Prognosis After First-Time Myocardial Infarction in Patients With Inflammatory Bowel Disease According to Disease Activity

Nationwide Cohort Study

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Background—Inflammatory bowel disease (IBD) is associated with increased cardiovascular risk. We examined the effect of active IBD on major adverse cardiovascular outcomes after myocardial infarction (MI).

Methods and Results—In nationwide registries, we identified 86 790 patients with first-time MI from the period 2002 to 2011. A total of 1030 patients had IBD, and we categorized their disease activity stages into either flare (120 days), persistent (>120 days) activity, or remission. Short-term mortality was estimated in a logistic regression-model, whereas risk of recurrent MI, all-cause mortality, and a composite of recurrent MI, cardiovascular death, and stroke were estimated by Cox regression-models. Odds ratio of death during hospitalization or within 30 days of discharge (n=13,339) corresponded to 3.29 (95% confidence interval [CI], 1.98–5.45) for patients in IBD flares, 1.62 (95% CI, 0.95–2.77) for persistent activity, and 0.97 (95% CI, 0.78–1.19) for remission when compared with the non-IBD group. Among 73,451 patients, including 863 with IBD, alive 30 days after discharge, IBD was associated with hazard ratios of 1.21 (95% CI, 0.99–1.49) for recurrent MI, 1.14 (95% CI, 1.01–1.28) for all-cause mortality, and 1.17 (95% CI, 1.03–1.34) for the composite end point. When compared with the non-IBD group, IBD flares, in particular, were associated with increased risks of recurrent MI (hazard ratio, 3.09; 95% CI, 1.79–5.32), all-cause mortality (hazard ratio, 2.25; 95% CI, 1.61–3.15), and the composite end point (hazard ratio, 2.04; 95% CI, 1.35–3.06), whereas no increased risk was identified in remission.

Conclusions—Active inflammatory bowel disease worsens prognosis after MI, in particular, in relation with flares.

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Key Words: colitis, ulcerative ■ Crohn’s disease ■ inflammatory bowel disease ■ myocardial infarction ■ prognosis
WHAT IS KNOWN

- Patients with inflammatory bowel disease are at increased risk of venous and arterial thrombotic events.

WHAT THE STUDY ADDS

- Inflammatory bowel disease flares at time of first myocardial infarction are associated with an increased short-term mortality.
- Inflammatory bowel disease is associated with modestly increased risk of death, and major adverse cardiovascular events among patients surviving a first-time myocardial infarction.
- Risk of recurrent myocardial infarction, death, and major adverse cardiovascular events in patients with inflammatory bowel disease after an MI was strongly correlated with IBD activity, including flares and persistent activity.

Methods

Settings and Data Sources

The study is a historical cohort study, and eligible subjects were identified through the use of nationwide registries covering the entire Danish population. The tax-funded government run healthcare system in Denmark provides free access to all citizens based on a unique and permanent civil registration number, which allows retrieval of data across the administrative registers. We retrieved information on hospitalizations, outpatient activities, and invasive procedures according to the Danish National Patient Registry. Admissions are registered by 1 primary diagnosis, and if appropriate, 21 secondary diagnoses, listed according to the International Classification of Diseases system, whereas invasive procedures are listed according to the Danish Register of Medicinal Product Statistics. The Danish Register of Medicinal Product Statistics holds information on drug quantity dispensed, strength and dispensing date for all prescriptions, registered according to the Anatomic Therapeutical Chemical classification since 1995. Partial reimbursement of drug expenses by the healthcare system yields a high validity of the registry. All deaths, including immediate, contributory, and underlying causes, are registered by International Classification of Diseases codes in the National Causes of Death Registry. Finally, information on birth date, vital status, sex, annual taxed income, and migration was obtained from the Danish Civil Registration System. Socioeconomic status was based on the mean annual taxed income in the 5 years before study inclusion for each patient, divided into quintiles, and included in the model as a categorical variable. All International Classification of Diseases and Anatomic Therapeutical Chemical codes used are available in Table I and II in the Data Supplement.

Study Population and IBD Disease Activity

The study cohort comprised subjects aged ≥30 years, hospitalized for a first-time MI between January 1, 2002 and December 31, 2011 (Figure 1). We categorized patients with MI according to the presence of IBD, defined as any hospitalization or outpatient admission for Crohn’s disease or ulcerative colitis at any point before MI hospitalization. The diagnostic coding of both MI and IBD in the Danish National Patient Registry has been validated with a positive predictive value of >90%. We further defined IBD activity by the use of surrogate markers including corticosteroid prescriptions, IBD hospital admissions, and treatment with tumor necrosis factor inhibitors. In a recent study from the UK General Practice Research Database, a new prescription for steroids had a positive predictive value of 85% for identification of an IBD flare, whereas the positive predictive value of remission in patients 120 days after last prescription was 91%. With the use of these IBD activity markers, we characterized 3 IBD activity stages, including flares, persistent activity, and remission, as done previously. A flare was set to last 120 days and was defined by new IBD activity after ≥120 days with no disease activity. Flares were succeeded by persistent activity after 120 days in case additional disease activity occurred within the flare period, and ended after 120 days without disease activity. Remission was present in patients with no disease activity or followed up flares and persistent activity after 120 days without disease activity. IBD activity was evaluated from 180 days before MI hospitalization and throughout follow-up (Figure 2).

Outcome Measures

The following study end points were examined: short-term mortality, recurrent MI, all-cause mortality, and a composite of cardiovascular death, recurrent MI, and stroke. Recurrent MI was defined as a new hospitalization with MI as primary diagnosis as previously validated with a positive predictive value of >90%. Short-term mortality was defined as death during the primary MI hospitalization or within 30 days of discharge, whereas for the other end points, subjects were required to be alive and were followed up from 30 days after primary MI discharge until event, migration, or end of study on December 31, 2011. The 30-day quarantine period after discharge was established to avoid capturing rehospitalizations for the initial MI and to allow patients time for claiming pharmacotherapy prescribed during the primary MI hospitalization.

Medical Treatment, Comorbidity, and Invasive Coronary Revascularization

Ongoing cardiovascular pharmacotherapy was identified by any claimed prescriptions in the period from 180 days before hospitalization for first-time MI and, for patients alive 30 days after discharge, until start of the follow-up period (ie, 30 days after discharge). We evaluated the use of aspirin, clopidogrel, vitamin K antagonists, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin 2 receptor antagonists, loop diuretics, spironolactone, statins, and glucose-lowering agents, (see Table II in the Data Supplement for Anatomic Therapeutical Chemical codes). Comorbidity was assessed by identifying discharge diagnostic codes from hospitalizations during the 12 months before admission for first-time MI according to the Ontario acute MI mortality prediction rules. Invasive coronary procedures, that is, percutaneous coronary intervention (PCI) including primary PCI and coronary artery bypass grafting, were identified for patients alive 30 days after discharge.

Statistical Analysis

Baseline characteristics were summarized as means with SDs for continuous variables and frequencies and percentages for categorical variables. The study population was defined at 2 time points. Patients were included at time of hospitalization for MI to assess short-term (30 days) mortality, and, subsequently, patients alive 30 days after discharge from MI hospitalization were identified to assess longer term adverse cardiovascular events. Baseline characteristics were defined at each time point (ie, at time of MI hospitalization [Table III in the Data Supplement] and 30 days after discharge for patients alive [Table I in the Data Supplement]). Investigating short-term mortality, a logistic regression model, adjusted for age, sex, year, socioeconomic status, and comorbidity, and cardiovascular pharmacotherapy as listed in Table III in the Data Supplement, was used to assess the odds ratios of short-term mortality, defined as death during hospitalization or within a 30-day postdischarge period, according to IBD activity stage at time of first-time MI, and with patients with MI without IBD as reference. Investigating longer term adverse cardiovascular risk, crude incidence rates (IRs; events per 100 person-years) were reported for patients with MI with and without IBD, and we further calculated IRs according to IBD disease...
activity stages. Cox regression models were used to estimate hazard ratios (HRs) comparing the risk in patients with IBD to the reference of patients with MI without IBD. Analyses were adjusted for age, sex, year, socioeconomic status, invasive procedures (PCI and coronary artery bypass grafting), comorbidity, and pharmacotherapy. To assess the IBD activity-dependent risk, we did Cox regression analyses modeling IBD activity as time-dependent covariates comprising the 3 defined stages of IBD disease activity; flare, persistent activity, and remission. The assumptions of the Cox model (proportionality, linearity of continuous variables, and no interactions) were tested, and the models were found valid. For sensitivity analyses, we changed flare duration from 120 days to 60 and 180 days, respectively, to assess the effect on disease activity-associated risk estimates, and we evaluated patients with ulcerative colitis and Crohn’s disease separately. Furthermore, to strengthen the validity of the MI diagnosis, we did an analysis only on invasively (PCI or coronary artery bypass grafting) managed patients. Finally, we did an analysis where we excluded patients with chronic obstructive pulmonary disease because of concerns of non-IBD reasons for glucocorticoid treatment in these patients. A 2-sided significance level of 0.05 was used. The study was conducted and reported according with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.24 All statistical analyses were performed with the SAS Statistical Software package version 9.2 (SAS Institute Inc, Cary, NC).

Ethics
Register-based studies do not require any ethical approval in Denmark. Individual patients were not identifiable as the personal identification numbers were encrypted. The Danish Data protection agency approved the study (reference no. 2007-58-0015, internal reference: 00916 GEH-2010-001).

Results

Short-Term Mortality Associated With IBD Disease Activity Stage
A total of 1030 patients with IBD and 85 760 patients without IBD were hospitalized for a first-time MI in the study period. A comparison of risk factors between IBD- and non-IBD patients is shown in Table III in the Data Supplement. Among 1030 patients with IBD, 110 had a flare, 89 had persistent activity, and 831 were in remission at time of hospitalization for MI. Death during hospitalization or within 30 days of discharge occurred in 167 (16.2%) patients with IBD and 13 172 (15.4%) without IBD, respectively. Among the fatal cases in the IBD group, 31 (28.2%) had a flare, 19 (21.3%) had persistent activity, and 117 (14.1%) were in remission at time of MI. Adjusted odds ratios of death during hospitalization or within 30 days of discharge according to IBD activity stages at time of first-time MI were 3.29 (95% confidence interval [CI], 1.98–5.45), 1.62 (95% CI, 0.95–2.77), and 0.97 (95% CI, 0.78–1.19) for flare, persistent activity, or remission, respectively.

Long-Term Risk of Adverse Cardiovascular End Points and Mortality
A total of 73 451 patients alive 30 days after first-time MI (mean age, 68.4 years; 36.9% women) were followed up for a mean period of 3.9 years (Figure 1). The population included 863 patients (1.2%) with IBD, who had a mean age of 68.5 years, and 42.3% were women. In general, there was a trend toward comorbidities being marginally more frequent among patients with IBD, while these subjects used less cardiovascular pharmacotherapy and had fewer coronary invasive procedures when compared with non-IBD patients (Table 1). Among patients with IBD, 368 (42.6%) patients had IBD activity, whereas the remaining patients stayed in remission (Table 2). Only 21 patients (1 with IBD) were lost to follow-up. We found no difference in risk associated with IBD in sex-stratified analyses on all outcomes (not shown).

Recurrent MI
Recurrent MI occurred in 7348 patients (94 with IBD), corresponding to IRs of 3.3 versus 2.7 per 100 person-years in patients with IBD versus non-IBD patients. Among patients with IBD 13 had a flare, 11 had persistent activity, and 70 had...
remission at time of recurrent MI and IRs varied considerably according to IBD disease activity stage (Figure 3). The overall risk of recurrent MI in patients with IBD was comparable with non-IBD patients with HR 1.21 (95% CI, 0.99–1.49). However, the risk was significantly increased in periods of active IBD with HR 3.09 (95% CI, 1.79–5.32) for IBD flares and HR 1.98 (95% CI, 1.09–3.61) for persistent activity, whereas no increased risk of recurrent MI was observed for patients with IBD in remission (HR 1.03; 95% CI, 0.81–1.31).

All-Cause Mortality
In patients alive 30 days after first-time MI discharge, a total of 21,330 patients, of whom 270 had IBD (34 with flares, 46 with persistent activity, and 190 with remission, respectively) died during follow-up. The IRs per 100 person-years were 8.7 and 7.4 in patients with and without IBD (Figure 3). The fully adjusted IBD-associated risk of all-cause mortality was modestly increased (HR, 1.14; 95% CI, 1.01–1.28), but the risk was more than doubled during flares (HR, 2.25; 95% CI, 1.61–3.15) and persistent activity (HR, 2.04; 95% CI, 1.53–2.73), whereas it remained similar to the non-IBD cohort during remission (HR, 0.95; 95% CI, 0.83–1.10).

Recurrent MI, Cardiovascular Death, and Stroke
The composite end point of recurrent MI, cardiovascular death, or stroke was met in 18,419 patients, of whom 226 had IBD (23 with flares, 28 with persistent activity, and 175 with remission, respectively). This corresponded to IRs per 100 person-years of 8.1 and 7.0, for patients with and without IBD, respectively. Overall, IBD was associated with a modestly increased risk of the composite end point (HR, 1.17; 95% CI, 1.03–1.34), and in analyses stratified on IBD activity stages, we observed a pattern similar to that observed for the other end points, with elevated risk during flares (HR, 2.04; 95% CI, 1.35–3.06) and persistent activity (HR, 1.73; 95% CI, 1.19–2.50), but not during remissions (HR, 1.06; 95% CI, 0.91–1.23).

Sensitivity Analyses
First, when we reduced flare duration to 60 days, the pattern of disease-activity–dependent risk persisted for recurrent MI (flare: HR, 2.07; 95% CI, 1.27–3.83; persistent activity: HR, 3.84; 95% CI, 1.60–9.23; and remission: HR, 1.11; 0.89–1.39), as well as for all-cause mortality and the composite end point (not shown). Similarly, when we extended flare duration to 180 days, increased risk remained associated with active disease for recurrent MI (flare: HR, 2.01; 95% CI, 1.78–5.08; persistent activity: HR, 1.88; 95% CI, 1.09–3.24; and remission: HR, 1.01; 95% CI, 0.80–1.29) and also for all-cause mortality and the composite end point (not shown). Second, in an analysis stratified by IBD entity, we found similar HRs for all adverse end points in patients with Crohn’s disease and ulcerative colitis, respectively (data not shown).

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and persistent activity (HR, 2.10; 95% CI, 1.05–4.21), but not in periods of remission (HR, 0.98; 95% CI, 0.76–1.27).

Discussion
In this nationwide cohort study of patients with first-time MI and a mean follow-up of 3.9 years, the risk of recurrent MI, stroke, and the composite end points was markedly increased for patients with IBD in periods of flares and persistent activity, while the risk during remission was comparable with that of patients with post-MI without IBD. In addition, we showed that an IBD flare at time of first-time MI was associated with higher odds ratios of death during the primary MI hospitalization or within 30 days of discharge. Overall, IBD was associated with a modestly increased risk of all-cause death, and the composite end point of recurrent MI, stroke, and cardiovascular death. No previous studies of post-MI prognosis in patients with IBD have been reported, but the association between IBD and worsened prognosis after MI is in line with findings in other chronic inflammatory diseases, including rheumatoid arthritis and psoriasis.25,26 The observation of a relationship between adverse cardiovascular events and active stages of IBD further suggests that inflammation plays a central role in the association between IBD and atherothrombotic events. Indeed, the arterial and systemic immune-inflammatory processes implicated in atherosclerosis and atherothrombotic events bear many resemblances to the intestinal and systemic inflammation seen in active IBD. For example, local target organ (artery or bowel) infiltration and activation of cells from both the innate and the adaptive immune response is associated with both conditions as are elevated circulating levels of high-sensitive C-reactive protein, platelet activation, and atherogenic lipid abnormalities.4,8,27

Our finding of an increased all-cause mortality in patients with post-MI and IBD parallels recent observations of a moderately increased all-cause mortality and cardiovascular mortality among Danish patients with IBD when compared with a random sample of the Danish population.28 However, we here considerably expand this observation by demonstrating that the increased mortality in patients with MI and IBD was present exclusively during active disease stages, whereas quiescent IBD did not carry any increased mortality risk.

The use of post-MI secondary pharmacological prevention was overall high in our study population with no apparent difference according to IBD status. The relatively low proportion of patients treated invasively during the index MI is likely to reflect, for example, that early coronary revascularization was not widely implemented during the early part of the current study and that patients with IBD may be at increased risk of type 2 MI (eg, because of anemia). Notably, slightly lower proportions among patients with IBD were treated with statins, platelet inhibitors, and invasive coronary revascularization when compared with patients with MI without IBD. This finding may reflect reluctance of physicians toward antithrombotic and invasive treatment in patients with active IBD because of, for example, concerns of bleeding. This reluctance may extend to in-hospital use of anticoagulant treatment in patients with IBD, but unfortunately we did not have information on this issue. Although the underlying reasons for this observation were not examined, significant chronic comorbidity has previously been associated with suboptimal post-MI care and this finding may be an example of the treatment-risk paradox (ie, that patients at increased risk receive less evidence-based treatment).29

Strengths and Limitations
The main strength of our study was the large nationwide unselected post-MI population, including, and the high validity of diagnose coding for IBD and MI in the Danish registries.17,18 We had extensive information on comorbidity and included only dispensed medication thereby avoiding recall bias. Limitations include the observational study design and lack of clinical information on individual patient characteristics, including the anatomic localization and extent of coronary artery disease and the use of anticoagulants during the MI hospitalization. Also, estimation of IBD activity was based on medical treatment and admissions, rather than on clinical criteria and inflammatory biomarkers. The flare duration of 120 days was arbitrary defined although based on clinical experience and this analysis strategy has previously used by us and

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<th>Recurrent MI</th>
<th>HR [95% CI]</th>
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<tr>
<td>IBD overall</td>
<td>1.21 (0.99-1.49)</td>
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<tr>
<td>Flare</td>
<td>3.09 (1.79-5.32)</td>
<td>9.2</td>
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<tr>
<td>Persistent activity</td>
<td>1.98 (1.09-3.61)</td>
<td>6.6</td>
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<tr>
<td>Remission</td>
<td>1.03 (0.81-1.30)</td>
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<th>All-cause mortality</th>
<th>HR [95% CI]</th>
<th>IR /100 py Events</th>
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<tr>
<td>IBD overall</td>
<td>1.14 (1.01-1.28)</td>
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<th>Re-MI, CV death, and stroke</th>
<th>HR [95% CI]</th>
<th>IR /100 py Events</th>
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<td>IBD overall</td>
<td>1.17 (1.03-1.28)</td>
<td>8.1</td>
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<tr>
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<td>Persistent activity</td>
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<tr>
<td>Remission</td>
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<td>No IBD</td>
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Conclusions

Patients with IBD have increased long-term risk of all-cause mortality and major adverse cardiovascular events after MI, and this risk is exclusively observed during active IBD, in particular, in relation with flares. The results support evidence indicating that increased clinical surveillance and treatment aimed at reduction of cardiovascular risk by reducing length and number of flares in patients with IBD may be warranted, especially for patients with prolonged or repeated disease activity. Prospective studies on the cardiovascular risk in IBD should incorporate inflammatory markers, and clinical information on risk factors such as ejection fraction, hemoglobin, smoking, and body mass index.

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Disclosures

None.

References

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Table 1: Diagnoses and treatment procedure codes used for defining the study population, comorbidities, and outcomes

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<td>Stroke</td>
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<td>CABG</td>
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<td>Treatment with TNF-α inhibitors</td>
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ICD-8: 8th revision of the International Classification of Diseases system
ICD-10: 10th revision of the International Classification of Diseases system
NCSP: The Nordic Medical Statistics Committees Classification of Surgical Procedures
PCI: Percutaneous coronary intervention
CABG: Coronary artery bypass grafting
TNF: Tumour necrosis factor
NCSP: Nordic Medico-Statistical Committee Classification of Surgical Procedures
**Supplementary Table 2**: Pharmacological treatment and Anatomical Therapeutical Chemical (ATC) codes

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>ATC codes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>BO1AC06, NO2BA01</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>BO1AC04</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>C07</td>
</tr>
<tr>
<td>Cholesterol-lowering agents</td>
<td>C10A</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>G45, I60-I69</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>J18.2, J81</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>BO11AA0</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>I12, I13, N18, T82.4, Z99.2</td>
</tr>
<tr>
<td>Glucose-lowering agents</td>
<td>I47-I49, I46.0, I46.9, R00.1</td>
</tr>
</tbody>
</table>

ACE inhibitors: Angiotensin-converting enzyme inhibitors  
ARBs: Angiotensin-II receptor blockers  
ATC: Anatomical Therapeutic Chemical classification system
Supplementary Table 3: Baseline characteristics of 86,790 patients admitted to hospital with first-time MI. IBD - inflammatory bowel disease; SD – standard deviation, ACE inhibitor – Angiotensin-converting enzyme inhibitor, ARB – angiotensin 2 receptor blocker.

<table>
<thead>
<tr>
<th></th>
<th>Patients with IBD n=1,030</th>
<th>No history of IBD n=85,760</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females (%)</strong></td>
<td>452 (43.9)</td>
<td>33,161 (38.7)</td>
</tr>
<tr>
<td><strong>Age, years (mean [SD])</strong></td>
<td>70.0 (13.4)</td>
<td>69.9 (13.7)</td>
</tr>
<tr>
<td><strong>Ulcerative colitis (%)</strong></td>
<td>781 (75.8)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Crohn’s disease (%)</strong></td>
<td>249 (24.2)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Comorbidity, No. (%)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients with IBD</th>
<th>No history of IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock</td>
<td>13 (1.3)</td>
<td>1,000 (1.2)</td>
</tr>
<tr>
<td>Diabetes with complications</td>
<td>67 (6.5)</td>
<td>4,286 (5.0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>109 (10.6)</td>
<td>10,083 (11.8)</td>
</tr>
<tr>
<td>Cancer</td>
<td>36 (3.5)</td>
<td>2,934 (3.4)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>74 (7.2)</td>
<td>5,255 (6.1)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>8 (0.8)</td>
<td>1,067 (1.2)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>20 (1.9)</td>
<td>1,343 (1.6)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>32 (3.1)</td>
<td>1,711 (2.0)</td>
</tr>
<tr>
<td>Cardiac dysrhythmia</td>
<td>136 (13.2)</td>
<td>9,601 (11.2)</td>
</tr>
</tbody>
</table>

**Concomitant pharmacotherapy, No. (%)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients with IBD</th>
<th>No history of IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>351 (34.1)</td>
<td>24,458 (28.5)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>30 (2.9)</td>
<td>1,745 (2.0)</td>
</tr>
<tr>
<td>Dual antiplatelet treatment</td>
<td>20 (1.9)</td>
<td>1,069 (1.3)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>249 (24.2)</td>
<td>17,154 (20.0)</td>
</tr>
<tr>
<td>Cholesterol-lowering agents</td>
<td>228 (22.1)</td>
<td>15,951 (18.6)</td>
</tr>
<tr>
<td>ACE Inhibitors/ARB</td>
<td>311 (30.2)</td>
<td>24,006 (28.0)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>224 (21.8)</td>
<td>14,768 (17.2)</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>50 (4.9)</td>
<td>3,774 (4.4)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>57 (5.5)</td>
<td>3,189 (3.7)</td>
</tr>
<tr>
<td>Glucose-lowering agents</td>
<td>143 (13.9)</td>
<td>10,130 (11.8)</td>
</tr>
</tbody>
</table>