Excess Recurrent Cardiac Events in Rheumatoid Arthritis Patients with Acute Coronary Syndrome.

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Abstract
Objectives: Cardiovascular mortality is increased in rheumatoid arthritis (RA). Possible reasons include increased incidence or prevalence of ischaemic heart disease (IHD) but also worse outcome of IHD, particularly after an acute coronary syndrome (ACS). We assessed the outcome of ACS in RA compared to case-matched controls in the context of underlying cardiac risk factors, clinical presentation and subsequent management.

Methods: 40 patients with RA and ACS identified from coronary care admission registers between 1990 and 2000 were case-matched as closely as possible for age, sex, classical cardiovascular risk factors, type and severity of ACS and admission date (+/- 3 months) with 40 controls. A standardised proforma was used for detailed case-note review.

Results: Age, sex, other cardiovascular risk factors, type and severity of presenting ACS were not significantly different between cases and controls. Recurrent cardiac events were commoner in RA (23/40, 57.5%) than controls (12/40, 30%) (p=0.013); there were 16/40 (40%) deaths in RA versus 6/40 (15%) in controls (p=0.012). Recurrent events occurred earlier in RA (log rank survival p=0.05). Presentation with chest pain occurred in all controls compared with 33/40 (82%) of RA patients (p=0.006); collapse occurred in 1 control (2.5%) versus 7/40 (17.5%) of RA patients (p=0.025). Treatment during the ACS was not significantly different in the two groups.

Conclusion: Recurrent ischaemic events and death occur more frequently after ACS in RA. Atypical presentation is commoner in RA. There is an urgent need to develop identification and intervention strategies for ACS specific to this high-risk group.
Introduction

Rheumatoid arthritis (RA) associates with increased overall mortality and reduced life expectancy. A major reason is increased cardiovascular mortality compared to the general population (1,2). Rheumatoid heart disease rarely has haemodynamic consequences, and is an unlikely cause for this. The most likely cause of cardiac death in RA, as in the general population, is atherosclerotic coronary artery disease (CAD) leading to ischaemic heart disease (IHD) (3).

Several studies have shown a higher incidence and/or prevalence of ischaemic cardiac pathologies such as myocardial infarction (MI), congestive heart failure (CHF) and coronary death in RA patients than in general population controls (4-8), and objective testing with myocardial perfusion imaging (9) has detected an increased background burden of stable IHD in RA.

In the general population, unstable angina and MI, collectively referred to as acute coronary syndromes (ACS), associate with an increased risk of further cardiac events (death, recurrent ACS, left ventricular failure, arrhythmia) and poor overall outcome (10). ACS are therefore an obvious target for intervention aiming to reduce mortality. Whether ACS have a worse prognosis in RA compared to controls, and potential reasons for this, has not been assessed systematically.

We hypothesised that patients with RA sustaining an ACS have a worse outcome than patients without RA who have a similar ACS. We assessed this in an observational, retrospective, case-controlled study in which we compared the outcome of a definite ACS in patients with RA with age and sex matched non-RA case controls. In order to explore possible causes of a difference in outcome, we investigated this in the context of cardiac risk factors, clinical presentation and subsequent management.

Patients and Methods

All Dudley Group of Hospitals (DGoH) patients who had had an ICD code for RA (ever) plus an ICD code for an ACS (within the period 01/01/1990 to 31/12/1999) were identified from discharge diagnosis coding using the hospital information system and cross-referenced with a separate Coronary Care Unit (CCU) admissions register. The DGoH at the time consisted of 4 hospitals with a catchment population of 380,000, of mixed socio-economic status in a mixed rural and urban setting, with an about average CVD prevalence for England and Wales. There were 2 CCUs with 14 acute and 24 post-acute beds and an excellent cardiac rehabilitation service (“Action Heart”). Patients notes were reviewed by a cardiologist and a rheumatologist to confirm the diagnoses of ACS and RA (see below). Only patients with first ever ACS were included in the study; those with a confirmed previous ACS were excluded. This process identified 40 RA patients for further study. Each RA case was matched for sex, as closely as possible for age and type of ACS to a non-RA control who also had a first ever ACS within 3 months of the respective RA patient (to allow for variations in CCU management practices over time). Diagnosis of RA required fulfilment of the 1987 ACR criteria applied retrospectively (11). First ACS (index event, occurring in the absence of any known previous acute event) was defined as follows:

I. Non ST elevation acute coronary syndrome (NSTEMI), which could be either of the following:- unstable angina (UA) - >20 minutes of typical cardiac pain at rest with or without typical electrocardiographic (ECG) change of IHD but without creatine kinase (MB fraction – CK-MB) cardiac enzyme rise; Non
Q wave myocardial infarction (NQWMI) - >20 minutes of typical cardiac pain, dyspnoea or collapse, with or without ECG change but with >2-fold transient increase in cardiac enzymes on serial testing.

II. ST elevation acute coronary syndrome (STEACS): as per non Q wave MI plus ST segment elevation in >2 contiguous leads (limb leads - 1mm, chest leads - 2mm) with subsequent Q wave formation or new Left Bundle Branch Block.

Troponin was not used in our definitions as most admissions predated its introduction into routine clinical practice. The definitions used in the present study largely correspond to the following current ACS definitions (12): UA in this study includes cases of ACS-unstable angina and ACS-minimal myocardial injury; NQWMI in this study includes current ACS-NQWMI; there is a possibility that some such events may have been classified as UA due to the reduced sensitivity of CK-MB compared to troponin; STEACS in this study correspond to current definition of QWMI.

Discharge diagnosis was defined as the final diagnosis used for coding, made on the basis of the above with the benefit of serial ECGs and cardiac enzymes as stated in the hospital discharge summary and confirmed with CCU records and by the cardiologist (MJB) as above (there were no cases of disagreement); however, the discharge diagnosis was not necessarily the “working diagnosis” made by the admitting doctor.

Killip Class is a clinical and prognostic marker of haemodynamic upset resulting from ACS. (Killip I: no clinical signs of cardiac decompensation; Killip II: heart failure with rales or S3 gallop or venous hypertension; Killip III: frank pulmonary oedema; Killip IV: hypotension (systolic blood pressure <= 90 mm Hg) cyanosis, oliguria, diaphoresis, pulmonary oedema) (13).

Outcomes were determined from review of hospital notes and information from death certificates. In the absence of definite evidence of death, direct contact was made with the patient, family or GP to verify whether the patient was still alive at the end of the study. For the purposes of the study, outcomes should have occurred up to the 31st of December 2001 and included: Death of any cause (as per part I of death certificate); Cardiovascular death (if cardiovascular cause stated on part I of death certificate); Recurrent ACS (the first ACS occurring after the index event); Recurrent Cardiac Events (cardiovascular death or recurrent ACS). A confirmed recurrent ACS occurring during the index admission was counted as a separate event. To avoid double-counting, any further events (e.g. third ACS) were not included in the analysis.

Data Collection: Data was collected using a standardized proforma to interrogate the notes and entered into a specifically designed spreadsheet. Patients were deemed to have entered the study at first presentation (index event) to CCU with ACS and the date and time was recorded. The following information was collected: demographics and classical cardiovascular risk factors (family history, smoking, past history of hypertension, diabetes mellitus or hypercholesterolaemia, systolic and diastolic blood pressure (BP), body mass index (BMI), serum total and HDL cholesterol), clinical presentation of index event, clinical severity of presentation (Killip class), treatment of index event in the first 24 hours, serological and ECG findings, discharge medication, risk assessment (exercise test, echocardiogram, myocardial perfusion imaging) and cardiac rehabilitation. Recurrent events were recorded and their time and date noted.

Statistical Analysis: was performed using SPSS statistical software ver.9.0 (SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th floor, Chicago, Illinois 60606). Results are presented as frequencies (%) or means with standard deviations (SD). Frequencies were
compared using $x^2$ test, or Fishers Exact test if n was <5 in one or more cells. Means were compared using student’s t-test or Mann-Whitney U test as appropriate, after tests for normality. Kaplan-Meier plots of probability of event free survival were made for each group and compared using a log rank survival comparison.

Results
Discharge diagnosis at index event
24/40 RA patients (60%) and 22/40 (55%) controls had a non-ST elevation ACS. The remaining patients in each group (RA: 16/40 – 40%; controls: 18/40 – 45%) had an ST-elevation ACS (p=0.65). The total observation period (mean ±SD from index event to study closure on 31/12/2001) was 2498 ±900 days for the RA group compared with 2297±741 days for the controls (p=0.28).

Classical Cardiac Risk Factors
At the index event, as intended, RA patients were matched to controls for age (years mean ±SD: RA: 65.2 ±15.1 vs controls: 68.1 ±11) (p=0.28) and sex (15/40 – 37.5% males in both groups). There were no significant differences between RA and controls in the frequency of the presence of any other classical cardiac risk factors, including smoking, diabetes, family history, hypertension, hypercholesterolaemia and clinical obesity (body mass index ≥30) (Table 1). All patients were Caucasian (this was not an inclusion criteria, however the local population has a particularly low proportion, ≤6%, of other ethnic groups).

Clinical Presentation
All 40 controls (100%) had chest pain on presentation, compared with 33/40 (82.5%) of patients with RA (p=0.003). Seven RA patients (17.5%) presented with collapse compared with only 1 control (2.5%) (p=0.025). Dyspnoea was present in 17 RA patients (42.5%) versus 14 controls (35%) (p=0.49). Serious arrhythmia occurred in 2/40 (5%) of RA patients compared with 1/40 (2.5%) of controls. Overall, the number of patients in each Killip class of clinical severity was similar in the 2 groups (Table 2).

Management
There were no significant differences between RA and controls in the frequency of patients receiving oxygen, diamorphine, heparin or beta-blockers in the first 24 hours after the index event. Of the patients who had an ST elevation ACS, thrombolysis was used in 8/16 (50%) in the RA group compared with 13/18 (72%) in the control group (p=0.18). Complete data on administration times for thrombolyis were available on 6/8 RA patients and 7/13 controls. The mean ±SD time from onset of symptoms to thrombolyis was 26±40 hours in RA compared with 6.2±12 hours in controls (p=0.09) and time from admission to thrombolyis was 5.8±10 hours in RA versus 3.3±9 hours in controls (p=0.12). Clinically silent ST-elevation ACS (Q wave MI) occurred in 2/16 RA patients but none of the 18 controls (p=0.25). These 2 RA patients were not thrombolyzed.

The frequency of use of angiotensin converting enzyme (ACE) inhibitors (12/40 RA patients v’s 8/40 controls), beta-blockers (13/40 RA patients v’s 15/40 controls), and/or statins (6/40 RA patients v’s 8/40 controls) on discharge after the index event was not significantly different between RA patients and controls.

Pre-discharge risk assessment with exercise testing occurred in 14/40 (35%) RA patients compared with 22/40 (55%) of the controls (p=0.06). There was no significant
difference in the frequency of usage of echocardiography (19/40 (47.5%) RA patients vs 12/40 (30%) controls), myocardial perfusion single photon emission computed tomography (10/40 (25%) RA patients vs 8/40 (20%) controls) or coronary angiography (2/40 (5%) RA patients vs 6/40 (15%) controls) between the 2 groups. No percutaneous coronary angioplasty was performed in either group and only one coronary artery bypass was performed in the control group with none in RA.

**Outcomes**

19/40 (47.5%) of the RA group died, compared with 10/40 (25%) of controls (p=0.036) (Table 3). 16/40 (40%) RA patients died due to a cardiovascular cause compared with 6/40 (15%) controls (p=0.012). Thus cardiovascular deaths represented 16/19 (84%) of all-cause mortality in RA, and 6/10 (60%) in controls (p=0.14) in these groups.

Non-cardiovascular deaths in the RA group were because of pneumonia (n=2) and perforated duodenal ulcer (n=1) and in the control group because of pneumonia (n=2), ampullary tumour (n=1) and old age (n=1).

Recurrent ACS occurred in 18/40 (45%) RA patients compared to 10/40 (25%) controls (p=0.011). Recurrent cardiac events (recurrent ACS or cardiovascular death) occurred in 23/40 (57.5%) RA patients compared with 12/40 (30%) controls (p=0.013) (Table 4). The median (interquartile range) from the index event to recurrent cardiac event was 149 (56-797) days in RA patients compared with 203 (47-577) in the controls (p=0.85). The probability of recurrent cardiac event-free survival was significantly lower in RA than controls (log rank survival p=0.05) (Figure 1).

**Predictors of Recurrent Cardiac Events**

The baseline characteristics at the index event were compared between patients who subsequently experienced recurrent cardiac events and those who did not.

In the control group, patients who experienced recurrent events were significantly older (74±10.3 years) than those who did not (65±10.7 years) (p=0.016) (Table 4). There were no significant differences in the frequency of any of the classical cardiovascular risk factors between the sub-groups within RA. The exact nature of the index ACS did not differ between patients who had a recurrent cardiac event and those who had not, within either RA or controls. Significantly more patients with recurrent cardiac events presented in Killip class II, in both groups: RA 14/23 (61%) vs 4/17 (24%) (p=0.02): and controls 7/12 (58%) vs 7/28 (25%) (p=0.04). The frequency of usage of various medications (including thrombolysis in patients with STEACS) was not different, with the exception of beta-blockers: within the RA group (but not controls) those prescribed beta-blockers were significantly less likely to suffer from a recurrent event. Risk assessment or exercise rehabilitation was not different between the groups.

**Discussion**

Previous studies have documented an increased cardiovascular mortality in RA (2;14-16). This could be either because CVD is commoner, or because it has a worse outcome in RA than in the general population. ACS account for most cardiovascular mortality both in the general population and in RA (6;8). The present study addressed specifically whether ACS has a worse outcome in RA and is the first to document that ACS associates with increased recurrent ischaemic events and death in this disease. This is a retrospective study in a relatively small sample rendering it prone to type II errors.
The multiple significance tests may also have lead to type I errors so results should be interpreted with caution. However, the great similarity between cases and controls for age, sex, classical cardiovascular risk factors, severity of presentation, type of ACS and period of treatment is a significant strength. The morbidity and mortality patterns seen in the control population in the present study are comparable to those reported in similarly treated contemporary populations (10), suggesting that our population was representative. Unrecognized MI and sudden deaths are more common in patients with RA so more patients with RA may have died prior to CCU (16) or been treated outside CCU. However this study did not set out to investigate the incidence of ACS in RA but the outcome in similarly managed patients with ACS, thus only patients admitted to CCU were included. Interestingly, the very low rates of post-ACS coronary angiography and revascularisation in this study, which reflect routine practice (due to low availability of these services) in UK District General Hospitals in the 1990s (10), provide a unique opportunity to study the “natural course” of events both in RA and controls.

RA patients may have worse “background atherosclerosis” compared even with subjects matched for classical cardiovascular risk factors. Continuous exposure to high-grade systemic inflammation may be linked to accelerated atherosclerosis (17). Evidence for this are available from studies assessing in vivo endothelial function (18), carotid intima-media thickness (19;20) arterial elasticity (21) and compressibility (22) which show earlier and more severe changes in RA than in age and sex-matched controls. However, arterial stenoses from advanced lesions may be “benign”, remaining clinically silent or giving stable symptoms (e.g. effort angina). Lesion size has no relation to thrombosis development, in fact most ACS develop at sites where atheroma causes <50% stenosis (23) and rupture is more likely at less stenotic lesions where wall tension is greater (24). It is the rupture of the fibrous cap, due to plaque instability, exposing the highly thrombogenic core material and leading to the sudden development of local thrombosis that leads to ACS. Plaque instability, rather than accelerated plaque formation, may be more important in the context of ACS (and its worse outcome) in RA.

There is currently no direct evidence that atheromatous plaques may be more unstable in patients with RA, but several mechanisms may contribute to this. Key inflammatory cytokines such as TNFα, IL1β and IFNγ involved in plaque rupture may be present at much higher levels in the “high-grade” inflammatory state of RA (17). The resulting inhibition of vascular smooth muscle cell proliferation and collagen synthesis by T cell-derived IFNγ (25;26), and collagen degradation from enhanced metalloproteinase (14) and free radical release by TNFα-activated macrophages, may make plaques particularly vulnerable in RA patients. CD25+ (IL-2 receptor-expressing, activated) T cells in atherectomy lesions relate to the severity of ACS (27) and are particularly prevalent in the peripheral blood of patients with RA (28). Patients with ACS also have an expanded population of CD4+CD28null cells, present in culprit lesions but not in stable plaques (29) which appears to represent senescent T cells with cytotoxic potential implicated in plaque rupture (30). These cells were first noticed in rheumatoid vasculitis. Their presence in high numbers has been linked to more advanced atherosclerotic changes and possibly plaque instability in RA (31), since in the presence of raised CRP they can be cytotoxic to endothelial cells (32). Levels of CRP are strongly linked with ACS outcome in the general population (33) for reasons that remain unclear. It may play a pathogenic role locally in the plaque as an endogenous activator of complement, foam cell formation from uptake of CRP-opsonized LDL by macrophages.
endothelial activation with enhanced expression of cellular adhesion molecules (35), MCP-1 induction (36) and sensitisation to damage from cytotoxic T cells (32). Acute stress leads to a rapid increase of CRP, particularly in patients with active RA; combined with haemostatic, rheologic and haemodynamic reactions over and above already high baseline levels, this could underlie the increased risk for re-infarction in this vulnerable patient group (37). An inflammation-induced dysregulated prothrombotic state (38;39) may also explain the higher recurrence rate observed in RA patients in this study.

Differences in pre-existing comorbidity, clinical presentation and subsequent management of ACS in the two populations may be equally important reasons for the worse outcomes observed in RA. It should be noted that the method of identifying controls resulted in a (non-significantly) longer total observation period in RA compared to controls: this may have allowed additional events to emerge. The presence of multiple physical and psychosocial co-morbidities is common in RA (7) and are bad prognostic factors in ACS. Depression, for example, itself a predictor of adverse outcome in ACS, is both commoner and more severe in patients suffering from both RA and CVD (40). Clinical presentation is also important, as it may lead to misdiagnosis and delayed therapy. A fifth of RA patients with ACS (compared with none in the control group) presented without chest pain, leading to later and less use of thrombolytic therapy. It appears that the previously noted silent IHD in RA (9, 39) may occur even in the context of ACS, whereas presentation with primary symptoms other than chest pain (for example collapse) is known to associate with poorer prognosis in the general population (41). It is possible that steroid, analgesic or NSAID use may have modified symptoms. Subsequent pharmacological management was not particularly different in the two groups. It is however interesting that specifically in RA, the lack of use of β-blockers may associate with recurrent events. Long term β-blockade reduces post-MI morbidity and mortality in unselected patients (42). RA patients have increased sympathetic activity (43), so β-blockers may be more beneficial in this group. Finally, few RA patients appear to receive appropriate post-ACS risk-assessment. We have previously suggested that physical disability may be an important referral barrier for risk-assessment with exercise testing or coronary angiography in patients with RA (44).

Diabetes mellitus (DM) is a recognized CHD risk factor. Over the past decade, aggressive therapy has translated into significantly improved ACS outcomes in DM. As in DM (44), we suggest that RA patients presenting with suspected ACS should be stratified as high-risk. In this study Killip class ≥II at presentation was associated with a poor outcome and may be a useful tool to identify patients at the highest risk. Admitting physicians need increased awareness of unusual presentations without chest pain. Post-ACS risk assessment strategies need to be more aggressive, and pharmacologically-stressed myocardial perfusion imaging (9) may be a good initial option for physically disabled patients unable to have exercise testing, as it is a highly sensitive and specific tool for predicting ACS recurrence in the general population (45). RA patients should not be discriminated from early intervention with coronary angioplasty and stenting. Strategies aimed at effectively controlling systemic inflammation and thus plaque stabilization with traditional anti-rheumatic drugs may already be reducing risk (46), but traditionally cardiovascular drugs, e.g. statins (47) need to be prospectively investigated in this high-risk group.
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Table 1. “Classical” cardiovascular risk factors in the RA and control populations.
(ns: not significant)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RA</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.2 (15.1)</td>
<td>68.5 (11)</td>
<td>ns</td>
</tr>
<tr>
<td>Male sex</td>
<td>15 (37.5%)</td>
<td>15 (37.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (10%)</td>
<td>8 (20%)</td>
<td>ns</td>
</tr>
<tr>
<td>Family history</td>
<td>11 (27.5%)</td>
<td>19 (47.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>4 (10%)</td>
<td>7 (17.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>11 (27.5%)</td>
<td>9 (22.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (35%)</td>
<td>19 (47.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index &gt;30</td>
<td>3 (7.5%)</td>
<td>5 (12.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Variable</td>
<td>RA n=40</td>
<td>Control n=40</td>
<td>p</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Presenting symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>33 (82.5%)</td>
<td>40 (100%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>17 (42.5%)</td>
<td>14 (35%)</td>
<td>ns</td>
</tr>
<tr>
<td>Collapse</td>
<td>7 (17.5%)</td>
<td>1 (2.5%)</td>
<td>0.025</td>
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<tr>
<td>Arrhythmia</td>
<td>2 (5%)</td>
<td>1 (2.5%)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Killip class (severity)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21 (52.5%)</td>
<td>26 (65%)</td>
<td>ns</td>
</tr>
<tr>
<td>II</td>
<td>18 (45%)</td>
<td>14 (35%)</td>
<td>ns</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>IV</td>
<td>1 (2.5%)</td>
<td>0</td>
<td>ns</td>
</tr>
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</table>

**Table 2.** Clinical presentation of index event for the RA and control populations studied. Results were analysed using the $\chi^2$ test or Fisher Exact test where $n<5$ in any cell. (ns: not significant)
<table>
<thead>
<tr>
<th>Variable</th>
<th>RA n=40</th>
<th>Control n=40</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Cardiac Events</td>
<td>23 (57.5%)</td>
<td>12 (30%)</td>
<td>0.013</td>
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<tr>
<td>Recurrent ACS</td>
<td>18 (45%)</td>
<td>10 (25%)</td>
<td>0.06</td>
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<tr>
<td>Cardiovascular Death</td>
<td>16 (40%)</td>
<td>6 (15%)</td>
<td>0.012</td>
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<tr>
<td>Death within 30 days of initial event</td>
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<td>2</td>
<td>0.162</td>
</tr>
<tr>
<td>Death of any cause</td>
<td>19 (47.5%)</td>
<td>10 (25%)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Table 3. Outcomes in rheumatoid and control patients. (ACS = acute coronary syndrome). Results were analysed using $x^2$ (ns = non significant).
Table 4. Classical cardiac risk factors, presentation, severity and treatment in RA and controls for those who suffered recurrent cardiac events compared with those who did not. Results were analysed using x^2 or Fisher exact test (if n=<5 in any cell). Age was analysed with t-test. (ns = non significant).

* Steroids defined as Prednisolone 7.5mg, or more, for more than 6 months ever.
Data is not available on controls for NSAID and steroid usage.
Figure 1. Kaplan Meier plots of the probability of event free survival for the RA and control populations. (log rank survival p=0.05)
Reference List


