)
OR model 2*	1.6 (1.0–2.5)	1.3 (0.8–2.1)	1.5 (0.7–3.2)	1.4 (1.0–2.0)

*ORs using no RA, within in each subgroup, as reference category.
†Logistic regression models: Model 1, adjusted for age, sex, hospital, inclusion year. Model 2 additionally adjusted for hypertension, hyperlipidaemia, diabetes mellitus, obesity and prior cardiovascular disease.
‡ACS, Acute coronary syndrome; RA, Rheumatoid arthritis.

transported by ambulance directly to the cardiac intensive care unit/catheterisation lab and by-pass the ED, the current study may not be representative of the total MI-population. However, we and others have shown that RA-patients with MI are more likely to have ST-elevation myocardial infarction (STEMI), compared to other patients with MI,[17] thus our results may in fact underestimate the global association between RA and ACS events.

Our study was population-based; the exposure, covariates and outcomes were register-based which minimise recall-bias. The in-patient diagnoses of MI in the NPR have been externally validated with a reported sensitivity above 90%[18] and the RA diagnoses in the NPR have been validated with an accuracy of 90%.[8] Patterns of seeking medical care vary between individuals.[19] Most RA patients have a regular contact with a rheumatologist and are therefore more used to hospital environment, which could lower the threshold for seeking care.[20] Limitations of the study include lack of information on smoking history and duration of chest pain at arrival, which both are important in the evaluation of chest pain. Finally, the observational design of the study cannot exclude the potential of residual confounding, several CIs had lower bounds close to 1, and the results should be interpreted accordingly.

In conclusion, RA is a risk factor for ACS also among patients presenting to the ED with chest pain as chief complaint. This increased risk was not readily explained by RA patients having more traditional ACS risk factors, and was attributable to more RA-patients presenting with an elevated initial hs-cTnT (>14 ng/L), but also to an association between RA and ACS among patients with an initial hs-cTnT between 5–14 ng/L. Clinically, our findings support the role and use of RA as a predictive factor in the clinical evaluation of patients with acute chest pain, especially so in patients with low to normal initial hs-cTnT levels, and few other ACS risk factors.

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Contributors PS, JA and MB designed the study. PS was responsible for acquisition of data. All authors contributed to analysis and interpretation of data. PS, JA and MB drafted the manuscript. All authors contributed with critical revision of the manuscript and important intellectual content. AD performed statistical analysis and data management. PS obtained funding. All authors agree to be accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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