Published in final edited form as:

Clin Gastroenterol Hepatol. 2011 October ; 9(10): 875–880. doi:10.1016/j.cgh.2011.06.032.

No Increased Risk of Myocardial Infarction Among Patients with Ulcerative Colitis or Crohn's Disease

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Abstract

BACKGROUND & AIMS—Patients with chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis have an increased risk of myocardial infarction (MI). Studies of the risk of MI among patients with inflammatory bowel disease (IBD) have provided inconsistent results. We aimed to determine the risk of first-time acute MI in patients with ulcerative colitis (UC) or Crohn's disease (CD) compared to patients from general practice.

METHODS—We conducted 2 retrospective cohort studies using the General Practice Research Database (GPRD). A total of 15,498 UC patients were matched to 144,605 patients from general practice patients (for age, sex, year of enrollment in the GPRD, and general practice of attendance) and followed for a mean of 4.7 years; 9,829 CD patients were matched to 92,987 patients from general practice and followed for a mean of 4.5 years. Univariable and multivariable Cox regression analyses were adjusted for age, sex, history of hypertension, diabetes mellitus, hypercholesterolemia, smoking status, body mass index, and aspirin use for each cohort.

RESULTS—Patients with UC had a significantly increased risk of first-time acute MI compared to patients from general practice in unadjusted, but not adjusted analysis (adjusted hazard ratio [HR] 1.11, 95% confidence interval [CI] 0.98–1.27). Patients with CD did not have an increased risk of MI in either unadjusted or adjusted analysis (adjusted HR 1.09, 95% CI 0.89–1.34).

CONCLUSIONS—Unlike some other chronic inflammatory diseases, IBD is not associated with an increased risk of MI.

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Disclosures: No authors have any potential conflicts that are relevant to the manuscript.

Writing Assistance: None

Author Contributions: Mark T. Osterman (study concept/design, acquisition of data, analysis/interpretation of data, drafting of the manuscript, statistical analysis); Yu-Xiao Yang (statistical analysis, critical revision of the manuscript); Colleen Brensinger (acquisition of data, critical revision of the manuscript); Kimbely A. Forde (acquisition of data, critical revision of the manuscript); Gary R. Lichtenstein (critical revision of the manuscript); James D. Lewis (study concept/design, analysis/interpretation of data, critical revision of the manuscript).

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Keywords

heart disease; inflammation; intestine; intestine; immune disorders

Introduction

There is a wealth of data demonstrating that inflammation plays a fundamental role in the development of myocardial infarction (MI). Inflammation is involved in all stages of atherosclerosis, from initiation and progression to eventual plaque rupture and thrombosis.¹ Integral to this process are inflammatory cells, adhesion molecules, chemoattractants, cytokines, and the CD40/CD40L pathway.^{1–3} C-reactive protein (CRP), clearly at least a marker of inflammation and MI risk, may also play a causal role in atherosclerosis and MI.²

Several chronic inflammatory diseases, most notably rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis, have been shown to be associated with an increased risk of MI.^{4–12} At present it is unclear whether patients with inflammatory bowel disease (IBD) are at increased risk of MI. Several population-based studies and one single-center study have shown conflicting results with respect to the risk of cardiovascular events or ischemic heart disease or death from these events in IBD patients compared to non-IBD patients.^{13–18}

Mechanistically, there are at least two potential links between IBD and atherosclerosis. One is CRP, which is often elevated in both processes. Another is the CD40/CD40L pathway, which induces an intense proinflammatory response by stimulating the expression of various adhesion molecules, chemoattractants, and cytokines. CD40 and CD40L are expressed by a variety of different cell types, including monocytes/macrophages, T and B cells, dendritic cells, endothelial cells, vascular smooth muscle cells, fibroblasts, and platelets.¹⁹ In atherosclerosis, the inflammation caused by the CD40-CD40L interaction is thought to lead to the formation of an unstable plaque and its subsequent rupture, resulting in thrombosis. In IBD, high platelet expression of CD40L is believed to trigger or amplify the proinflammatory response.²⁰

Thus, based on the observed association of other chronic inflammatory diseases with MI and the proposed molecular pathways linking IBD and atherosclerosis, we hypothesized that patients with IBD may be at increased risk of MI. The aims of this study were to determine the risk of first-time acute MI in patients with ulcerative colitis (UC) and Crohn's disease (CD) at the population level.

Methods

Study Population

The General Practice Research Database (GPRD) is a population-representative electronic medical record database in the United Kingdom (UK) and has been used extensively worldwide for epidemiological research. It was established in 1987 and comprises 5–7% of the UK population in any given year. As of August 2003, a total of nearly 9.4 million individuals had registered with the GPRD, encompassing over 40 million person-years of follow-up data.²¹ The age and sex distributions of participants in the GPRD are similar to that of the general UK population. More than 700 general practices have provided data for the GPRD since its inception. Each general practice must undergo formal training and display competence at entering data in order to be considered “up to standard.”

Many validation studies using the GPRD have been published concerning the exposure and outcome definitions employed in this study. Regarding the diagnosis of IBD, at least two studies including a total of 225 patients with IBD showed 92–94% accuracy of diagnostic recording, both for UC and CD.^{22,23} The diagnosis of first-time acute MI in the GPRD has also been validated by at least four studies including a total of more than 500 patients and reported greater than 90% accuracy of diagnostic recording.^{24–27}

Design

Approval from Institutional Review Board of the University of Pennsylvania and the Epidemiology and Pharmacology Core and Scientific and Ethical Advisory Group from the United Kingdom was obtained prior to commencement of the studies. We performed two separate retrospective cohort studies, and thus two distinct exposure groups were used: UC patients and CD patients. For each patient with these diseases, up to ten patients from the general population were randomly selected and then matched to the exposed patient on age, sex, year of enrollment in the GPRD, and general practice of attendance. Exclusion criteria included: age <18 years; history of MI, coronary artery disease, congestive heart failure, ventricular arrhythmia, or implantable cardiac defibrillator placement prior to the start of follow-up; and history of RA, SLE, or psoriasis.

Start of follow-up was defined by the latest of the following occurrences: 1) six months after registration with the GPRD (so as to avoid categorizing prevalent MI as incident MI);²⁸ 2) data entry being considered “up to standard;” or 3) diagnosis of UC or CD. End of follow-up was defined as the earliest of the following occurrences: 1) primary outcome; 2) end of study; 3) death; or 4) withdrawal from the GPRD.

Outcomes

The primary outcome was the risk of first-time acute MI. Secondary outcomes included: 1) the risk of early MI (defined liberally as ≤55 years of age) in UC or CD patients compared to general practice patients ≤55 years of age; and 2) the risk of MI among UC or CD patients with increased duration of disease (>5–10, >10–20, and >20 years), in which UC or CD patients with disease duration ≤5 years were used as the baseline comparator group (rather than the unexposed group of general practice patients).

Statistical Analysis

All analyses were performed using STATA version 10.0. Initial descriptive statistics, including demographic information, were calculated. Continuous variables were compared between the exposed and unexposed groups using a student's *t* test, and binary and categorical variables were compared between these groups using a χ^2 test. The primary and secondary analyses were performed using Cox proportional hazards multivariable regression. Potential confounding variables which were adjusted for in the models included: age; sex; history of hypertension, diabetes mellitus, or hypercholesterolemia (as defined by diagnosis codes or medication prescriptions for these conditions); smoking status (categorized as current or not current); body mass index ([BMI], categorized as normal, overweight, or obese, as defined by the World Health Organization²⁹); and aspirin use. All covariates were defined at the start of follow-up, except for aspirin use, which was adjusted for throughout the follow-up period as a time-varying covariate.

Based on prior studies in the GPRD which observed that 15–40% of patients had missing data with respect to smoking status and BMI,^{6,30,31} it was assumed that a number of patients in our study would also have missing data on these variables. For this reason, multiple sensitivity analyses were performed to account for these missing data. With respect to smoking status, for each primary or secondary analysis that was done, four separate

sensitivity analyses were done: 1) assigning a missing value indicator as the last category for the variable; 2) case deletion, in which patients with missing data were dropped from the analysis; 3) assigning all patients with missing data to be smokers; and 4) assigning all patients with missing data to be nonsmokers. With respect to BMI, for each primary or secondary analysis that was done, five separate sensitivity analyses were done: 1) assigning a missing value indicator as the last category for the variable; 2) case deletion; 3) assigning all patients with missing data to be of normal BMI; 4) assigning all patients with missing data to be overweight; and 5) assigning all patients with missing data to be obese. For both variables with missing data, it was decided *a priori* that the use of a missing value indicator would be the default method for all initial analyses.

Results

In the UC cohort, we identified 15,498 UC patients who were matched to 144,605 general practice patients on age, sex, calendar year of enrollment, and general practice of attendance. The demographic information of this cohort is shown in Table 1. The mean duration of UC at start of follow-up was 13.1 years, and patients in both groups were followed-up for a mean of 4.6–4.7 years. Although the two groups differed significantly from each other with respect to most variables (at least partially due to the very large sample sizes), most of the numerical differences were small. Larger differences were evident with respect to smoking status, where a larger proportion of UC patients were not current smokers, and BMI, where a larger proportion of general practice patients had missing data. In the CD cohort, we identified 9,829 CD patients who were matched to 92,987 general practice patients. The demographic information of this cohort is shown in Table 2. The mean duration of CD at start of follow-up was 11.7 years, and patients were followed-up for a mean of 4.4–4.5 years. Again, numerical differences between the two groups were small with respect to most variables, with the exception of smoking status, where CD patients were more likely to be current smokers, and BMI, where general practice patients were more likely to have missing data.

A total of 280 UC patients (1.8%) and 2,188 general practice patients (1.5%) developed their first MI during the study period. In unadjusted analysis, UC patients were found to have a slightly increased risk of first-time acute MI compared to the unexposed group, with a hazard ratio (HR) of 1.18 (95% confidence interval [CI], 1.03–1.34; $p = 0.014$). However, adjustment for age, sex, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, BMI, and aspirin use, revealed that UC patients had a risk of MI similar to that of general practice patients with HR of 1.11 (95% CI, 0.98–1.27; $p = 0.11$). In the CD cohort, 110 CD patients (1.1%) and 908 general practice patients (1.0%) developed their first MI during the study period. CD patients were found to have a risk of first-time acute MI similar to the unexposed group in both unadjusted (HR, 1.15; 95% CI, 0.94–1.41; $p = 0.17$) and adjusted analyses (HR, 1.11; 95% CI, 0.91–1.36; $p = 0.30$). As expected, in both the UC and CD cohort multivariable models (presented separately in Tables 3 and 4, respectively) in which each variable was adjusted for all other variables (including IBD subtype) to ascertain its independent association with MI, increased age (per 1-year increase), male sex, hypertension, diabetes mellitus, current smoking, and increased BMI each were independently associated with a significantly increased risk of MI (hypercholesterolemia was significantly associated with an increased risk of MI in the UC cohort only).

Two sets of subgroup analyses were done for each cohort: 1) examining the risk of early MI (≤ 55 years of age) in UC or CD patients compared to general practice patients ≤ 55 years of age; and 2) examining the risk of MI among only UC or CD patients with increasing duration of disease (in which UC or CD patients with disease duration ≤ 5 years were used as the baseline comparator group rather than unexposed general practice patients). With respect

to the risk of early MI, patients with UC or CD were not at increased risk compared to general practice patients, with HR of 0.78 (95% CI, 0.55–1.09; $p = 0.15$) for UC patients and 0.90 (95% CI, 0.57–1.42; $p = 0.64$) for CD patients (Table 5a). With respect to disease duration and risk of MI, UC patients with longer disease duration did not have a higher risk of MI than those with disease duration ≤ 5 years (although the HRs increased nonsignificantly over time), but among CD patients, the risk of MI decreased with longer disease duration and was significantly lower for those with >20 years of disease (Table 5b).

Multiple sensitivity analyses were done for each cohort to account for the high rates of missing data in the covariates, smoking status and BMI. In each case, the results of the primary and subgroup analyses did not change appreciably when compared to the default method of analysis in which patients with missing data were assigned a missing value indicator (data not shown). Also, since we observed slightly higher rates of several cardiac risk factors (history of hypertension, diabetes mellitus, and hypercholesterolemia) in the UC and CD patients, we redid all primary and subgroup analyses excluding aspirin users and found that the results were nearly identical (data not shown).

Discussion

Our two identically-designed retrospective cohort studies found that patients with UC or CD did not have an increased risk of first-time acute MI compared to general practice patients after adjustment for known cardiac risk factors, specifically age, sex, history of hypertension, diabetes mellitus, hypercholesterolemia, smoking status, BMI, and aspirin use. We also did not find an increased risk of early MI for UC or CD patients compared to the unexposed group. Finally, longer duration of IBD was not a risk factor for MI.

To our knowledge, this is the first population-representative study formally evaluating the risk of first-time acute MI in patients with IBD and also only the second study which adjusted for known cardiac risk factors. Earlier population-based studies, which examined cause-specific mortality in IBD and did not find an increase in death from cardiovascular events or ischemic heart disease,^{13–16} were limited by reporting only deaths but not events, lack of internal control groups, and lack of adjustment for known cardiac risk factors. A more recent population-based study, which examined a combined endpoint of ischemic heart disease (which included acute MI, old MI, and other forms of acute, subacute, and chronic ischemic heart disease) and reported a slightly increased risk in patients with UC and CD,¹⁷ also did not adjust for known cardiac risk factors. Our results are in keeping with those of a recent single-center retrospective cohort study which also did not find an increased risk of MI in IBD patients;¹⁸ the fact that the authors did observe higher rates of overall cardiovascular events may have been due to the inclusion of less rigorous endpoints in their combined outcome.

Several systemic chronic inflammatory diseases, especially RA, SLE, and psoriasis, have been found to be associated with an increased risk of ischemic heart disease. Multiple studies, including large population-based studies using the GPRD and designed similarly to our studies, have observed an increased risk of MI after adjustment for known cardiac risk factors in patients with RA, with a relative risk of 1.5–3.2,^{4–7} and SLE, with risk ratios of 2.3–2.7.^{6,8–11} Another GPRD study showed that patients with psoriasis are also at increased risk of MI.¹² Our hypothesis was that patients with CD, given its frequent systemic involvement, and possibly even UC, were at increased risk of myocardial infarction. However, we did not find this to be the case. Although it is currently not known mechanistically how RA, SLE, and psoriasis may predispose patients to ischemic heart disease, it is likely that differences in the inflammatory biology of these diseases as compared to UC and CD are at least partially responsible for this differential risk of MI. It is

also possible that the inflammatory milieu and platelet dysfunction in UC and CD are more conducive to the formation of venous thrombosis rather than arterial thrombosis, as several studies have reported an increased risk of venous thromboembolism in IBD patients.^{32–35} Our observation that a longer duration of CD was associated with a lower risk of MI among CD patients was an unexpected but interesting finding and warrants further investigation. Regardless, there was no evidence that longer duration of IBD increased the risk of MI.

Our study has several potential limitations. There were modest amounts of missing data on two covariates, smoking status and BMI. However, this issue was addressed rigorously via multiple sensitivity analyses which showed that even with the assignment of all missing values to the most extreme values, the results of all primary and subgroup analyses did not change appreciably. Misclassification bias is a potential concern in any database study. However, substantial misclassification of exposure or outcome is unlikely, given the numerous validation studies of the diagnostic accuracy of UC, CD, and first-time acute MI in the GPRD.^{22–27} Misclassification of aspirin use is possible, as over-the-counter aspirin use is not available in the GPRD. However, it has been suggested in two studies that daily regular aspirin use is largely captured by the GPRD.^{36,37} A slightly higher proportion of IBD patients had hypertension, diabetes mellitus, and hypercholesterolemia, compared to general practice patients. It is possible that this imbalance was due to preferential detection in IBD patients due to more frequent contact with healthcare professionals and that some general practice unexposed patients were misclassified as not having these conditions. However, it is unlikely that such misclassification would have a large impact on the results as the magnitude of difference in prevalence of these conditions between the IBD and unexposed cohorts was small. Alternatively, the slight imbalance of several traditional cardiac risk factors could be related to medical therapy of IBD, particularly treatment with corticosteroids. Of course, our adjusted models examined the association of IBD with MI after adjusting for these risk factors, suggesting that IBD itself is not an independent risk factor for MI. Thus, patients with IBD should be selected for primary and secondary prophylaxis for MI in the same manner as patients without IBD. Finally, as with all observational studies, there is always the possibility of residual confounding, in our case possibly from family history of early MI (about which there are limited data in the GPRD).

We elected not to censor follow-up after patients underwent surgery/colectomy for IBD. Although surgery reduces chronic inflammation for a period of time, most patients with CD have recurrence shortly after surgery. Patients with UC who undergo total proctocolectomy with creation of an ileal pouch may also have chronic inflammation. Importantly, even if the risk of MI was reduced following surgery, the relative low incidence of surgery would not be expected to have substantially biased the results.

The results of our study should be interpreted with two contextual points in mind. First, the average follow-up for patients in this study was less than five years. It is conceivable that with longer follow-up, different results may have been seen. Second, the IBD patients in this study were largely of the pre-anti-tumor necrosis factor (TNF) therapy era, and although infliximab and other anti-TNF agents have not been specifically linked to ischemic heart disease, the results may have been different had the study been conducted in the anti-TNF therapy era.

Lastly, it deserves mention that we considered the inclusion of corticosteroid use as a covariate in our analyses. However, we decided against this for a few reasons. The relationship between corticosteroid use and ischemic heart disease is unclear, as data addressing this issue have been conflicting.^{38–41} In addition, adjustment for corticosteroid use would have been very difficult for two reasons: 1) the majority of unexposed patients from the general practices would not be receiving corticosteroid therapy, thereby limiting

the ability to adjust for or match on corticosteroid exposure; and 2) information regarding prior corticosteroid exposure would be unavailable due to left-censoring.

In conclusion, we found that patients with UC or CD do not appear to be at elevated risk of MI compared to general practice patients. These results are contrary to those seen in other chronic inflammatory diseases, such as RA, SLE, and psoriasis. This difference in risk of MI may reflect differences in the underlying biology of UC and CD compared to RA, SLE, and psoriasis.

Acknowledgments

Grant Support: American Gastroenterological Association Fellow-Faculty Transition Award (MTO) and K24-DK078228 (JDL)

Abbreviations

CD	Crohn's disease
IBD	inflammatory bowel disease
MI	myocardial infarction
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
UC	ulcerative colitis

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Table 1

Baseline characteristics of UC cohort.

Variable	UC patients (n = 15,498)	General Population (n = 144,605)	p-value
Age (mean, y)	50.0	49.1	<0.001
Sex (% M/F)	48.4/51.6	48.0/52.0	0.28
Hypertension (%)	18.5	13.5	<0.001
Diabetes mellitus (%)	3.6	2.1	<0.001
Hypercholesterolemia (%)	2.1	1.5	<0.001
Smoking (%)			
Current	23.2	27.9	
Not current	55.3	39.8	
Missing	21.5	32.3	<0.001
Body mass index (%)			
Normal	32.7	26.6	
Overweight	26.4	23.0	
Obese	11.1	10.3	
Missing	29.9	40.1	<0.001
Aspirin use (% with ≥ 1 prescription)	7.1	6.1	<0.001
Follow-up time (mean, y)	4.6	4.7	0.01
Duration of disease (mean, y)	13.1	—	—

Table 2

Baseline characteristics of CD cohort.

Variable	CD patients (n = 9,829)	General Population (n = 92,987)	p-value
Age (mean, y)	44.2	43.3	<0.001
Sex (% M/F)	41.0/59.0	40.9/59.1	0.89
Hypertension (%)	14.5	10.5	<0.001
Diabetes mellitus (%)	1.9	1.7	0.09
Hypercholesterolemia (%)	1.3	1.1	0.10
Smoking (%)			
Current	37.0	28.9	
Not current	41.5	38.9	
Missing	21.6	32.2	<0.001
Body mass index (%)			
Normal	40.4	29.4	
Overweight	21.8	21.4	
Obese	8.2	9.7	
Missing	29.7	39.5	<0.001
Aspirin use (% with ≥ 1 prescription)	5.2	4.4	0.01
Follow-up time (mean, y)	4.4	4.5	0.08
Duration of disease (mean, y)	11.7	—	—

Table 3

Multivariable analysis for risk of MI in UC cohort.*

Variable	HR (95% CI), p-value
UC	1.11 (0.98–1.27), 0.11
Age (per 1-year increase)	1.07 (1.06–1.07), <0.001
Male sex	2.42 (2.22–2.63), <0.001
Hypertension	1.65 (1.50–1.81), <0.001
Diabetes mellitus	1.92 (1.64–2.24), <0.001
Hypercholesterolemia	1.65 (1.41–1.85), 0.002
Current smoking	1.30 (1.18–1.43), <0.001
BMI: Overweight	1.19 (1.06–1.33), 0.003
Obese	1.22 (1.06–1.40), 0.006
Aspirin use	1.60 (1.31–1.96), <0.001

* In this analysis, each variable was adjusted for all other variables to ascertain its independent association with MI.

Table 4

Multivariable analysis for risk of MI in CD cohort.*

Variable	HR (95% CI), p-value
CD	1.09 (0.89–1.34), 0.38
Age (per 1-year increase)	1.07 (1.07–1.08), <0.001
Male sex	2.43 (2.14–2.76), <0.001
Hypertension	1.66 (1.43–1.93), <0.001
Diabetes mellitus	1.89 (1.48–2.42), <0.001
Hypercholesterolemia	1.21 (0.79–1.84), 0.38
Current smoking	1.44 (1.25–1.67), <0.001
BMI: Overweight	1.19 (1.00–1.41), 0.052
Obese	1.32 (1.07–1.62), 0.010
Aspirin use	2.00 (1.40–2.85), <0.001

* In this analysis, each variable was adjusted for all other variables to ascertain its independent association with MI.

Table 5a

Subgroup analysis: risk of early MI in UC or CD patients compared to general practice patients.*

Cohort	HR (95% CI), p-value
UC	0.78 (0.55–1.09), 0.15
CD	0.90 (0.57–1.42), 0.64

* Adjusted for sex, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, BMI, and aspirin use. All patients in this analysis are ≤ 55 years of age.

Table 5b

Subgroup analysis: risk of MI in UC and CD patients by disease duration.*

Cohort	HR (95% CI), p-value
UC	
Disease duration (y)	
≤5	Reference
>5–10	1.00 (0.67–1.50), 1.00
>10–20	1.04 (0.74–1.46), 0.81
>20	1.21 (0.89–1.64), 0.22
CD	
Disease duration (y)	
≤5	Reference
>5–10	0.90 (0.51–1.57), 0.70
>10–20	0.66 (0.38–1.17), 0.16
>20	0.50 (0.27–0.95), 0.035

* Adjusted for age, sex, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, BMI, and aspirin use. Analysis is limited to patients with IBD.