Published in final edited form as:

Clin Gastroenterol Hepatol. 2016 August ; 14(8): 1120–1129.e6. doi:10.1016/j.cgh.2016.03.038.

Comparative Effectiveness and Safety of Anti-Tumor Necrosis Factor Agents in Biologic-Naïve Patients with Crohn's Disease

Siddharth Singh, M.D., M.S.[1,2,3], **Herbert C. Heien, M.S.**[4], **Lindsey R. Sangaralingham, M.P.H.**[4], **Stephanie R. Schilz, B.A.**[4], **Michael D. Kappelman, M.D., M.P.H.**[5], **Nilay D. Shah, Ph.D.**[4,6,7], and **Edward V. Loftus Jr., M.D.**[1]

[1]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

[2]Division of Gastroenterology, University of California San Diego, La Jolla, CA

[3]Division of Biomedical Informatics, University of California San Diego, La Jolla, CA

[4]Robert D and Patricia E Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN

[5]Division of Pediatric Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, NC

[6]Division of Health Care Policy and Research, Department of Health Services Research, Mayo Clinic, Rochester, MN

[7]Optum Labs, Cambridge, MA

Abstract

Background & Aims—Inhibitors of tumor necrosis factor (anti-TNF agents) are the most effective therapy for Crohn's disease (CD). We evaluated the real-world comparative effectiveness and safety of different anti-TNF agents (infliximab, adalimumab, and certolizumab pegol) in biologic-naïve patients with CD in a retrospective, propensity-matched cohort study using a national administrative claims database (Optum Labs Data Warehouse).

Corresponding author: Siddharth Singh, M.D., M.S. Assistant Professor of Medicine, Division of Gastroenterology; Division of Biomedical Informatics, University of California San Diego 9500 Gilman Drive, La Jolla, CA 92093, sis040@ucsd.edu, Phone: 858-657-5271, Fax: 858-657-7259.

Author Contributions:

- Study concept and design: SS, NDS, EVL
- Acquisition of data: SS, LRS, HCH, SRS
- Analysis and interpretation of data: SS, LRS, HCH, SRS
- Drafting of the manuscript: SS
- Critical revision of the manuscript for important intellectual content: LRS, HCH, SRS, MDK, NDS, EVL
- Approval of the final manuscript: SS, LRS, HCH, SRS, MDK, NDS, EVL• Study supervision: SS

Methods—We identified 3205 biologic-naïve CD patients (mean age, 41±15 years; 45% male; median follow-up period after anti-TNF therapy, 19 months; 44.5% on infliximab and 38.9% on adalimumab) who received their first prescription for an anti-TNF agent (infliximab, adalimumab, or certolizumab pegol) after a 12-month period without any anti-TNF treatment (baseline), and with a minimum follow-up period of 6-months after their initial anti-TNF prescription, between 2006 and 2014. The primary outcomes were all-cause and CD-related hospitalization, abdominal surgery, corticosteroid use, and serious infections. We performed a propensity-matched, Cox proportional hazard analysis, accounting for baseline demographics, healthcare utilization, comorbidities, and use of CD-related medication.

Results—Compared to adalimumab-treated patients, infliximab-treated patients had a lower risk of CD-related hospitalization (adjusted hazard ratio [aHR], 0.80; 95% confidence interval [CI], 0.66–0.98), abdominal surgery (aHR, 0.76; 95% CI, 0.58–0.99), and corticosteroid use (aHR, 0.85; 95% CI, 0.75–0.96). Compared to certolizumab pegol-treated patients, infliximab-treated patients had a lower risk of all-cause hospitalization (aHR, 0.70; 95% CI, 0.52–0.95) and CD-related hospitalization (aHR, 0.59; 95% CI, 0.39–0.90). Adalimumab-treated patients had outcomes comparable to those of certolizumab pegol-treated patients. All agents had comparable risk of serious infections.

Conclusion—In a retrospective analysis of a large cohort of biologic-naïve patients with CD, we found infliximab to be superior to adalimumab and certolizumab pegol for patient-relevant outcomes, without increased risk of serious infections.

Keywords

biologics; real-world effectiveness; database analysis; propensity matching

INTRODUCTION

Biologic therapy with anti-tumor necrosis factor-α (anti-TNF) agents such as infliximab (IFX), adalimumab (ADA) and certolizumab pegol (CZP), alone or in combination with immunomodulators, is currently the most effective treatment in inducing and maintaining clinical remission in patients with CD, and has been shown to decrease risk of hospitalization and surgery.[1–7] In the absence of head-to-head trials, there is a significant unmet need among patients and clinicians to understand the relative effectiveness and safety of different anti-TNF medications. Current decisions on the choice of anti-TNF agent are primarily driven by insurance coverage and patient and physician preferences. There are differences in the molecular construct, dosing and route of administration of these agents, and in comparing CZP with ADA or IFX, subtle differences in mechanism of action, and hence, it is conceivable that there may be differences in efficacy.[8]

We sought to study the real-world comparative effectiveness and safety of different anti-TNF agents in biologic-naïve adult patients with CD, using a propensity-score matched retrospective cohort study, in a nationally representative administrative database of privately insured individuals derived from the Optum Labs Data Warehouse.[9] Using patient-relevant outcomes of risk of all-cause and CD-related hospitalizations, abdominal surgery, need for corticosteroids, and risk of serious infections, the results of this study might assist

consumers, clinicians, purchasers, and policy makers to make informed decisions and potentially identify the need for additional clinical trial to improve the treatment of patients with IBD.

METHODS

Data Sources

We conducted a retrospective analysis of medical and pharmacy administrative claims from a large database, Optum Labs Data Warehouse, which includes privately insured and Medicare Advantage enrollees throughout the United States.[9] The database contains data on more than 100 million enrollees, from geographically diverse regions across the United States, with greatest representation from the South and Midwest. Medical claims include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes; ICD-9 procedure codes; Current Procedural Terminology, Fourth Edition (CPT-4) procedure codes; Healthcare Common Procedure Coding System (HCPCS) procedure codes; site of service codes; and provider specialty codes. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996, and because this study involved analysis of preexisting de-identified data, it was exempted from institutional review board approval.

Study Population

We identified all patients who filled a prescription for an anti-TNF agent or received an infusion for an anti-TNF agent in the clinic setting between January 1, 2006 to June 30, 2014. Our study cohort was comprised of adult patients (≥18 years of age) with: (a) at least one ICD-9 diagnosis code for CD (ICD 555.x) in the baseline period (prior to index date of anti-TNF prescription), either from an inpatient or outpatient visit, (b) continuous health plan enrollment with pharmacy benefits, with no anti-TNF prescription in the 12 months prior to index date (to identify a group of anti-TNF-naïve patients), and at least a 6-month minimum follow-up after index date. We excluded patients with a concomitant diagnosis of rheumatoid arthritis, ankylosing spondylitis, psoriasis or psoriatic arthritis, within the previous 12 months of anti-TNF prescription date, as competing causes for prescribing anti-TNF agents. Figure 1 shows the flow of patients for identification of the cohort, and Supplementary Figure 1 outlines the general study scheme.

Exposures and Outcomes of Interest

The primary exposures of interest were IFX, ADA or CZP prescription for CD. We considered patients as being continuously exposed from the index date (date of first prescription of anti-TNF agent) for the duration of their prescription. Patients were followed until occurrence of outcome of interest (see below), disenrollment from healthcare plan or completion of study (last date of follow-up, December 31, 2014) or discontinuation of index anti-TNF (absence of new prescription for a period of >4 months [for IFX] or >3 months [for ADA or CZP]).

The primary outcomes of interest were:

Effectiveness Outcomes

a) All-cause hospitalization

b) CD-related hospitalization, with CD either as the primary diagnosis, or as a secondary diagnosis if the primary diagnosis was related to a gastrointestinal symptom (abdominal pain, diarrhea, nausea, vomiting, constipation, gastrointestinal bleeding)

c) CD-related surgery, including intestinal or perianal surgical procedure (identified using established procedural codes [available upon request])

d) Corticosteroid prescription, occurring at least 60 days after the start of anti-TNF therapy (to minimize confounding by disease severity)

e) Persistence on the index anti-TNF agent at 6-months (prescription of index anti-TNF agent between 140–220 days after index date) and 12-months (prescription of index anti-TNF agent between 325–405 days after index date). Persistence on index anti-TNF agent at 12m was assessed only in patients who were followed at least 12m after initiation of anti-TNF therapy.

Safety Outcomes

f) Hospitalization for serious or opportunistic infections as primary diagnosis (available upon request).

If the index anti-TNF agent was started during an inpatient hospitalization, then that hospitalization was not counted as an outcome; only inpatient admissions which were >23 hours in duration were regarded as outcomes (to avoid misclassifying observation visits for IFX infusions as outcome).

Covariates of Interest

Independent variables of interest included measures of healthcare utilization, comorbidities including surrogate markers of disease severity, and overall medication burden, including use of IBD-related medications, in the baseline period (prior to initiation of the index anti-TNF agent) (Supplementary Appendix). Patients were classified as being on anti-TNF-based combination immunomodulator therapy if they received immunomodulator prescriptions within 30 days before and/or after anti-TNF index start date.

Statistical Analysis

We examined the relative effectiveness of IFX, ADA and CZP on the risk of all-cause and CD-related hospitalization, abdominal surgery, corticosteroid use and serious infections, using two statistical approaches. **First**, our primary analysis was performed using 1:1 propensity score matching without replacement to adjust for differences in baseline covariates.[10] The matching was performed in three separate models for patients exposed to IFX (vs. ADA), IFX (vs. CZP) and CZP (vs. ADA). The propensity score model included demographic variables (age categories, sex, census region), date of initiation of index anti-TNF, comorbidity index, healthcare utilization (as described above), surrogate markers of disease severity, medication class count, and IBD-related medications. We performed a

paired t-test for continuous variables, a McNemar test for dichotomous variables, and a Bowker's test for categorical variables with more than two levels; then, we measured the standardized difference of each covariate in the propensity score model, and variables were considered to be different across treatment if after propensity score matching the standardized difference was greater than 10%. In order to correct for any remaining imbalance after the propensity score analysis was performed, we included remaining covariates that were shown to be different across treatment groups into the final multivariate Cox proportional hazard models for assessment of the outcomes of interest. **Second**, we performed an inverse probability-of-treatment weight (IPTW) analysis where the IPTW was applied to each observation in the Cox model in order to assess the relative effectiveness between IFX, ADA, and CZP. The IPTW analysis was derived by utilizing the propensity score on all observations before matching.[11] In contrast to propensity-score matching in which the sample size usually decreases (as a result of matching), this type of modeling allowed us to retain all identified patients in the analysis, resulting in increased power.

We calculated hazard ratios (HR) with 95% confidence intervals (CI) for each outcome of interest separately, and patients were censored at time of treatment discontinuation or switching (to another anti-TNF agent), health plan disenrollment or end of observation period. We created the analytic dataset in SAS 9.3 and used Stata SE software (version 13.0) for statistical analysis.

We performed multiple sensitivity analyses to assess the robustness of our findings, as detailed in the Supplementary Appendix.

RESULTS

Characteristics of Patients

We identified 3205 biologic-naïve patients with CD, of whom 1427, 1248 and 530 patients were treated with IFX, ADA and CZP, respectively, as the index anti-TNF agent. Table 1 describes the baseline demographic, clinical, treatment characteristics and healthcare utilization of the overall cohort and the three subgroups. Median follow-up after starting index anti-TNF agent was 19 months (interquartile range [IQR], 10–35). Only 6.3% of patients were >65 years old. Overall, the groups were comparable with regard to demographic, clinical variables, CD-related medication use and healthcare utilization in the baseline period. About 4.7% of patients had undergone an abdominal surgery in the preceding 12 months, with CZP-treated patients more likely to have undergone surgery (7.4%) as compared to ADA- (4.9%) or IFX-treated (3.7%) patients ($p<0.001$). The proportion of patients on anti-TNF-based combination therapy (immunomodulator prescriptions within 30 days before and/or after anti-TNF index start date) was higher in IFX-treated patients as compared to ADA- or CZP-treated patients (IFX vs. ADA vs. CZP: 32% vs. 26% vs. 26%).

After propensity score matching, these groups were more balanced, with no significant difference in clinical variables, healthcare utilization or CD-related medication use (Supplementary Table 1A–C). Only a small number of variables fell outside a standardized

difference of 0.10 (Supplementary Figures 2A–C). These variables were additionally adjusted for in the propensity score-matched multivariable Cox proportional hazard analysis.

Comparative effectiveness and safety of infliximab vs. adalimumab

A total of 1020 patients treated with IFX were propensity score-matched to 1020 ADA-treated patients. On unadjusted analysis, the risks of all-cause and CD-related hospitalization, abdominal surgery and corticosteroid prescription were lower in IFX-treated patients compared to ADA-treated patients (Figure 2A–E). On Cox proportional hazard analysis, after additional adjustment for variables not balanced through propensity score matching, we observed that the risks of CD-related hospitalization (aHR, 0.81; 95% CI, 0.66–1.00), abdominal surgery (aHR, 0.73; 95% CI, 0.56–0.97) and corticosteroid use >60 days after initiation of anti-TNF therapy (aHR, 0.85; 95% CI, 0.75–0.96) were significantly lower in IFX-treated patients compared to ADA-treated patients (Table 2). Although the risk of all-cause hospitalization (aHR, 0.86; 95% CI, 0.74–1.01) was numerically lower in the IFX-treated patients, this was not statistically significant. The risk of serious infections requiring hospitalization was not significantly different in IFX- and ADA-treated patients (aHR, 0.88; 95% CI, 0.48–1.64). Persistence on index IFX and ADA was comparable at 6-months (IFX vs. ADA, 78% vs. 78%, p=0.83) and 12-months (55% vs. 55%, p=0.79).

The overall results were similar on stratified analysis by anti-TNF monotherapy or concomitant immunomodulator therapy, although several of the results were not statistically significant in the latter strata likely due to loss of statistical power (Supplementary Table 2). On sensitivity analysis limiting only to patients with at least a 3-year baseline anti-TNF-free period, the overall summary estimates were comparable to the primary analysis for CD-related hospitalization (aHR, 0.85), abdominal surgery (aHR, 0.75) and corticosteroid use (aHR, 0.87), although the results were not statistically significant (Table 2). The results were similar when restricting analysis to patients without inpatient hospitalization within 30 days prior to initiation of anti-TNF agents (Supplementary Table 3). The overall results were also comparable to the primary propensity-score matched analysis, when using inverse probability-of-treatment weight analysis (Supplementary Table 4).

Comparative effectiveness and safety of infliximab vs. certolizumab pegol

A total of 253 patients treated with IFX were propensity-score matched to 253 CZP-treated patients. On unadjusted analysis, the risks of all-cause and CD-related hospitalization, abdominal surgery and corticosteroid prescription were lower in IFX-treated patients compared to CZP-treated patients (Figure 3A–E). On Cox proportional hazard analysis, we observed that the risks of all-cause and CD-related hospitalization were significantly lower in IFX-treated patients compared to CZP-treated patients (Table 2). Although the risks of abdominal surgery and corticosteroid prescription were numerically lower, these differences were not statistically significant. The risk of serious infections requiring hospitalization was not significantly different in IFX- and CZP-treated patients. Persistence on index IFX was higher compared to index CZP, both at 6-months (IFX vs. CZP, 78% vs. 70%, p=0.03) and 12-months (53% vs. 42%, p=0.01).

The overall results were similar in the stratified analysis by anti-TNF monotherapy or concomitant immunomodulator therapy (Supplementary Table 2). On sensitivity analysis limiting only to patients with at least a 3-year baseline anti-TNF-free period, the overall summary estimate was comparable to the primary analysis for corticosteroid use, although the results were not statistically significant (Table 2). The results were similar when restricting analysis to patients without inpatient hospitalization within 30 days prior to initiation of anti-TNF agents (Supplementary Table 3). The overall results were also comparable to the primary propensity-score matched analysis, when using inverse probability-of-treatment weight analysis (Supplementary Table 4).

Comparative effectiveness and safety of certolizumab pegol vs. adalimumab

A total of 523 patients treated with CZP were propensity-score matched to 523 ADA-treated patients. The risks of all-cause hospitalization, CD-related hospitalization, abdominal surgery and new corticosteroid prescription were higher in CZP-treated patients as compared to ADA-treated patients (Figures 4A–E). On Cox proportional hazard analysis, after additional adjustment for variables not balanced through propensity score matching, we observed that the risk of all-cause hospitalization was statistically higher in CZP-treated patients compared to ADA-treated patients. The risks of CD-related hospitalization, abdominal surgery, corticosteroid prescription and serious infections were numerically higher in CZP-treated patients compared to ADA-treated patients, but these differences were not statistically significant. Persistence on index CZP was lower compared to index ADA, at both 6-months (CZP vs. ADA, 72% vs. 78%, p=0.04) and 12-months (56% vs. 43%, p<0.001).

The overall results were stable when the analysis was stratified by anti-TNF monotherapy or concomitant immunomodulator therapy (Supplementary Table 2), and on multiple sensitivity analyses (Table 2, Supplementary Table 3). The overall results were also comparable to the primary propensity-score matched analysis, when using inverse probability-of-treatment weight analysis (Supplementary Table 4).

DISCUSSION

While anti-TNF-based therapy is the most effective treatment for CD, there are limited data on the comparative effectiveness and safety of different anti-TNF agents. In this nationally representative, propensity score-matched retrospective cohort study of 3,205 biologic-naïve patients with CD, we made several key observations. **First**, we observed that IFX-treated patients had lower risks of CD-related hospitalization, abdominal surgery and corticosteroid use compared to patients treated with ADA or CZP as the index anti-TNF agent. **Second**, patients started on IFX or ADA as the index anti-TNF agent were more likely to stay on their index agent at 6- and 12-months as compared to CZP-treated patients, even after adjusting for calendar year of prescription. **Third**, there was no significant difference in the risk of serious infections requiring hospitalization in IFX-, ADA- or CZP-treated patients. Based on the findings of our observational study, IFX may be superior to other anti-TNF agents for the treatment of CD. This is one of the largest observational comparative effectiveness studies in a contemporary cohort of biologic-naïve Crohn’s disease patients,

with patient-centered effectiveness and safety outcomes, assessed with robust complementary statistical approaches, with several stratified and/or sensitivity analyses.

These results were consistent on: (a) different statistical approaches including propensity score-matched analysis and inverse probability-of-treatment weighted analysis; (b) stratified analysis based on use of anti-TNF monotherapy or concomitant immunomodulator therapy; (c) sensitivity analysis after excluding patients without inpatient hospitalization in the preceding 30 days (to minimize misclassification of non-responders and confounding by disease severity); and (d) on restricting the analysis to patients with at least a 3-year baseline anti-TNF-free period (to minimize misclassification of anti-TNF-naivety).

Indirect treatment comparison network meta-analyses have suggested that in a subset of biologic-naïve patients with CD, IFX may be superior to CZP but comparable to ADA for induction of remission, but all agents are comparable for maintenance of remission.[12, 13] However, there are considerable differences in trial designs (no trials of standard IFX induction dosing, differences in design of maintenance trials, etc.) and co-interventions, with no head-to-head trials, all of which decrease the quality of evidence from these network meta-analyses. Moreover, all of these trials had restrictive inclusion criteria and were short-term (maximum maintenance therapy, 1 year), and hence, not representative of real-world patient-relevant outcomes.

Our findings are consistent with, and expand upon, those of a recent retrospective cohort study, using the U.S. Medicare database. Osterman and colleagues found a lower risk of surgery in IFX-treated patients as compared to ADA-treated patients (5.5 vs. 6.9 surgeries per 100 person-years, respectively), although this difference was not statistically significant.[14] In this Medicare population, approximately 45% patients were above 65 years of age. Among patients younger than 65 years, IFX use was associated with a lower risk of surgery compared to ADA use (adjusted odds ratio [OR], 0.66; 95% CI, 0.47–0.93). With a smaller sample size, the investigators also did not observe a statistically significant difference in risk of CD-related hospitalization, although the point estimate favored IFX (IFX vs. ADA: adjusted OR, 0.88; 95% CI, 0.72–1.07). Similar to our observation, the rate of persistence on index anti-TNF agent at 6 months was comparable for IFX and ADA in their cohort (49% vs. 47%); numerically, their overall persistence rates were lower compared to ours (78%), perhaps due to their older population who is at a higher risk of adverse events.

Despite all three anti-TNF agents having a similar mechanism of action, there are subtle differences in pharmacokinetics, which may explain these results. IFX, administered intravenously, is dosed based on body weight, whereas ADA- and CZP- have a fixed dose administered subcutaneously. In a retrospective cohort study, Bhalme *et al* observed differences in the rates of dose escalation due to therapeutic failure based on body mass index (BMI) in ADA-treated, but not IFX-treated, patients with CD.[15] In an exploratory analysis of trials of ADA in patients with psoriasis, the response rate decreased progressively with increasing quartile of weight, from 74–79% in the lowest quartile to 62–71% in the highest quartile.[16] In contrast, in a pooled analysis of 3 randomized controlled trials of IFX in psoriasis, the response rates were comparable in normal weight, overweight and obese

patients (78% vs. 78% vs. 74%, p=not significant). CZP, in contrast to both ADA and IFX, has a slightly different mechanism of action, and does not have complement-mediated or antibody-mediated cell-dependent cytotoxicity due to absence of IgG1-Fc portion.[8] Hence, the clinical response to CZP may be different from ADA and IFX.

Our findings must be interpreted with caution, given the limitations associated with our study design. First, this was an observational, not an interventional study, and hence, there may be unmeasured confounders across groups. The potential for unmeasured confounding by severity is of particular importance, as administrative data do not include objective measures of disease severity such as endoscopic or biochemical markers; however, this is unlikely to significantly impact our findings, since anti-TNF agents are conventionally used for similar levels of disease activity. To the extent that IFX may preferentially be used among sicker patients, we may have underestimated the comparative benefits of IFX versus ADA or CZP. We also did not have data on baseline cigarette smoking status and weight, both of which can influence outcomes; however, there is no clear reason why tobacco use would be differential across exposure groups. Second, there is potential for misclassification of patients as anti-TNF-naïve, since the baseline period required that patients not have received another anti-TNF agent only 1 year prior to index date. It is well known that the response to a second anti-TNF agent is generally inferior to that of the first anti-TNF agent, and likewise, response decreases for the 3rd anti-TNF agent as compared to the second.[17] We tried to minimize potential misclassification of biologic-naïve status by performing a sensitivity analysis increasing the baseline anti-TNF-free period to 3 years, and observed similar summary estimates for patient-relevant outcomes; however, we can not fully validate that patients were truly biologic-naïve. Third, both baseline covariates and outcomes were measured using administrative claims codes and may be subject to errors. Other prognostic factors influencing response to therapy such as disease duration, dose and frequency intensification, and effect of therapeutic drug monitoring could not be assessed. Fourth, we excluded patients with competing diagnoses for which anti-TNF agents may be used, such as spondyloarthropathy; however, with such an approach, we may have missed some patients with overlapping IBD and spondyloarthropathy who had been prescribed anti-TNF primarily for their bowel disease instead of their rheumatological condition.

In conclusion, using a propensity-matched retrospective observational cohort study, we observed that IFX may be superior to ADA and CZP for patient-relevant outcomes such as risk of hospitalization, surgery and need for corticosteroids, with comparable safety profile, in patients with CD. Future prospective cohort studies with adjustment for baseline objective measures of disease severity and pragmatic randomized controlled trials are warranted to confirm these observations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures: This study was made possible by support from (a) the American College of Gastroenterology Clinical Research Award 2014 to SS, and (b) the Center for the Science of Health Care Delivery, Mayo Clinic, and a CTSA

Grant UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. Dr. Loftus has consulted for and has received research support from Janssen Biotech, AbbVie, and UCB Pharma. Dr. Kappelman has consulted for and has received research support from Janssen Biotech and AbbVie. None of the other authors have any relevant financial disclosures.

References

1. Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. N Engl J Med. 2013; 369:754–62. [PubMed: 23964937]
2. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010; 362:1383–95. [PubMed: 20393175]
3. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007; 132:52–65. [PubMed: 17241859]
4. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med. 2007; 357:228–38. [PubMed: 17634458]
5. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med. 2007; 146:829–38. [PubMed: 17470824]
6. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med. 2007; 357:239–50. [PubMed: 17634459]
7. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. 1997; 337:1029–35. [PubMed: 9321530]
8. Nestorov I. Clinical pharmacokinetics of TNF antagonists: how do they differ? Semin Arthritis Rheum. 2005; 34:12–8. [PubMed: 15852249]
9. Wallace PJ, Shah ND, Dennen T, et al. Optum Labs: building a novel node in the learning health care system. Health Aff (Millwood). 2014; 33:1187–94. [PubMed: 25006145]
10. Borah BJ, Moriarty JP, Crown WH, et al. Applications of propensity score methods in observational comparative effectiveness and safety research: where have we come and where should we go? J Comp Eff Res. 2014; 3:63–78. [PubMed: 24266593]
11. Sugihara M. Survival analysis using inverse probability of treatment weighted methods based on the generalized propensity score. Pharm Stat. 2010; 9:21–34. [PubMed: 19199275]
12. Singh S, Garg SK, Pardi DS, et al. Comparative efficacy of biologic therapy in biologic-naive patients with Crohn disease: a systematic review and network meta-analysis. Mayo Clin Proc. 2014; 89:1621–35. [PubMed: 25441399]
13. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology. 2015; 148:344–54 e5. quiz e14–5. [PubMed: 25448924]
14. Osterman MT, Haynes K, Delzell E, et al. Comparative effectiveness of infliximab and adalimumab for Crohn's disease. Clin Gastroenterol Hepatol. 2014; 12:811–817 e3. [PubMed: 23811254]
15. Bhalme M, Sharma A, Keld R, et al. Does weight-adjusted anti-tumour necrosis factor treatment favour obese patients with Crohn's disease? Eur J Gastroenterol Hepatol. 2013; 25:543–9. [PubMed: 23337170]
16. Puig L. Obesity and psoriasis: body weight and body mass index influence the response to biological treatment. J Eur Acad Dermatol Venereol. 2011; 25:1007–11. [PubMed: 21492252]
17. Gisbert JP, Marin AC, McNicholl AG, et al. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015; 41:613–23. [PubMed: 25652884]

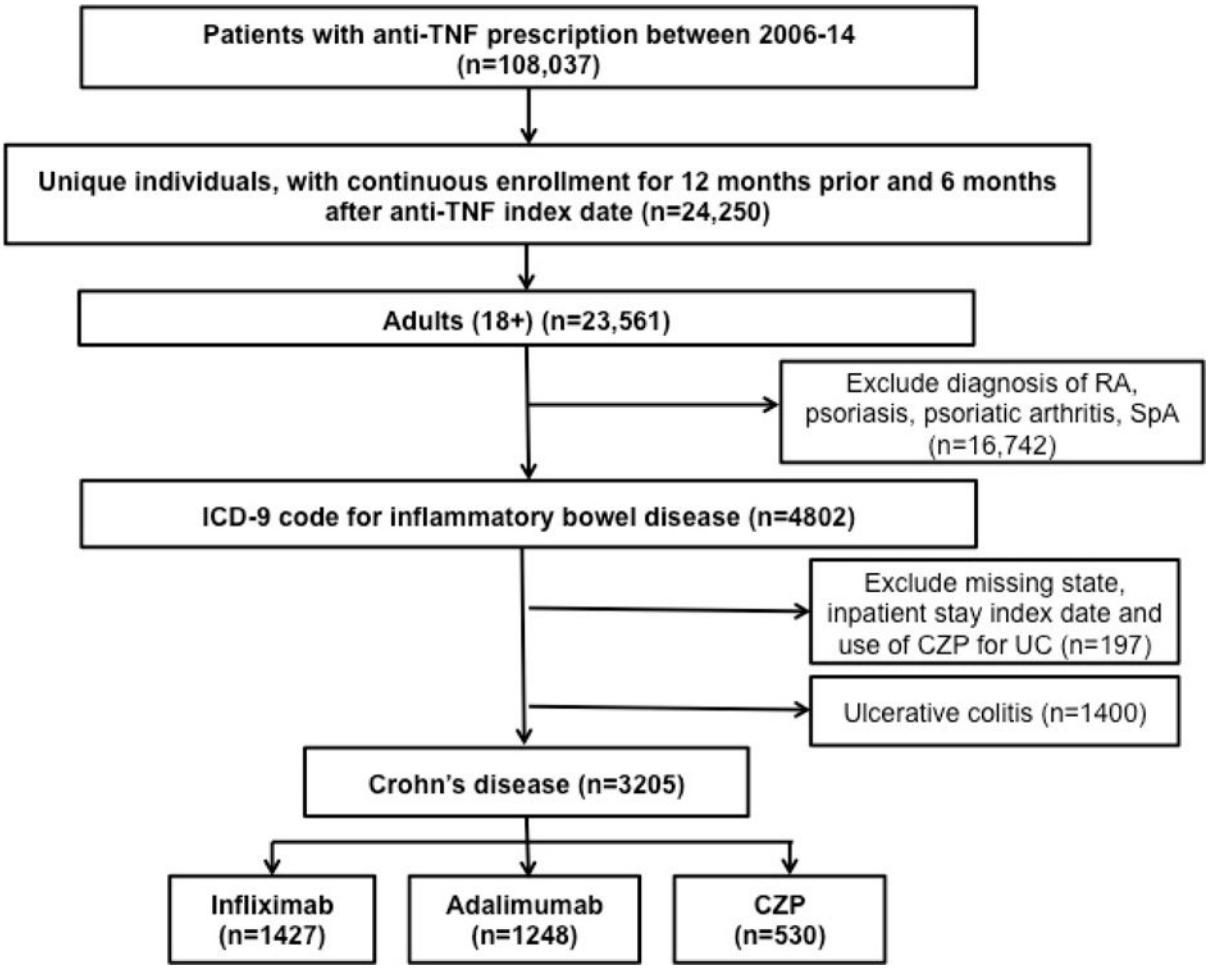
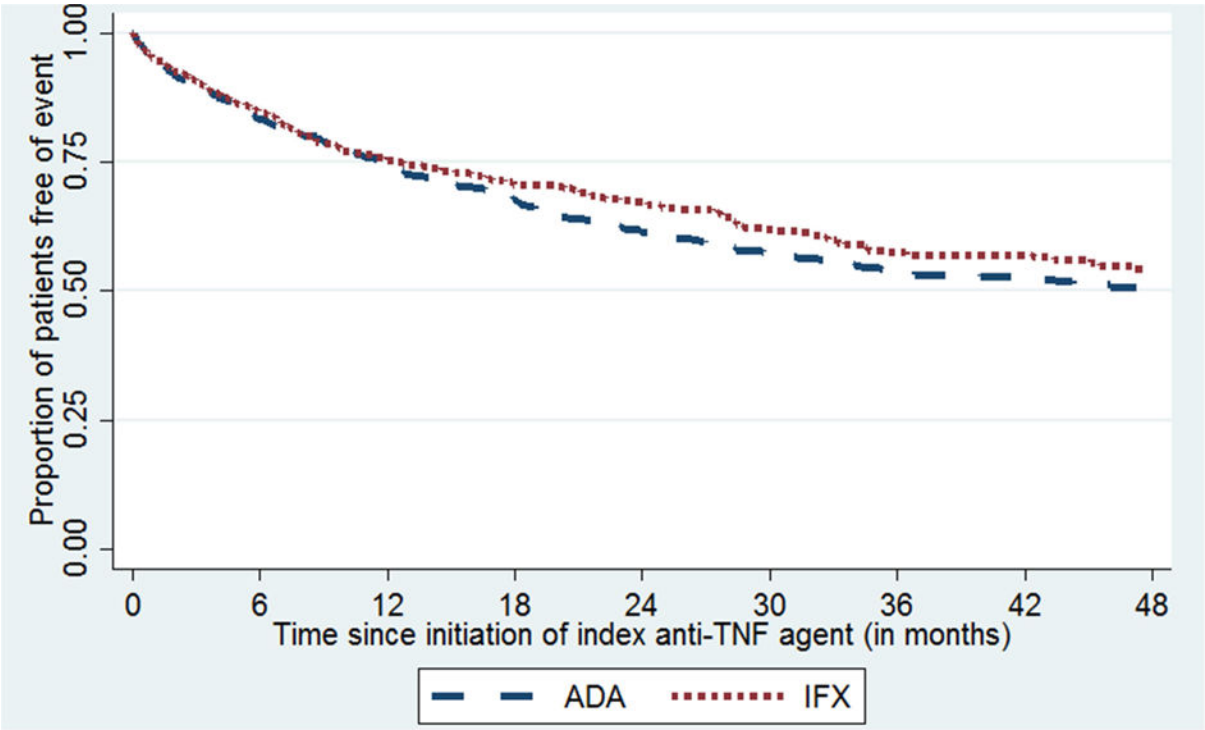
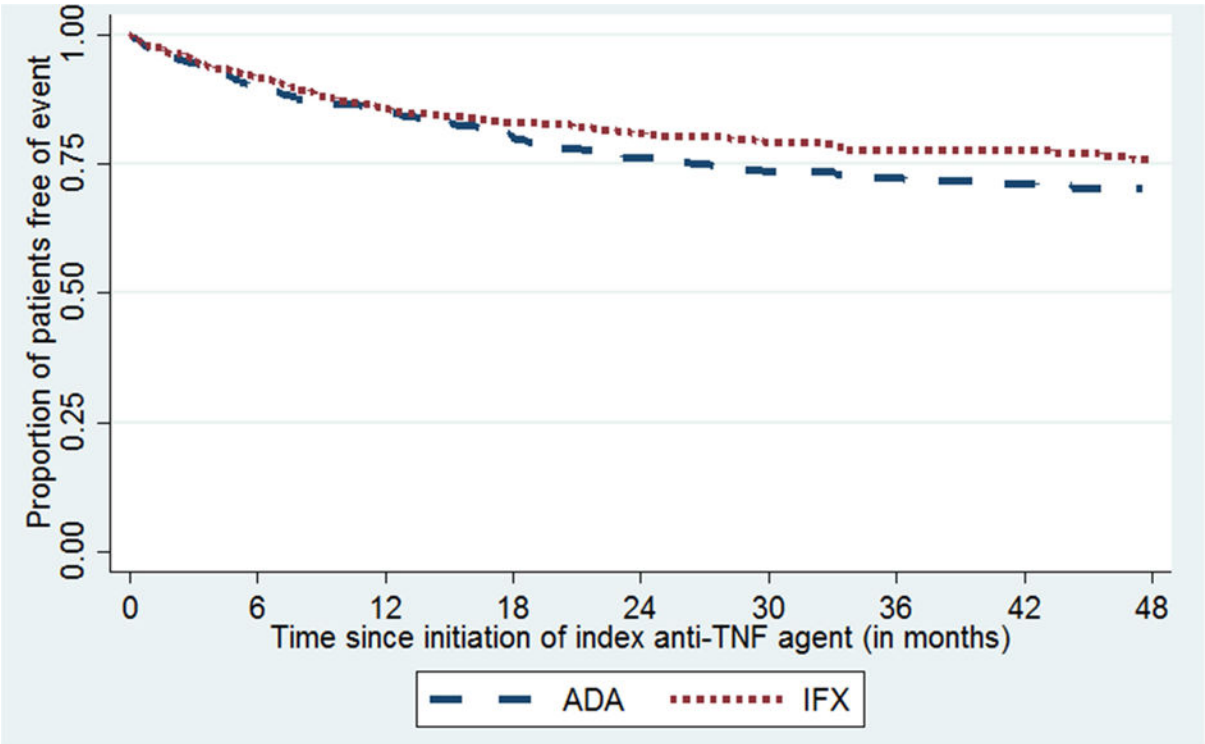
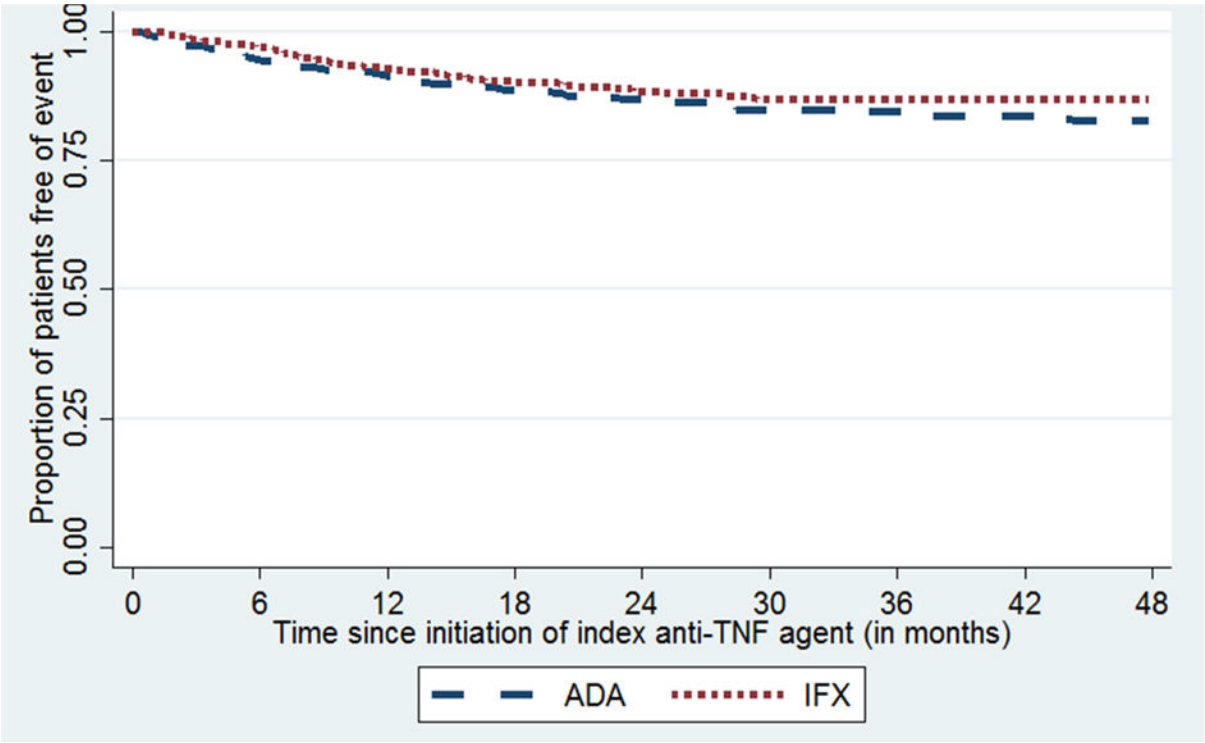


Figure 1.
Flow of patients for identification of the anti-TNF-naive Crohn's disease cohort.







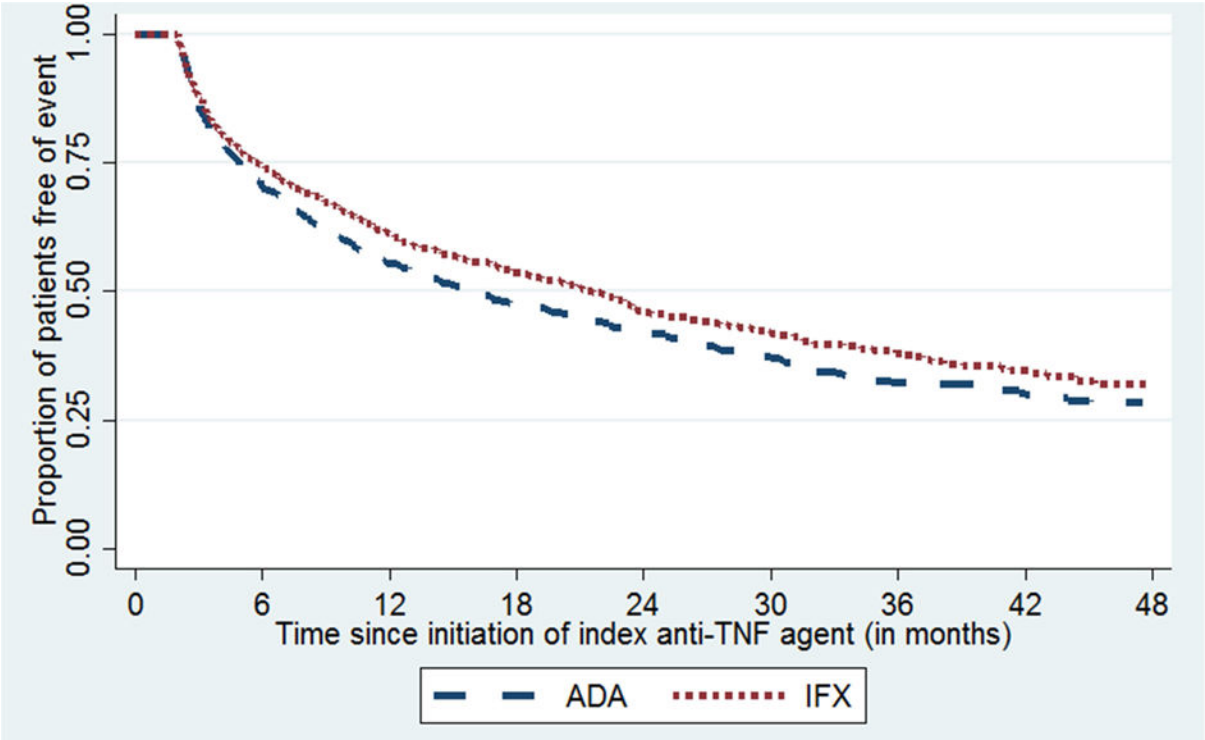
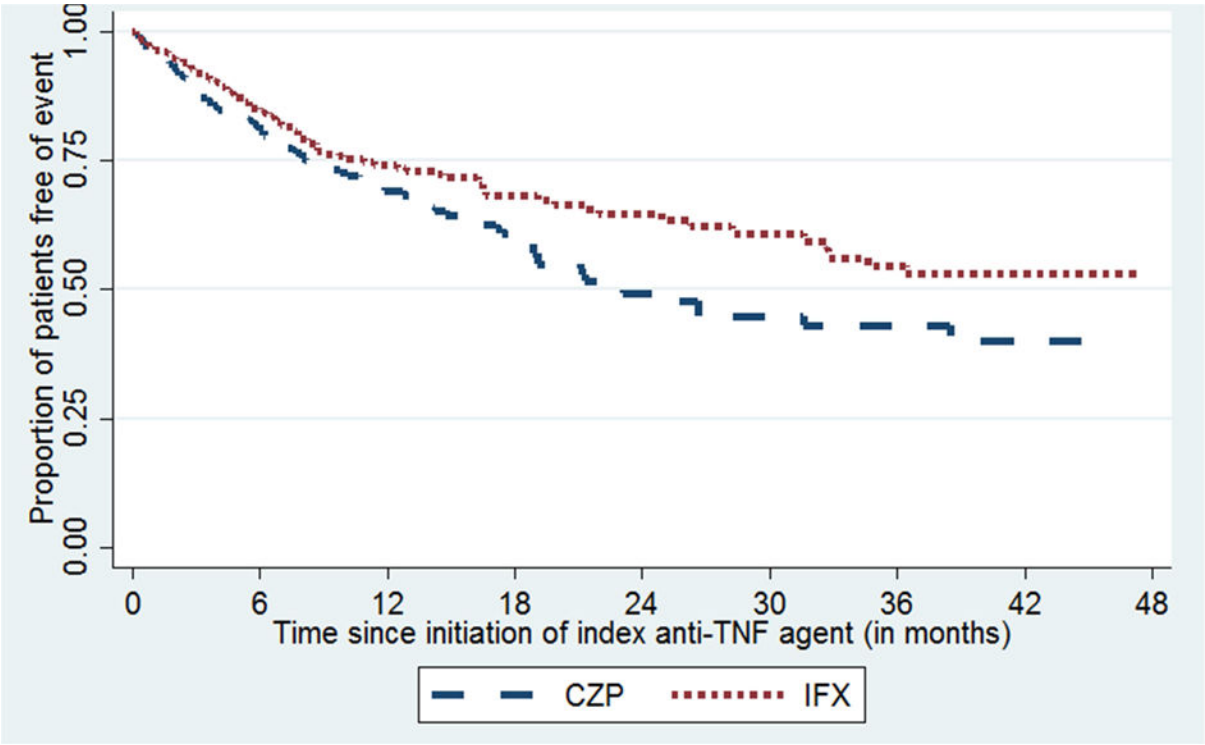
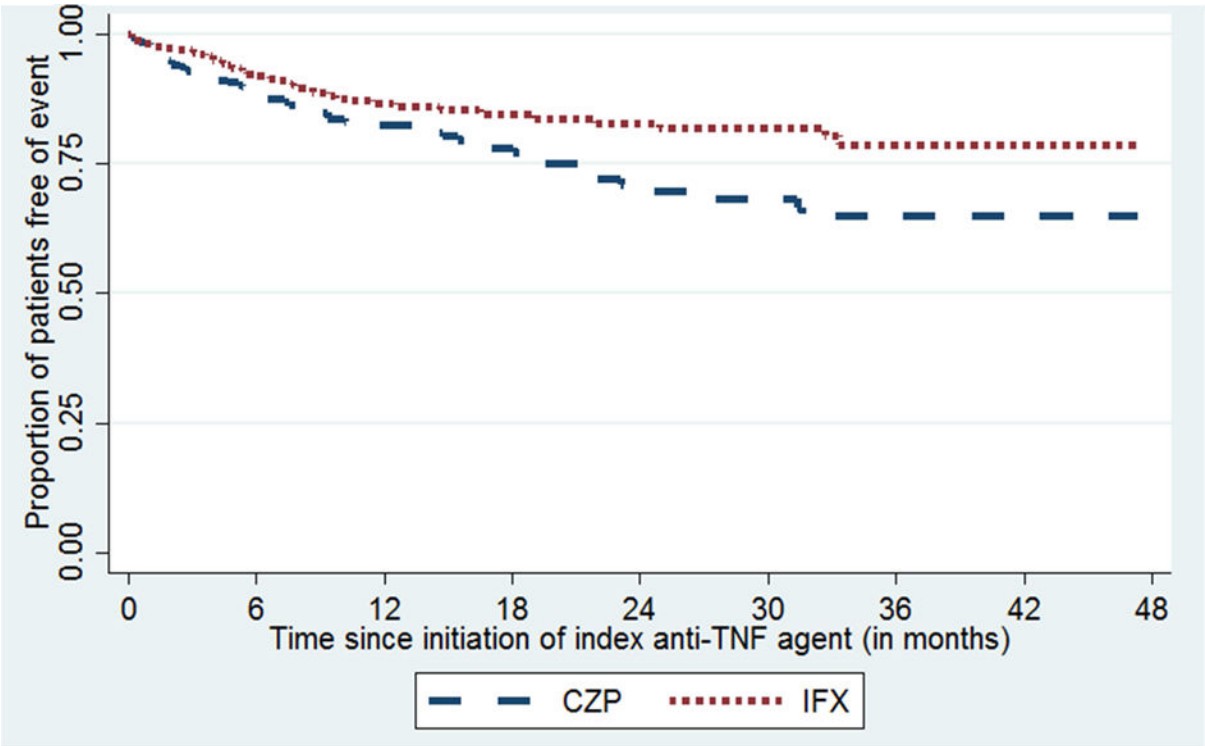
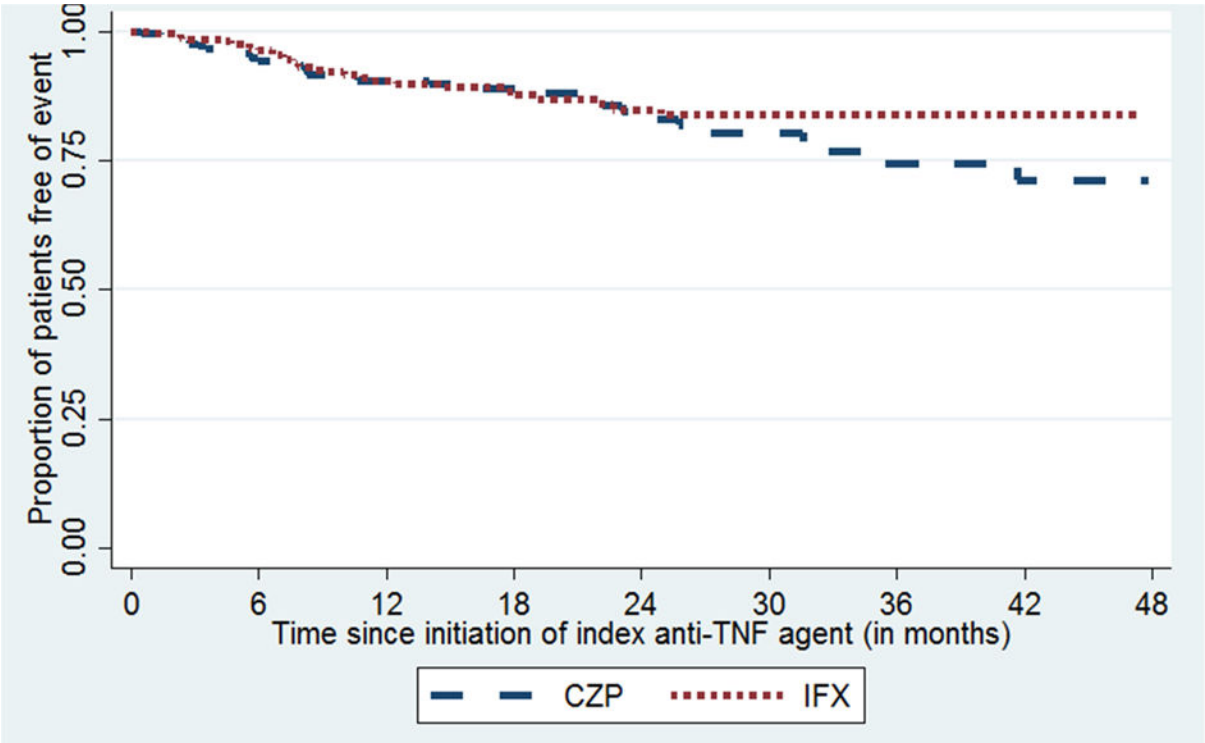


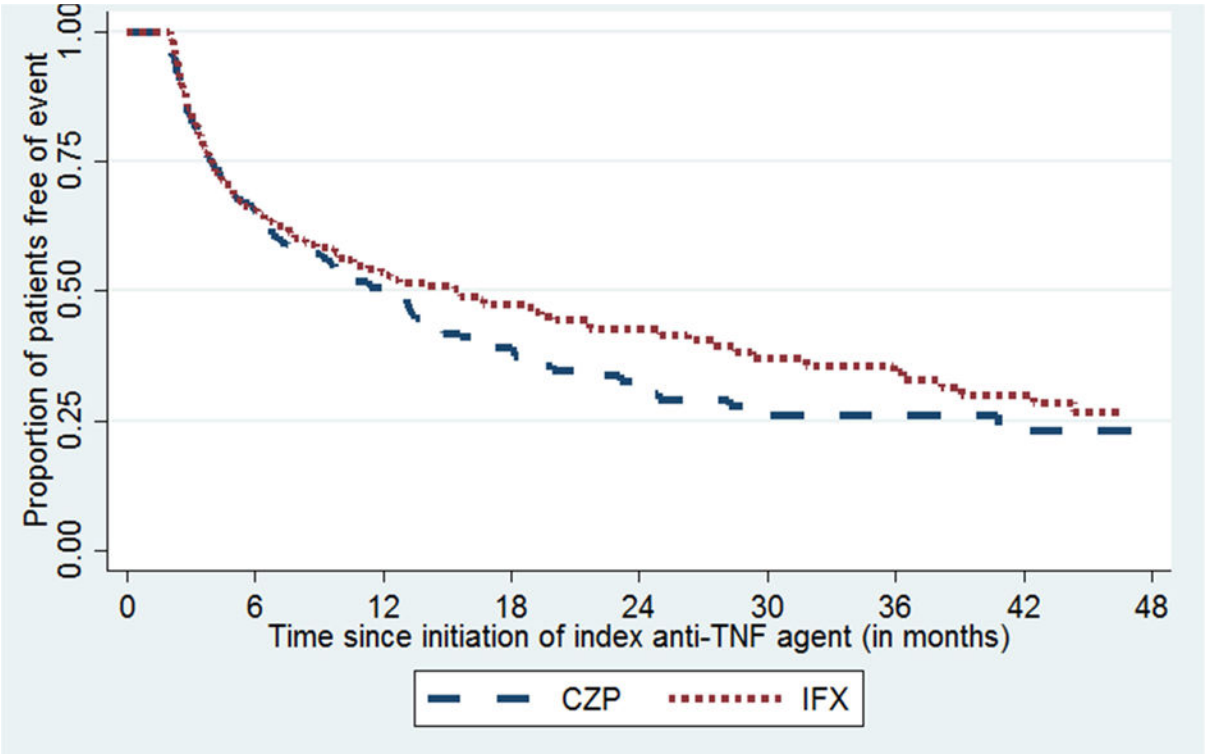
Figure 2.

Survival free of **(a)** all-cause hospitalization, **(b)** Crohn's disease-related hospitalization, **(c)** CD-related abdominal surgery, **(d)** corticosteroid prescription (at least 60 days after index anti-TNF agent) and **(e)** hospitalization for serious infection, in comparing propensity-score matched cohort of patients treated with infliximab (IFX) vs. adalimumab (ADA) as the first-line index anti-TNF agent. IP refers to inpatient hospitalization.









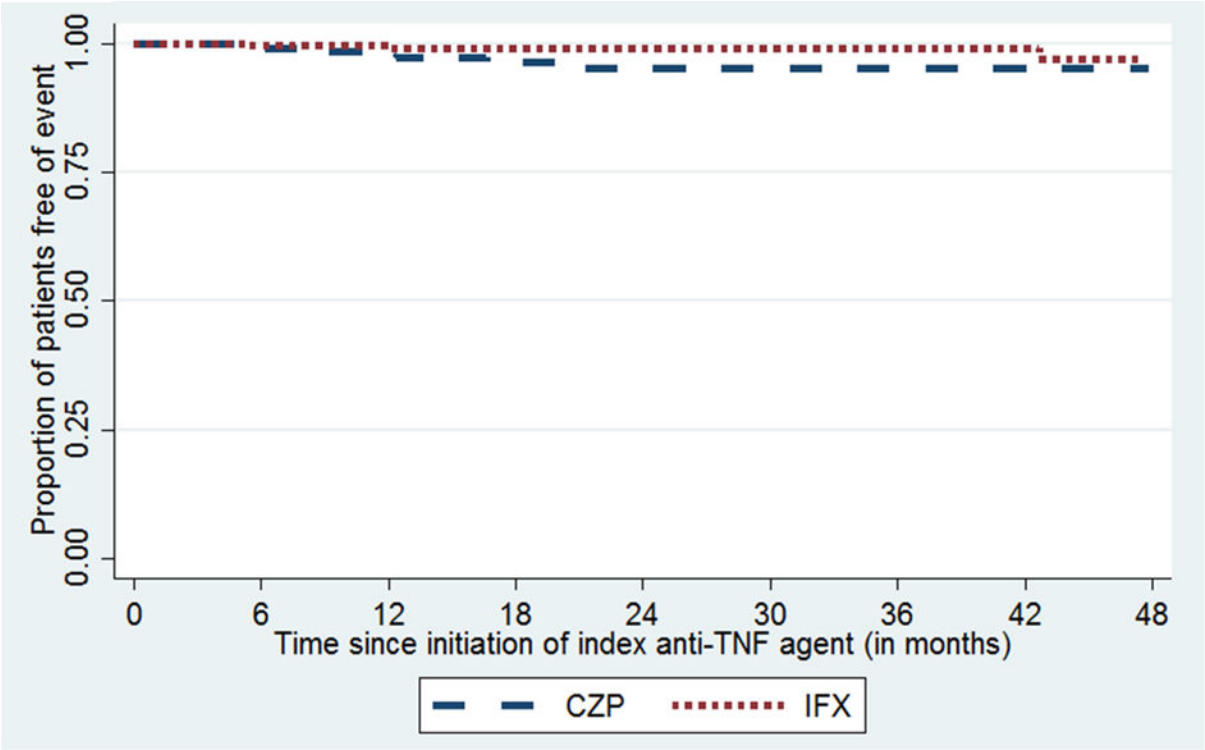
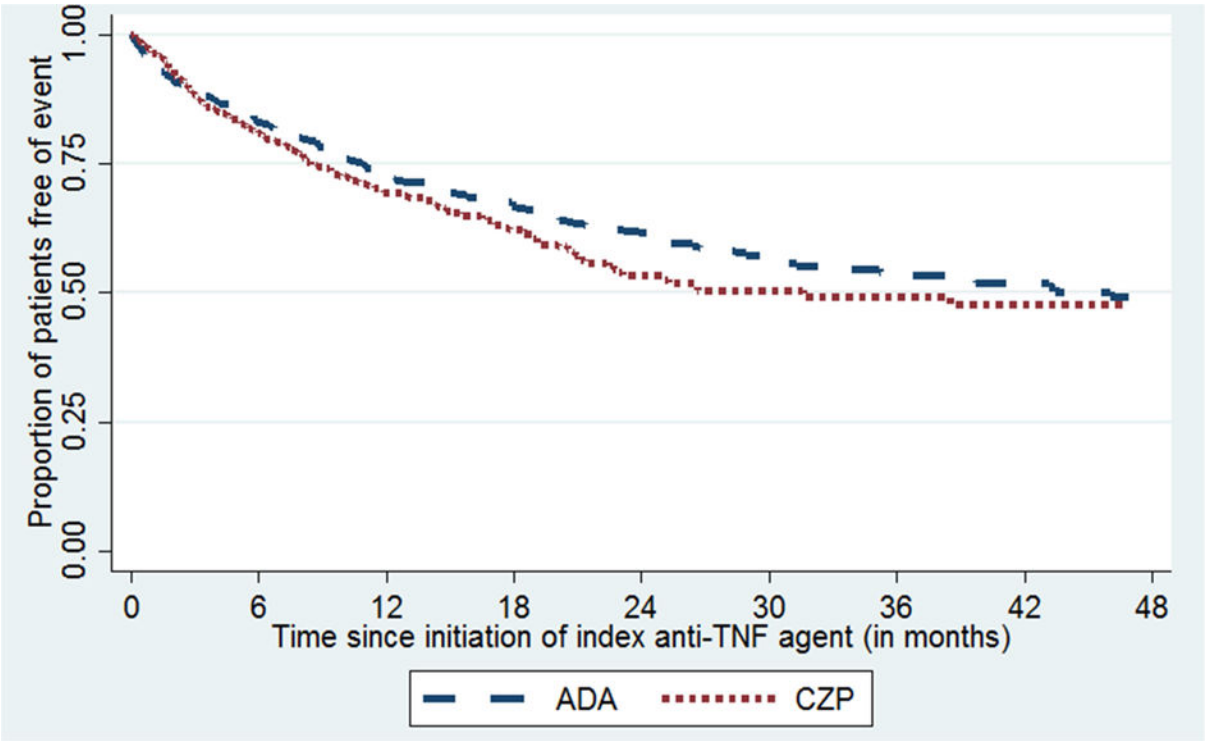
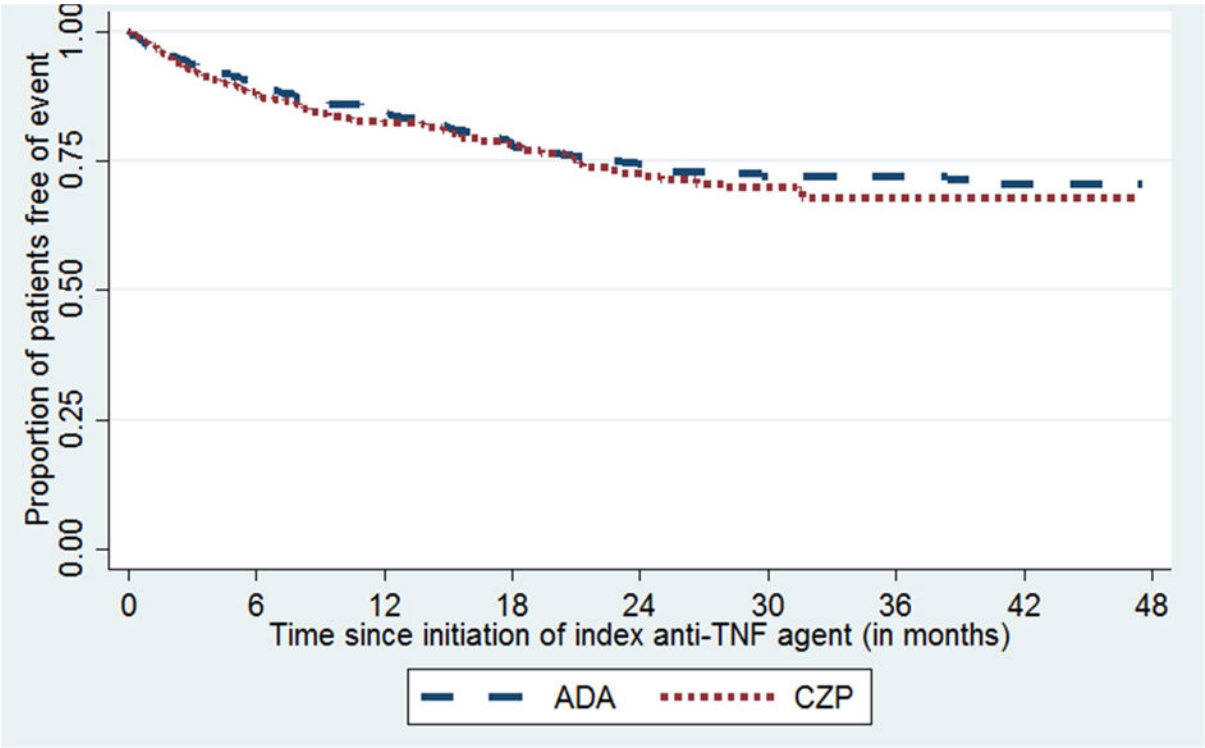
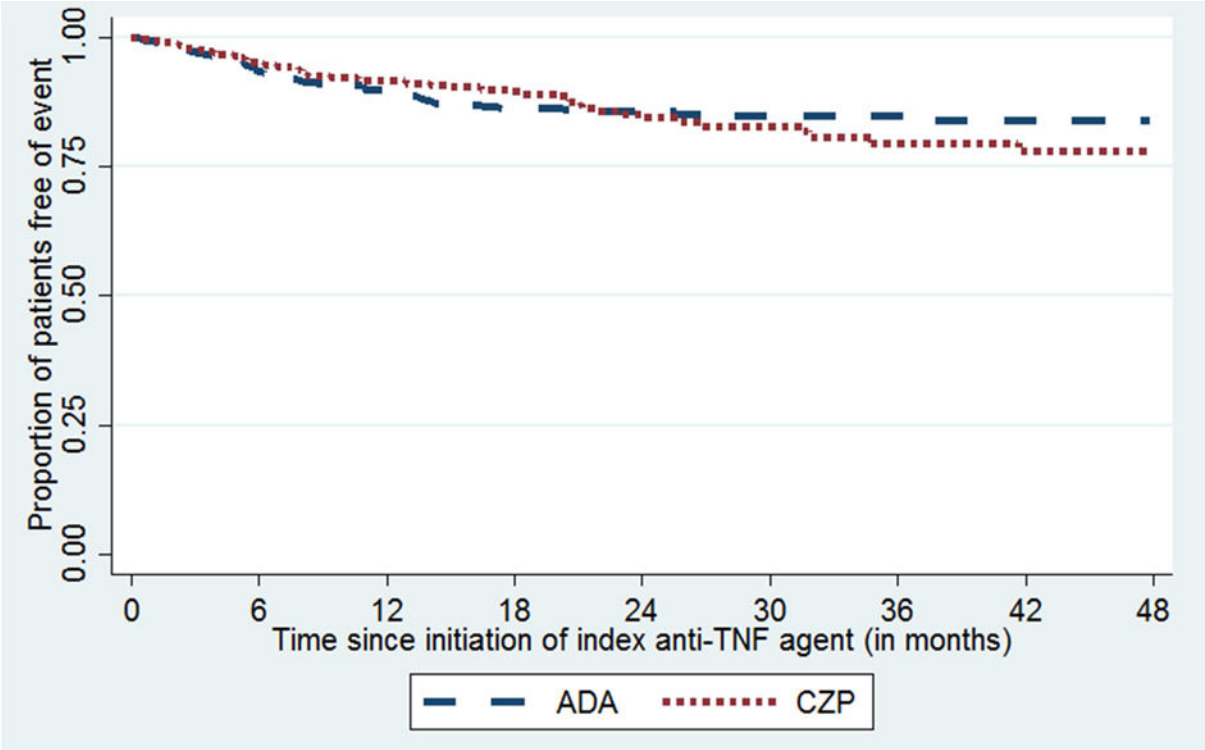


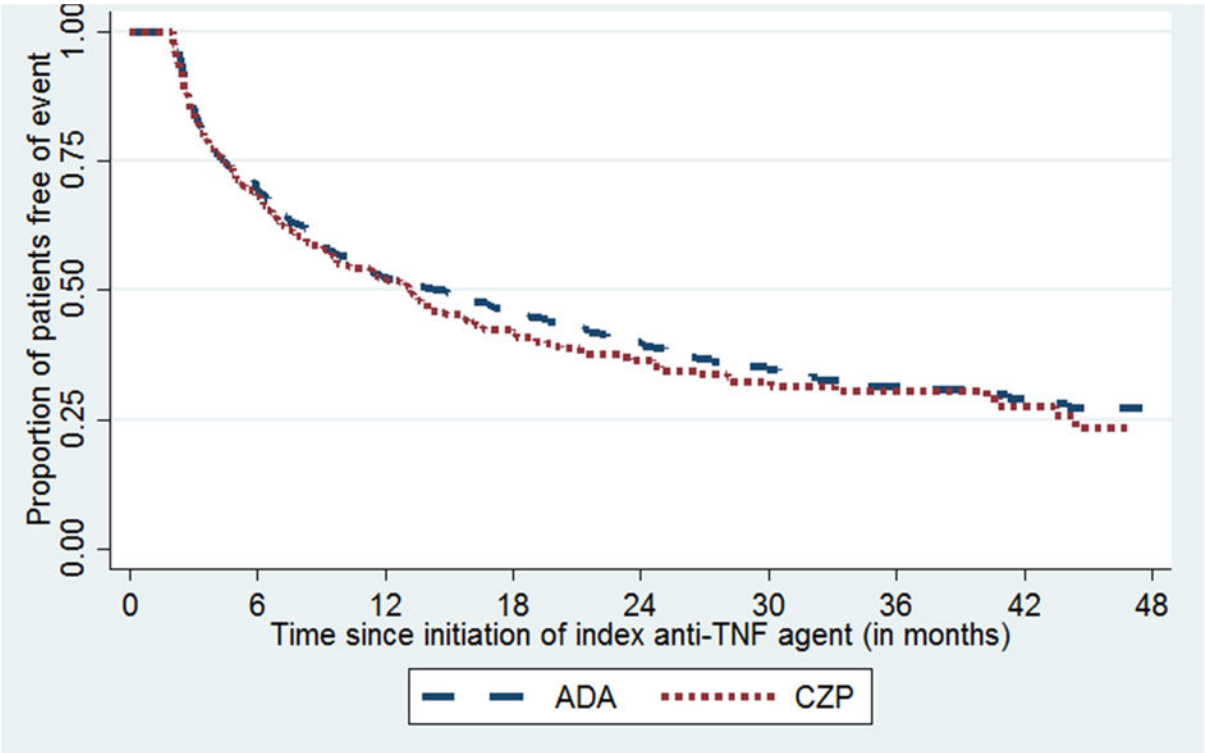
Figure 3.

Survival free of **(a)** all-cause hospitalization, **(b)** Crohn's disease-related hospitalization, **(c)** CD-related abdominal surgery, **(d)** corticosteroid prescription (at least 60 days after index anti-TNF agent) and **(e)** hospitalization for serious infection, in comparing propensity-score matched cohort of patients treated with infliximab vs. certolizumab pegol as first-line index anti-TNF agent. IP refers to inpatient hospitalization.









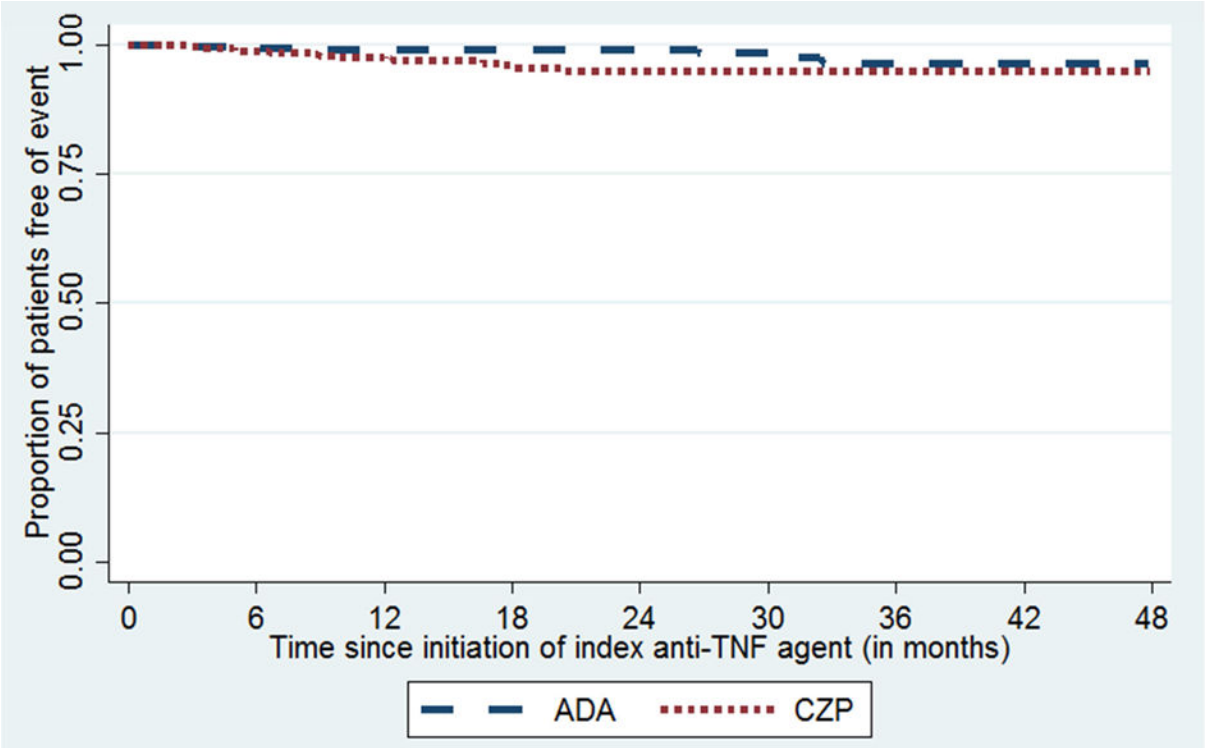


Figure 4.

Survival free of **(a)** all-cause hospitalization, **(b)** Crohn's disease-related hospitalization, **(c)** CD-related abdominal surgery, **(d)** corticosteroid prescription (at least 60 days after index anti-TNF agent) and **(e)** hospitalization for serious infection, in comparing propensity-score matched cohort of patients treated with certolizumab pegol vs. adalimumab as first-line index anti-TNF agent. IP refers to inpatient hospitalization.

Table 1

Baseline demographic characteristics, healthcare utilization and IBD-related medication use in the 12 months prior to initiation of anti-TNF agents (figures in bold represent statistically significant difference between groups)

Variable	Infliximab (n=1427)	Adalimumab (n=1248)	Certolizumab pegol (n=530)	p-value (for difference between groups)
Demographic variables				
Mean age ± SD, years	41±15	40±14	41±14	0.39
Sex (% males)	46	44	46	0.85
Median follow-up after starting anti-TNF, months (IQR)	**19 (10–35)**	**21 (11–38)**	**15 (8–27)**	**<0.001**
Healthcare utilization (in 12 months prior to starting anti-TNF)				
Median outpatient visits (IQR)	8 (5–12)	8 (5–12)	8 (5–12)	0.64
Emergency room visits (% pts with ≥1)	42	41	42	0.92
Inpatient visits (% pts with ≥1)	35	34	32	0.41
Imaging (% of pts with ≥1)	**46**	**48**	**53**	**0.02**
Endoscopic procedures (% pts with ≥1)	**60**	**60**	**67**	**0.01**
Prior abdominal surgery (% pts with ≥1)	**4**	**5**	**7**	**0.006**
Perianal CD * (%)	12.6	12.7	13.2	0.94
Median generic medication count (IQR)	6 (4–8)	6 (4–9)	6 (4–9)	0.39
IBD-related medication use (in 12 months prior to starting anti-TNF)				
Mesalamine, oral, %	52	49	49	0.41
Steroids • **Any prior use, %** • Recent (in 90 days prior to anti-TNF), %	 **65** 50	 **71** 52	 **72** 56	 **<0.001** 0.07
Immunomodulators • Any prior use, % • **Concurrent (index date ± 30 days), %**	 45 **32**	 44 **26**	 43 **26**	 0.51 **0.004**
Narcotics, %	49	51	52	0.22

* based on ICD-9 codes, 565.x and 566.x

Abbreviations: IQR-interquartile range, n-number of patients, pts-patients, SD-standard deviation, TNF-tumor necrosis factor

Table 2

Propensity-matched analysis (1:1) of the comparative effectiveness and safety of (A) infliximab vs. adalimumab, (B) infliximab vs. certolizumab pegol and (C) certolizumab pegol vs. adalimumab and in biologic-naïve patients with Crohn's disease, with 1-year baseline anti-TNF-free period (primary analysis) and 2- and 3-year baseline anti-TNF-free period (sensitivity analysis) (figures in bold represent statistically significant difference between groups)

Outcomes of interest	**(A.) Infliximab vs. Adalimumab**					
	1-year baseline (N=2040)		**2-year baseline (N=1318)**		**3-year baseline (N=884)**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All-cause hospitalization	0.86 (0.74, 1.01)	0.063	0.92 (0.76, 1.12)	0.415	0.98 (0.77, 1.23)	0.847
CD-related hospitalization	**0.81 (0.66, 1.00)**	**0.048**	0.94 (0.73, 1.22)	0.654	0.85 (0.63, 1.15)	0.286
Abdominal surgery	**0.73 (0.56, 0.97)**	**0.029**	0.76 (0.53, 1.08)	0.128	0.74 (0.50, 1.08)	0.122
New steroid use • Any time after anti-TNF initiation • >60d after anti-TNF initiation	 0.90 (0.80, 1.01) 0.85 (0.75, 0.96)	 0.069 0.011	 0.96 (0.83, 1.11) 0.91 (0.79, 1.06)	 0.582 0.240	 0.97 (0.82, 1.15) 0.87 (0.73, 1.04)	 0.715 0.128
Serious Infection	0.88 (0.48, 1.64)	0.690	0.79 (0.37, 1.66)	0.531	0.72 (0.26, 2.02)	0.535
	(B.) Infliximab vs. Certolizumab pegol					
	1-year baseline (N=506)		**2-year baseline (N=418)**		**3-year baseline (N=296)**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All-cause hospitalization	**0.68 (0.46, 1.00)**	**0.050**	**0.57 (0.38, 0.87)**	**0.009**	1.03 (0.66, 1.58)	0.913
CD-related hospitalization	**0.54 (0.32, 0.91)**	**0.020**	0.69 (0.41, 1.16)	0.163	1.19 (0.66, 2.14)	0.563
Abdominal surgery	0.59 (0.30, 1.17)	0.133	**0.48 (0.25, 0.94)**	**0.031**	0.93 (0.47, 1.83)	0.822
New steroid use • Any time after anti-TNF initiation • >60d after anti-TNF initiation	 0.88 (0.68, 1.14) 0.78 (0.59, 1.03)	 0.317 0.078	 0.86 (0.66, 1.12) 0.85 (0.63, 1.16)	 0.269 0.303	 0.97 (0.68, 1.39 0.86 (0.58, 1.28)	 0.881 0.456
Serious Infection	0.47 (0.08, 2.75)	0.406	0.28 (0.05, 1.54)	0.143	0.52 (0.11, 2.55)	0.417
	(C.) Certolizumab pegol vs. Adalimumab					
	1-year baseline (N=1046)		**2-year baseline (N=752)**		**3-year baseline (N=508)**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
All-cause hospitalization	**1.30 (1.03, 1.64)**	**0.025**	**1.41 (1.06, 1.86)**	**0.017**	1.38 (0.99, 1.94)	0.060
CD-related hospitalization	1.19 (0.89, 1.57)	0.243	**1.45 (1.02, 2.07)**	**0.040**	1.36 (0.88, 2.08)	0.164
Abdominal surgery	1.13 (0.75, 1.69)	0.557	**1.70 (1.05, 2.75)**	**0.032**	1.40 (0.87, 2.26)	0.169

Outcomes of interest	(A.) Infliximab vs. Adalimumab					
	1-year baseline (N=2040)		2-year baseline (N=1318)		3-year baseline (N=884)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
New steroid use • Any time after anti-TNF initiation • >60d after anti-TNF initiation	1.07 (0.90, 1.29) 1.20 (1.00, 1.46)	0.439 0.054	0.96 (0.78, 1.19) 0.98 (0.78, 1.23)	0.729 0.865	0.99 (0.77, 1.27) 0.91 (0.70, 1.19)	0.934 0.481
Serious Infection	2.06 (0.98, 4.35)	0.058	1.25 (0.51, 3.02)	0.629	1.84 (0.44, 7.66)	0.401

Abbreviations: CD-Crohn's disease, CI-confidence interval, HR-hazard ratio, N=number of patients