Inflammatory Bowel Disease Is Associated With an Increased Risk of Hospitalization for Heart Failure: A Danish Nationwide Cohort Study

Kristensen et al: Heart Failure in Patients with IBD

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Journal Subject Codes: Heart failure:[110] Congestive, Etiology:[8] Epidemiology
Abstract

Background—Inflammatory bowel disease (IBD) has been linked to adverse cardiovascular events, but a relation to heart failure is uncertain. We investigated the IBD-associated risk of heart failure in a nationwide setting.

Methods and Results—A total of 5,436,647 Danish citizens, with no history of IBD or heart failure, were included on 1 January 1997 and followed until first hospitalization for heart failure, death, or 31 December 2011. Of these subjects, 23,681 developed IBD for which disease activity was determined continuously throughout the study. The risk of hospitalization for heart failure was estimated with a Poisson regression model adjusting for comorbidity and cardiovascular pharmacotherapy as time-dependent covariates. During a mean follow-up of 11.8 years in the reference population and 6.4 years in the IBD group, hospitalization for heart failure occurred in 553 subjects with IBD, and 171,405 in the reference population. Patients with IBD had a 37% increased risk of hospitalization for heart failure (incidence rate ratio [IRR] 1.37, 95% confidence interval [CI] 1.26-1.49) compared to the reference population. IBD activity-specific analyses showed markedly increased risk of heart failure hospitalization during flares (IRR 2.54, 95% CI 2.13-3.04) and persistent activity (IRR 2.73, 95% CI 2.25-3.33]) but not in IBD remission (IRR 1.04, 95% CI 0.94-1.16).

Conclusions—In a nationwide cohort, IBD was associated with an increased risk of hospitalization for heart failure, and this risk was strongly correlated to periods of active disease. The mechanisms underlying this finding warrant further studies.

Key Words: Crohn’s disease; heart failure, inflammation, inflammatory bowel disease; ulcerative colitis
Heart failure is among the most frequent hospital discharge diagnoses of patients 65 years of age or older, constituting a considerable health care burden with an expected increased prevalence in the future.\textsuperscript{1-3} Inflammatory bowel disease (IBD) is characterized by intestinal inflammation and periodical flares with increased disease activity, and along with other chronic inflammatory diseases, IBD has been linked to an increased risk of cardiovascular disease, including myocardial infarction, stroke and atrial fibrillation.\textsuperscript{4-9} Research has provided evidence that inflammatory activation plays a role in the development and progression of heart failure, and the prothrombotic state associated with inflammation has been suggested as a causal link between IBD and atherothrombosis.\textsuperscript{10-17} In addition, intestinal inflammation in IBD, especially during flares, may contribute to the development of heart failure by translocation of bacterial lipopolysaccharides from the bowel to the circulatory system that elicit production of proinflammatory mediators and tissue injury including myocardial damage.\textsuperscript{10-11} However, whether IBD is associated with an increased risk of heart failure has not been explored previously. We therefore determined the IBD-associated risk of developing heart failure and the importance of IBD disease activity by evaluating all first-time hospitalizations for heart failure in a Danish nationwide cohort.

\textbf{Methods}

\textit{Setting and data sources}

This is a historical cohort study utilizing existing registries of the entire Danish population followed from 1997 until 2011. Eligible subjects were identified by use of the Civil Person Registration system, which contains information on birth date, gender, vital status, annual taxed income, and migration status, registered according to each citizen’s unique and permanent civil registration number. All contacts with the public health care system are based on this registration number and thus allowed us to do individual level-linkage across the
nationwide hospital and drug prescription registers.\textsuperscript{18} The National Patient Register holds information on all in-hospital contacts since 1978, and all outpatient activity since 1995.\textsuperscript{19} Each contact is coded by up to four diagnoses, with the main reason for hospitalization as the primary diagnosis, listed according to the International Classification of Diseases, 8\textsuperscript{th} revision (ICD-8) until 1994 and the 10\textsuperscript{th} revision (ICD-10) thereafter. The Danish Register of Medicinal Product Statistics holds information on all drug prescriptions since 1995, including information on amount, strength and dispensing date using the Anatomical Therapeutical Chemical (ATC) classification. Partial reimbursement of drug expenses ensures complete and accurate registration by Danish pharmacies.\textsuperscript{20}

Study Subjects

The study cohort comprised all Danish citizens aged 18 years or older with no history of IBD or prior hospitalizations for heart failure. Eligible subjects were included on 1 January 1997 or on their 18\textsuperscript{th} birthday, and followed until first hospitalization for heart failure, death, or 31 December 2011 (Figure 1). We identified individuals with new-onset IBD by a combined criteria of a first-time diagnosis of IBD i.e. Crohn’s disease or ulcerative colitis, and a claimed prescription of IBD pharmacotherapy (Supplemental Tables) within the period from one year before, to one year after diagnosis. We used the latest of either the date of prescription or diagnosis as date of IBD onset, to avoid including risk time conditioned on future events, and we excluded subjects who received IBD pharmacotherapy (apart from glucocorticoids) more than one year prior to the date of IBD diagnosis.

IBD activity

In patients with IBD, hospitalizations with IBD as primary diagnosis, initiation of biological anti-tumor necrosis factor (TNF) treatment and claimed prescription of glucocorticoids were used as surrogate markers for disease activity (Supplemental Tables). By combined use of these markers, disease stages of remission, flare and persistent activity were defined. Patients
were defined as in remission starting 120 days after last disease activity (IBD hospitalization, anti-TNF treatment or glucocorticoid prescription), and remission continued in the absence of further disease activity. Disease activity following a remission period defined a flare which was set to 120 days duration. Likewise, the first 120 days following onset of IBD was defined as a flare. Finally, we defined periods of persistent activity, which succeeded flares if additional disease activity occurred within the 120 days from flare start (Figure 2).

Study endpoint

The endpoint for the study was first hospitalization for heart failure, recorded as discharge diagnosis in the National Patient Registry.

Comorbidity and pharmacotherapy

Baseline comorbidity was registered by hospitalizations in the five years prior to study start, and baseline pharmacotherapy was defined by at least one dispensed prescription in the two years preceding study inclusion. Both comorbidity and pharmacotherapy was continuously updated throughout follow-up. We evaluated the following comorbidities: Diabetes, atrial fibrillation, chronic obstructive pulmonary disease, renal disease, hypertension, vascular disease and thromboembolism (Supplemental Table 1). Pharmacotherapy included glucose-lowering agents, lipid-lowering agents, platelet inhibitors, and (for sensitivity analyses) loop-diuretics (Supplemental Table 2). Hypertension was defined by treatment with at least two of the following classes of antihypertensive drugs within a 90 day period: α-adrenergic blockers, non-loop diuretics, vasodilators, β-blockers, calcium channel blockers, and renin-angiotensin system inhibitors, as previously validated with a positive predictive value of >80%. Hypertension and diabetes were defined by either drug prescriptions or hospital diagnoses, whichever came first.
Statistical analyses

Baseline characteristics were presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. Incidence rates (IRs) of hospitalization for heart failure were presented per 1,000 person-years for subjects with and without IBD, respectively. We fitted two Poisson regression models to calculate incidence rate ratios (IRR) of heart failure comparing the IBD group, with the reference population. The primary model was adjusted for age, sex, calendar year, income, comorbidity, and pharmacotherapy, all determined as time-dependent variables, whereas the second model solely adjusted for age, sex and calendar-year. Two models were explored in order to assess the influence of comorbidities such as vascular disease, which is more prevalent in IBD, and hereby potentially acts as intermediates. Time bands were split in 1-year periods from 1 January 1997, and age was updated in each time band split. In IBD activity analyses, we categorized exposure time as flare, persistent activity, or remission. The assumption of a constant rate of examined variables within each time-band was tested and confirmed by demonstrating the same results with a finer split of 6 months (not shown). Interactions were tested and found be absent unless otherwise reported. The assumption of linearity of continuous variables was tested by demonstrating that quartiles of these variables did not add to the prognostic value of the model. For sensitivity analyses, we did a 1:5 age- and sex-matched cohort analysis where we included IBD subjects as well as matched controls at time of IBD onset, and followed them until hospitalization for heart failure, death or 31 December 2011. Further, we changed the definition of the study endpoint to a prescription of loop diuretics and/or a heart failure discharge diagnosis (as done previously), and only hospitalizations with a primary diagnosis of heart failure, respectively. Further we excluded IBD patients with more than one annual hospital admission, on average, during follow-up, and we also performed analyses excluding patients with chronic obstructive pulmonary
disease to evaluate the effects of potential misclassification of flares due to pulmonary indications for glucocorticoids. Finally, we varied the assumed flare duration to 60 and 180 days compared to the 120 days used for the primary analyses to assess effects on the disease activity-dependent risk estimates. SAS version 9.2 and Stata version 11.1 were used for statistical analyses. The study was conducted and reported according with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.22

Ethics

Register-based studies do not require 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, suite no. 00916 GEH-2010-001).

Results

From 1 January 1997, we included 5,436,647 Danish citizens, aged 18 years and older, and with no history of IBD or prior hospitalizations for heart failure. Of these, 23,681 patients developed new-onset IBD throughout follow-up, and constituted the IBD group. Mean age in the IBD group was 38.3 years compared to 40.7 years in the reference population and females comprised 53.7% and 50.7% of the IBD group and the reference population, respectively. Despite these differences, baseline comorbidity and pharmacotherapy were comparable in the two groups. Ulcerative colitis comprised 73.3% and Crohn’s disease the remaining 26.7% of the IBD group (Table 1). Hospitalization for heart failure occurred in 553 patients with IBD and 171,405 subjects from the reference population, which corresponded to crude IRs of 3.68 and 2.69 per 1000 person-years, respectively. The IRR of hospitalization for heart failure in the IBD group as compared to the reference population was 1.37, 95% confidence interval [CI] 1.26-1.49) in the fully adjusted analysis (Figure 3). The increased risk associated with
IBD was consistent in the analysis only adjusted for age, sex and calendar-year (IRR 1.62, 95% CI 1.49-1.76). In patients with IBD, flares comprised 10.4%, persistent activity 4.7%, and remission the remaining 84.9% of the follow-up, respectively (Table 2). At time of hospitalization for heart failure, 120 patients were in IBD flares, 100 patients had persistent activity, and the remaining 333 patients were in remission. This disease activity-dependent association corresponded to a 2.5 fold incidence of heart failure during flares (IRR 2.54, 95% CI 2.13-3.04) and almost 3-fold increase during persistent activity (IRR 2.74, 95% CI 2.25-3.33), whereas risk of hospitalization for heart failure in IBD patients in remission was comparable to the reference population (IRR 1.04, 95% CI 0.94-1.16). In stratified analyses, no significant difference (p=0.11) was observed between patients with ulcerative colitis (IRR 1.33, 95% CI 1.21-1.46) and Crohn’s disease (IRR 1.57, 95% CI 1.31-1.89).

Sensitivity analyses

In age- and sex-matched analyses, we included 23,681 patients with IBD and 116,862 matched controls, who had 553 and 1,773 hospitalizations for HF, respectively. This analysis showed an IBD-associated IRR of 1.29, 95% CI 1.17-1.42, and IRRs 2.19, 95% CI 1.82-2.62 and 2.40, 95% CI 1.96-2.95 during flares and persistent activity, respectively, and IRR 1.02, 95% CI 0.90-1.15 during remission. When the main study endpoint was modified to include either a hospital discharge diagnosis of heart failure or prescription for a loop diuretic, the IBD-associated increased risk persisted (IRR 1.56, 95% CI 1.49-1.63) as did the pattern of increased risk during active stages of IBD (flare [IRR 3.76, 95% CI, 3.44-4.11] and persistent activity [IRR 3.48, 95% CI, 3.08-3.93]) and with only a slightly increased risk in remission periods (IRR 1.12, 95% CI 1.06-1.19). Further, in an analysis where the main endpoint was a primary hospital discharge diagnoses of heart failure, the increased risk in IBD patients persisted (IRR 1.21, 95% CI 1.07-1.36). The IBD-associated risk of heart failure hospitalization remained when we excluded IBD patients with more than one annual hospital
admission (not shown) as well as when we excluded patients with COPD (IRR 1.23, 95% CI 1.11-1.39), with a similar activity dependent increased incidence in flares (IRR 2.03, 95% CI 1.59-2.58) and persistent activity (IRR 1.90, 95% CI, 1.43-2.54). Finally, when we increased flare duration to 180 days, risk estimates were only marginally reduced during flares (IRR 2.44, 95% CI 2.07-2.88), persistent activity (IRR 2.45, 95% CI 2.03-2.96), and remission (IRR 1.01, 95% CI 0.90-1.13), whereas a shortened duration of a flare to 60 days lead to increased risk estimates during flares (IRR 2.90, 95% CI 2.41-3.48) and persistent activity (IRR 3.16, 95% CI 2.41-4.16).

Discussion

In this nationwide cohort study, we found a significantly increased risk of first heart failure hospitalization in patients with IBD. Importantly, we demonstrated a 2.5-fold increased risk in active stages of IBD (flares and persistent activity), whereas risk during remission periods was comparable to the reference population. The increased risk in patients with IBD was more pronounced in analyses solely adjusted for age and sex, but was not considerably changed in analyses that included time-dependent adjustments for pharmacotherapy and comorbidity, i.e., including effects of potential mediators of heart failure, such as ischemic heart disease and atrial fibrillation. Further, the increased risk was consistent in sensitivity analyses with modified heart failure endpoints, and exclusion of patients with COPD, respectively.

The present study is the first to demonstrate an association between IBD, in particular active stages of the disease, and hospitalization for heart failure. Inflammation is likely to be an important mechanism underlying this finding and inflammatory activation may play a central role in the pathogenesis of heart failure through an array of mechanisms that can contribute to, for example, myocardial injury and endothelial dysfunction. Further, inflammation
also contributes to a prothrombotic state and even low-grade systemic inflammation is associated with increased risk of atherothrombotic events.\textsuperscript{14, 17, 22, 23} IBD is characterized by inappropriate immune-mediated intestinal and systemic inflammatory activity, but other mechanisms that can increase the risk of heart failure in patients with IBD might be considered as well.\textsuperscript{4, 5} In this regard, the well-known high prevalence of anemia, as well as the increased use of glucocorticoids, and susceptibility to surgical interventions and infections during IBD flares should be considered. The role of glucocorticoids in cardiovascular disease remains controversial, but these agents may, for example, diminish myocardial recovery from ischemic injury by inhibition of angiogenesis and enhancement of tissue fibrosis, which may contribute to development of heart failure.\textsuperscript{24, 25} However, in a large cohort of patients with rheumatoid arthritis, glucocorticoids were not associated with an increased risk of heart failure which indicates that in this regard, their beneficial anti-inflammatory effects counterbalance adverse effects.\textsuperscript{26} Of interest, biological anti-TNF treatment, which is used frequently in IBD patients, was recently found not to be associated with increased risk of heart failure in patients with rheumatoid arthritis and in patients with chronic heart failure, these agents have failed to show any clinical efficacy, probably owing, in part, to the well-known redundancy of inflammatory pathways and the overall complexity of heart failure pathogenesis.\textsuperscript{27-30}

\textit{Strengths and limitations}

The main strength of our study was the large unselected nationwide population, and the extensive information on comorbidity and pharmacotherapy, which included only dispensed medication, i.e., avoidance of recall-bias. The high validity of the diagnostic coding for IBD was further strengthened by our criteria for initiation of IBD pharmacotherapy.\textsuperscript{31} To address differences in the distribution of age and sex between IBD patients and the reference population, we performed a matched analysis, which yielded similar IBD-associated risk
estimates and hereby supported the findings from our primary analysis. The diagnostic coding of heart failure in the Danish registries holds a high specificity of 99% but similar to the EuroHeart Failure survey programme, the sensitivity of the HF diagnosis was low (30-50%). The low sensitivity of the heart failure diagnosis made our study more susceptible to surveillance bias, i.e., subjects with IBD because of more frequent health care contacts are more likely to be diagnosed with heart failure, or diagnosed at an earlier stage. This risk was particularly present during active stages of IBD, and we cannot refute that surveillance bias led to overestimation of risk of heart failure during IBD flares. However, to counter this critical issue we did sensitivity analyses with use of a combined endpoint of loop diuretics and/or heart failure diagnosis (to increase the sensitivity of the heart failure end point) and found similar results. The increased risk of hospitalization for heart failure persisted in an analysis with the endpoint restricted to primary hospitalizations for heart failure, as well as in an analysis where we excluded patients with IBD with more than one annual hospital visit, on average, during follow-up. Major limitations include the lack of clinical information on individual patient characteristics, including the anatomical localization and extent of IBD. Further, we based the estimation of IBD disease activity on medical treatment and admissions, rather than on clinical criteria and inflammatory biomarkers, and since we used IBD treatment to establish disease activity it is possible that systemic IBD treatment, e.g., with glucocorticoids, may have contributed to the increased risk of heart failure during periods of IBD activity. We also lacked information on important cardiovascular risk factors including left ventricular function, obesity, physical activity, blood pressure and smoking although some of these unmeasured confounders were adjusted for, in part, by use of time-dependent surrogates including statins for hyperlipidemia, antihypertensive treatment for hypertension, and COPD for smoking, respectively. The flare duration of 120 days was arbitrarily defined, although this analysis strategy has previously been used by us and others
and we found comparable results in analyses with use of flare durations of 60 and 180 days, respectively.\textsuperscript{16, 34, 35}

\textit{Conclusion}

In a nationwide cohort, IBD was associated with an increased risk of hospitalization for heart failure, and this risk was strongly correlated to periods of active disease. The mechanisms underlying this finding warrant further studies.

\textbf{Sources of Funding}

This study was funded by an unrestricted grant from the P. Carl Petersens Foundation (ref. 13076). Dr. Gislason is supported by an independent research scholarship from the Novo Nordisk Foundation.

\textbf{Disclosures}

None.

\textbf{References}


Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Reference population (n=5,412,966)</th>
<th>IBD patients (n=23,681)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females (%)</td>
<td>2,742,284 (50.7)</td>
<td>12,723 (53.7)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>40.7 (19.6)</td>
<td>38.3 (18.3)</td>
</tr>
<tr>
<td>Mean follow-up time, years</td>
<td>11.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>-</td>
<td>17,359 (73.3)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>-</td>
<td>6,322 (26.7)</td>
</tr>
</tbody>
</table>

Pharmacotherapy (%)

<table>
<thead>
<tr>
<th></th>
<th>Reference population</th>
<th>IBD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive agents</td>
<td>149,818 (2.8)</td>
<td>657 (2.8)</td>
</tr>
<tr>
<td>Cholesterol-lowering agents</td>
<td>30,871 (0.6)</td>
<td>175 (0.7)</td>
</tr>
<tr>
<td>Glucose-lowering agents</td>
<td>74,362 (1.4)</td>
<td>254 (1.1)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>198,730 (3.7)</td>
<td>752 (3.2)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>161,744 (3.0)</td>
<td>621 (2.6)</td>
</tr>
</tbody>
</table>

Comorbidity (%)

<table>
<thead>
<tr>
<th></th>
<th>Reference population</th>
<th>IBD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>38,192 (0.7)</td>
<td>150 (0.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>80,679 (1.5)</td>
<td>270 (1.1)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29,225 (0.5)</td>
<td>92 (0.4)</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>47,961 (0.9)</td>
<td>168 (0.7)</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>44,333 (0.8)</td>
<td>191 (0.4)</td>
</tr>
<tr>
<td>COPD</td>
<td>24,896 (0.5)</td>
<td>89 (0.4)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>4,607 (0.1)</td>
<td>22 (0.1)</td>
</tr>
</tbody>
</table>

IBD – inflammatory bowel disease, COPD - chronic obstructive pulmonary disease
Table 2. Disease activity periods and follow-up time in study cohort with inflammatory bowel disease (IBD)

<table>
<thead>
<tr>
<th>Disease activity periods (n [%])</th>
<th>Mean duration (days)</th>
<th>Total duration of follow-up (person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flare</td>
<td>50,221 (42.8)</td>
<td>115.6</td>
</tr>
<tr>
<td>Persistent activity</td>
<td>20,360 (17.4)</td>
<td>128.1</td>
</tr>
<tr>
<td>Remission</td>
<td>46,718 (39.8)</td>
<td>1,011.3</td>
</tr>
<tr>
<td>Total</td>
<td>117,299 (100)</td>
<td>474.5</td>
</tr>
</tbody>
</table>
Figure Legends

**Figure 1.** Flowchart of the study population. 
IBD – inflammatory bowel disease.

**Figure 2.** Example of disease activity in a patient with inflammatory bowel disease (IBD) throughout the study period. 
TNF – tumor necrosis factor.

**Figure 3.** Risk of hospitalization for heart failure in patients with inflammatory bowel disease (IBD) compared to the reference population. 
IR - incidence rate, py – person-years, *adjusted for age, sex, calendar-year, income, cardiovascular pharmacotherapy, and comorbidity."
Danish population aged ≥ 18 years on January 1, 1997
n = 5,482,798

Excluded at baseline:
Prevalent heart failure or IBD
n = 46,151

Study cohort n = 5,436,647

IBD group
n = 23,681

Reference population
n = 5,412,966
**Study start**
1 January 1997

**IBD onset**

- **Flare**
- **Remission**
- **Persistent activity**

**IBD diagnosis + pharmacotherapy**

120 days

**IBD activity**

120 days

**IBD disease stage**

**End of study**
31 December 2011

**Activity markers:**
- Prescription for glucocorticoids
- IBD hospitalizations
- Biological anti-TNF treatment
Hospitalization for heart failure

Reference population
IRD (age-, sex- and year-adjusted)
IRD (fully adjusted*)

Stages of disease activity
Flare
Persistent activity
Remission

Incidence rate ratio (IRR)
(Horizontal bars indicate 95% confidence interval [CI])

<table>
<thead>
<tr>
<th></th>
<th>IRR [95% CI]</th>
<th>IR /1000 py</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>1.00 (ref.)</td>
<td>2.69</td>
<td>171,405</td>
</tr>
<tr>
<td>Age-, sex-, and year-adjusted</td>
<td>1.62 (1.49-1.76)</td>
<td>3.68</td>
<td>553</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.37 (1.26-1.49)</td>
<td>3.68</td>
<td>553</td>
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**Supplementary Table 1**: Diagnoses and procedure codes used in the study.

<table>
<thead>
<tr>
<th>Study population</th>
<th>ICD-10 / ICD-8</th>
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<td>Inflammatory bowel disease</td>
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<td>Ulcerative colitis</td>
<td>K51 / 569.05, 563.19</td>
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<td>Crohn’s disease</td>
<td>K50 / 563.01</td>
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<td>Study outcome</td>
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<tr>
<td>Heart Failure</td>
<td>I42, I43, I50 / 110, 517</td>
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<td>Comorbidity</td>
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<td>Vascular disease</td>
<td>I21, I22, I70.0, I70.2 - I70.9 / 410, 440</td>
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<td>Diabetes</td>
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<td>J42, J44 / 490-492</td>
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<td>I48 / 427.9</td>
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<td>I26, I63, I64, I74, G45.8 G45.9 / 433-438, 444, 450</td>
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<td>Coronary revascularization</td>
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<td>PCI</td>
<td>KFNG</td>
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<td>Primary PCI</td>
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<td>CABG</td>
<td>KFNA, KFNB, KFNC, KFNE</td>
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<tr>
<td>Biological anti-TNF treatment</td>
<td>BHJ18A</td>
</tr>
</tbody>
</table>

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
**Supplementary Table 2**: Anatomical, Therapeutical, Chemical (ATC codes) used in the study.

<table>
<thead>
<tr>
<th>IBD pharmacotherapy</th>
<th>ATC codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>L04AX01</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>L01BA01 / L04AX03</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>A07EC01</td>
</tr>
<tr>
<td>5-ASA</td>
<td>A07EC02</td>
</tr>
<tr>
<td>6-mercaptopurine</td>
<td>L01BB02</td>
</tr>
<tr>
<td>Rectal glucocorticoids</td>
<td>A07EA</td>
</tr>
<tr>
<td>Oral glucocorticoids</td>
<td>H02AB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other pharmacotherapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol-lowering agents</td>
<td>C10A</td>
</tr>
<tr>
<td>Glucose-lowering agents</td>
<td>A10</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>B01AC04, B01AC06, N02BA01</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>α-adrenergic blockers (C02A, C02B, C02C), non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52), vasodilators (C02DB, C02DD, C02DG), β-blockers (C07), calcium channel blockers (C07F, C08, C09BB, 09DB), renin-angiotensin system inhibitors (C09)</td>
</tr>
</tbody>
</table>

IBD – inflammatory bowel disease, 5-ASA – 5-aminosalicylic acid.