Longterm Outcomes and Treatment After Myocardial Infarction in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the risk profiles, treatment, and outcomes of patients with rheumatoid arthritis (RA) with myocardial infarction (MI) and matched MI patients without RA.

Methods. We used a population-based cohort of Olmsted County, Minnesota, residents with MI from the period 1979-2009. We identified 77 patients who fulfilled the American College of Rheumatology 1987 criteria for RA and 154 MI patients without RA matched for age, sex, and calendar year. Data collection from medical records included RA and MI characteristics, antirheumatic and cardioprotective medications, reperfusion therapy, and outcomes (mortality, heart failure, and recurrent ischemia).

Results. The mean age at MI was 72.4 years and 55% of patients were female in both cohorts. Cardiovascular risk factor profiles, MI characteristics, and treatment with reperfusion therapy or cardioprotective medications were similar in MI patients with and those without RA. Patients with RA experienced poorer longterm outcomes compared to patients without RA — for mortality: hazard ratio (HR) 1.47; 95% CI 1.04, 2.08; and for recurrent ischemia: HR 1.51; 95% CI 1.04, 2.18.

Conclusion. MI patients with RA received similar treatment with reperfusion therapy and cardioprotective medications and had similar short-term outcomes compared to patients without RA. Patients with RA had poorer longterm outcomes. Despite similar treatment, MI patients with RA had worse longterm outcomes than MI patients without RA. (First Release Feb 15 2013; J Rheumatol 2013;40:605–10; doi:10.3899/jrheum.120941)

Key Indexing Terms:
RHEUMATOID ARTHRITIS MYOCARDIAL INFARCTION TREATMENT

Cardiovascular (CV) disease is implicated as a major cause of morbidity and mortality in rheumatoid arthritis (RA)[1,2,3,4,5,6,7,8,9]. RA is associated with systemic inflammation, contributing to the increased CV disease risk in patients with RA[10,11]. A well-powered observational study demonstrated impaired prognosis after acute coronary events in patients with RA compared to the general population[12]. Subsequent studies indicated that patients with RA may be less likely to receive reperfusion therapy and may also be less likely to receive appropriate medical management[13]. In addition to short-term mortality, longterm mortality in MI patients with RA may be worse than in MI patients without RA. Two small studies have demonstrated that despite similarity in short-term mortality outcomes after MI, patients with RA have poorer longterm outcomes than patients without RA[14,15]. The aim of our study was to elucidate these findings by assessing the CV disease risk profile, use of treatment (e.g., reperfusion therapy and cardioprotective medication use), and outcomes (mortality, heart failure, and recurrent ischemia) after MI in patients with and without RA.

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Supported by the US National Institutes of Health, US National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR46849), and US National Heart, Lung and Blood Institute (R01 HL59205), and by the Rochester Epidemiology Project (R01 AG034676, National Institute on Aging).

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Accepted for publication December 20, 2012.

MATERIALS AND METHODS

Study population. Our study used the resources of the Rochester Epidemiology Project, a diagnostic indexing linkage system that allows access to complete (inpatient and outpatient) medical records of all healthcare providers for the population of Olmsted County, Minnesota, USA[16].

The study population comprised a retrospectively identified cohort of Olmsted County residents with incident MI between January 1, 1979, and January 1, 2010. MI was defined using standardized epidemiologic criteria and Minnesota coding of the electrocardiogram (ECG)[17,18,19]. All patients with RA were identified within the MI cohort using the 1987 American College of Rheumatology (ACR) classification criteria for RA[20]. The RA incidence date was defined as the first date of fulfillment of 4 of the 7 ACR diagnostic criteria. For patients with incident MI who moved to Olmsted County with prevalent RA, the incidence date of RA was estimated from

medical record documentation. For each patient with RA, 2 MI patients without RA were randomly selected from all patients with MI of similar age and sex with an MI in the same calendar year. The inpatient and outpatient medical records were reviewed longitudinally from the onset of MI until the subject's death, migration from Olmsted County, or September 1, 2011, for collection of CV data (as described below). A separate abstractor reviewed the medical records of patients with RA beginning with the date of diagnosis of RA to collect data on RA disease characteristics.

Data collection. Clinical diagnoses were used to ascertain hypertension, diabetes mellitus, and hyperlipidemia. Previous physician diagnoses of cerebrovascular disease and peripheral vascular disease were also collected. Body mass index (BMI) was calculated using the height and weight at onset of MI, and obesity was defined as BMI ≥ 30 kg/m^2. MI characteristics and severity were classified using the Killip class II-IV. ECG findings were documented and categorized into anterior MI, ST-segment elevation MI, and presence of Q waves. Heart failure was defined based on the Framingham criteria[21]. Recurrent ischemia was defined as hospitalization for recurrent MI or unstable angina using physician's diagnosis. Reperfusion or revascularization therapy was defined as the use of thrombolytic therapy, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) within the same hospitalization. Medical treatment during hospitalization and at discharge was documented and included aspirin, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers, beta blockers, statins, other lipid-lowering medications, aspirin, and other antiplatelet agents.

All subjects (irrespective of residency status) were tracked nationally to ascertain vital status, and death certificates were obtained from the respective states for subjects who died outside Minnesota. The underlying cause of death was coded from national mortality statistics and grouped according to *International Classification of Diseases*, 9th Revision (ICD-9) and ICD-10 chapters. Cardiovascular death was defined as ICD-9 codes 390-459 and ICD-10 codes I00-I99 according to the American Heart Association classification[22].

RA characteristics. Data were collected on RA disease characteristics present on or before the date of onset of MI including rheumatoid factor (RF), anticitrullinated protein antibodies (ACPA), presence of rheumatoid nodules, erosions/destructive changes on radiographs, and severe extra-articular disease. Severe extraarticular disease was defined, according to the Malmö criteria, as the presence of pericarditis, pleuritis, Felty's syndrome, vasculitis, neuropathy, scleritis, episcleritis, and glomerulonephritis[23]. Data were collected on use of antirheumatic medication at the time of onset of MI including corticosteroids, disease-modifying antirheumatic drugs (DMARD), and biologic agents.

Statistical analysis. Descriptive statistics (percentages, means, etc.) were used to summarize the data. Characteristics of patients with and without RA at the time of MI were compared using conditional logistic regression models, accounting for the matched structure of the cohorts. In addition, short-term (30-day) outcomes were analyzed using conditional logistic regression, with results summarized using OR, instead of hazard ratios (HR) from Cox models, because censoring was not an issue for short-term outcomes. Kaplan-Meier methods were used to estimate the rate of development of each outcome after MI to account for censoring. Log-rank tests were used to compare the rate of development of each outcome between those with and those without RA. Cox proportional hazards models were used to examine the associations between RA disease characteristics at the time of MI and the development of the outcomes of interest during followup, and results were summarized using HR. In these analyses, patients who had heart failure prior to MI were excluded from the analyses of the development of heart failure during followup. The proportional hazards assumption was examined using the Schoenfeld residuals, and tested using methods by Grambsch and Therneau[24]. No violations of the proportional hazards assumption were found. Analyses were conducted using the R program (R Project for Statistical Computing) and SAS version 9.2 (SAS Institute Inc.).

RESULTS

Characteristics of the study population. The study population consisted of 77 MI patients with RA and 154 MI patients without RA. The mean age at MI was 72.4 years and 55% were female in both cohorts (Table 1). CV disease risk factors including hypertension, dyslipidemia, diabetes mellitus, smoking status, obesity, previous revascularization procedures, cerebrovascular disease, and peripheral vascular disease were assessed — no significant differences between cohorts were found. At the time of MI, there were fewer current smokers among the patients with RA than in those without RA, but this difference did not reach statistical significance (12% vs 21%; p = 0.06). MI characteristics and severity were similar in both groups, with Killip class II-IV in 36% of patients with RA and 35% of patients without RA (p = 0.92). ECG findings were also similar among patients with and without RA.

Treatment with reperfusion therapy and cardioprotective medications. Treatment of patients with and those without RA was similar (Table 2). Reperfusion therapy occurred at similar rates in both groups. When subcategorized by type of reperfusion therapy (i.e., thrombolytics, CABG, and PCI), there were no significant differences in treatment between the 2 groups. Treatment with cardioprotective medications (aspirin, ACE inhibitors, beta blockers, and statins) was assessed both during hospitalization and at discharge from the hospital. During hospitalization, there was a trend toward lower rates of patients with RA receiving each treatment, but these differences did not reach statistical significance. At the time of discharge, there were no significant differences between patients with and without RA. The

Table 1. Characteristics of 77 patients with rheumatoid arthritis (RA) and 154 patients without RA at onset of myocardial infarction (MI).

Characteristic	MI Patients with RA, n = 77	MI Patients without RA, n = 154	p
Age, yrs, mean ± SD	72.4 ± 12.2	72.4 ± 12.2	1.0
Women, n (%)	42 (55)	84 (55)	1.0
Medical history, n (%)			
Hypertension	55 (71)	99 (63)	0.26
Dyslipidemia	31 (40)	62 (40)	0.91
Diabetes mellitus	21 (27)	41 (26)	0.92
Current smoking	9 (12)	32 (21)	0.06
Obesity (body mass index ≥ 30 kg/m^2)	26 (33)	45 (29)	0.48
Revascularization procedures	21 (27)	41 (27)	0.91
Cerebrovascular disease	18 (23)	33 (21)	0.73
Peripheral vascular disease	16 (21)	39 (25)	0.45
MI characteristics and severity, n (%)			
Killip class II–IV	28 (36)	55 (35)	0.92
Electrocardiogram, n (%)			
Anterior MI	25 (32)	50 (32)	0.92
ST-segment elevation	16 (21)	43 (28)	0.24
Presence of Q waves	34 (44)	68 (44)	0.96

Table 2. Treatment of myocardial infarction (MI) patients with and without rheumatoid arthritis (RA).

Treatment	MI Patients with RA, n = 77	MI Patients without RA, n = 154	OR (95% CI)
Reperfusion therapy, n (%)	39 (50)	73 (47)	1.19 (0.63, 2.23)
Medications during hospitalization, n (%)			
Aspirin	56 (72)	127 (81)	0.44 (0.18, 1.09)
ACE inhibitor	25 (32)	58 (37)	0.78 (0.41, 1.48)
Beta blocker	54 (69)	115 (74)	0.83 (0.40, 1.71)
Statin	24 (31)	61 (39)	0.58 (0.25, 1.30)
Other lipid-lowering agents	0 (0)	5 (3)	0.30 (0.0, 1.64)
Other antiplatelet agents	31 (40)	71 (46)	0.71 (0.36, 1.38)
Medications at discharge, n (%)			
Aspirin	49 (63)	99 (63)	0.93 (0.45, 1.95)
ACE inhibitor	23 (29)	51 (33)	0.91 (0.46, 1.78)
Beta blocker	48 (62)	92 (59)	1.45 (0.67, 3.13)
Statin	29 (37)	58 (37)	1.12 (0.50, 2.48)
Other lipid-lowering agents	0 (0)	3 (2)	0.52 (0.0, 3.43)
Other antiplatelet agents	29 (40)	55 (39)	1.07 (0.56, 2.09)

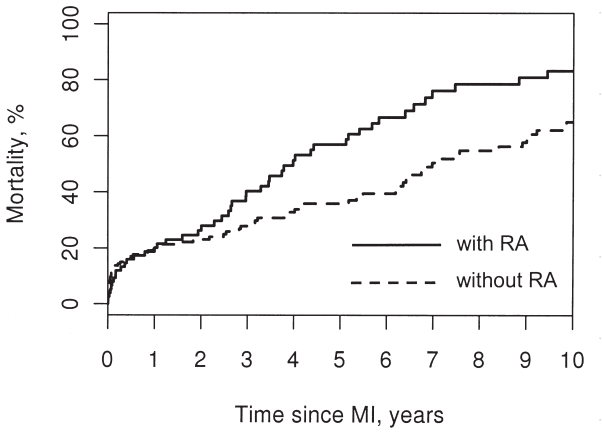
ACE: angiotensin-converting enzyme.

duration of hospitalization after MI shortened over time in both groups, with no evidence of differences in patients with RA compared to those without RA (8.3 ± 7.2 days vs 7.7 ± 7.7 days, respectively; p = 0.55).

Outcomes. We assessed outcomes of death, recurrent ischemia, and heart failure following MI. During hospitalization, 4 (5%) patients with RA and 13 (8%) patients without RA died (p = 0.37). During a median followup of 2.6 years among the patients with RA [interquartile range (IQR) 1.0, 5.6 yrs] and a median followup of 2.7 years among the patients without RA (IQR 0.9, 6.6 yrs), 55 with RA and 85 of those without RA died, corresponding to a higher death rate among the patients with RA compared to those without RA (HR 1.47; 95% CI 1.04, 2.08). Although the short-term mortality was somewhat, but not significantly, lower among patients with RA than those without RA, with 30-day case fatality rates of 6% among patients with RA and 12% among patients without RA (OR 0.41; 95% CI 0.13, 1.31; p = 0.13), by 1 year after MI, the mortality rates were similar in both groups (19% vs 20%). By 5 years, mortality rates were significantly higher among patients with RA (57% ± 6%) compared to those without RA (36% ± 4%; log-rank p = 0.036; Figure 1).

Cause of death information was available in all but 5 of the patients who died. CV causes were found in 28 (53% of 52) deaths among patients with RA and in 40 (49% of 82) deaths among patients without RA. In both groups, the early deaths were predominately CV, and the later deaths were predominantly non-CV. However, there was no apparent difference between groups in the proportion of deaths due to CV causes.

Recurrent ischemia. Recurrent ischemia was more common among patients with RA compared to patients without RA

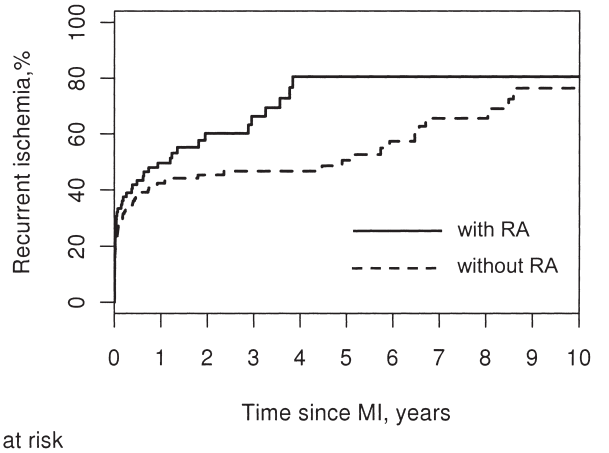


No. at risk

RA	77	44	26	15	9	7
Non-RA	154	82	66	47	31	23

Figure 1. Cumulative incidence of mortality after myocardial infarction (MI) among 77 patients with rheumatoid arthritis (RA) and 154 patients without RA (55 deaths in patients with RA; 85 deaths in patients without RA; log-rank p = 0.036).

(HR 1.51; 95% CI 1.04, 2.18). A total of 48 patients with RA and 76 without RA developed recurrent ischemia during followup, with no difference in the 30-day rates of recurrent ischemia (32% among patients with RA vs 25% among patients without RA; p = 0.24). There were minimal differences in the cumulative incidence of recurrent ischemia at 1 year after MI: 50% (± 6%) among patients with RA and 42% (± 4%) among patients without RA. By 5 years after MI, this difference in cumulative incidence of recurrent ischemia was more pronounced, with 80% (± 7%) in patients with RA and 50% (± 5%) in patients without RA (log-rank p = 0.043; Figure 2).



No. at risk

RA	77	16	5	3	2	2
Non-RA	153	42	31	18	10	5

Figure 2. Cumulative incidence of recurrent ischemia after myocardial infarction (MI) among 77 patients with RA and 153 patients without RA (recurrent ischemia occurred in 48 patients with RA and 76 patients without RA; log-rank p = 0.043).

Heart failure. Among the 64 patients with RA and 127 patients without RA who did not have heart failure at the time of MI, the development of heart failure after MI was similar among patients with and without RA (HR 1.30; 95% CI 0.81, 2.10). During followup, 28 patients with RA and 45 without RA developed heart failure, and there was no difference in 30-day event rates (31% in both groups). By 5 years after MI, the cumulative incidence of developing heart failure was higher among patients with RA (57% ± 8%) than those without RA (35% ± 4%), but this difference did not reach statistical significance (log-rank p = 0.24). Because our study spans several decades, calendar trends in outcomes (mortality, heart failure, and recurrent ischemia) were also examined. Improvements in outcomes over calendar time were similar in both groups, with no evidence that the rate of improvement in outcomes after MI differed in patients with RA compared to patients without RA (p > 0.7 for all outcomes).

RA disease characteristics and association with outcomes. Associations between RA disease characteristics and outcomes (mortality, recurrent ischemia, and heart failure) were assessed in MI patients with RA (Table 3). No significant associations were found for any of the RA disease characteristics examined (presence of RF and/or ACPA, duration of RA, presence of severe extraarticular disease, or use of DMARD and corticosteroids). There were several HR in the 1.5–2.0 range, but CI were wide, indicating our study may have been underpowered to detect associations between RA disease characteristics and MI outcomes. The use of biologic agents could not be assessed because only 2 patients with RA in this cohort were exposed to biologic agents.

DISCUSSION

In this population-based study of MI patients with and without RA, we found no significant differences in risk factor profile, MI treatment, or use of cardioprotective medications, but there was a trend toward lower short-term mortality in patients with RA than in those without RA. Patients with RA experienced significantly poorer longterm outcomes compared to patients without RA and there was no evidence that this disparity between groups had improved over time. Despite this, although our study was underpowered, we did not find an association between RA disease characteristics and mortality, recurrent ischemia, or heart failure. These findings indicate that despite having similar treatment, MI patients with RA have worse longterm outcomes than do MI patients without RA.

Several studies have recently demonstrated a disparity in treatment of MI patients with RA compared to those without RA. A recent observational study demonstrated that MI patients with RA were less likely than MI patients without RA to be treated with reperfusion therapy and were also less likely to receive beta blockers or lipid-lowering agents[13]. Another study found that fewer patients with RA received treatment with cardioprotective drugs during and after hospitalization, although this difference did not reach statistical significance[14]. In contrast, other studies have described increased rates of PCI in MI patients with RA[25]. Our study did not demonstrate a significant difference in use of reperfusion therapy during hospitalization or use of cardioprotective medication after discharge from the hospital. This may be explained by institutional variation in treatment of patients with and without RA. Rates of PCI and CABG as well as outcomes vary, based on geographic location[26,27,28]. Our results may not be generalizable to other geographic regions. Others have postulated that treatment of MI patients with RA has changed over time, affecting outcomes[29].

There is evidence from a prospective observational study that patients who developed RA after 1980 were less likely to experience an MI or to die of a fatal MI than patients who developed RA before 1980, and the rate of fatal MI in patients who developed RA after 1980 was not statistically

Table 3. Risk factors for mortality, heart failure, and recurrent ischemia among 77 patients with rheumatoid arthritis (RA) and myocardial infarction (MI). Models adjusted for age at MI, sex, and year of MI.

RA Characteristics at Onset of MI	N (%) or mean ± SD	Mortality HR (95% CI)	Heart Failure† HR (95% CI)	Recurrent Ischemia HR (95% CI)
RF and/or ACPA-positive	54 (70)	1.36 (0.73, 2.54)	1.19 (0.52, 2.73)	0.96 (0.51, 1.80)
Duration of RA, yrs**	14.0 ± 9.5	1.23 (0.92, 1.65)	1.27 (0.86, 1.88)	0.95 (0.69, 1.32)
Rheumatoid nodules	63 (82)	1.29 (0.56, 2.97)	1.11 (0.40, 3.07)	0.72 (0.35, 1.49)
Erosions/destructive changes	65 (84)	1.76 (0.71, 4.35)	1.84 (0.54, 6.30)	1.60 (0.66, 3.85)
Severe extraarticular disease	63 (82)	1.42 (0.63, 3.20)	0.99 (0.36, 2.69)	0.98 (0.46, 2.08)
Methotrexate	17 (22)	0.83 (0.42, 1.66)	0.93 (0.37, 2.38)	0.91 (0.43, 1.93)
Hydroxychloroquine	9 (12)	1.75 (0.67, 4.59)	0.67 (0.15, 2.88)	0.82 (0.28, 2.37)
Other nonbiologic DMARD	10 (13)	2.36 (0.84, 6.62)	0.45 (0.06, 3.52)	1.09 (0.40, 2.95)
Corticosteroids	25 (32)	1.24 (0.68, 2.27)	0.75 (0.32, 1.73)	1.47 (0.79, 2.72)

† Among 64 patients without heart failure prior to myocardial infarction. ** Hazard ratio (HR) per 10-year increase in disease duration. RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; DMARD: disease-modifying antirheumatic drugs.

different from the general population[29]. We found no differences in the relative improvement of outcomes (mortality, heart failure, and recurrent ischemia) over calendar time in patients with RA compared to patients without RA. This may be explained by a difference in timing of the cohorts. In the aforementioned study[29], differences were found in patients who developed RA after 1980 compared to those who developed it earlier. Our study included patients who had an MI in 1979 or later.

We found that 30-day mortality was somewhat lower among MI patients with RA compared to MI patients without RA, although this finding was not statistically significant. We found that 30-day recurrent ischemia and heart failure were similar between the 2 groups. We found no differences in rates of reperfusion therapy after MI, but other reports suggest that short-term mortality may be dependent on therapy choice while hospitalized. In one report, MI patients with RA were less likely to receive reperfusion therapy than MI patients without RA, and an increased 30-day case fatality rate was found in the patients with RA[12,13]. In contrast, another report showed that MI patients with RA were more likely to have PCI than MI patients without RA, and a decreased in-hospital mortality rate was found in patients with RA[25]. Yet another cross-sectional study of all patients with RA who underwent revascularization found decreased in-hospital mortality in patients with RA[30]. The disparity of these results might be explained by differences in study design and in case mix, which may have led to differences in the use of PCI in these cohorts.

Additionally, we found increased longterm mortality and recurrent ischemic events in patients with RA compared to those without RA. These findings correspond to previous studies showing increased longterm mortality in MI patients with RA[1,31]. In a recent study of post-MI patients, patients with RA who received similar treatment to patients without RA had increased case fatality at 10 years, but no difference in short-term survival[14]. Similar treatment between patients with and without RA may result in similar short-term outcomes; however, longterm outcomes between patients with and without RA remain disparate. This difference in longterm outcomes suggests RA disease characteristics may play a role in determining the longterm mortality after MI in RA. We were unable to demonstrate significant associations between RA disease characteristics and mortality, recurrent ischemia, or heart failure after MI, likely because of limited statistical power. Previous studies have demonstrated associations between RA severity and CV mortality, but none have examined predictors of mortality after MI in RA[32,33]. If RA disease characteristics do indeed play a role in determining longterm survival after MI in persons with RA, this would argue for a more personalized, disease-specific approach to post-MI management for patients with RA, similar to post-MI management in patients with diabetes mellitus.

Our study has several potential limitations. In this retrospective study, we were limited to information available from medical records for evaluation of risk factors and outcomes. Risk factors and outcomes were not measured at regular intervals and were dependent on physician documentation. This limitation was minimized using the Rochester Epidemiology Project database and standardized case ascertainment. Data on treatment therapy of modifiable risk factors was not collected, because of changes of diagnosis and treatment guidelines over the time period of our study. Data on nonsteroidal antiinflammatory agents was not collected because use of this over-the-counter medication is frequently not documented in medical records. Finally, we were unable to obtain data on the disease activity of patients at the time of MI. Erythrocyte sedimentation rate was documented in less than half the cohort in the months prior to MI, and no other measure of disease activity was consistently used or documented over the study time period.

The statistical power of our study was adequate for comparisons between cohorts, but limited when examining associations within the RA cohort, such as associations between RA disease characteristics and outcomes after MI. It may have been underpowered to detect associations between RA disease characteristics and MI outcomes.

As this was an observational study, we cannot rule out the possibility of confounding by indications/contraindications of medication use with the risk of fatality and heart failure. Further, the population of Olmsted County, Minnesota, is predominately white, so our conclusions may not be generalizable to other more diverse populations[34]. Strengths of the study include the population-based longitudinal design with longterm followup of both cohorts.

Our study did not demonstrate a significant difference in treatment of MI patients with and those without RA, including reperfusion therapy and use of cardioprotective medications. The 30-day case fatality rate was somewhat lower among patients with RA compared to those without RA, but 30-day rates of recurrent ischemia and heart failure were similar between MI patients with and those without RA.

The increase in longterm mortality in patients with RA compared to patients without RA indicates that early similarity in post-MI treatment changes outcomes over time. MI patients with RA may benefit from closer monitoring and treatment of their rheumatologic disease as well as their CV disease to optimize their CV disease outcomes. More research is needed to understand the determinants of longterm outcomes after MI in patients with RA, in particular, the role of RA disease characteristics.

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