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Effect of Inflammatory Bowel Disease–Related Characteristics and Treatment Interventions on Cardiovascular Disease Incidence

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Abstract: *Background:* An association between inflammatory bowel disease (IBD) and cardiovascular diseases has been shown in multiple studies. However, little is known about the effect of IBD-related characteristics on cardiovascular events. *Methods:* The authors conducted a retrospective, nested case-control study of IBD patients who presented to the institution from 2000 to 2004, allowing for a 10-year follow-up period. One hundred eleven patients who developed cardiovascular events (cases) and 222 patients who did not develop cardiovascular events (cases) were included in the study after matching for Framingham cardiovascular risk score (2008). Relationships between predictor variables and cardiovascular outcome were assessed by conditional logistic regression. *Results:* The cases and controls were similar in age, gender, smoking and cholesterol level. There was no difference in disease subtype (ulcerative colitis or Crohn's disease). On conditional logistic regression, thiopurine treatment (odds ratio [OR]: 0.42, 95% confidence interval [CI]: 0.19–0.87; $P = 0.02$) was associated with decreased cardiovascular events and tumor necrosis factor alpha antagonist use (OR: 2.63, 95% CI: 1.49–4.63; $P = 0.001$) was associated with increased cardiovascular events. Although not statistically significant, disease-related surgery (OR: 0.57, 95% CI: 0.32–1.02; $P = 0.06$) was associated with decreased cardiovascular events and disease-related hospitalization (OR: 1.58, 95% CI: 0.96–2.57; $P = 0.07$) was associated with increased incidence of cardiovascular disorders. *Conclusions:* The authors observed decreased incidence of cardiovascular diseases in patients with IBD who were treated with thiopurines and increased incidence of cardiovascular outcomes among patients treated with tumor necrosis factor alpha antagonist.

Key Indexing Terms: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Coronary artery disease; Thiopurine; Biological agents. **[Am J Med Sci 2015;350(3):175–180.]**

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder associated with intestinal and extraintestinal manifestations. Cardiovascular disorders have increased incidence among patients suffering from chronic inflammatory diseases.[1] Among IBD patients, studies have been contradictory with some studies showing increased cardiovascular events,[1] whereas others have not shown increased risk.[2] Although the pathogenic link between IBD and cardiovascular disorders is not well known, inflammation is considered to be the general mechanism of pathogenesis in both disorders. In addition, inflammatory markers that are increased in patients with IBD have been associated with cardiovascular diseases[3] and multiple studies have shown IBD patients to be at increased risk of developing cardiovascular events.[1]

Furthermore, vascular alterations are common in IBD patients. Early arterial wall alterations have been observed in IBD patients, marked by increased carotid artery intima-media thickness which is a marker of atherogenesis.[4] Even children with IBD have early endothelial dysfunction based on increased intima-media thickness and reduced flow-mediated dilatation.[5] On the contrary, some studies in the past have not shown increased cardiovascular disease risk among IBD patients.[2,6] Therefore, the current evidence is not sufficient to definitively conclude that IBD patients are at increased risk of developing cardiovascular disorders.[6]

However, increased inflammation among IBD patients has been shown to increase the risk of cardiovascular diseases. A nationwide cohort study from Denmark showed increased risk of cardiovascular death during active IBD.[7] Another retrospective study by Yarur et al[8] showed increased risk of coronary artery disease in IBD patients compared with the general population despite having lower burden of traditional risk factors.

Despite the increasing knowledge that inflammation in IBD is associated with increased risk of cardiovascular diseases, the disease-related characteristics and the effect of anti-inflammatory medications used in IBD on cardiovascular disease incidence are poorly understood. Furthermore, most studies so far have focused on acute coronary events rather than the long-term evolution of cardiovascular diseases in IBD.

The aim of the present study was to explore the effect of disease-related characteristics, including disease activity, severity and treatment, on cardiovascular disease incidence among IBD patients over a 10-year follow-up period.

METHODS

This study was approved by the Henry Ford Hospital Institutional Review Board.

Subject Identification and Data Collection

The authors used Henry Ford Hospital medical record databases that contain medical and demographic information for patients evaluated at Henry Ford Health System. These databases were used to identify patients who presented with IBD from January 1, 2000, to December 31, 2004, to allow for a 10-year follow-up period. *International Classification of Diseases, Ninth Revision*, codes 555.x and 556.x were used to identify patients with IBD.

Cases and Controls

The inclusion criteria included the following: (1) age at presentation between 30 and 74 years, (2) histological evidence of IBD and (3) follow-up data available for greater than 5 years.

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Exclusion criterion was medical history of cardiovascular or cerebrovascular disease. Records for a cohort of 2,525 IBD cases who had been evaluated in the IBD clinic at Henry Ford Hospital from 2000 to 2004 were reviewed. A total of 1,188 patients were excluded because they did not meet the inclusion criteria or had history of cardiovascular or cerebrovascular disease. One thousand three hundred thirty-seven patients met the study criteria. There were 111 patients who subsequently developed cardiovascular diseases.

Framingham risk score (2008) was used to measure the baseline general cardiovascular disease risk for all patients included in the study. Patients between the age of 30 and 74 years were selected because the Framingham risk score (2008) applies to this age group. The Framingham risk score (2008) is a validated risk score that is used to calculate the risk of developing general cardiovascular disorders over a period of 10 years.[9] The score is based on age, gender, smoking status, total cholesterol level, high-density lipoprotein (HDL) level and systolic blood pressure.

A total of 111 cases with cardiovascular disorders were identified and matched for Framingham risk score with 2 controls for each case. Cases were defined as patients who developed incidental cardiovascular diseases, including coronary artery disease, heart failure, stroke or peripheral artery disease on objective testing. Some patients developed multiple cardiovascular conditions. Cases were identified by reviewing medical records for objective evidence of cardiovascular disease (ejection fraction less than 40% on echocardiography, computed tomography scan head or magnetic resonance imaging brain with evidence of stroke, carotid artery Doppler ultrasound with atherosclerotic narrowing, ankle-brachial index suggestive of peripheral artery disease, computed tomography angiography with coronary calcification, fixed wall motion abnormality on echocardiography, cardiac stress test suggestive of coronary artery disease). Controls were chosen from IBD patients in the cohort who did not develop cardiovascular diseases. Physician notes from the hospital and from outside health-care facilities were also reviewed when available for history of cardiovascular disease. None of the control patients had any history of cardiovascular disorders. Cases and controls were propensity matched for Framingham risk score (2008) by "nearest neighbor method."

Variables and Outcomes

Information regarding age at presentation, gender and race (white, black or other) was extracted. Lifetime history of smoking more than 1 pack year or current smoker was recorded. Colonoscopy results on extent of anatomical disease involvement were also collected. Histopathology results for intestinal tissue obtained during colonoscopy were reviewed for active inflammation during the follow-up period. The total cholesterol and HDL and low-density lipoprotein levels were collected during the initial clinic visit. Patient records were reviewed for blood pressure at initial presentation. All the recorded blood pressures, glycated hemoglobin levels and cholesterol levels during the follow-up period were also reviewed for the development of diabetes, hypertension and/or hyperlipidemia during the follow-up period. These data were used to calculate the Framingham risk score (2008) for cardiovascular risk prediction.

Disease characteristic was divided as follows: ulcerative colitis (UC) patients were divided into panulcerative colitis and non-panulcerative colitis. Crohn's disease (CD) patients were divided into inflammatory disease or fistulizing/stricturing disease. Age at onset of disease was also abstracted. Colonoscopy reports were reviewed for histological evidence of active inflammation during the follow-up period, and data regarding need for disease-related hospitalization were also reviewed from medical records for identifying patients with active inflammation during the follow-up period. Peak erythrocyte sedimentation rate (ESR) was also abstracted as a marker of inflammation.

Data regarding the use of IBD-related medications, including 5-aminosalicylates, corticosteroids, thiopurines (6-mercaptopurine and azathioprine) and antitumor necrosis factor agents (infliximab, adalimumab and certolizumab pegol), were collected. Only medications used before the development of cardiovascular events were included.

The primary outcome of this study was a composite of cardiovascular events, including coronary artery disease, heart failure, peripheral vascular disease and stroke. Composite outcomes are often used in studies with cardiovascular endpoint.

Statistical Analyses

R software, version 3.0.1, for all statistical analyses was used. Continuous variables were summarized using medians and interquartile range (IQR), and categorical variables were expressed as proportions. Categorical variables were analyzed using the χ^2 test and fisher's exact test, and continuous variables were analyzed using t test or Wilcoxon signed rank test for parametric and nonparametric data, respectively. Framingham risk score was used as a continuous variable. Cases and controls were matched for the Framingham risk score (2008) using the nearest neighbor method.

Variables with a P value less than 0.1 on univariate conditional logistic regression analysis were included in the multivariate conditional logistic regression model.

Secondary analysis comparing patients who developed hard cardiovascular endpoints (myocardial infarction, stroke and heart failure) with the control population was also conducted. Predictor variables were identified using univariate logistic regression. Variables with P value less than 0.1 in the univariate model were included in the multivariate logistic regression model.

The effect was expressed as odds ratio (OR) with 95% confidence interval (CI), along with P values.

RESULTS

The median age for the cases was 56 years (IQR, 47.5–64.5), and the median age of the controls was 54 years (IQR, 46–62). Data involving 3,410 patient years were reviewed for final analysis. The cases consisted of 64.86% Caucasian and 53.15% were men. The controls consisted of 58.5% Caucasians and 46.85% were men. The mean systolic blood pressures on initial presentation were 133.1 mm Hg for cases and 134 mm Hg for controls. The median Framingham risk score for general cardiovascular disease risk (2008) for cases was 14.54 (IQR, 6.66–24.58) and for controls was 13.41 (IQR, 6.62–20.44). The median follow-up period for cases was 9.53 years (IQR, 9.19–10.22). The median follow-up for controls was 9.82 years (IQR, 8.9–12.19) (Table 1). Of the cohort, 111 patients developed cardiovascular events. There were 67 cases of coronary artery disease, 23 cases of stroke, 25 cases of heart failure and 31 cases of peripheral vascular disease. Some patients had multiple cardiovascular events.

Cases and controls were matched for Framingham risk score (2008) for cardiovascular risk. Matching was done using the nearest neighbor method. There was no difference in the median Framingham score between the cases and controls (14.54 versus 13.41, $P = 0.27$).

The median age at IBD diagnosis for cases was 45 years (IQR, 32.5–53.5) and for controls was 44 years (IQR, 31.25–52).

TABLE 1. Demographic and clinical characteristics of cases and controls

Demographics	Cases (n = 111)	Controls (n = 222)	P
Age, median (IQR), yr	56 (47.5–64.5)	54 (46–62)	0.15
Male	59 (53.15%)	52 (46.85%)	0.97
HDL, median (IQR), mg/dL	51 (41–59)	53 (43–64.75)	0.22
Smoking	44 (39.64%)	67 (30.18%)	0.49
Total cholesterol, median (IQR), mg/dL	198 (167.5–226)	199.5 (174–231.8)	0.37
Hypertension	63 (56.76%)	106 (47.75%)	0.15
Diabetes mellitus	13 (11.71%)	31 (13.96%)	0.69
Framingham score (IQR)	14.54 (6.66–24.58)	13.41 (6.62–20.44)	0.27
CD	46 (41.44%)	81 (36.49%)	0.45
Stricturing CD	11 (9.9%)	22 (9.9%)	0.83
UC	66 (59.46%)	141 (63.51%)	0.55
Pancolonic UC	36 (32.43%)	73 (32.88%)	0.84
IBD duration (IQR)	9 (5–17.5)	9 (4–18)	0.43
Age at onset (IQR)	45 (32.5–53.5)	44 (31.25–52)	0.68
ESR (IQR)	45 (23–59.5)	40 (24–53)	0.12
Hospitalization	69 (62.16%)	115 (51.8%)	0.09
Hospitalization frequency			
No hospitalization	42 (37.84%)	107 (48.19%)	0.14
1–3 hospitalization	68 (61.26%)	111 (50%)	
>3 hospitalization	1 (0.9%)	4 (1.8%)	
Active inflammation on biopsy	82 (73.87%)	147 (66.22%)	0.19
Disease-related surgery	22 (19.82%)	68 (30.63%)	0.05
5-ASA	83 (74.78%)	170 (76.58%)	0.82
Steroids	47 (42.34%)	112 (50.45%)	0.2
Thiopurines	11 (9.91%)	48 (20.62%)	0.01
TNF antagonist	36 (32.43%)	41 (18.47%)	0.007

CD, Crohn's disease; UC, ulcerative colitis.

Proportion of patients with pancolitis and fistulizing/stricturing CD was similar between the cases and controls (Table 1). The disease activity during the follow-up period was evaluated using the need for disease-related hospitalization, peak ESR level and the presence of active inflammation on biopsy samples obtained during colonoscopy. The median ESR level for cases was 45 mm/hr (IQR, 23–59.5) and 40 mm/hr (IQR, 24–53) for controls. The need for disease-related hospitalization and the presence of active inflammation on biopsy were also higher among the cases compared with the controls (Table 1).

There was no difference between cases and controls in the use of sulfa medications or steroids (Table 1). Tumor necrosis factor (TNF) alpha antagonist use was more common among the cases compared with controls (36 versus 41, $P = 0.004$). Thiopurine use was less common among patients with cardiovascular events (11 versus 48, $P = 0.01$). Some patients were on multiple medications.

On univariate conditional logistic regression, disease-related hospitalization (OR: 1.59, 95% CI: 0.92–2.77; $P = 0.06$), active inflammation on biopsy during the follow-up period (OR: 1.19, 95% CI: 1.05–3.97; $P = 0.04$) and TNF-alpha antagonist use (OR: 2.6, 95% CI: 1.37–4.95; $P = 0.004$) were associated with increased risk of cardiovascular events. Disease-related surgery (OR: 0.55, 95% CI: 0.27–1.1; $P = 0.09$) and thiopurine use (OR: 0.45, 95% CI: 0.19–1.06; $P = 0.07$) were associated with decreased risk of cardiovascular events. Variables with P value less than 0.1 were included in the multivariate regression model. On multivariate conditional logistic regression, thiopurine use was associated with decreased odds of developing cardiovascular diseases (OR: 0.39, 95% CI: 0.19–0.83; $P = 0.01$) and TNF-alpha antagonist use was associated with increased odds of developing cardiovascular diseases (OR: 2.59, 95% CI: 1.49–4.51; $P = 0.001$). Although not statistically significant, history of disease-related surgery was associated with decreased cardiovascular events (OR: 0.56, 95% CI: 0.32–1.01; $P = 0.053$) and need for disease-related hospitalization was associated with increased risk of cardiovascular events (OR: 1.59, 95% CI: 0.97–2.58; $P = 0.06$) (Table 2).

On secondary analysis, patients who developed cardiovascular events (myocardial infarction, stroke and heart failure) were compared with the control group. On univariate logistic regression, HDL, hypertension, Framingham risk score, steroid use, thiopurine and TNF-alpha antagonist use were associated with cardiovascular events at a predefined P value <0.1 (Table 3). On multivariate logistic regression, HDL was slightly protective against cardiovascular events (OR: 0.98, 95% CI: 0.96–0.99; $P = 0.03$), thiopurine use was associated with decreased cardiovascular events (OR: 0.28, 95% CI: 0.08–0.73; $P = 0.047$) and TNF-alpha antagonist use was associated with increased cardiovascular events (OR: 3.42, 95% CI: 1.74–6.75; $P = 0.0004$).

DISCUSSION

Development of atherosclerotic lesions is influenced by major inflammatory factors that encompass components of both the innate and the acquired immune systems. There is

TABLE 2. Conditional logistic regression for combined cardiovascular outcome

Characteristics	Univariate logistic regression OR (95% CI)	P	Multivariate logistic regression OR (95% CI)	P
Age	1.01 (0.98–1.04)	0.59		
Gender (male vs. female)	1.03 (0.58–1.81)	0.93		
HDL	0.99 (0.98–1.01)	0.46		
Smoking	1.2 (0.67–2.17)	0.54		
Total cholesterol	0.99 (0.99–1.01)	0.99		
Hypertension	1.26 (0.69–2.28)	0.45		
Diabetes mellitus	0.83 (0.33–2.09)	0.69		
Framingham score	1.19 (0.83–1.72)	0.33		
IBD subtype				
CD	1.06 (0.61–1.87)	0.83		
UC	0.98 (0.56–1.71)	0.94		
Stricturing CD	0.91 (0.59–1.38)	0.65		
Pancolonic UC	1.13 (0.69–1.93)	0.66		
Age at onset	0.99 (0.97–1.01)	0.51		
IBD duration	1.01 (0.99–1.04)	0.24		
ESR	1.01 (0.99–1.02)	0.17		
Hospitalization	1.59 (0.92–2.77)	0.09	1.59 (0.97–2.58)	0.06
Hospitalization frequency (0 vs. 1–3 vs. more than 3 admissions)	1.19 (0.62–2.29)	0.6		
Active inflammation on biopsy	2.04 (1.05–3.97)	0.04	1.53 (0.89–2.6)	0.12
Surgery	0.55 (0.27–1.1)	0.09	0.56 (0.32–1.01)	0.053
5-ASA	0.98 (0.53–1.81)	0.94		
Steroids	0.65 (0.37–1.12)	0.12		
Thiopurines	0.45 (0.19–1.06)	0.07	0.39 (0.19–0.83)	0.01
TNF antagonist	2.6 (1.37–4.95)	0.004	2.59 (1.49–4.51)	0.001

CD, Crohn's disease; UC, ulcerative colitis.

substantial evidence supporting the role of metabolic disturbances combined with dysregulated inflammation as the mechanism of atherosclerosis in coronary arteries.[10] There is also evidence that patients with IBD are at increased risk of cardiovascular diseases[1] despite having lower burden of traditional risk factors.[8] However, the disease-related characteristics and the effect of medications on cardiovascular system remain poorly understood. In this study, increased cardiovascular outcomes among IBD patients with increased disease activity as observed by TNF-alpha antagonist use and disease-related hospitalization were observed. Paradoxically, decreased cardiovascular disease incidence was observed among patients treated with thiopurines and those requiring disease-related surgery. Age at onset of IBD and disease characteristics (pancolitis versus non-pancolitis for UC and stricturing/fistulizing versus inflammatory for CD) were also used as surrogate disease severity parameters. These variables are known to predict severity of disease in IBD.[11] Furthermore, the presence of histological evidence of inflammation during the follow-up period, need for disease-related hospitalization and peak ESR levels were used as surrogate markers of disease activity. There was no difference between cases and controls in peak ESR levels and disease characteristics (pancolitis versus non-pancolitis for UC and stricturing/fistulizing versus inflammatory for CD) (Table 1).

Despite the increased understanding of various immunological pathways, the exact mechanisms that link cardiovascular disorders and IBD remain unknown. However, there are several immunological dysfunctions that are common in both IBD and cardiovascular disorders. Inflammatory cytokines, including interleukin 1, interleukin 6 and TNF, are involved in the pathogenesis of IBD[12]; these cytokines are also known to play a role in the development of cardiovascular disorders.[13] In fact, c-reactive protein, which is a marker of inflammation and found in higher concentrations in patients with active IBD, has also been shown to be a modifiable cardiovascular risk factor.[14] Toll-like receptors (TLR) and autophagy are recently discovered immunological mechanisms, which have been found to be dysfunctional in both IBD and cardiovascular disorders. TLRs are expressed on a large number of immune cells and play an essential role in the activation of the innate immune response to microbial pathogens. Dysfunction in the interaction between TLRs plays a role in the pathogenesis of both coronary artery disease and IBD.[15] Autophagy is another mechanism that can explain the association between cardiovascular events and CD. Both cardiovascular disorders and CD have defects in autophagy.[16] Although these similarities in immunological disorders do not mean causation, it does point to common pathogenic links between cardiovascular disorders and IBD.

In this study, the authors found increased odds of developing cardiovascular diseases in patients treated with TNF-alpha antagonists. This is most likely because TNF-alpha antagonist use is a marker of IBD severity and activity. IBD patients with the most severe disease activity, which is not well controlled with other medications, are treated with TNF-alpha antagonists. This finding lends further support that patients with severe IBD are at increased risk of developing cardiovascular disorders. However, there have been reports of cardiovascular events in patients using TNF-alpha antagonist,[17,18] and heart failure in particular has been strongly linked to these medications.[19] However, there have also been reports of improvement in

TABLE 3. Logistic regression analysis for combined cardiovascular events (heart failure, myocardial infarction and stroke)

Characteristics	Univariate logistic regression OR (95% CI)	Multivariate logistic regression P	OR (95% CI)	P
Age	1 (0.98–1.03)	0.77		
Gender (female vs. male)	0.6 (0.32–1.1)	0.11		
HDL	0.98 (0.96–0.99)	0.053	0.97 (0.95–0.99)	0.03
Smoking	1.38 (0.76–2.51)	0.29		
Total cholesterol	0.99 (0.99–1.003)	0.31		
Hypertension	2.31 (1.26–4.37)	0.008	1.87 (0.92–3.9)	0.09
Diabetes mellitus	1.03 (0.42–2.28)	0.95		
Framingham score	1.02 (0.99–1.04)	0.06	1 (0.98–1.03)	0.77
IBD subtype				
CD	1.04 (0.56–1.9)	0.89		
UC	1.03 (0.57–1.93)	0.91		
Stricturing CD	0.96 (0.61–1.48)	0.86		
Pancolonic UC	1.32 (0.71–2.41)	0.37		
Age at onset	0.99 (0.98–1.02)	0.86		
IBD duration	1.01 (0.98–1.04)	0.57		
ESR	1.01 (0.99–1.02)	0.33		
Hospitalization	1.15 (0.64–2.09)	0.63		
Hospitalization frequency (0 vs. 1–3 vs. more than 3 admissions)	1.07 (0.61–1.86)	0.82		
Active inflammation on biopsy	1.08 (0.58–2.05)	0.82		
Surgery	0.55 (0.26–1.1)	0.1		
5-ASA	0.84 (0.44–1.67)	0.59		
Steroids	0.55 (0.29–0.99)	0.05	0.74 (0.38–1.44)	0.38
Thiopurines	0.28 (0.08–0.73)	0.019	0.31 (0.08–0.89)	0.047
Biological agents	3.31 (1.76–6.21)	0.0002	3.42 (1.74–6.75)	0.0004

CD, Crohn's disease; UC, ulcerative colitis.

cardiovascular parameters with TNF-alpha antagonist use.[20] Animal studies have shown deceleration of atherosclerosis with these medications[21]; however, this has not translated into convincing human studies. Moreover, there have been reports of cardiovascular events after TNF-alpha antagonist infusion.[22] Therefore, the effect of these medications on the heart remains controversial. These medications are being increasingly used in the management of IBD patients, and their long-term effect on the cardiovascular system should be further investigated.

The authors also observed a trend toward increased incidence of cardiovascular disorders among patients requiring disease-related hospitalization. This is consistent with previous studies that have shown increased cardiovascular events with active IBD.[7] Therefore, patients with severe IBD activity requiring hospitalization are at increased risk of cardiovascular disorders.

They also observed decreased cardiovascular events in patients treated with thiopurines, which is not consistent with their current understanding that increased inflammation leads to cardiovascular disorders because thiopurines are often used in IBD patients who do not respond to treatment with 5-aminosalicylate medications and have frequent exacerbations. This finding could be because of strong immunomodulatory effects of this class of medications. Immunomodulatory medications are helpful in delaying the progression of atherosclerosis, and there are several medications such as angiotensin receptor antagonists and statins with pleiotropic effects that have been shown to decrease cardiovascular mortality. However, the effect of immunomodulating drugs on development of atherosclerosis is not well understood.[23] Several immunomodulatory medications are being studied for prevention of cardiovascular diseases. Thiopurines have been used in IBD for decades and still form the mainstay of treatment for many patients.[24] Azathioprine has been shown to be a strong inducer of T-cell apoptosis,[25] and treatment with thiopurine is associated with a reduction of interferon γ + T cells in IBD patients who responded to treatment.[26] Coronary artery disease is also mediated by T cells, and $CD4^{+}CD28$null T cells, which are characterized by increased interferon γ levels, are prominent in patients with acute coronary syndromes.[27] These findings suggest that thiopurines could have a potentially protective effect on the cardiovascular system by inhibiting deleterious T-cell–mediated effects on the heart.

Furthermore, although not statistically significant, the authors found patients with history of disease-related surgery to have a strong trend toward lower cardiovascular disease incidence. This effect could be because surgical resection of inflamed bowel removes the nidus of inflammation and thereby decreases the harmful effects of inflammation on the cardiovascular system. Therefore, proper selection of patients for surgical treatment may not only spare them from intolerable disease-related symptoms but also protect from harmful effects of inflammation on the heart.

Furthermore, the decreased incidence of cardiovascular events among thiopurine users and increased incidence among TNF-alpha antagonist users were significant on secondary analysis comparing patients with only hard cardiovascular endpoints (myocardial infarction, stroke and heart failure) and the control group. This further lends support to the robustness of their findings.

The main drawback of this study is its retrospective design. It is also a single tertiary center study. The cohort

comprised of patients between the age of 30 and 74 years and did not include younger or older patients because the Framingham risk score is applicable only in this age group. Therefore, the results of this study do not apply to patients who are younger or older than this cohort. Another important drawback of this study is that the severity of IBD was measured using surrogate markers and not evaluated directly because of the retrospective nature of the study. Finally, the tests that were performed and medications that were administered were part of routine clinical care and not study interventions.

CONCLUSIONS

Increased cardiovascular disease incidence was observed in patients treated with TNF-alpha antagonists and patients requiring disease-related hospitalization over the follow-up period, supporting the role of inflammation in cardiovascular events in patients with IBD. Paradoxically, decreased incidence of cardiovascular disease in patients treated with thiopurines and patients who underwent disease-related surgery was also observed.

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