CRE-MI Methods Group journal club: Prevalent new-user cohort design

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Today’s paper

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Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis

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The prevalent new-user cohort design is useful for assessing the effectiveness of a medication in the absence of an active comparator. Alternative approaches, particularly in the presence of informative censoring, include a variant of this design based on never users of the study drug and the marginal structural Cox model approach. We compared these approaches in assessing the effectiveness of proton pump inhibitors (PPIs) in reducing mortality among patients with idiopathic pulmonary fibrosis (IPF) using a cohort of IPF patients identified in the United Kingdom's Clinical Practice Research Datalink and diagnosed between 2003 and 2016. The cohort included 2,944 IPF patients, 1,916 of whom initiated use of PPIs during follow-up. There were 2,136 deaths (mortality rate = 25.8 per 100 person-years). Using the conventional prevalent new-user design, we found a hazard ratio for death associated with PPI use compared with nonuse of 1.07 (95% confidence interval (CI): 0.94, 1.22). The variant of the prevalent new-user design comparing PPI users with never users found a hazard ratio of 0.82 (95% CI: 0.73, 0.91), while the marginal structural Cox model found a hazard ratio of 1.08 (95% CI: 0.85, 1.38). The marginal structural model and the conventional prevalent new-user design, both accounting for informative censoring, produced similar results. However, the prevalent new-user design variant based on never users introduced selection bias and should be avoided.

cohort studies; comparative effectiveness research; idiopathic pulmonary fibrosis; informative censoring; pharmacoepidemiology; proton pump inhibitors

Abbreviations: CI, confidence interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; IPCW, inverse probability of censoring weights; IPF, idiopathic pulmonary fibrosis; IPTW, inverse probability of treatment weights; MSCM, marginal structural Cox model; ONS, Office for National Statistics; PPI, proton pump inhibitor; TCPS, time-conditional propensity score.

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease associated with a poor prognosis; median survival is 2–5 years after diagnosis (1–3). Because of a potential effect of acid reflux on the progression of IPF, proton pump inhibitors (PPIs) are used to treat this disease and have been given conditional recommendations in international IPF treatment guidelines (4). These recommendations were based on several observational studies that assessed the effectiveness of PPIs among patients with IPF, with particular interest in survival (5, 6). Subsequent studies continued to evaluate the effectiveness of PPIs in IPF (7–13). However, several of these studies were affected by immortal time bias or presented other limitations, such as a small sample size or a short study period (14).

In a recent study, Tran et al. (15) used a large population-based database and a prevalent new-user cohort design that allowed them to specifically circumvent these limitations while assessing the effectiveness of a drug in the absence of an active comparator. The prevalent new-user cohort design originally received its name because of its ability to compare new users of a medication of interest with prevalent users of an older established drug. For example, patients who switched from the comparison drug to the drug of interest and patients who were prevalent users of the comparison

- T. Tran and S. Suissa. **Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis.** *American Journal of Epidemiology*, 190(5):928–938, May 2021. doi:10.1093/aje/kwaa242.

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Talk outline

- Paper background
- Prevalent new-user cohort method in detail
- Adjusting for informative censoring
- Results
- What does the PNUC method estimate?
- Loose ends

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Introduction

- Question: Are PPIs efficacious in idiopathic pulmonary fibrosis?
- Contention: Effects seen in earlier studies are due to bias
- Data: UK linked GP and hospital data (CPRD-GOLD/HES/ONS), $n = 2944$
- Outcomes: All-cause mortality, respiratory death, hospitalisation
- Covariates: Demographics, comorbidity, medicines (all time-varying)

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Idiopathic Pulmonary Fibrosis (IPF)

- Progressive scarring of the lungs, cause unknown
- Average life expectancy after diagnosis about four years
- Pirfenidone (2008) and nintedanib (2014) slow progression
- Proton pump inhibitors also guideline recommended (weak evidence)

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Review: Active comparator new-user cohort design

- Confounding by indication (inactive comparator)
- Healthy adherer bias (prevalent users)

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Why *prevalent* new-user?

- Increase sample size if few treatment-naive patients
- Better external validity e.g. disease progression
- Key feature: conditioning on length of exposure

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Prevalent new-user cohort design step by step

1. Defining the base cohort
2. Forming exposure sets
3. Estimating the propensity score
4. Matching and forming the analysis cohort
5. Estimating the causal effect

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Defining exposure sets and estimating the propensity score

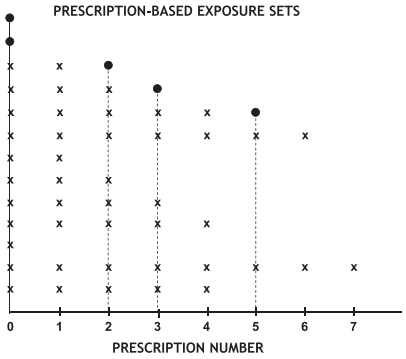

Figure 3. Depiction of a base cohort formed of 13 subjects with prescription-based exposure sets defined by the number of comparator drug prescriptions (**x**) before the first study drug prescription (●) was given

Suissa et al. (2017)

Matching

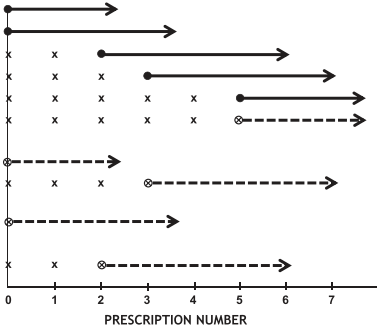

Figure 4. Depiction of the final prevalent new-user comparative cohort with comparator drug subjects matched to study drug subjects on the number of comparator drug prescriptions (x) before the first study drug prescription (●) was given, with the arrows indicating the follow-up period for outcomes

Suissa et al. (2017)

Informative censoring

- In this study, “prevalent user” = IPF patient *not* treated with PPI
- Follow-up of prevalent users is censored if PPI treatment starts
- Starting PPI = patient is sicker (but still alive)

Adjusting for informative censoring

- Option 1: Restriction
  - exclude PPI ever users from prevalent cohort
- Option 2: Weighting
  - use inverse probability of censoring weights (IPCW)
  - estimate from logistic regression model (*à la* propensity)

Results 1

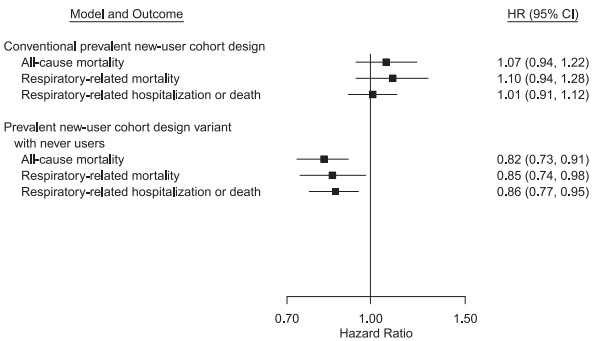

Figure 3. Hazard ratios (HRs) for respiratory-disease–related hospitalization and mortality associated with proton pump inhibitor use (compared with no use) obtained using 3 different study designs in a cohort of patients with idiopathic pulmonary fibrosis, United Kingdom, 2003–2016. Bars, 95% confidence intervals (CIs).

Marginal Structural Cox Model

- All patients followed from IPF diagnosis
- Exposure and covariates assessed in each person-month
- Inverse probability of treatment weights (IPTW)
- Inverse probability of censoring weigts (IPCW)
- Estimation with weighted time-dependent Cox model

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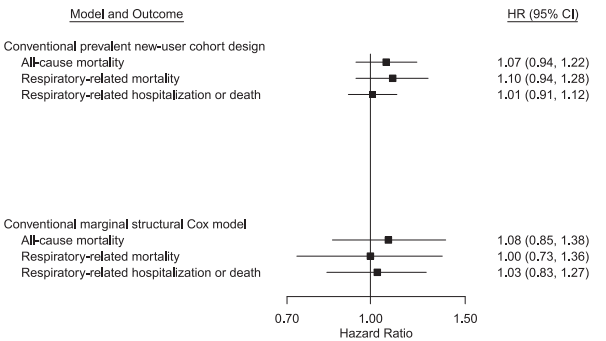
Results 2



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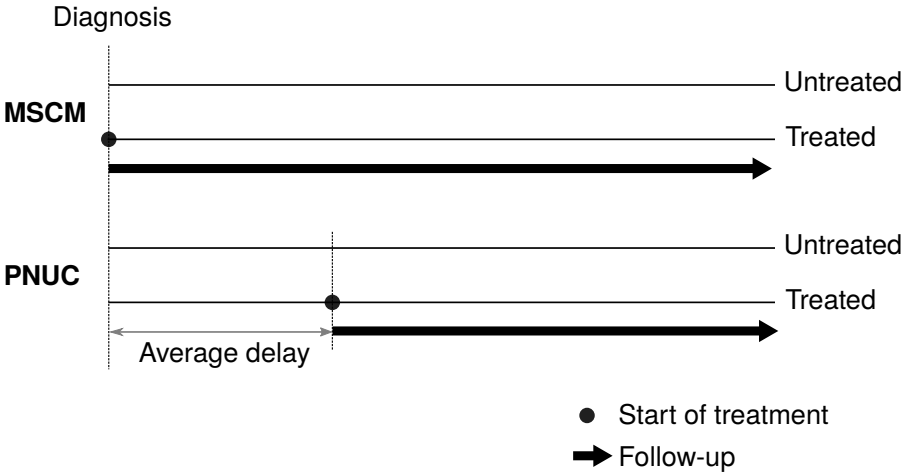
Estimands


Diagnosis
MSCM
Untreated
Treated
PNUC
Untreated
Treated
Average delay
Start of treatment
Follow-up

Scenarios

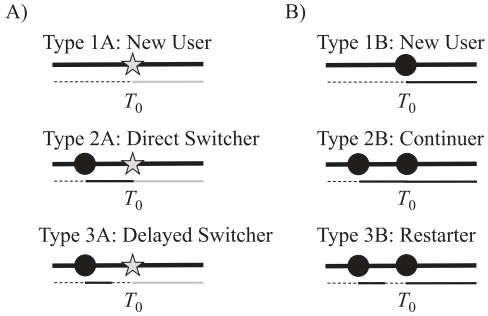


Figure 1. Infographic showing treatment histories of various types of initiators of treatment A and users of B. Panel A includes the initiators of treatment A (types 1A–3A) and panel B includes the 3 corresponding individuals taking treatment B that would be "ideal" counterfactual contrasts for types 1A–3A. Gray stars represent prescriptions for A, while black circles represent prescriptions for B. Below each set of prescriptions is a secondary timeline showing time with no treatment (dashed black), time treated with A (gray), and time treated with B (solid black).

Webster-Clark et al. (2020)

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Loose ends

- Sampling with/without replacement
- Conditioning on length of exposure vs entire history
- Positivity and matching
- Estimating the propensity score
- See also: `https://pharmacoepi.unc.edu/wp-content/uploads/sites/6788/2020/12/Webster-Clark_Michael_PNU.pdf`

Discussion

- Have you used the prevalent new-user cohort design or the marginal structural Cox model approach? If so, please tell us about it.
- Would you use either of these methods for your current research interests? What do you see as the barriers to using them?

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Other business

- Suggestions for articles or topics to discuss
- Volunteers to present
- Comments on format, timing, frequency and audience for the journal club

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