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Early Ileocecal Resection for Crohn's Disease Is Associated With Improved Long-term Outcomes Compared With Anti-Tumor Necrosis Factor Therapy: A Population-Based Cohort Study

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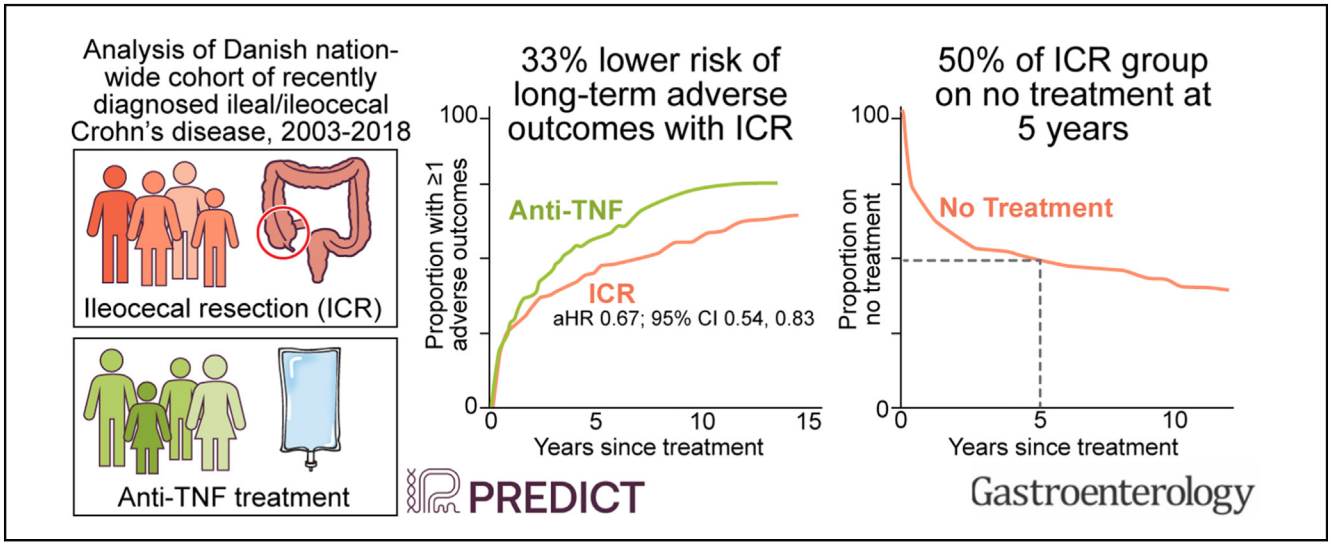
This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e25. Learning Objective: Upon completion of this CME activity, successful learners will be able to understand the role of and outcomes with early ileocecal resection, relative to anti-tumor necrosis factor therapy, as primary treatment in Crohn's disease.



BACKGROUND & AIMS: Early Crohn's disease (CD) treatment involves anti-tumor necrosis factor (TNF) agents, whereas ileocecal resection (ICR) is reserved for complicated CD or treatment failure. We compared long-term outcomes of primary ICR and anti-TNF therapy for ileocecal CD. **METHODS:** Using cross-linked nation-wide registers, we identified all individuals diagnosed with ileal or ileocecal CD between 2003 and 2018 and treated with ICR or anti-TNF agents within 1 year of diagnosis. The primary outcome was a composite of ≥1 of the following: CD-related hospitalization, systemic corticosteroid exposure, CD-related surgery, and perianal CD. We conducted adjusted Cox's proportional hazards regression analyses and determined the cumulative risk of different treatments after primary ICR or anti-TNF therapy. **RESULTS:** Of 16,443 individuals diagnosed with CD, 1279 individuals fulfilled the inclusion criteria. Of these, 45.4% underwent ICR and 54.6% received anti-TNF. The composite outcome occurred in 273 individuals (incidence rate, 110/1000 person-years) in the ICR group and in 318 individuals (incidence rate, 202/1000 person-years) in the anti-TNF group. The risk of the composite outcome was 33% lower with ICR compared with anti-TNF (adjusted hazard ratio, 0.67; 95% confidence interval, 0.54–0.83). ICR was associated with reduced risk of systemic corticosteroid exposure and CD-related surgery, but not other secondary outcomes. The proportion of individuals on immunomodulator, anti-TNF, who underwent subsequent resection, or were on no therapy 5 years post-ICR was 46.3%, 16.8%, 1.8%, and 49.7%, respectively. **CONCLUSION:** These data suggest that ICR may have a role as first-line therapy in CD management and challenge the current paradigm of reserving surgery for complicated CD refractory or intolerant to medications. Yet, given inherent biases associated with observational data, our findings should be interpreted and applied cautiously in clinical decision making.

Keywords: Anti-Tumor Necrosis Factor Agent; Crohn's Disease; Ileocecal Resection; Inflammatory Bowel Disease; Surgery.

Abbreviations used in this paper: **aHR, adjusted hazard ratio; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; ICR, ileocecal resection; IMM, immunomodulator; IQR, interquartile range; LIR!C, Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Recurrent Distal Ileitis in Crohn's Disease trial; PY, person-years; TNF, tumor necrosis factor.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The Laparoscopic Ileocaecal Resection versus Infliximab for Terminal Ileitis in Crohn's disease (LIR!C) randomized clinical trial has demonstrated comparable quality of life with ileocaecal resection and infliximab as a first-line treatment for limited, nonstricturing ileocecal Crohn's disease at 1 year of follow-up, and improved outcomes with ileocaecal resection on retrospective analysis of long-term follow-up data. However, in the real world, the long-term impact of early ileocaecal resection for Crohn's Disease, compared with medical therapy, remains largely unexplored.

NEW FINDINGS

Using nationwide data from an unselected population-based cohort with long-term follow, we report that the risk of the composite outcome including hospitalization, repeat Crohn's disease-related surgery, systemic corticosteroid exposure, and perianal Crohn's disease was 33% lower with ileocaecal resection compared with anti-tumor necrosis factor agents as primary therapy. Of individuals who underwent ileocaecal resection, approximately half were on no treatment at 5 years of follow-up.

LIMITATIONS

Limitations include the use of administrative data secondarily for the purpose of research, lack of data on disease progression-associated variables such as smoking, confounding by indication, and limited generalizability to other populations.

CLINICAL RESEARCH RELEVANCE

We report improved long-term outcomes with ileocaecal resection compared with anti-tumor necrosis factor as primary treatment for early ileal and ileocecal Crohn's disease. A substantial subset of patients was on no medication 5 years after ileocaecal resection. Identifying clinical characteristics of these patients will help personalize inflammatory bowel disease care.

BASIC RESEARCH RELEVANCE

Molecular analyses in biological samples to predict outcomes after ileocaecal resection will further improve personalized inflammatory bowel disease care.

Early and effective treatment of Crohn's disease (CD) is critical to preventing disease progression and improving long-term outcomes.[1,2] Anti-tumor necrosis factor (anti-TNF) therapy is the mainstay of moderate to severe CD management.[3,4] However, it most often warrants indefinite continuation of treatment and is associated with loss of response, adverse events, and health care costs.[5–8] Although surgical management is traditionally recommended in complicated CD or for patients nonresponsive to or intolerant of medications,[9] interest in early surgery for management of CD ileitis is growing.

In the Laparoscopic Ileocolic Resection Versus Infliximab Treatment of Recurrent Distal Ileitis in Crohn's Disease (LIR!C) randomized clinical trial, the improvement in quality of life with ileocecal resection (ICR) was comparable to infliximab as a first-line treatment for limited, nonstricturing ileocecal CD at 1 year of follow-up.[10] Retrospective analysis of long-term data (median, 5 years) demonstrated that individuals in the ICR group (n = 69) did not require repeat surgery and, furthermore, that most were on no medical treatment, contrary to the anti-TNF group (n = 65), of whom 31 (48%) required surgery and the remaining were maintained on a biologic medication.[11] However, in the real world, the long-term impact of early ICR for CD remains largely unexplored.

In this study, we used longitudinal real-world data to compare long-term outcomes of ICR and anti-TNF therapy as primary treatment for ileal or ileocecal CD, initiated within 1 year of diagnosis.

Materials and Methods

Study Population

We conducted a nationwide cohort study for which the source population of all individuals who lived in Denmark between January 1, 2003, and December 31, 2018 (the study period), was identified through the Danish Civil Registration System. This registry prospectively records demographic and vital data of all residents of Denmark with continuous updates and links to other registries through a unique personal identification number. Using the cross-linked Danish National Patient Registry and the Danish National Prescription Registry, we identified all Danish residents who were diagnosed with CD during the study period and who underwent ICR or anti-TNF therapy as the primary treatment within 30 days before and 1 year after CD diagnosis. We used the International Classification of Disease, 10th Edition, to identify disease diagnoses, the Nordic Classification of Surgical Procedures to identify surgical procedures, and Anatomical Therapeutic Chemical codes and hospital procedure codes to identify medications.

We then leveraged the cross-linked Danish Pathology Register to identify individuals with confirmed ileal or ileocecal inflammation, based on Systematized Nomenclature of Medicine codes. We included patients who had confirmed inflammation or a CD diagnosis code on endoscopic biopsy or surgical specimen from the ileal or ileocecal region within 1 year before to 30 days after the primary treatment. This was done to align CD phenotypes in the ICR and anti-TNF groups. Definitions of all variables and relevant codes are recorded in the Supplementary Table 1.

Exposure

The exposure of interest was the primary treatment of CD by ICR or anti-TNF (yes, no). Individuals were assigned the first of the 2 treatments that they received, regardless of whether they received the opposite treatment at a later stage. Individuals who were diagnosed with CD before the start of the study period, who did not receive either treatment within 30 days before and 1 year after CD diagnosis, or those who were treated with biologic medications or underwent CD-related operations before ICR or anti-TNF were excluded. Also excluded were individuals who were diagnosed with perianal CD before the primary treatment and those who did not live in Denmark at least 1 year before the primary treatment.

Outcomes

The primary outcome was a composite of ≥1 of the following outcomes >30 days after the primary treatment: CD-related

hospitalization (yes, no), systemic corticosteroid exposure (yes, no), major CD-related surgery (yes, no), and perianal CD (yes, no) (Supplementary Table 1). A lag period of 30 days was chosen while defining the outcome to increase the probability of the outcome being associated with the exposure rather than reflecting treatment complications or disease manifestations present before the primary treatment. Secondary outcomes were CD-related hospitalization, systemic corticosteroid exposure, major CD-related surgery, and perianal CD, each >30 days after primary treatment and each analyzed as a separate outcome.

In a separate descriptive analysis, we examined in the ICR group the subsequent use of immunomodulator (IMM), anti-TNF, intestinal resection, or no treatment. Correspondingly, in the infliximab group, we determined subsequent switch to another biologic (other anti-TNF, ustekinumab, or vedolizumab), ICR, or continuation of infliximab.

Covariates

The demographic covariates included sex (female, male), age at CD diagnosis (operationalized as continuous or categorical, as described below), calendar year of primary treatment (2003–2007, 2008–2012, 2013–2018), and timing of the primary treatment relative to CD diagnosis (0 to 1 month before, 0 to 1 month after, 1 to 5 months after, 5 to 12 months after). As a measure of comorbid conditions in the year before the primary treatment, we ascertained the number of hospital contacts for any indication (0–1, 2–5, 6–10, >10) and the number of unique prescription medications (0–1, 2–5, 6–10, >10). We determined systemic corticosteroid (yes, no) and IMM exposure (yes, no) in the year before the primary treatment as an indicator of CD severity. Last, we determined the proportion of individuals who were diagnosed with complicated CD, defined as intestinal stenosis, ileus, internal fistula, or abscess (yes, no), in the year before the primary treatment. Definitions of all variables and relevant codes are recorded in Supplementary Table 1.

Statistical Analysis

We monitored all individuals from 30 days after the initiation of the primary treatment until the composite outcome (≥1 of the following: CD-related hospitalization, systemic corticosteroid exposure, CD-related surgery, perianal CD diagnosis), death, emigration, or December 31, 2018, whichever occurred first. Kaplan-Meier survival analyses were used to compare the proportion of individuals who experienced the composite outcome in the ICR and anti-TNF groups. We conducted 2 multifactor-adjusted Cox's proportional hazards regression analyses to estimate the adjusted hazard ratios (aHRs) for the composite outcome (models 1 and 2). In model 1, we adjusted for age at diagnosis (operationalized as a continuous variable with basis splines with 3 degrees of freedom), sex, and year of treatment, which were selected a priori. In model 2, we additionally adjusted for the number of hospital contacts for any indication, the number of unique prescription medications, systemic corticosteroid exposure, and IMM exposure, all in the 1 year before primary treatment, because the distribution of these variables was different between the ICR and anti-TNF groups. We did not adjust for complicated CD in the year preceding primary treatment given small number of individuals with complicated CD in anti-TNF group. Supplementary Figure 1 shows a directed acyclic graph depicting the hypothesized relationship between the index treatment and adverse long-term outcomes.

We conducted corresponding analyses for each secondary outcome. A time-stratified Cox's regression was conducted and found insignificant ($P = .13$) relative to the adjusted model without time stratification. This result provides support to the proportional hazards assumption.

To study interaction effects, we next examined whether the treatment effect was modified by age at CD diagnosis (<17, 17–40, >40 years), sex, year of treatment (2003–2010, 2011–2018), systemic corticosteroid exposure, and IMM exposure, the latter 2 in the 1 year before the primary treatment. We conducted sensitivity analyses excluding individuals diagnosed with CD at age <18 years, excluding individuals who received primary treatment before CD diagnosis, excluding ICR from the surgery outcome, excluding individuals with complicated CD (a diagnosis code of ileus, stenosis, internal fistula, or abscess before treatment and those who received treatment at or before CD diagnosis) and those who received treatment in the first time period (2003–2007), and finally, changing the composite outcome definition to include systemic corticosteroid exposure ≥8 weeks after the primary treatment to avoid including as an outcome a tapering course of corticosteroids that may have been initiated with the primary treatment.

Additional robustness analysis included a propensity-weighted analysis to mitigate confounding by indication. Cases were weighted according to their propensity scores using the standardized mortality ratio method.[12] Propensity score regression included the following covariates: age at CD diagnosis, sex, the number of unique prescription medications, the number of hospital contacts for any indication, systemic corticosteroid exposure, and IMM exposure in the year preceding primary treatment.

Last, we determined the Kaplan-Meier cumulative incidence estimate of being started on an IMM or an anti-TNF, or undergoing another ICR, and the survival estimate for no treatment in the primary ICR group, and the cumulative incidence estimate of being switched to another biologic agent or undergoing ICR, and the survival estimate for continuing infliximab, among individuals initiated on infliximab as the primary treatment. We conducted all statistical analyses using the programming language R 4.1.3 and the R package survival 3.4 (R Foundation for Statistical Computing).[13]

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. After approval by the Danish Data Protection Agency, all analyses were conducted on a secure server provided by the Danish Health Data Authority. Registry data-based research is exempt from ethical approval in Denmark.

Results

Cohort Characteristics

Of 16,443 individuals who were diagnosed with CD between 2003 and 2018, 1279 fulfilled the inclusion criteria (Figure 1). Of these, 581 individuals (45.4%) underwent ICR and 698 (54.6%) received anti-TNF as the primary treatment between 30 days before and 1 year after the CD diagnosis. The 581 individuals who underwent ICR as primary treatment received open (437 [75.2%]) or laparoscopic (144 [24.8%]) ICR. The 698 individuals in the anti-

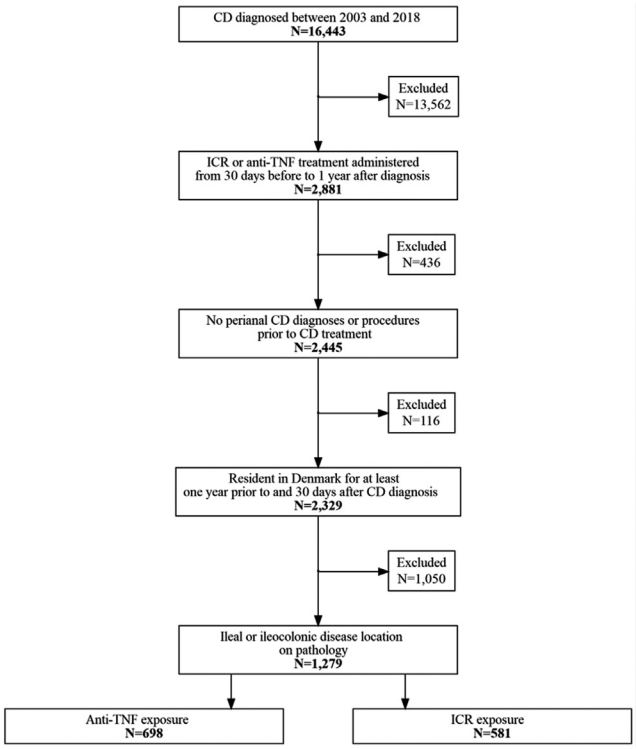

Figure 1. Patient flow diagram.

TNF group received adalimumab (46 [6.6%]), and infliximab (633 [90.7%]); there were 19 individuals (2.7%) where the administered anti-TNF type was either golimumab or not recorded.

The baseline characteristics of the cohort are described in Table 1. The median age of those in the ICR and anti-TNF groups was 30 years (interquartile range [IQR], 22–51 years) and 22 years (IQR, 17–31 years), respectively. In the ICR group, compared with the anti-TNF group, complicated CD was more common (123 [21.2%] vs 12 [1.7%] individuals). ICR remained relatively stable, whereas anti-TNF use increased over time. ICR was more likely than anti-TNF treatment to occur within 1 month before and after diagnosis. Systemic corticosteroid and IMM use were more common in the year before primary treatment with anti-TNF.

Composite Outcome With Ileocecal Resection vs Anti-Tumor Necrosis Factor as Primary Treatment

On a total of 2474 person-years (PY) of follow-up, the composite outcome occurred in 273 individuals (incidence rate, 110/1000 PY) in the ICR group. In contrast, in the anti-TNF group, on 1575 PY of follow up, the composite outcome occurred in 318 individuals (incidence rate, 202/1000 PY). The median follow-up until the composite outcome was 1.86 years (IQR, 0.49–4.50 years). The Kaplan-Meier survival curve (Figure 2) demonstrates that the proportion of individuals who experienced the composite outcome was lower in those treated with ICR than with anti-TNF therapy during follow-up.

On Cox's proportional hazards regression analysis, the aHR of the composite outcome for ICR, compared with anti-TNF, as primary treatment was 0.72 (95% confidence interval [CI], 0.60–0.86) after adjusting for age, sex, and calendar year (Table 2). After additionally adjusting for the number of prior hospitalizations, number of unique prescription medications, systemic corticosteroid, and IMM exposure, the estimate for ICR was similar (aHR, 0.67; 95% CI, 0.54– 0.83).

Table 1. Demographic and Clinical Characteristics of the Study Cohort Included in the Follow-up Analysis

Characteristic	ICR (n = 581)	Anti-TNF (n = 698)
Sex		
Female	337 (58.0)	404 (57.9)
Male	244 (42.0)	294 (42.1)
Age at CD diagnosis, *y*		
<17	40 (6.9)	138 (19.8)
17–40	336 (57.8)	470 (67.3)
>40	205 (35.3)	90 (12.9)
Calendar year of primary treatment		
2003–2007	186 (32.0)	30 (4.3)
2008–2012	174 (29.9)	150 (21.5)
2013–2018	221 (38.0)	518 (74.2)
Timing of primary treatment relative to diagnosis		
0–1 month before	88 (15.1)	5 (0.7)
0–1 month after	203 (34.9)	91 (13.0)
1–5 months after	205 (35.3)	399 (57.2)
5–12 months after	85 (14.6)	203 (29.1)
In the year preceding primary treatment		
Complicated CD[a]		
Yes	123 (21.2)	12 (1.7)
No	458 (78.8)	686 (98.3)
Hospital contacts, n		
0–1	48 (8.3)	36 (5.2)
2–5	203 (34.9)	366 (52.4)
6–10	227 (39.1)	232 (33.2)
>10	103 (17.7)	64 (9.2)
Unique medications, n		
0–1	93 (16.0)	60 (8.6)
2–5	230 (39.6)	296 (42.4)
6–10	184 (31.7)	251 (36.0)
>10	74 (12.7)	91 (13.0)
Systemic corticosteroid exposure		
Yes	199 (34.3)	474 (67.9)
No	382 (65.7)	224 (32.1)
Immunomodulator exposure		
Yes	105 (18.1)	389 (55.7)
No	476 (81.9)	309 (44.3)

NOTE. Data are presented as n (%).
[a]Defined as stricture, ileus, internal fistula, or abscess.

Secondary Outcomes With Ileocecal Resection vs Anti-Tumor Necrosis Factor as Primary Treatment

Kaplan-Meier curves demonstrate a lower risk of CD-related hospitalization, systemic corticosteroid use, and

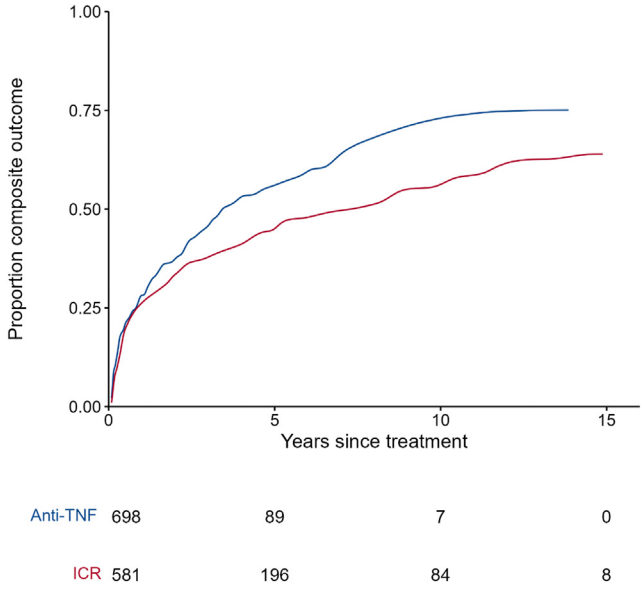

Figure 2. Kaplan-Meier cumulative incidence estimates of the composite outcome including CD-related hospitalization, systemic corticosteroid exposure, CD-related surgery, and perianal CD in the groups who underwent ICR or received anti-TNF therapy as primary treatment for CD within one year of diagnosis.

CD-related surgery in the ICR group compared with anti-TNF therapy (Figure 3). The risk of perianal CD was slightly lower in the ICR group. The risk of hospitalization and of a subsequent CD-related surgery were similar in the 2 groups during the first year of follow-up and increased in the anti-TNF group relative to the ICR group thereafter.

Compared with anti-TNF therapy, ICR as primary treatment was associated with lower risks of systemic corticosteroid exposure (aHR, 0.61; 95% CI 0.49–0.77) and CD-related surgery (aHR, 0.49; 95% CI, 0.36–0.67) but not of CD-related hospitalization (aHR, 0.84; 95% CI, 0.68–1.04) or perianal CD diagnosis (aHR, 0.62; 95% CI, 0.37–1.04) after adjusting for age, sex, and calendar year. After adjusting for number of prior hospitalizations, number of unique prescription medications, systemic corticosteroid, and IMM exposure, the estimates remained consistent (Table 2).

Subgroup and Sensitivity Analyses

On analyses stratified by sex, systemic corticosteroid use, immunomodulator use, and year of treatment, the HRs for the composite outcome were lower with ICR compared with anti-TNF in each subgroup, with consistent effect estimates after adjusting for age, sex, and calendar year (Figure 4). On stratifying by age at CD diagnosis, the risk of the composite outcome was lower with ICR compared with anti-TNF in age-groups 17 to 40 years and >40 years, but there was no difference in the composite outcome in those aged <17 years. Yet, the *P* value for the interaction term was not statistically significant ($P = .46$), suggesting that age did not modify the effect, and of note, the number of participants and events in the ICR group in children were low.

All sensitivity analyses are reported in Supplementary Table 2. After children (aHR, 0.65; 95% CI, 0.52–0.82) and individuals who were diagnosed with CD at the time of ICR (aHR, 0.66; 95% CI, 0.53–0.81) were excluded, the effect estimates were consistent with those in the main analyses. After ICR was excluded from the surgery outcome, the aHR for the secondary outcome CD-related surgery was 1.06 (95% CI, 0.68–1.65), whereas the HR for the composite outcome was consistent with the main analysis (aHR, 0.67; 95% CI, 0.54–0.83).

Table 2. Unadjusted Incidence Rates, Adjusted Hazard Ratios, and 95% Confidence Intervals for Each Outcome in the Ileocecal Resection Group Compared With the Anti-Tumor Necrosis Factor Group

							ICR vs Anti-TNF					
	ICR			Anti-TNF			Model 1[a]			Model 2[b]		
Outcome	Events	PY	IR	Events	PY	IR	aHR	95% CI		aHR	95% CI	
Primary outcome												
Composite outcome[c]	273	2474	110	318	1575	202	0.72	0.60	0.86	0.67	0.54	0.83
Secondary outcomes												
CD-related hospitalization	190	3039	63	215	1964	109	0.84	0.68	1.04	0.79	0.61	1.01
Systemic corticosteroids	162	3415	47	193	2155	90	0.61	0.49	0.77	0.71	0.54	0.92
CD-related surgery	82	3932	21	123	2397	51	0.49	0.36	0.67	0.56	0.39	0.80
Perianal CD	30	4229	7	40	2682	15	0.62	0.37	1.04	0.70	0.38	1.30

IR, incidence rate.
[a]Adjusted for age at diagnosis, sex, and year of treatment.
[b]Adjusted for age at diagnosis, sex, year of treatment, and the number of hospital contacts for any indication, the number of unique prescription medications, systemic corticosteroid exposure, and immunomodulator exposure, all in the year before primary treatment.
[c]The composite outcome is defined as ≥1 secondary outcomes of CD-related hospitalization, systemic corticosteroids, CD-related surgery, and perianal CD.

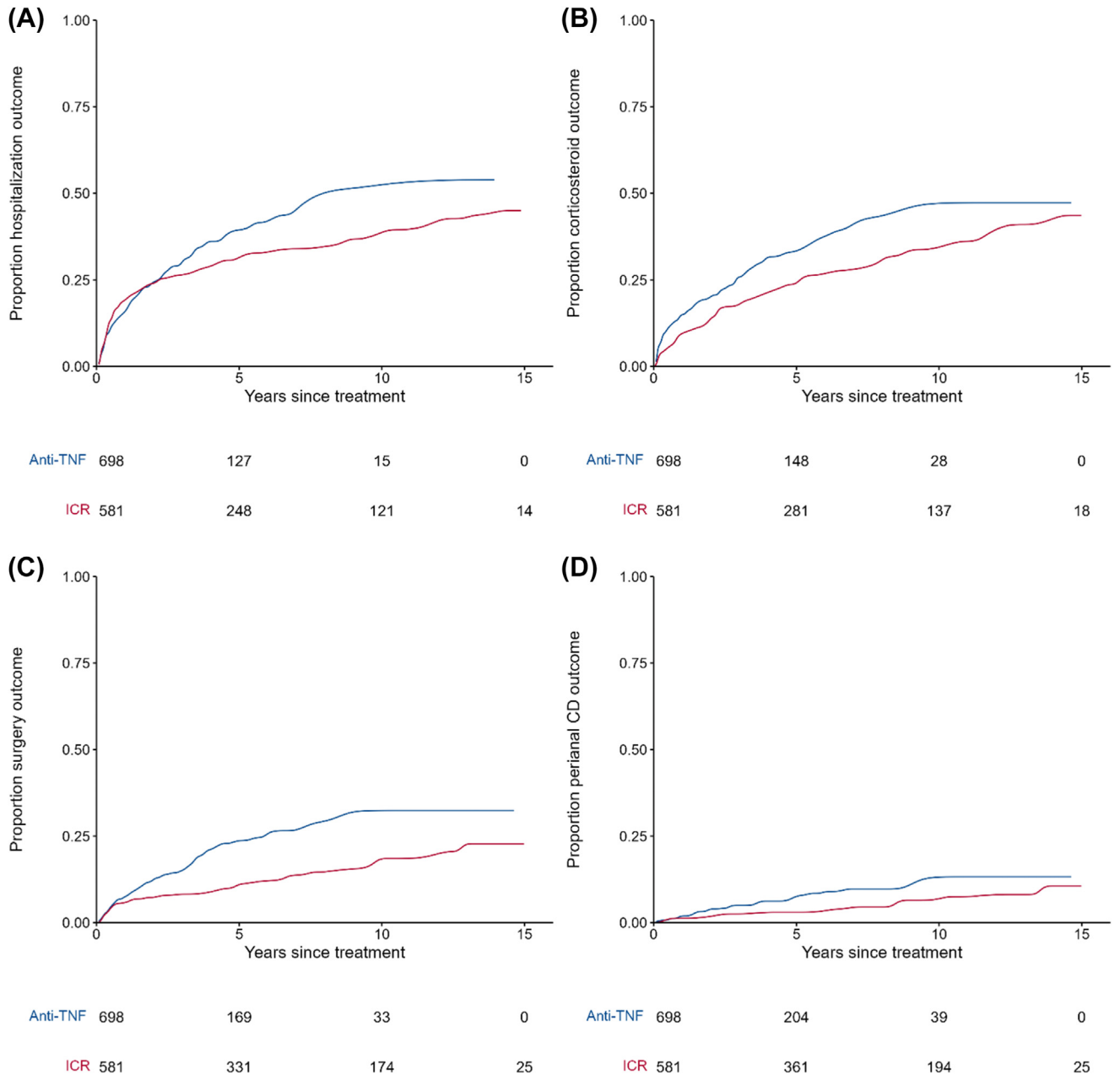

Figure 3. Kaplan-Meier cumulative incidence estimates of secondary outcomes (*A*) CD-related hospitalization, (*B*) systemic corticosteroid exposure, (*C*) CD-related surgery, and (*D*) perianal CD in the groups that underwent ICR and received anti-TNF therapy as primary treatment for CD within 1 year of diagnosis.

The effect estimates for the composite outcome remained consistent after individuals with complicated CD (aHR, 0.64; 95% CI, 0.50–0.80) and those treated in the first time period (aHR, 0.69; 95% CI 0.55, 0.87) were excluded. On changing the composite outcome definition to include systemic corticosteroid exposure $\geq$8 weeks after the primary treatment, the effect estimate remained consistent (aHR, 0.72; 95% CI, 0.58–0.89). Finally, effect estimates remained consistent on propensity-weighted analysis (aHR, 0.63; 95% CI, 0.47–0.84) (Supplementary Table 3). All HRs are defined for the ICR group relative to the anti-TNF group.

Of individuals who underwent ICR, the Kaplan-Meier estimate of the proportion who postoperatively initiated IMM, initiated anti-TNF treatment, underwent another intestinal resection, or were on no treatment at 5 years of postoperative follow-up was 46.3%, 16.8%, 1.8% and 49.7%, respectively (Figure 5*A*). Of those who were initiated on infliximab as primary therapy, the Kaplan-Meier estimate of the proportion who underwent ICR, switched to a different biologic agent, or continued infliximab at 5 years of follow-up was 17.7%, 40.8%, and 47.3%, respectively (Figure 5*B*). In the ICR group, of those initiated on IMM, anti-TNF, or no treatment at 5 years of post-ICR follow-up,

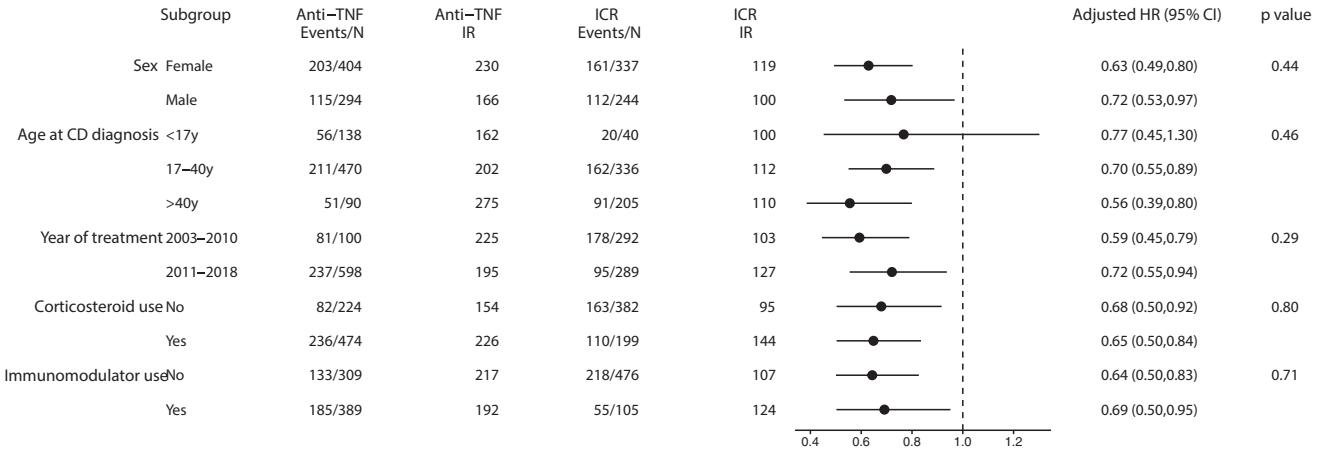

Figure 4. Unadjusted incidence rates (IR) and aHR for the composite outcome for the ICR group compared with the anti-TNF group, stratified by sex, age at diagnosis, year of treatment, corticosteroid use, and IMM use, all in the year before primary treatment. The HRs are adjusted for age at diagnosis, sex, year of treatment, the number of hospital contacts for any indication, the number of unique prescription medications, systemic corticosteroid exposure, and IMM exposure, all in the year before primary treatment. When stratifying by age, age was adjusted for in discretized age categories. The *P* values are *P* for interaction.

there were no clear differences in sex distribution (IMM [n = 255]: 54.5% female; anti-TNF [n = 86]: 58.1% female; and no treatment [n = 192]: 54.7% female) or median age of CD diagnosis (IMM: 27 years [IQR, 20–43 years]; anti-TNF: 26 years [IQR, 20–43 years], and no treatment: 34 years [IQR, 23–57 years]).

Discussion

In this nationwide cohort study with long-term follow-up, we demonstrate that early ICR compared with anti-TNF therapy for ileal or ileocecal CD treatment was associated with a 33% risk reduction in the rate of the composite outcome of ≥1 of the following: hospitalization, systemic corticosteroid use, CD-related major surgery, and perianal CD after adjusting for potential confounders. The aHR of the secondary outcomes of systemic corticosteroid use and CD-related major surgery were similarly reduced with ICR. For the secondary outcomes of hospitalization and perianal CD, the risk estimates were numerically lower with ICR, but there was no statistically significant difference between the 2 treatments.

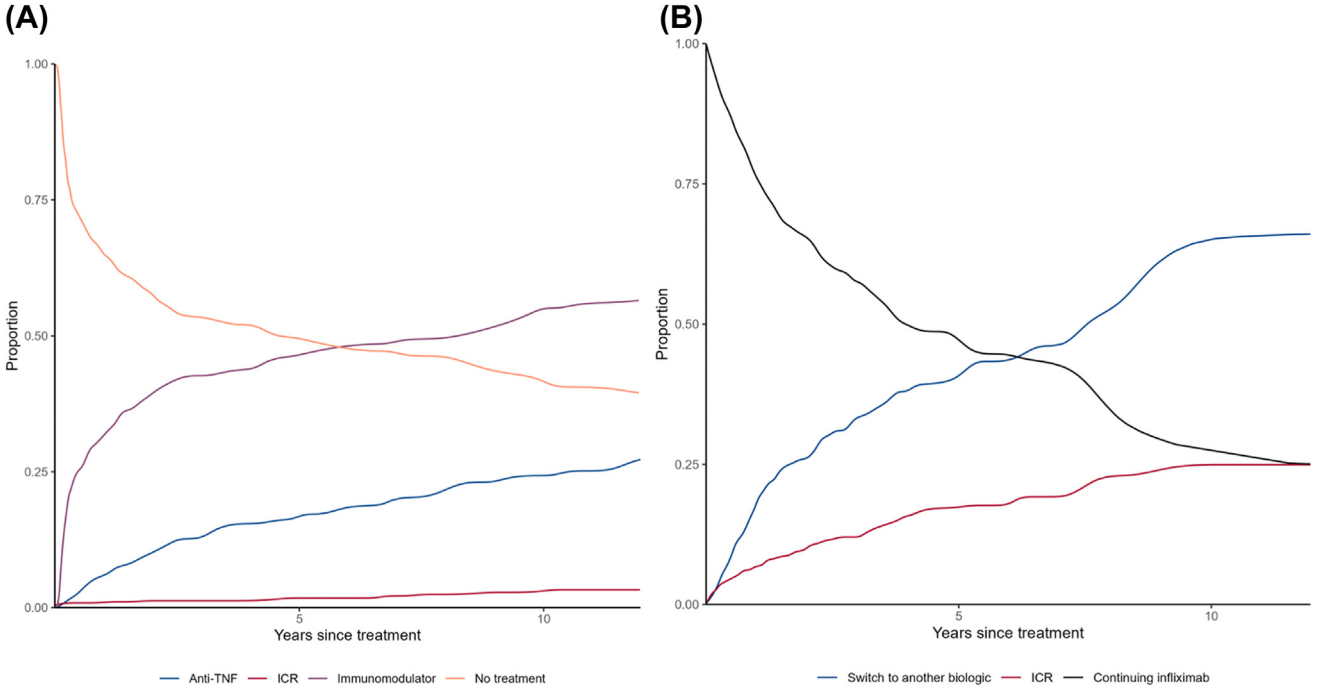

Figure 5. Kaplan-Meier cumulative incidence and survival estimates for different medical treatments and surgery after primary therapy of (*A*) ICR and (*B*) anti-TNF therapy. The outcomes (*A*) anti-TNF, ICR, and immunomodulator and (*B*) switch to another biologic and ICR are not mutually exclusive.

To our knowledge, these are the first real-world data in a population-based cohort with long-term follow-up of early ICR compared with anti-TNF therapy for newly diagnosed ileal and ileocecal CD. Results from smaller retrospective studies, consistent with our findings, have reported that early surgery in CD is safe and associated with improved clinical outcomes.[14–16] In the LIR!C open-label, randomized controlled trial, adults with nonstricturing ileocecal CD, in whom treatment with corticosteroids or IMM had previously failed, were assigned to ICR (n = 70) or infliximab (n = 73). Quality of life at 12 months, measured using the Inflammatory Bowel Disease Questionnaire, was comparable in the 2 arms.[10] In the Swedish Crohn trial, a randomized trial terminated early due to slow enrollment, clinical remission was similar, quality of life was improved in the ICR arm (n = 18) compared with the IMM arm (n = 18).[17]

On retrospective analysis of the long-term LIR!C trial follow-up data (median, 63.5 months; IQR, 39.0–94.5 months), 0 of 69 individuals in the ICR group and 31 of 65 (48%) individuals in the infliximab group underwent a CD-related surgery.[11] In a separate study of early compared with later surgery for CD, the former was associated with lower risk of subsequent surgery.[18] Further, relative to anti-TNF therapy, ICR was a cost-effective treatment option.[19] From the patient's perspective as well, surgery is likely to be an acceptable option.[20]

There are further notable points of consideration. Kaplan-Meier curves for the secondary outcomes indicate that the hazards of CD-related hospitalization and CD-related surgery were comparable in the ICR and anti-TNF groups in the first year of follow-up, and the 2 curves diverged over time. These findings are consistent with clinical observations; postoperative complications necessitating hospital contact and subsequent surgery are likely to occur early after surgery, whereas loss of response with anti-TNF agents occurs progressively over time.[5] Overall, while the decreased risk of hospitalization did not attain statistical significance. ICR was associated with a 44% lower risk of subsequent CD-related surgery compared with anti-TNF treatment. Certainly, repeated surgery is associated with morbidity, direct and indirect costs, and loss of quality of life.[21,22] Similarly, a 29% reduction in the risk of systemic corticosteroid exposure after ICR is a meaningful secondary outcome. Corticosteroids are associated with extensive adverse effects, and steroid-sparing remains an important long-term goal of CD maintenance therapy.[9,23]

Overall, our cohort largely represents uncomplicated CD. Before ICR, 21% were diagnosed with a stricture, ileus, internal fistula, or abscess, indicative of complicated CD and representative of the real world. In contrast, only 1.7% in the anti-TNF group had complicated CD. Further, on excluding complicated CD in a sensitivity analysis, the effect estimates remained consistent. Additional stratified, sensitivity and propensity score-weighted analyses showed a consistent protective effect of ICR for the composite outcome across subgroups, supporting the robustness of our findings. Of note, a large majority of patients in our study cohort underwent open surgery rather than laparoscopic surgery, which is likely to bias our results towards the null. With a shift toward laparoscopic surgery in recent times, outcomes are likely to be further improved.

On analysis of subsequent treatment with an IMM, an anti-TNF agent, or subsequent intestinal resection in the ICR group, we noted reduced need for immunosuppression and anti-TNF and that very few individuals underwent a second resection, consistent with long-term LIR!C and other data.[11,14] Subsequent medical treatment and surgery among those who received primary infliximab treatment is also consistent with LIR!C data, with 18% of individuals undergoing ICR after infliximab treatment. Here, we would like to underscore that primary ICR in early CD is distinct from later ICR after failure of medical therapy; whereas the latter is considered as an adverse outcome, the former is not. Half of all individuals in the ICR group were on no therapy at 5 years of follow-up. This novel finding of a subgroup of individuals with limited CD that required no therapy after early ICR suggests a potentially curative role of timely surgery in the right patient. This is in contrast to infliximab, after initiation of which, 18% needed an ICR, 41% switched to a different biologic agent, and 47% continued on infliximab at 5 years of follow-up. Demographic characteristics of those on no treatment after ICR were comparable to those who were initiated on treatment in our study.

Granular prospective data to characterize CD phenotype and patient characteristics associated with lack of postoperative CD progression will help clinicians better understand which patients would benefit most from early ICR and help advance personalized CD therapeutics. The indication for IMM or anti-TNF treatment (postoperative prevention of CD vs treatment of active disease) cannot be ascertained from our data. However, these are consistent with data from the LIR!C trial and others indicating reduced need for immunosuppression and anti-TNF after early ICR for CD.[11,14] In the LIR!C trial, 15 of 69 individuals (22%) in the ICR arm were on no treatment during the follow-up period of 63.5 months (IQR, 39.0–94.5 months).[11]

The strengths of our study include the nationwide and unselected cohort of individuals with CD, large sample size, confirmed disease location based on pathology, and prospective follow-up for up to 23 years. We adjusted for relevant covariates and conducted stratified and sensitivity analyses, along with propensity score-weighted analysis, demonstrating the robustness of our findings.

Our study also has some limitations. We lack data on certain clinical risk factors for disease progression, such as smoking, as well as endoscopy and radiology data. A large majority of individuals in the anti-TNF group were on infliximab, which may be different from prescription patterns elsewhere, but it is likely to bias results toward the null, considering the effectiveness of infliximab relative to other biologic agents.[3]

There is also a risk of unmeasured and residual confounding, and we cannot completely rule out confounding by indication. Given inherent biases associated with observational data, our findings should be interpreted and applied cautiously in clinical decision making.

Conclusion

In summary, we demonstrate improved long-term outcomes with ICR, compared with anti-TNF, as primary treatment for early ileal and ileocecal CD and that a substantial subset of patients was on no medication 5 years after ICR. These data suggest that ICR may have a role as first-line therapy in CD management and challenge the current paradigm of reserving surgery for complicated CD refractory or intolerant to medications.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://dx.doi.org/10.1053/j.gastro.2023.05.051.

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Conflicts of interest
The authors disclose no conflicts.

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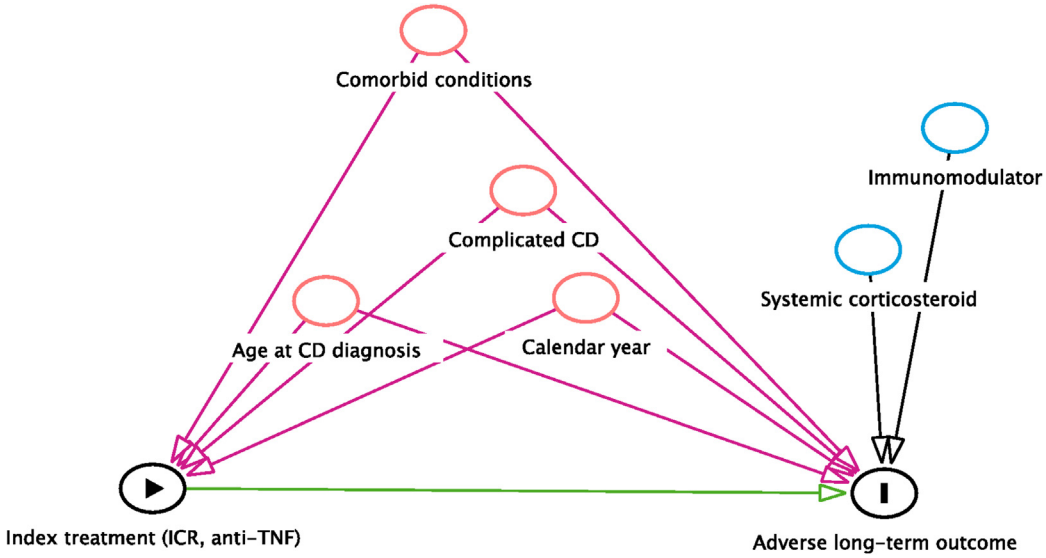
Data Availability
The data underlying this article are available in the article and in its online Supplementary Material. The study is based on data from the Danish nationwide registers (https://sundhedsdatastyrelsen.dk). The register data are protected by the Danish Act on Processing of Personal Data and are accessed through application to and approval from the Danish Data Protection Agency and the Danish Health Data Authority.



Supplementary Figure 1. Directed acyclic graph depicts the hypothesized relationship between index treatment (ileocecal resection or anti-TNF therapy) and adverse long-term outcomes, defined as CD-related hospitalization, systemic corticosteroid use, CD-related surgery, and perianal CD. The *green node* represents the exposure, the *blue nodes* represent the outcome or ancestor of the outcome, and the *pink nodes* represent confounders, which are causes of exposure and outcome, but not on the causal pathway.

Supplementary Table 1. Definitions and Relevant Codes for all Included Variables

Variable	Definitions and codes	Source
CD-related hospitalization	Inpatient contact[a] with (A) diagnosis of ICD-10: K50 or (B) diagnosis of K50 and (A) diagnosis of 1 the following	Danish National Patient Registry
Abdominal pain	ICD-10: R100, R101, R102C, R103	
Nausea and vomiting	ICD-10: R11	
Noninfectious gastroenteritis	ICD-10: K529 (excl. K529B1)	
Rectal or anal bleeding	ICD-10: K625	
Fistula	ICD-10: K603–605, K316E, K632, N822–825, N828F	
Abscess	ICD-10: K610–14, K630, K650A, K650G, K650H, L023C	
Stenosis	ICD-10: K264, K566+F+G	
Ileus and subileus	ICD-10: K566C, K567	
Ileal or ileocecal CD	Topology codes (disease location): T65200–T65902, T67011, T67100–T67310, T67965 Disease codes (diagnostic codes): S6214, S6216 Morphology codes (presence of inflammation): M41–M44, M463, M47	Danish Pathology Register
Corticosteroids		
Corticosteroids	ATC: H02AB04, H02AB06, H02AB07, H02AB09	Danish National Prescription Registry
Immunomodulators		
Immunomodulators	Azathioprine (ATC: L04AX01; C_OPR: BWHB83), mercaptopurine (ATC: L01BB02), methotrexate (ATC: L04AX03/L01BA01; C_OPR: BWHA115)	
Perianal CD		
Diagnoses	ICD-10: K60.3–5, K61, K62.4	Danish National Patient Registry
Procedures	SKS: KJHD2*; KJHD3*; KJHD42; KJHD43; KJHD46; KJHD6*; KJHD99; KJHA00;	
CD-related surgery		
Intestinal resections	NCSP: KJGB, KJFB (excluding KJFB10+13)	
Enteroenterostomy	NCSP: KJFC	
Enterostomy	NCSP: KJFF	
Colectomy	NCSP: KJFH	
Intestinal stricture-plasty	NCSP: KJFA60, KJFA61, KJFA63	
Other local intestinal surgery	NCSP: KJFA96, KJFA97	
Other intestinal surgery	NCSP: KJFW	
Stenosis surgery without resection or adhesiolysis	NCSP: KJFL	
Minor surgery (included in the definition of perianal CD, not included in the CD-related surgery outcome)		
Anal or perianal incision or excision	NCSP: KJHA00	
Incision or excision of anal fistula	NCSP: KJHD30, KJHD33, KJHD20, KJHD23, KJHD60	
Incision and drainage of pelvic abscess	NCSP: KJAJ00	
Closing of intestinal fistulas	NCSP: KKCH30, KKDH50, KJFA76, KJFA86	
Percutaneous drainage of intraperitoneal abscess	NCSP: KTJA40	
Dilatation of intestine or anus	NCSP: KJFA58, KJFA38, KJGA58, KJHD00	

NOTE. Diagnosis codes follow the Danish classification system SKS (Sundhedsvæsenets Klassifikationssystem), which builds on ICD-10, but adds subdiagnoses to some ICD-10 codes.
ATC, Anatomical Therapeutic Chemical; ICD, International Classification of Diseases, 10th Edition; NCSP, NOMESCO (Nordic Medico-Statistical Committee) Classification of Surgical Procedures.

Supplementary Table 2. Sensitivity Analyses With Unadjusted Incidence Rates, Adjusted Hazard Ratios, and 95% Confidence Intervals for the Composite Outcome in the Ileocecal Resection Group Compared With the Anti-Tumor Necrosis Factor Group

	ICR			Anti-TNF					
Analysis description	Events	PY	IR	Events	PY	IR	aHR[a]	95% CI	
Excluding CD diagnosis at age <18 years	253	2273	111.3	262	1230	213	0.65	0.52	0.82
Excluding treatment before diagnosis	258	2376	108.6	316	1568	202	0.66	0.53	0.81
Excluding ICR as surgery outcome	273	2474	110.3	316	1580	200	0.67	0.54	0.83
Excluding complicated CD	200	1894	105.6	310	1541	201	0.64	0.50	0.80
Excluding 2003–2007	152	1266	120.1	292	1463	200	0.69	0.55	0.87
Changing composite outcome definition to include systemic corticosteroid exposure ≥8 weeks after the primary treatment	272	2493	109.1	302	1636	185	0.72	0.58	0.89
Propensity weighted analysis	273	2474	110.3	257	1173	219	0.63	0.47	0.84

NOTE. The outcome in each analysis is the composite outcome, defined as ≥1 secondary outcomes of CD-related hospitalization, systemic corticosteroids, CD-related surgery, and perianal CD.
IR, incidence rate.
[a]Adjusted for age at diagnosis, sex, year of treatment, the number of hospital contacts for any indication, the number of unique prescription medications, systemic corticosteroid exposure, and immunomodulator exposure, all in the year before primary treatment.

Supplementary Table 3. Distribution of Baseline Characteristics After Propensity Score Weighting

Characteristic	ICR (n = 581)	Anti-TNF (n = 584)
Sex		
Female	337 (58)	359 (61)
Male	244 (42)	225 (39)
Age at CD diagnosis		
17 years	40 (6.9)	46 (7.8)
17–40 years	336 (58)	348 (60)
	205 (35)	190 (33)
In the year preceding index treatment		
Hospital contacts, n		
0–1	48 (8.3)	18 (3.0)
2–5	203 (35)	274 (47)
6–10	227 (39)	180 (31)
>10	103 (18)	112 (19)
Different medications, n		
0–1	93 (16)	108 (18)
2–5	230 (40)	198 (34)
6–10	184 (32)	173 (30)
	74 (13)	105 (18)
Systemic corticosteroid use		
Yes	199 (34)	235 (40)
No	382 (66)	349 (60)
Immunomodulator use		
Yes	105 (18)	116 (20)
No	476 (82)	468 (80)

NOTE. Data are presented as n (%).