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Steroid Exposure, Acute Coronary Syndrome, and Inflammatory Bowel Disease: Insights into the Inflammatory Milieu

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Abstract

Background—Steroids are anti-inflammatory agents commonly used to treat inflammatory bowel disease. Inflammation plays a critical role in the pathophysiology of both inflammatory bowel disease and acute coronary syndrome. We examined the relationship between steroid use in patients with inflammatory bowel disease and acute coronary syndrome.

Methods—In 177 patients with inflammatory bowel disease (mean age 67, 75% male, 44% Crohn's disease, 56% ulcerative colitis), we performed a 1:2 case-control study matched for age, sex and inflammatory bowel disease type and compared 59 patients with inflammatory bowel disease with acute coronary syndrome to 118 patients with inflammatory bowel disease without acute coronary syndrome. Steroid use was defined as current or prior exposure. Acute coronary syndrome was defined as myocardial infarction or unstable angina, confirmed by cardiac biomarkers and coronary angiography.

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All authors had access to the data and a role in the development of the manuscript

CONFLICT OF INTEREST:

The other authors report no conflict of interest.

Results—In patients with inflammatory bowel disease, 34% with acute coronary syndrome had exposure to steroids versus 58% without acute coronary syndrome ($p<0.01$). Steroid exposure reduced the adjusted odds of acute coronary syndrome by 82% (odds ratio [OR] 0.39, 95% CI 0.20-0.74; adjusted OR 0.18, 95% CI 0.06-0.51) in patients with inflammatory bowel disease, 77% in Crohn's disease (OR 0.36, 95% CI 0.14-0.92; adjusted OR 0.23, 95% CI 0.06-0.98), and 78% in ulcerative colitis (OR 0.41, 95% CI 0.16-1.04; adjusted OR 0.22, 95% CI 0.06-0.90). There was no association between other inflammatory bowel disease medications and acute coronary syndrome.

Conclusions—In patients with inflammatory bowel disease, steroid use significantly reduces the odds of acute coronary syndrome. These findings provide further mechanistic insight into the inflammatory processes involved in inflammatory bowel disease and acute coronary syndrome.

Keywords

Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Steroids; Acute Coronary Syndrome

INTRODUCTION

Inflammation plays a critical role in the pathophysiology of inflammatory bowel disease, including Crohn's disease and ulcerative colitis, as well as coronary artery disease (1, 2). The pathogenesis of inflammatory bowel disease involves a cascade of dysfunctional immune-mediated processes in genetically predisposed individuals. Inflammation is involved in all stages of coronary atherosclerosis and acute coronary syndromes, from initiation and progression to eventual plaque rupture and thrombosis(1). There is some evidence in the literature that supports a shared interaction between these two different diseases, with patients with inflammatory bowel disease, regardless of inflammatory bowel disease type, having a higher incidence of coronary artery disease compared to patients without inflammatory bowel disease (3-5).

Steroids are anti-inflammatory agents, which are commonly used for the treatment of acute inflammatory bowel disease flares. Other medications for inflammatory bowel disease include biological agents such as infliximab and immunomodifiers such as azathioprine, 6-Mercaptopurines and methotrexate(6). Steroids are able to modulate the immune response via interactions with glucocorticoid receptors in the cell nucleus leading to the inhibition of signaling and subsequent expression of inflammatory adhesion molecules(7). Although there is a relationship between inflammatory bowel disease and coronary artery disease regarding inflammation, there is controversy regarding the impact of steroids in patients with inflammatory bowel disease and the development of subsequent cardiovascular events (8-10). Furthermore, current inflammatory bowel disease management guidelines do not include any specific recommendations for primary prevention of coronary artery disease(6).

Therefore, this case:control study aims to (1) investigate the relationship between steroid use in patients with inflammatory bowel disease and the development of acute coronary syndrome and (2) examine the relationship between inflammatory bowel disease medications other than steroids and the development of acute coronary syndrome.

METHODS

Study Population

In this case-control study, patients with inflammatory bowel disease were identified using the Research Patient Data Registry (Partners HealthCare, Boston, Massachusetts), a centralized clinical data registry with medical information from Partners HealthCare. Figure 1 summarizes the study schema and inclusion/exclusion of patients. Patients were initially screened for a diagnosis of inflammatory bowel disease (Crohn's disease or ulcerative colitis) and a first presentation of acute coronary syndrome (acute myocardial infarction or unstable angina) who also underwent coronary angiography between January 2005 and July 2011. We determined if it was a first presentation of acute coronary syndrome by confirming in the patients' medical record from the Partners HealthCare network, which included all available clinical notes, electrocardiograms, non-invasive imaging studies, coronary angiography, and cardiothoracic surgical reports, to ensure that there was no previous documentation of acute coronary syndrome. For the inflammatory bowel disease diagnosis, both newly diagnosed and long standing cases were included. Of the 430 patients screened, 59 patients with both inflammatory bowel disease and acute coronary syndrome were selected as 'cases'. A separate Research Patient Data Registry search was then conducted to identify 'controls' with a diagnosis of inflammatory bowel disease but no previous history of coronary artery disease. Two control patients were matched to each case on the basis of age (± 3 years), gender and inflammatory bowel disease type. The local Institutional Review Board approved the study protocol.

Definition of Inflammatory Bowel Disease

The diagnosis of inflammatory bowel disease, either Crohn's disease or ulcerative colitis, was established by a physician, as documented in the electronic medical records and was confirmed using clinical, histological, endoscopic or imaging studies. Such studies included colonoscopies, sigmoidoscopies or gastro-intestinal biopsies.

Definition of Steroid Use

The primary predictor of interest in this study was steroid use, which was determined by review of the medical record. We classified steroid use into the following three categories: current (taking steroids at the time of acute coronary syndrome for cases and at the corresponding time point for controls), former (use of steroids during any time prior to acute coronary syndrome for cases or corresponding time point for controls) and never (no steroids taken at any time or no mention of steroid use in the medical record prior to acute coronary syndrome for cases or at the corresponding time point for controls). Steroid use was indicated primarily for the treatment of acute inflammatory bowel disease flares. However, other reasons for steroid use such as allergic reactions and asthma were also included. Steroid use included oral prednisone and intravenous methylprednisolone, budesonide or dexamethasone. Inhaled and topical steroid usage was not included in the analysis due to the limited systemic effects of both these modes of application. Steroid duration was defined as the cumulative duration of steroid use in months. Study participants were classified as having either chronic or non-chronic exposure to steroids. Chronic steroid exposure was defined as a cumulative steroid exposure for ≥ 90 days. Study participants

with a cumulative exposure to steroids of < 90 days were classified as having non-chronic exposure.

Use of Non-steroid Inflammatory Bowel Disease Medications

We also examined the relationship between the use of other inflammatory bowel disease medications and development of acute coronary syndrome in our patient population. Other inflammatory bowel disease medications included those not classified as steroids such as aminosalicylates (5-aminosalicylic acid), immune modifiers (azathioprine, 6-Mercaptopurine, and methotrexate) and biologic therapies (infliximab and adalimumab). Use of non-steroid inflammatory bowel disease medications were defined as taking any of these three classes of inflammatory bowel disease medications if documentation was present in the medical record at the time of acute coronary syndrome for cases and at the corresponding time point for controls.

Definition of Acute Coronary Syndrome

For study cases, acute coronary syndrome was established using their primary diagnosis of either unstable angina or acute myocardial infarction. Unstable angina was defined as patients with ischemic symptoms suggestive of cardiac ischemia with no elevation in troponin, with or without electrocardiographic changes indicative of ischemia such as ST segment depression or new T wave inversion. Acute myocardial infarction was defined as either an ST elevation myocardial infarction or non-ST elevation myocardial infarction. For every case, we confirmed the diagnosis of acute myocardial infarction with documented elevation in cardiac troponin and evidence of a culprit lesion on coronary angiography. Only patients with a first acute coronary syndrome event were included after the diagnosis of inflammatory bowel disease. The acute coronary syndrome event could be recent or remote from the time of inflammatory bowel disease diagnosis.

Covariates of Interest

We collected data on several covariates of interest including cardiovascular risk factors, coexisting medical conditions, cardiac medications and laboratory values, if reported in the medical record. Cardiovascular risk factors included dyslipidemia, hypertension, family history of coronary artery disease, body mass index, smoking, diabetes, and history of stroke or transient ischemic attack. Co-existing medical conditions included renal insufficiency as well as autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Cardiac medications consisted of aspirin, beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, statins, nicotinic acid and its derivatives, and fibrates. Laboratory values were collected for plasma creatinine to enable calculation of estimated glomerular filtration rate, white blood cell count, platelets and high sensitivity C-reactive protein. Death and cause of death were determined from medical records.

STATISTICAL ANALYSIS

Continuous data are presented as mean±standard deviation or median (interquartile range) as appropriate, and categorical variables are expressed as frequencies and percentages. For between group comparisons, we used Student's t-test or Wilcoxon rank sum for continuous

variables and a Fisher's exact test for categorical data, as appropriate. Conditional logistic regression was used to determine the association between steroid use and acute coronary syndrome. For the multivariable analyses, we included all univariate variables that may be associated with acute coronary syndrome ($p < 0.10$). For inflammatory bowel disease, we adjusted for body mass index, diabetes, dyslipidemia, smoking, family history of coronary artery disease, white blood count and aspirin. We performed similar analyses by inflammatory bowel disease type and forced in body mass index. For Crohn's disease, we adjusted for body mass index, white blood count, and dyslipidemia. For ulcerative colitis, we adjusted for body mass index, diabetes, smoking, family history of coronary artery disease, and aspirin. A two-sided p -value of < 0.05 was considered statistically significant. Statistical analyses were performed using SAS (Version 9.2, SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical characteristics and laboratory results of patients with inflammatory bowel disease with and without acute coronary syndrome are shown in Table 1. Body mass index and white blood count were significantly higher in patients with acute coronary syndrome compared to patients without acute coronary syndrome (both $p < 0.05$). Patients with acute coronary syndrome also had more cardiac risk factors including diabetes, dyslipidemia, smoking, and family history of coronary artery disease compared to patients without acute coronary syndrome (all $p < 0.05$). Patient characteristics stratified by inflammatory bowel disease type are shown in Table 2. Although there was no difference in cardiac risk factors between Crohn's disease patients with and without acute coronary syndrome, there were a greater percentage of ulcerative colitis patients with acute coronary syndrome who had diabetes, smoking history and family history of coronary artery disease compared to ulcerative colitis patients without acute coronary syndrome (all $p < 0.01$). White blood count was higher among Crohn's disease patients with acute coronary syndrome than among Crohn's disease patients without acute coronary syndrome ($p = 0.02$).

Inflammatory bowel disease and cardiac medication use for patients with inflammatory bowel disease with and without acute coronary syndrome is shown in Table 3. In 6 patients, steroids were used for non-inflammatory bowel disease indications that included asthma, osteoarthritis, sterile peritonitis and anaphylaxis. The proportion of steroid use (either current or former) was found to be significantly higher in patients with inflammatory bowel disease without acute coronary syndrome (58%) compared to those with acute coronary syndrome (34%, both $p < 0.01$). Steroid exposure, both chronic and non-chronic was significantly higher among patients with inflammatory bowel disease without acute coronary syndrome compared to patients with acute coronary syndrome ($p < 0.01$). There were no significant differences found between the two groups for non-steroid inflammatory bowel disease medications. The only cardiac medication found to be significant was aspirin, where patients with inflammatory bowel disease with acute coronary syndrome had significantly higher aspirin use compared to patients with inflammatory bowel disease without acute coronary syndrome ($p < 0.01$).

Table 4 shows inflammatory bowel disease and cardiac medication use stratified by inflammatory bowel disease type. Crohn's disease patients without acute coronary syndrome had a significantly higher proportion of current or former steroid use compared to Crohn's disease patients without acute coronary syndrome ($p<0.03$). Among those with ulcerative colitis, patients with acute coronary syndrome had a significantly smaller proportion of current steroid use compared to ulcerative colitis patients without acute coronary syndrome ($p<0.03$). Also, ulcerative colitis patients with acute coronary syndrome had a significantly higher proportion of aspirin use than ulcerative colitis patients without acute coronary syndrome ($p<0.01$).

Figure 2 depicts the association between steroid use and acute coronary syndrome. In unadjusted analysis, steroid use reduced the odds of acute coronary syndrome in patients with inflammatory bowel disease by 61% (crude odds ratio [OR] 0.39, 95% confidence interval [CI] 0.20-0.74, $p<0.01$). In adjusted analysis, steroid use reduced the odds of acute coronary syndrome by 82% (adjusted OR 0.18, 95% CI 0.06-0.51, $p<0.01$) in patients with inflammatory bowel disease, 77% reduction in Crohn's disease (adjusted OR 0.23, 95% CI 0.06-0.98, $p=0.045$), and 78% reduction in ulcerative colitis (adjusted OR 0.22, 95% CI 0.06-0.90, $p=0.035$).

Of the 59 inflammatory bowel disease cases with acute coronary syndrome, there were 25 (42%) ST elevation myocardial infarctions, 25 (42%) non-ST elevation myocardial infarctions, 9 (15%) with unstable angina and 10 (17%) deaths; 2 of the deaths were from cardiac causes, 1 from non-cardiac causes and 7 from unknown causes. Of the 118 control patients with inflammatory bowel disease without acute coronary syndrome, there were 6 (5%) deaths; 4 of the deaths were from non-cardiac causes and 2 were unknown. Patients with inflammatory bowel disease with acute coronary syndrome had a significantly higher all-cause mortality than those without acute coronary syndrome (17% vs. 5%, OR= 3.7, 95% CI 1.3-11.0, $p=0.02$).

DISCUSSION

This study, which explored the associations between steroid use and the development of acute coronary syndrome in patients with known inflammatory bowel disease, found that any exposure to steroids may be protective against acute coronary syndrome. Such exposure reduced the odds of acute coronary syndrome by 82% after adjustment of cardiovascular risk factors of diabetes, dyslipidemia, smoking, family history of coronary artery disease, body mass index as well as aspirin use and white blood count. This held true regardless of inflammatory bowel disease type. Furthermore, inflammatory bowel disease medications other than steroids were found not to affect the development of acute coronary syndrome.

The interplay between a pro-inflammatory state in inflammatory bowel disease, effects of corticosteroids, immunosuppressive and biologic agents and the development of subsequent coronary artery disease in patients with inflammatory bowel disease is complex. With inflammatory bowel disease, there is an interruption of the balance between endogenous host factors including the innate and adaptive immune responses as well as intestinal epithelial cell barrier function and exogenous factors such as commensal intestinal flora

which leads to a state of severe inflammation (11). Inflammation is involved in all stages of coronary atherosclerosis and elevated levels of systemic biomarkers for inflammation have been found to predict coronary events in population studies and in individuals with angina (12, 13). However, there are conflicting results in the literature regarding the risk of atherothrombotic disease including coronary artery disease and cerebral vascular events in patients with inflammatory bowel disease. Some studies conclude there is no increased risk of ischemic heart disease or cardiovascular deaths in patients with inflammatory bowel disease compared to controls (14-17) while others have found that patients with inflammatory bowel disease have more major cardiovascular events including myocardial infarction compared to matched controls free of inflammatory bowel disease (3, 4, 8, 18). Furthermore, studies investigating what factors contribute or are associated with the development of cardiovascular morbidity and mortality among patients with inflammatory bowel disease are lacking(19). The strength of our study is that our entire patient population had documented inflammatory bowel disease and we specifically evaluated patients with inflammatory bowel disease with and without acute coronary syndrome in a study setting matched for age, sex and inflammatory bowel disease type.

While the identification and treatment of cardiovascular risk factors such as diabetes, obesity, family history of coronary artery disease and smoking are important, the presence of these traditional cardiovascular risk factors may not provide a full assessment of cardiac risk in patients with inflammatory bowel disease. There is some evidence that aside from hypertension, traditional cardiovascular risk factors may have a smaller impact on cardiovascular disease outcomes in patients with inflammatory bowel disease compared to patients without inflammatory bowel disease(8). Inflammation is known to be an important factor in the development of acute coronary syndrome. Thus the role of a chronic inflammatory state in patients with inflammatory bowel disease may in part provide a possible explanation for increased cardiovascular events among patients with inflammatory bowel disease compared to patients without inflammatory bowel disease. Studies have demonstrated that non-traditional risk factors such as white blood count were higher in patients with inflammatory bowel disease and associated with the development of coronary artery disease(8). Our study supports the inflammatory hypothesis as evident by patients with inflammatory bowel disease with acute coronary syndrome having higher white blood counts compared to patients with inflammatory bowel disease without acute coronary syndrome. On the contrary high-sensitivity C-reactive protein, another marker of inflammation was not different between the two groups, however this may be due to small number of samples available from our study population.

The major anti-inflammatory effects of corticosteroids appear to be due largely to interactions between activated glucocorticoid receptors and transcription factors that mediate the expression of inflammatory genes. Excessive exposure to steroids may lead to adverse metabolic, endocrine, and neuropsychiatric side effects, and also poses a hypothetical increased cardiovascular risk due to sympathetic activation of the renin-aldosterone-angiotensin system(7). However this adverse relationship between corticosteroid use and development of ischemic heart disease is contentious(8-10). In a population-based Scottish cohort study of >150,000 subjects, higher cardiovascular risk was found to be in patients with exposure to high dose (>7.5mg) prednisolone compared to subjects not taking steroids;

however, this was not limited to patients with inflammatory bowel disease(10). In contrast, a recent longitudinal cohort study of 356 patients with inflammatory bowel disease with 712 matched controls without inflammatory bowel disease showed that although inflammatory bowel disease was associated with increased coronary artery disease events despite lower rates of selected traditional risk factors (hypertension, diabetes, dyslipidemia, obesity), steroid exposure and dose did not increase the risk of coronary artery disease(8). Elevated white blood count was a risk factor for associated incident coronary artery disease events in the inflammatory bowel disease group(8). Furthermore, a nation-wide Danish matched cohort study of 20,795 newly diagnosed patients with inflammatory bowel disease observed a higher risk of myocardial infarction, stroke and cardiovascular death in periods of active disease including flares and persistent activity compared to non-inflammatory bowel disease controls from the general population(18). Corticosteroid prescriptions, along with initiation of biological treatment and hospitalizations with inflammatory bowel disease as primary diagnosis, were used as surrogate markers for disease activity with periods free of such events defined as remission(18). There was no increased cardiovascular risk for patients with inflammatory bowel disease in remission periods. In sum, there seems to be a signal among patients with inflammatory bowel disease that periods of increased inflammation and severe disease are associated with a higher risk of acute coronary syndrome(20). In our study where all patients had inflammatory bowel disease and thus a baseline pro-inflammatory state, our observation that steroid exposure (whether for inflammatory bowel disease indications or not) reduced the odds of developing acute coronary syndrome further supports the notion that systemic reduction of inflammation with steroids has beneficial effects in the pathophysiology of coronary atherosclerosis.

Our study did not find a relationship between the use of other inflammatory bowel disease medications and the subsequent development of acute coronary syndrome. A similar finding where there was no increased risk of acute myocardial infarction, stroke or cardiovascular death in patients with inflammatory bowel disease taking immune modifiers including 6-Mercaptopurine, azathioprine and/or methotrexate was reported in a recent study of >20,000 patients with inflammatory bowel disease(19). This finding may be partially explained by the differing modes of actions of these non-steroid inflammatory bowel disease medications that differ from those involved in the pathogenesis of coronary atherosclerosis. In contrast, others have found that the risk of ischemic heart disease was lower among patients with inflammatory bowel disease taking 5-aminosalicylic acid, thiopurines and tumor necrosis factor alpha compared to non-users(18). There is still uncertainty as to whether other inflammatory bowel disease medications aside from steroids affect cardiovascular risk and outcomes, and if so, how these drugs affect a person's cardiovascular risk profile. Further studies exploring these questions are needed.

Our finding that suggests that steroid use reduces the odds of acute coronary syndrome in patients with inflammatory bowel disease is an important one. However, studies that involve the administration of this drug to reduce the risk of acute coronary syndrome may be risky given the side effect profile of corticosteroids. In addition to our findings, the importance of screening for risk stratification, investigation and treatment of cardiovascular risk factors in this patient population remains of paramount importance. Furthermore, prudent and judicious use of corticosteroids in patients with inflammatory bowel disease is necessary to ensure

optimal patient care to maximize the benefits of this medication while minimizing side effects.

Limitations

This is a small retrospective study. However, the unique feature is that all patients, both with and without acute coronary syndrome have a diagnosis of inflammatory bowel disease. Although steroid exposure has previously been used as a proxy for inflammatory bowel disease activity and severity in other studies, our subjects were not matched for disease severity and our covariate of interest was history of steroid exposure. Hence we are unable to determine if patients with inflammatory bowel disease with more severe disease had more acute coronary syndrome. The retrospective nature of this study and incomplete information on biomarkers, inflammatory bowel disease activity, flares and severity were limitations. Additionally, there may be other confounders that we did not capture in our covariates of interest that may at least partly explain the association that we observed. Despite these limitations our study found a strong association between steroid exposure and reduced acute coronary syndrome in patients with inflammatory bowel disease. Larger prospective studies of patients with inflammatory bowel disease are needed to validate our findings.

CONCLUSION

This study that compared patients with inflammatory bowel disease with and without acute coronary syndrome found an association between steroid exposure and a significantly reduced the odds of acute coronary syndrome. However, the use of aminosalicylates, immune modifiers and biologic therapies did not affect acute coronary syndrome events. These findings provide further mechanistic insight into the inflammatory processes involved in both inflammatory bowel disease and acute coronary syndrome. Future trials targeted at reducing the inflammatory process in this cohort are warranted.

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REFERENCES

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005; 352(16):1685–95. [PubMed: 15843671]
2. Rogler G. Update in inflammatory bowel disease pathogenesis. *Curr Opin Gastroenterol*. 2004; 20(4):311–7. [PubMed: 15703658]
3. Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. *Clin Gastroenterol Hepatol*. 2008; 6(1):41–5. [PubMed: 18063423]
4. Haapamaki J, Roine RP, Turunen U, et al. Increased risk for coronary heart disease, asthma, and connective tissue diseases in inflammatory bowel disease. *J Crohns Colitis*. 2011; 5(1):41–7. [PubMed: 21272803]

5. Roifman I, Beck PL, Anderson TJ, et al. Chronic inflammatory diseases and cardiovascular risk: a systematic review. *Can J Cardiol.* 2011; 27(2):174–82. [PubMed: 21459266]
6. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut.* 2004; 53(Suppl 5):V1–16. [PubMed: 15306569]
7. Hayashi R, Wada H, Ito K, Adcock IM. Effects of glucocorticoids on gene transcription. *Eur J Pharmacol.* 2004; 500(1-3):51–62. [PubMed: 15464020]
8. Yarur AJ, Deshpande AR, Pechman DM, et al. Inflammatory bowel disease is associated with an increased incidence of cardiovascular events. *Am J Gastroenterol.* 2011; 106(4):741–7. [PubMed: 21386828]
9. Souverein PC, Berard A, Van Staa TP, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart.* 2004; 90(8):859–65. [PubMed: 15253953]
10. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med.* 2004; 141(10):764–70. [PubMed: 15545676]
11. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature.* 2007; 448(7152):427–34. [PubMed: 17653185]
12. Haverkate F, Thompson SG, Pyke SD, et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet.* 1997; 349(9050):462–6. [PubMed: 9040576]
13. Koenig W, Sund M, Frohlich M, et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation.* 1999; 99(2):237–42. [PubMed: 9892589]
14. Dorn SD, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. *Am J Gastroenterol.* 2007; 102(3):662–7. [PubMed: 17156143]
15. Ha C, Magowan S, Accortt NA, et al. Risk of arterial thrombotic events in inflammatory bowel disease. *Am J Gastroenterol.* 2009; 104(6):1445–51. [PubMed: 19491858]
16. Osterman MT, Yang YX, Brensinger C, et al. No increased risk of myocardial infarction among patients with ulcerative colitis or Crohn's disease. *Clin Gastroenterol Hepatol.* 2011; 9(10):875–80. [PubMed: 21749853]
17. Sridhar AR, Parasa S, Navaneethan U, et al. Comprehensive study of cardiovascular morbidity in hospitalized inflammatory bowel disease patients. *J Crohns Colitis.* 2011; 5(4):287–94. [PubMed: 21683298]
18. Rungoe C, Basit S, Ranthe MF, et al. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. *Gut.* 2013; 62(5):689–94. [PubMed: 22961677]
19. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death--a Danish nationwide cohort study. *PLoS One.* 2013; 8(2):e56944. [PubMed: 23457642]
20. Walker BR. Glucocorticoids and cardiovascular disease. *Eur J Endocrinol.* 2007; 157(5):545–59. [PubMed: 17984234]

Clinical Significance

- Acute coronary syndrome, an ominous sequelae of coronary artery disease, and inflammatory bowel disease may be precipitated by a heightened inflammatory state.
- Steroid exposure is associated with a reduction in acute coronary syndrome in patients with inflammatory bowel disease
- Our findings support the inflammatory hypothesis in the atherosclerosis cascade and suggest that reducing inflammatory burden in patients with inflammatory bowel disease may reduce future incidence of acute coronary syndrome.

Figure 1.
 Study schema and population.

Figure 2. Association between acute coronary syndrome and steroid exposure among patients with inflammatory bowel disease and by inflammatory bowel disease type

For inflammatory bowel disease, adjusted analysis included body mass index, diabetes, dyslipidemia, smoking, family history of coronary artery disease, white blood count and aspirin. For Crohn's disease, adjusted analysis included body mass index, white blood count, and dyslipidemia. For ulcerative colitis, adjusted analysis included body mass index, diabetes, smoking, family history of coronary artery disease, and aspirin.

Table 1
Patient Characteristics of Patients with Inflammatory Bowel Disease with and without Acute Coronary Syndrome

	Acute Coronary Syndrome (n=59)		No Acute Coronary Syndrome (n=118)	P value
Demographics				
Age, yrs	67 ± 10		67 ± 10	0.71
Male, gender, n (%)	44 (75)		88 (75)	1.00
Race, Caucasian, n (%)	56 (95)		113 (96)	1.00
Body Mass Index (kg/m²)	29.2 ± 5.9		27.2 ± 5.9	0.04
Cardiac Risk Factors				
Diabetes mellitus, n (%)	21 (36)		16 (14)	<0.01
Hypertension, n (%)	36 (61)		60 (51)	0.27
Dyslipidemia, n (%)	33 (56)		46 (39)	0.04
Smoking: Current or Former, n (%)	42 (71)		62 (53)	0.02
Family History of Coronary Artery Disease, n (%)	11 (19)		7 (6)	0.02
Co-existing medical diseases				
Renal Insufficiency, n (%)	3 (5)		6 (5)	1.00
Rheumatoid Arthritis, n (%)	2 (3)		3 (3)	1.00
Systemic Lupus Erythematosus, n (%)	0 (0)		1 (1)	1.00
Laboratory				
White Blood Cell count (th/cmm)	10.2 ± 4.4		8.2 ± 6.5	0.02
Platelets (th/cumm)	264.1 ± 95.3		276.0 ± 121.7	0.48
Plasma Creatinine (mg/dl)	1.2 ± 1.0		1.2 ± 0.2	0.62
Estimated Glomerular Filtration Rate (mL/min)	73.9 ± 25.3		71.6 ± 24.2	0.56
High sensitivity C-reactive Protein, median [interquartile range] (mg/L) *	9.1 [2.2, 28.3]		3.3 [1.3, 16.0]	0.12

* High sensitivity C-reactive Protein levels were available in 16 patients with ACS and 58 patients without ACS.

Table 2

Patient Characteristics by Inflammatory Bowel Disease Type

	Crohn's Disease (n=78)		Ulcerative Colitis (n=99)		P value
	Acute Coronary Syndrome (n=26)	No Acute Coronary Syndrome (n=52)	Acute Coronary Syndrome (n=33)	No Acute Coronary Syndrome (n=66)	P value
Demographics					
Age, yrs	70 ± 9	71 ± 9	64 ± 11	65 ± 11	0.85
Male, gender, n (%)	18 (69)	36 (69)	26 (79)	52 (79)	1.00
Race, Caucasian, n (%)	25 (96)	51 (98)	31 (94)	62 (94)	1.00
Body Mass Index (kg/ m ²)	28.3 ± 6.4	26.1 ± 6.0	29.8 ± 5.6	28.0 ± 4.8	0.13
Cardiac Risk Factors					
Diabetes mellitus, n (%)	9 (35)	9 (17)	12 (36)	7 (11)	0.01
Hypertension, n (%)	16 (62)	24 (46)	20 (61)	36 (55)	0.67
Dyslipidemia, n (%)	14 (54)	16 (31)	19 (58)	30 (46)	0.29
Smoking: Current or Former, n (%)	18 (69)	32 (62)	24 (73)	30 (46)	0.01
Family History of Coronary Artery Disease, n (%)	4 (15)	4 (8)	7 (21)	3 (5)	0.01
Co-existing medical diseases					
Renal Insufficiency, n (%)	1 (4)	4 (8)	2 (6)	2 (3)	0.60
Rheumatoid Arthritis, n (%)	1 (4)	1 (2)	1 (3)	2 (3)	1.00
Systemic Lupus Erythematosus, n (%)	0 (0)	0 (0)	0 (0)	1 (2)	1.00
Laboratories					
White Blood Cell count (th/cmm)	10.6 ± 5.7	7.6 ± 2.8	9.9 ± 3.0	8.6 ± 8.2	0.27
Platelets (th/cumm)	283.8 ± 97.1	286.8 ± 139.8	248.6 ± 92.4	267.5 ± 105.6	0.39
Plasma Creatinine (mg/dl)	1.1 ± 0.29	1.1 ± 0.41	1.3 ± 1.3	1.2 ± 0.6	0.62
Estimated Glomerular Filtration Rate (mL/min)	67.7 ± 21.1	69.9 ± 23.1	78.9 ± 27.6	73.0 ± 25.1	0.30
High sensitivity C-reactive Protein, median [interquartile range] (mg/L)	19.6 [2.4, 156.4] (n=5)	4.5 [1.2, 15.1] (n=31)	5.7 [1.7, 25.9] (n=11)	2.3 [1.5, 17.7] (n=27)	0.43

Table 3

Medication use in Patients with inflammatory bowel disease with and without acute coronary syndrome

	Acute Coronary Syndrome (n=59)	No Acute Coronary Syndrome (n=118)	P value
Steroid Use*			
Current or Former, n (%)	20 (34)	68 (58)	<0.01
Current, n (%)	6 (10)	32 (27)	<0.01
Steroid Exposure, n (%)			
Chronic (> 90 days)	10 (17)	40 (34)	
Not Chronic (< 90 days)	2 (3)	13 (11)	<0.01
Exposed, duration unknown	8 (14)	15 (13)	
Never	39 (66)	50 (42)	
Steroid Duration (months, median [interquartile range])**	13 [5, 30]	18 [3, 96]	0.58
Other Inflammatory Bowel Disease Medications			
Aminosalicylates (5-aminosalicylic acid), n (%)	29 (45)	66 (56)	0.27
Immune Modifiers (Azathioprine, 6-Mercaptopurine, Methotrexate), n (%)	6 (10)	19 (16)	0.20
Biologic Therapy (Infliximab, Adalimumab), n (%)	2 (3)	8 (7)	0.28
Cardiac Medications			
Aspirin, n (%)	25 (42)	25 (21)	<0.01
Beta Blockers, n (%)	19 (32)	24 (20)	0.10
Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blocker, n (%)	21 (36)	30 (25)	0.16
Statins, n (%)	18 (31)	39 (33)	0.44
Niacin and/or Fibrates, n (%)	2 (3)	4 (3)	1.00

* 6 patients had steroid use for non-inflammatory bowel disease indications and included: asthma (2), osteoarthritis (1), sterile peritonitis (1), uveitis (1), and anaphylaxis (1)

** Steroid duration was available in 12 patients with acute coronary syndrome and 53 patients without acute coronary syndrome.

Table 4

Medication use in Patients with Inflammatory Bowel Disease with and without Acute Coronary Syndrome as stratified by Inflammatory Bowel Disease Type

	Crohn's Disease (n=78)		P value	Ulcerative Colitis (n=99)		P value
	Acute Coronary Syndrome (n=26)	No Acute Coronary Syndrome (n=52)		Acute Coronary Syndrome (n=33)	No Acute Coronary Syndrome (n=66)	
Steroid Use						
Current or Former, n (%)	10 (39)	35 (67)	0.03	10 (30)	33 (50)	0.09
Current, n (%)	4 (15)	16 (31)	0.17	2 (6)	16 (24)	0.03
Steroid Exposure, n (%)			0.11			0.08
Chronic (> 90 days)	5 (19)	20 (39)		5 (15)	20 (30)	
Not Chronic (< 90 days)	2 (8)	7 (14)		0 (0)	6 (9)	
Exposed, duration unknown	3 (12)	8 (15)		5 (15)	7 (11)	
Never	16 (62)	17 (33)		23 (70)	33 (50)	
Steroid Duration (months, median [interquartile range])	12 [0.3, 24] (n=7)	24 [2, 168] (n=27)	0.12	36 [12, 96] (n=5)	12 [3, 60] (n=26)	0.27
Other Inflammatory Bowel Disease Medications						
Aminosalicylates (5-aminosalicylic acid), n (%)	10 (39)	29 (56)	0.14	19 (58)	37 (56)	1.00
Immune Modifiers (Azathioprine, 6-Mercaptopurine, Methotrexate), n (%)	3 (12)	9 (17)	0.74	3 (9)	10 (15)	0.53
Biologic Therapy (Infliximab, Adalimumab), n (%)	1 (4)	6 (12)	0.41	1 (3)	2 (3)	1.00
Cardiac Medications						
Aspirin, n (%)	11 (42)	16 (31)	0.33	14 (42)	9 (14)	<0.01
Beta Blockers, n (%)	8 (31)	12 (23)	0.58	11 (33)	12 (18)	0.13
Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blocker, n (%)	12 (46)	18 (35)	0.34	9 (27)	12 (18)	0.31
Statins, n (%)	7 (27)	14 (27)	1.00	11 (33)	25 (38)	0.82
Niacin and/or Fibrates, n (%)	1 (4)	3 (6)	1.00	1 (3)	1 (2)	1.00