Assessing the effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a rare and progressive chronic lung disease that is associated with poor prognosis, with an estimated median survival of 2-5 years after diagnosis. In the last decade, advances in IPF treatment were made and two medications – nintedanib and pirfenidone – are now available to treat mild to moderate IPF. While these medications slow disease progression, they are expensive – costs in Canada are approximately $40,000/year - and need to be used with caution in patients with renal disease or increased cardiovascular risk. Thus, the search for other effective and affordable treatment options for patients with IPF is still ongoing. Current IPF treatment guidelines now conditionally recommend anti-acid therapy, mainly consisting of proton pump inhibitors, to treat IPF regardless of the presence of gastroesophageal reflux. The biological rationale for the recommendation is based on the high prevalence of gastroesophageal reflux disease in patients with IPF, which is hypothesized to contribute to the IPF disease progression through microaspiration of acid reflux. However, the evidence supporting the use of these drugs in the current treatment guidelines for IPF is inconsistent, based on several observational studies reporting highly beneficial effects on survival, with others reporting no effect. Thus, uncertainty remains regarding the beneficial effects of PPIs in IPF. The overarching goal of my thesis was to evaluate the effectiveness of PPIs on survival and other major outcomes in patients with IPF while addressing methodological issues that were present in previous studies.

In the first manuscript, I present a methodological review of observational studies examining the association of anti-acid therapy and survival in patients with IPF, with a particular focus on immortal time bias. We identified ten observational studies. Four of the five studies reporting beneficial effects of anti-acid therapy use on mortality were affected by immortal time bias (pooled hazard ratio (HR) = 0.46, 95% confidence interval (CI) 0.30-0.69), while the fifth was

insufficiently detailed to assess its methods. The five studies that were free of immortal time bias reported no effect of anti-acid therapy on mortality (pooled HR = 0.99, 95% CI 0.81-1.22) but had other limitations, such as short duration of follow-up, small sample size or lack of generalizability. Thus, the relationship between anti-acid therapy, including PPIs, and survival remains uncertain due to the methodological and size limitations in the existing observational studies.

In the second manuscript, I used data from the United Kingdom's Clinical Practice Research Datalink linked to the Hospital Episode Statistics and Office for National Statistics databases to evaluate whether the use of PPIs is indeed beneficial with regard to mortality and respiratory-related hospitalizations, when compared to non-use in patients with IPF. Using the prevalent new-user cohort design to match 1852 PPI users to an equal number of non-users, I found no beneficial effect of PPIs on all-cause mortality (HR = 1.07, 95% CI 0.94-1.22), respiratory-related mortality (HR = 1.10, 95%, CI 0.94-1.28) or respiratory hospitalizations (HR = 1.00, 95% CI 0.86-1.16) compared with no PPI use in patients with IPF. Because PPIs are commonly used medications, approximately 65% of patients with IPF were using PPIs at some point after their IPF diagnosis, leading to potential informative censoring. This was accounted for by weighted analysis.

In the third manuscript, I therefore explored two alternative approaches to address informative censoring and compared these to the conventional prevalent new-user cohort design in comparing the effectiveness of PPIs on mortality in patients with IPF. The first approach used a variation of this design by only matching to uncensored non-users (never-users). The second approach used a marginal structural model approach. The HR for all-cause mortality of 1.07 (95% CI 0.94-1.22) with PPI use using the conventional prevalent new-user design, was 0.82 (95% CI 0.73-0.91) using the variant based on never-users, and 1.08 (95% CI 0.85-1.38) using the marginal structural model. The results suggest that the prevalent new-user design and the marginal structural model produce

similar results, when accounting for informative censoring. However, the variant that compares users to never-users introduces selection bias and should be avoided.

In sum, my thesis shows that immortal time bias is present in many observational studies of the treatment of IPF, which led to spurious findings on the effectiveness of PPIs in IPF. Properly designed and analyzed studies show that PPIs are not as beneficial in treating IPF as previously stated. Additionally, my thesis contributes to the advancement of alternative study designs that could be used in comparative effectiveness observational studies when there is no active comparator and when informative censoring is present.

Résumé

La fibrose pulmonaire idiopathique (FPI) est une maladie évolutive rare associée à un pronostic sombre. La survie médiane est estimée à deux à cinq ans après le diagnostic. Durant la dernière décennie, grâce à la recherche sur des traitements potentiels, deux médicaments, soit le nintedanib et la pirfénidone, sont maintenant approuvés pour traiter la FPI d'intensité faible à modérée. Bien que ces médicaments ralentissent la progression de la maladie, ils sont coûteux – environ 40 000 $ par année au Canada – et doivent être utilisés avec prudence chez les patients atteints d'une néphropathie ou ayant un risque cardiovasculaire accru. La recherche d'autres options de traitement de la FPI efficaces et abordables est donc loin d'être terminée. Les directives cliniques de traitement de la FPI recommandent maintenant conditionnellement un traitement antiacide, principalement par des inhibiteurs de la pompe à protons (IPP), qu'il y ait ou non reflux gastro-œsophagien. D'un point de vue biologique, la recommandation est basée sur la forte prévalence de cette affection chez les personnes atteintes de FPI : on croit que le reflux gastro-œsophagien contribuerait à l'évolution de la FPI par des microaspirations de reflux acide. Cependant, les données probantes à l'appui de ces traitements cités dans les directives cliniques sont contradictoires : plusieurs études observationnelles rapportent un effet hautement bénéfique sur la survie, alors que d'autres ne constatent aucun effet. Par conséquent, la présence d'effets bénéfiques des IPP sur l'évolution de la FPI demeure incertaine. L'objectif global de mon projet de recherche de doctorat était d'évaluer l'effet des IPP sur la survie et d'autres issues majeures chez les patients atteints de FPI, tout en mettant en évidence des problèmes méthodologiques présents dans les études précédentes.

Dans le premier manuscrit, je présente une revue des méthodes d'études observationnelles qui se sont penchées sur l'association entre les traitements antiacides et la survie chez les patients atteints

de FPI, particulièrement en ce qui a trait au biais du sujet immortel. Nous avons retenu dix études observationnelles. Quatre des cinq études rapportant un effet bénéfique des traitements antiacides sur la mortalité présentaient un biais du sujet immortel (rapport de risque [RR] combiné = 0,46; intervalle de confiance [IC] à 95 % : 0,30-0,69), alors que la cinquième n'était pas assez détaillée pour permettre une évaluation des méthodes. Quant aux cinq études qui ne présentaient aucun biais du sujet immortel, elles n'ont observé aucun effet (RR combiné = 0,99; IC à 95 % : 0,81-1,22), mais présentaient d'autres limites, notamment une courte durée de suivi, une petite taille d'échantillon ou une faible généralisabilité. Par conséquent, l'existence d'une relation entre les traitements antiacides, dont les IPP, et la survie demeure incertaine en raison des limites méthodologiques et de la faible taille des études observationnelles existantes.

Dans le deuxième manuscrit, j'ai utilisé des données tirées de la base de données britannique Clinical Practice Research Datalink liées aux bases Hospital Episode Statistics et Office for National Statistics pour déterminer si la prise d'IPP avait effectivement un effet bénéfique sur la mortalité et le taux d'hospitalisation pour des problèmes respiratoires des patients atteints de FPI, comparativement à des patients ne prenant pas d'IPP. Un plan d'étude de cohortes de nouveaux utilisateurs prévalents a été utilisé pour jumeler 1 852 patients prenant des IPP à un nombre égal de patients n'en prenant pas; aucun effet bénéfique des IPP n'a été observé chez les patients atteints de FPI sur la mortalité, toutes causes confondues (RR = 1,07; IC à 95 % : 0,94-1,22), la mortalité liée à des problèmes respiratoires (RR = 1,10; IC à 95 % : 0,94-1,28) ou les hospitalisations pour des problèmes respiratoires (RR = 1,00; IC à 95 % : 0,86-1,16). Comme les IPP sont des médicaments couramment prescrits, environ 65 % des patients atteints de FPI ont pris des IPP à un moment ou à un autre après leur diagnostic, ce qui pourrait avoir entraîné une censure informative. Nous en avons tenu compte par une analyse pondérée.

Dans le troisième manuscrit, j'ai donc mis à l'essai deux autres approches visant à tenir compte de la censure informative, et comparé leurs résultats à ceux du plan conventionnel d'étude de cohortes de nouveaux utilisateurs prévalents pour la mesure de l'effet des IPP sur la mortalité chez les patients atteints de FPI. La première approche consistait en une variation du plan conventionnel qui n'utilisait que des non-utilisateurs non censurés pour le jumelage (sujets jamais exposés). La seconde approche utilisait un modèle structurel marginal. Alors que le RR associé à la mortalité, toutes causes confondues était de 1,07 (IC à 95 % : 0,94-1,22) chez les sujets prenant des IPP selon le plan conventionnel de nouveaux utilisateurs prévalents, il était de 0,82 (IC à 95 % : 0,73-0,91) avec la variante basée sur les sujets jamais exposés et de 1,08 (IC à 95 % : 0,85-1,38) avec le modèle structurel marginal. Ces résultats semblent indiquer que le plan conventionnel et le modèle structurel marginal produisent des résultats similaires lorsqu'on tient compte de la censure informative. Toutefois, la variante comparant des utilisateurs à des sujets jamais exposés introduit un biais de sélection, et devrait donc être évitée.

En conclusion, mon projet de recherche a montré que le biais du sujet immortel est présent dans beaucoup d'études observationnelles sur le traitement de la FPI, ce qui mène à de fausses conclusions sur l'efficacité des IPP comme traitement. Dans les études correctement conçues et analysées, les IPP n'ont pas un effet sur la FPI aussi bénéfique qu'initialement rapporté. Par ailleurs, ma thèse préconise le recours à d'autres plans d'étude applicables aux études observationnelles sur l'efficacité comparée qui pourraient être utilisés dans ce type d'études en absence de comparateur actif et en présence de censure informative.

List of abbreviations

ATS	American Thoracic Society
BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
ERS	European Respiratory Society
GERD	gastroesophageal reflux disease
GP	general practitioner
HES	Hospital Episode Statistics
HR	hazard ratio
HRCT	high-resolution computed tomography
ICD	International Classification of Diseases
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IR	incidence rate
IPCW	inverse probability of censoring weight
IPTW	inverse probability of treatment weight
MSCM	marginal structural Cox model
ONS	Office for National Statistics
OPCS	Office of Population Censuses and Surveys classification of interventions and procedures
PPI	proton pump inhibitor

RCT	randomized controlled trials
SD	standard deviation
ROBINS-I	Risk of Bias in Non-Randomized Studies – of Interventions
TCPS	time-conditional propensity score
UK	United Kingdom
UTS	up-to-standard

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Contribution of authors

Manuscript 1:

I developed the research question for this methodological review with the assistance of Dr. Suissa. I was solely responsible for the systematic search, the extraction of the data, the in-depth review and quality assessment of the included studies and the draft version of the manuscript. Dr. Suissa was involved in the review and quality assessment, provided valuable feedback, and reviewed the manuscript for important intellectual content.

Manuscript 2:

The research question of this study was developed by Drs. Assayag, Suissa and me. I developed the study design and analysis plan with the support of my supervisor Dr. Suissa. I drafted the study protocol and was responsible for all aspects of the study, including the preparation of the data for analysis, completing all of the data analyses, interpretation of the results, and drafting the manuscript. Drs. Assayag and Ernst also contributed to the discussions of the study design. All co-authors were involved in the interpretation of the findings, and critically reviewed the manuscript for important intellectual content.

Manuscript 3:

The idea and the objective of this study was developed by Dr. Suissa and me. I drafted the study protocol, carried out the analyses, interpreted the results, and drafted the manuscript. Dr. Suissa was involved in finalizing the methods, interpretation of the findings, and reviewed several drafts of the manuscript.

Statement of originality

This dissertation makes an original contribution to research on the effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis and to methods in comparative effectiveness research in pharmacoepidemiology. Despite a conditional recommendation for anti-acid therapy in international IPF treatment guidelines, uncertainties remained whether the recommendation was warranted. Additionally, previously published studies on the effectiveness of anti-acids in idiopathic pulmonary fibrosis produced inconsistent findings with regard to survival. In this dissertation, I elucidated these inconsistencies and addressed limitation of these studies in a methodological review in manuscript 1. I further estimated the effect of proton pump inhibitors on mortality and hospitalization in patients with IPF in manuscript 2 using a novel study design approach in comparative effectiveness research and data from a large longitudinal population-based database to address shortcomings in previously published studies. Finally, in manuscript 3, I provide and discuss alternative approaches in comparative effectiveness research in the absence of an active comparator and a significant amount of informative censoring, which can be applied in future pharmacoepidemiology research.

I attest that while I received guidance from my supervisor and thesis committee members on the substantive and methodological aspects of my thesis, the work presented in this dissertation is my own.

1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial lung disease which is usually diagnosed in people above 60 years of age and is associated with poor prognosis, with a median survival of 2-5 years after diagnosis (1-4). IPF has gained more attention in the last decade due to the development of two medications to treat IPF – pirfenidone and nintedanib (5, 6). These two anti-fibrotic medications slow the decline in lung function but can also lead to gastrointestinal and cutaneous side effects (7, 8). Despite the advances in treatment, the search for other treatment options continues. This is mainly due to the indication of the anti-fibrotic drugs which are recommended as treatment for mild to moderate IPF and need to be used with caution in patients with renal or hepatic impairment, and patients with increased cardiovascular risk (9, 10). Additionally, the costs for pirfenidone and nintedanib are quite high, with estimated costs around $ 40,000/year in Canada (11).

The 2015 updated international treatment guidelines for IPF conditionally recommend proton pump inhibitors (PPIs) as a treatment for IPF but acknowledge that the recommendation is based on weak evidence (6). Thus, without strong evidence from randomized controlled trials (RCTs) or high-quality observational studies, PPIs were given the same level of recommendation as the two IPF-specific drugs (nintedanib and pirfenidone). PPIs are normally indicated for acid gastroesophageal reflux disease (GERD) which is hypothesized to contribute to the disease progression in IPF. According to the guidelines, possible improved lung function and survival and low cost make PPIs an attractive treatment choice for IPF (6). However, this treatment recommendation, regardless of the presence of GERD, was based on very few case and observational studies (12-14). Subsequent observational studies reported conflicting results on lung function, hospitalization, and survival (15-25). Limitations of these studies include small

sample size, short study follow-up, and immortal time bias. There are no RCTs that have assessed the effectiveness of PPIs in patients with IPF with regard to mortality and hospitalization. Indeed, all-cause mortality as a primary endpoint for IPF in RCTs has been discussed and found to be both impractical and cost-prohibitive (26, 27). The paucity of high-quality evidence and the lack of population-based studies with sufficient sample size and long study follow-up underline the need for further investigation of PPIs as a treatment option for IPF.

1.1 Research objectives

The primary goal of this doctoral dissertation was to evaluate the effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis on major health outcomes, including all-cause mortality, while addressing methodological issues in previous studies. The specific objectives were to:

1. Conduct a methodological review of observational studies examining the association of anti-acid therapy and mortality, with a focus on immortal time bias.
2. Assess whether the use of proton pump inhibitors, compared to no use, is associated with all-cause mortality, respiratory-related mortality, or respiratory-related hospitalizations.
3. Explore alternative study designs and data analytical techniques when no active comparator is available and informative censoring is present, illustrated in a comparative effectiveness study of proton pump inhibitors on mortality in patients with IPF.

1.2 Structure

This is a manuscript-based thesis containing 7 chapters. In chapter 1, I present the rationale and objectives of this thesis. Chapter 2 provides background information on IPF and on the previous research of PPIs as a treatment option in IPF. In chapter 3, I describe the data sources and methods

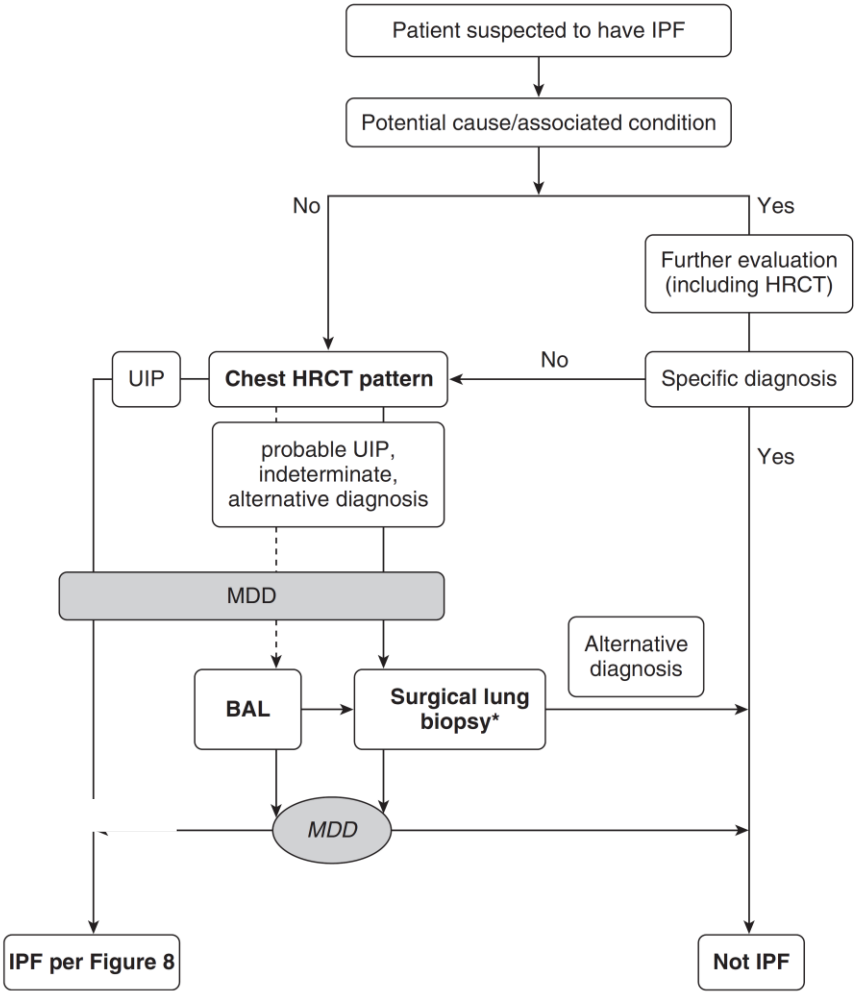
used in this thesis. In chapter 4, I present a methodological review on the effectiveness of anti-acid therapy on mortality in IPF. In chapter 5, I analyze the association between PPIs and survival outcomes in patients with IPF in a population-based cohort. In chapter 6, I explore alternative methods which address different approaches to account for informative censoring in comparative effectiveness research. Chapter 7 summarizes the main findings and contributions of this thesis and discusses opportunities for future research.

2 Literature review

2.1 Epidemiology of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is a specific form of interstitial pneumonia and the most common (17-37%) interstitial lung disease (ILD) (3, 5, 28-30). ILDs consist of a heterogeneous group of lung disorders that are classified together because of similar clinical, radiographic, histopathologic, and physiologic presentations. The pathobiology of ILDs can be of an inflammatory or fibrotic nature, leading to differential disease progression and response to treatments. Classification schemes of ILDs, including diagnostic criteria, have changed over time. IPF was first defined as a distinct clinical entity by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in an international consensus statement in 2002, which resulted in standardized diagnostic criteria and terminology for IPF (31, 32). In 2011, a joint official statement released by the ATS, the ERS, the Japanese Respiratory Society, and the Latin American Thoracic Association uniformly defined IPF as "a specific form of chronic progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs" (5). Since then, an update of the statement in 2013 underlines the distinction of IPF from other ILDs (29) and the most recent update in 2018 led to new recommendations regarding the diagnosis of IPF (33). Generally, IPF diagnosis requires the careful exclusion of other known causes of ILDs, such as connective tissue disease or domestic or occupational environmental factors, and the presence of a usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT) scanning of the chest or a combination of certain HRCT patterns and histopathological changes. While multidisciplinary discussion between a pulmonologist, radiologist, and pathologist was initially always required for diagnostic decision-making, it is now only suggested to improve diagnostic accuracy (Figure 2.1) (33).

Figure 2.1 Diagnostic algorithm for idiopathic pulmonary fibrosis presented in the International Clinical Practice Guidelines 2018 (33).



Abbreviations: BAL, bronchoalveolar lavage; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; UIP, usual interstitial pneumonia.

Each year, approximately 6,000 individuals in Canada (incidence rate 9.0-18.7 per 100,000 person-years) (34) and 5,000 in the United Kingdom (UK) (incidence rate 4.6-7.4 per 100,000 person-years) (3, 35) are diagnosed with IPF. The prevalence is 20.0-41.8 (34) and 15.0-25.0 (36) per 100,000 persons, respectively. The worldwide prevalence of IPF is estimated to be 2 to 29 cases per 100,000 persons in the general population (5), and the incidence seems to be increasing,

particularly among older adults age 75 years or older (3, 5). However, the increase could very likely be a result of an ageing population and changes in diagnostic criteria. Currently, there are about 15,000 patients affected by IPF in the UK, with approximately 5,000 dying every year (3). The quality of life in patients with IPF is often poor due to knowledge of poor prognosis, debilitating respiratory symptoms, and limitation of physical activity but also the lack of treatment options (1, 37). Additionally, patients suffer from various comorbidities that may affect the course of the disease. Common comorbidities in IPF include pulmonary hypertension, gastroesophageal reflux disease, obstructive sleep apnea, obesity, diabetes, emphysema, chronic obstructive pulmonary disease (COPD), coronary artery disease, arrhythmia, lung cancer, and depression (5, 38). The natural course of IPF varies among patients, with an estimated median survival of 2-5 years (1, 30). Increasing respiratory symptoms, worsening pulmonary function, progressive fibrosis on HRCT, and acute respiratory decline are signs of disease progression. Most patients die of respiratory failure or cardiovascular disease (2, 39).

2.2 Treatment options for idiopathic pulmonary fibrosis

Treatment recommendations for IPF have changed over time due to the development of new drugs, better understanding of the underlying pathological mechanisms, and new scientific findings. Despite weak evidence, previous guidelines recommended anti-inflammatory drugs, such as corticosteroids, in combination with immunosuppressants for treatment of IPF. However, there were no clear benefits from such therapies and prognosis for these patients remained poor (40, 41). Moreover, some previously widely used treatments for IPF were even found to be harmful, such as triple therapy with prednisone, azathioprine, and *N*-acetylcysteine, causing an increased risk of death compared to placebo (42, 43). It is now hypothesized that injuries to alveolar epithelial cells trigger aberrant fibroblast and epithelial cell response - with little or no inflammatory component

- which are suspected to lead to fibrotic lesions and progressive fibrosis in IPF (44). Still, there are no strong recommendations in favor of a specific drug class.

As the cause of IPF is unclear, it is difficult to develop targeted interventions. Treatment choices depend on the severity of disease and need to be reassessed as the disease progresses. Since 2015, evidence-based guidelines for diagnosis and treatment of IPF recommend the use of the anti-fibrotic drugs pirfenidone and nintedanib as treatment for mild to moderate IPF (6). In double-blind RCTs, pirfenidone and nintedanib reduced the annual rate of decline in lung function measured by forced vital capacity (45, 46).While these two drugs slow disease progression, they do not reverse or abate the scarring of lung tissue and may not even reduce symptoms of IPF, such as dyspnea or persistent dry cough, nor do they improve quality of life (8). The only therapy reported to improve disease prognosis is lung transplantation (47), which can only be considered in highly selected patients (5, 41, 48). Other pharmacological treatment recommendations for IPF include anti-acids which are recommended as treatment for IPF regardless of the GERD status of patients - even though the biological mechanism for benefit of these drugs in IPF is not clearly understood.

Additional treatment approaches can be used to improve the symptoms of IPF, including supplemental oxygen and pulmonary rehabilitation. Corticosteroids should only be used in patients with IPF who have acute exacerbations of their lung fibrosis and unstable IPF (5). The long-term goal is to understand the etiology and pathophysiology of IPF, in order to ultimately identify treatment targets.

2.3 Anti-acid treatment for idiopathic pulmonary fibrosis

The relationship between gastroesophageal reflux and pulmonary fibrosis was reported 40 years ago, yet the pathological mechanism remains unclear (49). Abnormal acid gastroesophageal reflux is more common (60 ± 22%) in patients with IPF (50-52) compared to the general population (10-30%) (53, 54). However, many patients are asymptomatic (55). Abnormal acid reflux is hypothesized to be a contributing factor to the development of IPF (50) as gastric juices secreted by the digestive system can reach the respiratory system through repeated reflux and micro-aspiration, and potentially lead to airway disorders (49, 56). Furthermore, animal studies have shown that introduction of acid into the airways of animal models induced pulmonary fibrosis (57, 58). This led to the hypothesis that treatments for GERD might reduce the stimulus for fibrosis in the lung through prevention of acid gastric reflux, and subsequently lead to a modification of IPF disease progression (59). In a case series in 2006, four newly diagnosed IPF patients were treated solely with PPIs over a period of 2-6 years. Pulmonary function tests were regularly performed during follow-up. Patients all had less severe IPF and remained stable when adhering to PPIs which led to the conclusion that further investigations of treatment for acid GER in IPF patients are needed (12).

Despite the lack of evidence, anti-acids such as PPIs or histamine-2 blocker receptor antagonists (H2 blocker) have been conditionally recommended since 2011 by the official IPF treatment guidelines due to their low cost and the possibility of improved lung function and survival (5, 6). Though it was acknowledged that the recommendations were based on weak evidence which mostly focused on PPIs. Subsequent pre-clinical, interventional, and observational studies have been performed to assess the effect of any anti-acid treatment or PPIs only on lung function, IPF symptoms, and mortality (14, 16-21, 25, 60).

2.3.1 Observational studies of anti-acid treatment in IPF

Manuscript 1 is a methodological review, providing a detailed summary and review of observational studies evaluating the effectiveness of anti-acid treatment in IPF. Briefly, since 2011 eleven observational studies have been published evaluating the effect of anti-acid treatment or PPIs alone on all-cause or IPF-related mortality in patients with IPF (14, 16-25). Other outcomes included in these studies were hospital admissions, acute exacerbations, infections, or change in pulmonary function tests.

There were two different approaches to obtain data for these observational studies: first, cohort studies using databases from hospitals, tertiary care centres, IPF registries or population-based health care databases, and second, post-hoc analyses of data from RCTs evaluating other IPF treatments that collected data on anti-acid treatment at the time of randomization. While the first approach (seven studies) produced results ranging from large reductions in mortality associated with use of anti-acid therapy to no association (hazard ratios (HR) ranging from 0.23 to 1.12), the second (four studies) consistently reported no association between anti-acid treatment and mortality (HRs ranging from 0.61 to 1.33). However, the maximum follow-up within the post-hoc analyses was 1 year which is likely to be insufficient to assess the outcome of all-cause mortality. Moreover, the sample sizes in these observational studies ranged from 69 –786 patients with IPF, which furthermore raises the question as to whether the studies were sufficiently powered to detect differences in all-cause mortality. The inconsistent results - particularly with regards to mortality – call for further investigation between the use of anti-acid therapy and survival in IPF. The existing discrepancies between effect estimates from previous observational studies may result from methodological limitations in the design of the study, including small sample size, short follow-up, and immortal time bias. This bias is often present in observational cohort studies which

classify patients into exposure groups based on medication use during follow-up using a time-fixed exposure definition and report highly beneficial drug effects on survival compared to non-users. Such findings are likely a result of immortal time during follow-up in which subjects cannot experience the outcome (61, 62).

One systematic review summarized the findings of treatment of gastroesophageal reflux in patients with IPF (63) and found that treatment of gastroesophageal reflux was associated with a reduction in IPF-related mortality but not all-cause mortality when compared to no use. Quality assessment of the included studies showed that the quality of evidence was low. However, quality assessment tools for systematic reviews, such as the ROBINS-I (Risk of Bias in Non-Randomized Studies – of Interventions) do not adequately assess biases in pharmacoepidemiology such as immortal time bias (64). Other guidelines for the reporting of observational studies include the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) and the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) statements, which also do not capture biases in pharmacoepidemiology (65, 66). A recent extension of the RECORD statement now specifies reporting guidelines specific to pharmacoepidemiologic research (RECORD-PE) (67). However, RECORD-PE was not available when the reviews on anti-acid treatment in IPF were conducted. Thus, the full extent of the bias in current observational studies of anti-acid treatment and mortality outcomes may not have been fully evaluated.

2.4 Proton pump inhibitors in idiopathic pulmonary fibrosis

My research focuses on PPIs as these represent the most commonly used therapy in acid-related disorders. Furthermore, researchers have suggested that PPIs may have molecular regulatory

properties that go beyond gastric acid suppression, including possible anti-inflammatory, anti-oxidant, and anti-fibrotic effects (17, 68, 69).

Even though anti-acid treatment, including PPIs, were given a conditional recommendation in the IPF treatment guidelines of 2011 and 2015, the evidence supporting this recommendation was based on studies either providing weak evidence or featuring methodological limitations. Hence, it remains unclear whether these recommendations are warranted. With research on pre-clinical data supporting a potential pleiotropic effect of PPIs and the uncertainty regarding the validity of existing observational studies, there is need for more robust evidence, particularly for well-designed RCTs, to assess the effectiveness of PPIs in IPF (69, 70) .

2.4.1 Randomized controlled trials

The suppression of gastric acids may also reduce cough in patients with IPF (71). Therefore, a pilot trial (NCT02085018) in the UK evaluated the feasibility of assessing the effect of the PPI omeprazole in a double-blind RCT. This study randomized patients with IPF to omeprazole or placebo and objectively measured the frequency of cough after 90 days of treatment. Forty-five patients with IPF were recruited within two years, with 23 randomised to omeprazole and 22 to placebo. The results showed that the mean cough frequency was 39.1% lower (95% confidence interval (CI) -66.0%, 9.3%) in the omeprazole group compared with placebo. Omeprazole was well-tolerated in this small sample.

While this trial showed that a large RCT of PPIs for cough would be feasible, all-cause mortality as a primary endpoint for IPF in RCTs has been discussed and found to be both impractical and cost-prohibitive (26, 27). The reasons for this conclusion lie in the low mortality rate from any cause in patients with mild or moderate IPF, which would require a large study sample size and

long duration of follow-up. Furthermore, due to the low incidence and prevalence of IPF, a longer enrollment period would also be necessary. However, trials with long duration will lead to increased cost and increased likelihood of loss to follow-up, limiting the feasibility of long-term RCTs in IPF. Therefore, observational studies are pragmatic alternatives to assess the effectiveness of PPIs in IPF on survival.

2.5 Comparative effectiveness research in the presence of informative censoring

In the absence of an active comparator, no use of treatment is commonly used as the comparison group. In time-to-event analyses to minimize exposure misclassification and to avoid immortal time bias, exposure can be assessed in a time-fixed manner after identifying an appropriate time for cohort entry for the comparison groups or can be defined in a time-dependent manner (61, 62). For example, in a cohort study, patients are considered unexposed until the initiation of the exposure of interest and exposed from then on until the end of follow-up. However, if exposure is highly prevalent, such as commonly used PPIs, this exposure definition leads to censoring in a very large number of patients who start as non-users and then initiate PPIs. If mortality is the study outcome, deaths will occur more frequently in exposed patients by design, as patients need to be alive to receive a PPI prescription. Thus, censoring cannot be assumed to be independent from mortality, leading to informative censoring. The issue of informative censoring has not been addressed before in observational studies evaluating the effectiveness of PPIs on mortality in IPF. As there are different approaches to account for informative censoring, such as inverse probability of treatment weighting (72) or only using uncensored patients (73), research to explore the feasibility of these alternative approaches is needed.

2.6 Conclusion

The prevalence of GERD is higher in patients with IPF compared to the general population. GERD may also contribute to the progression of IPF through microaspiration. As treatment options for IPF are limited, medications to treat GERD have been explored as a treatment for IPF. Current treatment guidelines for IPF give a conditional recommendation for anti-acid therapy based on potential survival benefits. However, the evidence is weak and subsequent studies evaluating the effectiveness of anti-acid therapy in IPF have found inconsistent results, likely due to methodological shortcomings which require an in-depth review. PPIs in particular have gained more interest as they may have molecular properties that go beyond acid suppression, highlighting the need for a well-designed study. As RCTs with the primary outcome of all-cause mortality in IPF are not feasible, a well-designed observational study is needed to assess the effectiveness of PPIs in IPF. However, as PPIs are commonly used drugs, informative censoring has to be considered in time-to-event analyses comparing PPIs to no use. Alternative study designs and analytical techniques that address the issue of informative censoring need to be evaluated in the context of the effectiveness of PPIs in IPF.

3 Overview of data and methods

3.1 Data sources

Manuscripts 2 and 3 in this thesis used data from the UK Clinical Practice Research Datalink (CPRD) GOLD linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases.

3.1.1 Clinical Practice Research Datalink

The CPRD GOLD was established in 1987 and is a primary care database that contains anonymized longitudinal data of routinely collected electronic medical records of more than 11 million people enrolled in around 680 consented general practices. The average duration of follow-up in the CPRD is 9 years (74, 75). The database covers approximately 7% of the population in the UK and is representative of the UK population in terms of age, sex, and ethnicity. Primary care general practitioners (GPs) function as gatekeepers of care in the UK National Health service and act as the first point of contact for any non-emergency health-related issues. Patients can then be referred to secondary care and information from secondary care, including diagnoses, are reported back to the GP (75). Due to its comprehensive and longitudinal data from routine clinical practice, the CPRD is used by researchers worldwide for epidemiologic studies, including pharmacoepidemiology studies (76).

GPs are specifically trained on the systematic recording of data. Data from practices are only used for research after routine quality checks and when deemed "up-to-standard" (UTS) by the CPRD, i.e. the practice provides continuous high quality data (74, 75). The UTS date is a practice-based quality metric that aids in selecting research-quality patients who are then considered 'acceptable' for research purposes, i.e. with continuous follow-up and sufficient data recording (75).

Medical diagnoses, laboratory procedures, symptoms, and medical history are recorded using the Read code classification, and drugs prescribed by GPs are coded based on the UK Prescription Pricing Authority dictionary. The CPRD also contains information on anthropometric variables (such as body mass index (BMI), and lifestyle variables (such as smoking and alcohol use), and its data have been previously validated and shown to be of high quality (74, 75, 77).

Numerous studies have illustrated the high quality of the data, which have been used to study the epidemiology of respiratory and chronic diseases (78, 79). The diagnostic codes for cryptogenic fibrosing alveolitis, the term formerly used for IPF in the UK, have been found to be accurate (proportion of true positives: 95%) in this database when compared to hospital letters (80). The CPRD and another UK primary care database (The Health Improvement Network) which is similar in structure and content to the CPRD have been used in previous IPF studies (3, 35, 81-85).

3.1.2 Hospital Episode Statistics and Office for National Statistics Databases

The HES contains information on dates of hospital admissions and discharge diagnoses, including primary and secondary diagnoses (coded using the International Statistical Classification of Diseases and Health-Related Problems, 10th Revision (ICD-10)) and hospital-related procedures (coded using the Office of Population Censuses and Surveys classification of interventions and procedures, 4th version). The linkage of the HES to the CPRD is possible from April 1, 1997, onward, and is limited to English general practices that have consented to the linkage scheme (currently representing 76% of all English practices) (75, 77). Finally, the ONS provides death registration data from January 2, 1998 on, and contains the electronic death certificates of all citizens living in England and Wales and provides information on the official date and the cause

of death (coded using ICD-10 classifications) (86). Approximately 60% of the population in the CPRD database can be linked to the HES and ONS mortality data (75, 87).

3.1.3 Strengths and limitations

The strengths and limitations of the CPRD for research purposes have been discussed previously (75, 76). The CPRD is a representative population-based database with a large number of patients and long follow-up. This enables the study of both rare and chronic disease but also research questions to assess long-term outcomes. The database routinely undergoes quality checks and provides unique data, such as information on smoking status or laboratory procedures. Furthermore, the linkage to HES for hospitalization data and ONS for death registration data further enrich the available data in the CPRD.

Despite these strengths, the CPRD does have a few limitations. First, even though prescription data in the CPRD are well documented, there is no data available on PPI prescriptions written in hospital, by specialists, or on over-the-counter use (only short-term and low doses (88, 89)) leading to potential exposure misclassification. However, secondary care-initiated treatment is usually continued by GPs (90, 91). Additionally, prescription medications are free without any co-payment at dispensation for patients older than 60 years in England (92). There is also no information on whether the prescribed PPIs were dispensed and whether the patient adhered to prescribed medications. In the case of a chronic disease where any management may bring relief to the patient, this may not be a major limitation as these patients likely fill their prescriptions and take their prescribed medications. Second, medical reports from specialists (e.g. respirologists) must be entered manually into the database. Thus, information on diagnoses, tests or other medical procedures performed outside of primary care may be missing, Third, data on routinely collected

information, such as BMI, blood pressure, smoking or alcohol intake may be missing. However, an initiative to incentivize such data entries among GPs was introduced in 2004 and the amount of recordings for such key variables has increased since then (75). Moreover, missing data on an important risk factor in patients with a lung disorder such as smoking is likely to be small.

3.2 Cohort formation

3.2.1 Base cohort

A population-based retrospective cohort of newly diagnosed IPF patients served as the base cohort for manuscripts 2 and 3. The accrual period for IPF diagnoses started on January 1, 2003, the year after the international consensus statement of the definition of IPF (32), and ended on December 31, 2016. Patients were identified according to diagnostic codes for IPF in the CPRD. Read Codes included the term "idiopathic pulmonary fibrosis", but also the terms "diffuse pulmonary fibrosis", "cryptogenic fibrosing alveolitis" and "idiopathic fibrosing alveolitis" (Table 3.1), which reflect the clinical terms for IPF commonly used in the UK over the last 20 years. Patients were not considered to have IPF if they had any record of specific recognized causes of interstitial lung diseases, including connective tissue diseases, allergic alveolitis, sarcoidosis, and asbestosis prior to their IPF diagnosis. Patients were only included if they had at least one year of observation time in the CPRD prior to IPF diagnosis, were enrolled at a UTS practice, aged 40 years or older at the time of IPF diagnosis, and if they were linkable to the HES and ONS database. Patients were furthermore excluded if they had a lung transplantation prior to IPF diagnosis or if there were data entry inconsistencies, such an IPF diagnosis that was recorded on or after their date of death or transferred out date (the date when a patient left a CPRD practice). Entry into the base cohort was defined as the date of the first recorded diagnosis of IPF in the CPRD.

3.2.2 Exposure definition

The first PPI prescription after IPF diagnosis recorded in the CPRD database was used to define the treatment group in manuscripts 2 and 3. All available PPIs on the UK market were considered, including omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazole, rabeprazole, and ilaprazole. As PPIs are the most commonly used anti-acid treatments and the alternatives, such as H2-blockers, are used infrequently, no use of PPIs was defined as the comparison group in the absence of an active comparator, which also follows the comparisons used in all other observational studies to date.

3.2.3 Prevalent new-user cohort design

In manuscript 2 and 3, the base cohort served to create the study cohort using the prevalent new-user cohort design, which is a new study design, developed for comparative effectiveness research (93). This study design is an appropriate approach when new-users in the comparison group are not comparable to new-users in the exposure group or difficult to identify. This design can therefore be used when there is no active comparator.

For example, in a study comparing PPI use to non-PPI use in IPF, the study cohort entry for users of PPIs would be the date of the first PPI prescription after IPF diagnosis. However, cohort entry for non-users is more difficult to define. Cohort entry defined at IPF diagnosis could lead to selection bias due to differential follow-up. Particularly, if severely ill patients die soon after their IPF diagnosis and thus do not have the opportunity to receive a PPI prescription. Furthermore, patients who were prescribed a PPI after their IPF diagnosis and newly diagnosed IPF patients are likely at a different time point in their duration of disease and their risk regarding health outcomes may thus be differential, which introduces confounding. The prevalent new-user cohort design

allows to define cohort entry for unexposed patients at a time point that is comparable to the first PPI prescription in exposed patients, making the two comparison groups concurrently similar.

In this approach, exposed and unexposed patients from the base cohort are 1:1 matched based on time-based exposure sets and time-conditional propensity scores. On average, exposed and unexposed patients in this study cohort have equivalent duration of disease and are similar regarding other characteristics due to matching. The main difference between the two comparison groups is the decision made by the GP to prescribe a PPI in the exposed group but not in the unexposed group.

3.2.4 Time-conditional propensity scores

Time-conditional propensity scores (TCPS) were computed to identify the unexposed match for PPI users within time-based exposure sets. Exposure sets in the prevalent new-user cohort design were used to determine the time points at which covariates – time-varying and time-fixed patient characteristics prior to the first PPI prescription or corresponding physician visit - were measured to compute the TCPS of initiating a PPI (93). TCPS were estimated using conditional logistic regression to conserve the matching induced by the exposure set. Covariates included in the TCPS are listed in Table 3.2. The verification of the positivity assumption was performed within each exposure set, i.e. the TCPS of the PPI user was within the range of the TCPS of the members in the corresponding exposure set.

3.2.5 Study cohort formation

The prevalent new-user cohort design was used to create the study cohorts in manuscripts 2 and 3. Figure 3.1 illustrates the formation of the study cohort in manuscript 2, which I describe here in

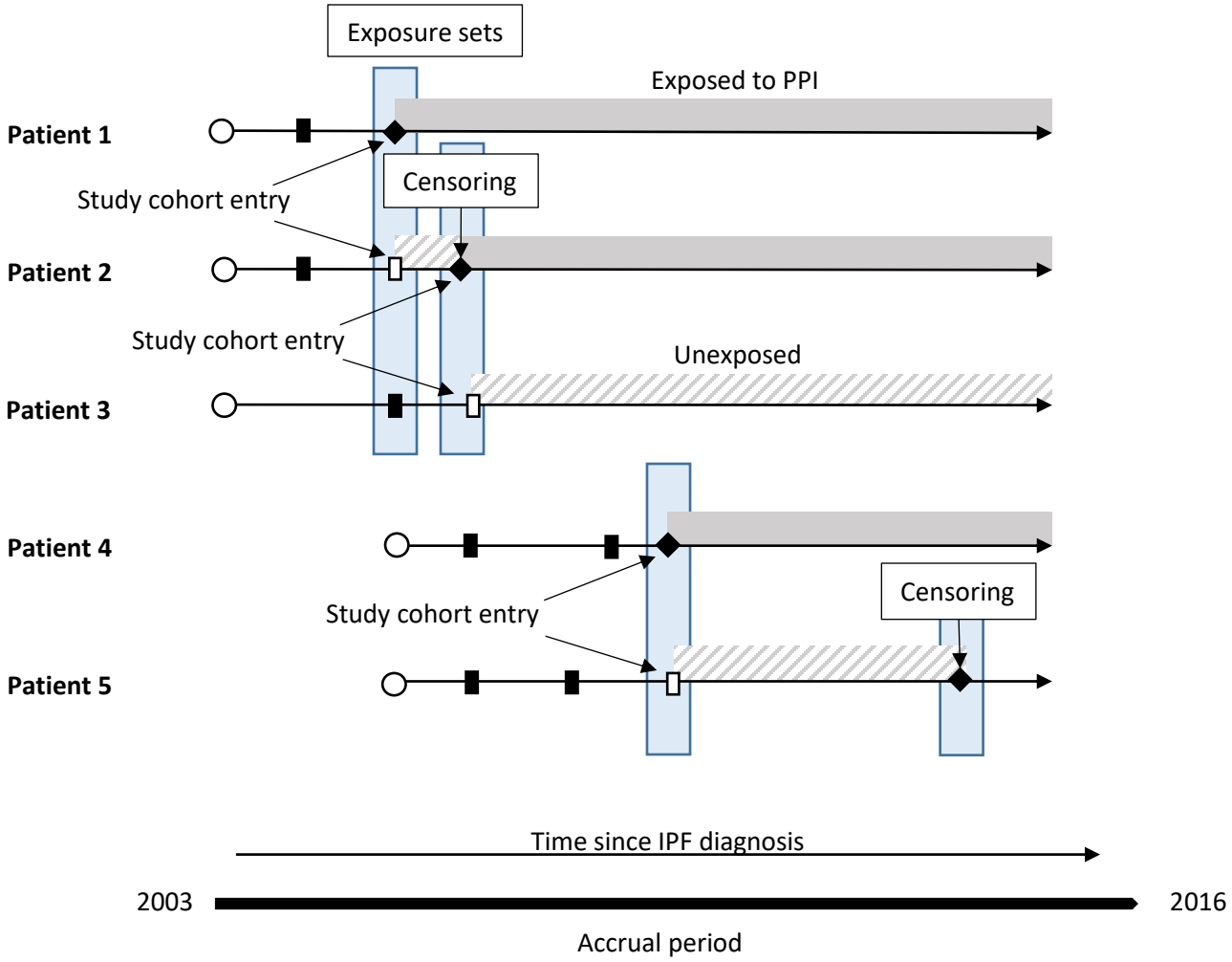
more detail: To build the study cohort, I identified all first PPI prescriptions after IPF diagnosis in the base cohort and ordered them chronologically according to IPF disease duration. Time-based exposure sets were then created, which were defined as time intervals (± 1 month) around the date of the first PPI prescription since IPF diagnosis. These exposure sets served as the relevant time interval to identify potential matches. Physician visits were chosen as the relevant reference time point as unexposed patients could have received a PPI prescription during that visit. Physician visits were any contacts with the GP recorded in the CPRD that could have led to a PPI prescription, which included consultations, other diagnoses, or immunizations. All unexposed patients with a record of a physician visit within the given time interval belonged to the corresponding exposure set. For example, a patient received his first PPI prescription three months after IPF diagnosis on March 1, 2010 (PPI user). All patients with a physician visit between two to four months after diagnosis and February 1, 2010 and April 1, 2010 and no prior PPI prescription since IPF diagnosis belonged to the exposure set of the PPI user.

After, identifying the PPI user and all potential reference patients, TCPS were computed, to identify the best match within an exposure set based on nearest-neighbour matching. The matched PPI user and non-user were then included in the study cohort. Once, a non-user had been matched, that patient was removed from the pool of potential reference patients for subsequent exposure sets. Using this approach, I matched PPI users 1:1 to a non-user within the same exposure set. If a PPI user did not have any unexposed physician visits recorded in his exposure set, the PPI user could not be matched and was not included in the study cohort. Matched non-users who initiated a PPI during follow-up were censored at the date of their first PPI prescription and could enter the cohort as a PPI user. Thus, one patient could have been included as a non-user and a PPI user in

the study. Study cohort entry was the date of the first PPI prescription for PPI users or the corresponding matched physician visit for non-users within the same exposure set**.**

Figure 3.1 depicts the formation of a study cohort using the prevalent new-user cohort design. Each line represents one patient in the base cohort of patients diagnosed with IPF between 2003 and 2016. Patient 1 enters the study cohort as a PPI user after being matched to Patient 2 based on the time-based exposure set around the time of his first PPI prescription and TCPS matching. Patient 2 is first included as a non-user, censored at the date of his first prescription, and then included as a PPI user in this cohort after being matched to Patient 3 who enters the cohort as a non-user. Patient 4 (PPI user) is matched to Patient 5 (non-user). Patient 5 was also censored at his first PPI prescription but could not be matched due to lack of any reference patients. Thus, three PPI users and three matched non-users are included in the study cohort.

Figure 3.1 Illustration of the prevalent new-user cohort design: PPI users are matched 1:1 to non-users based on exposure sets and time-conditional propensity score

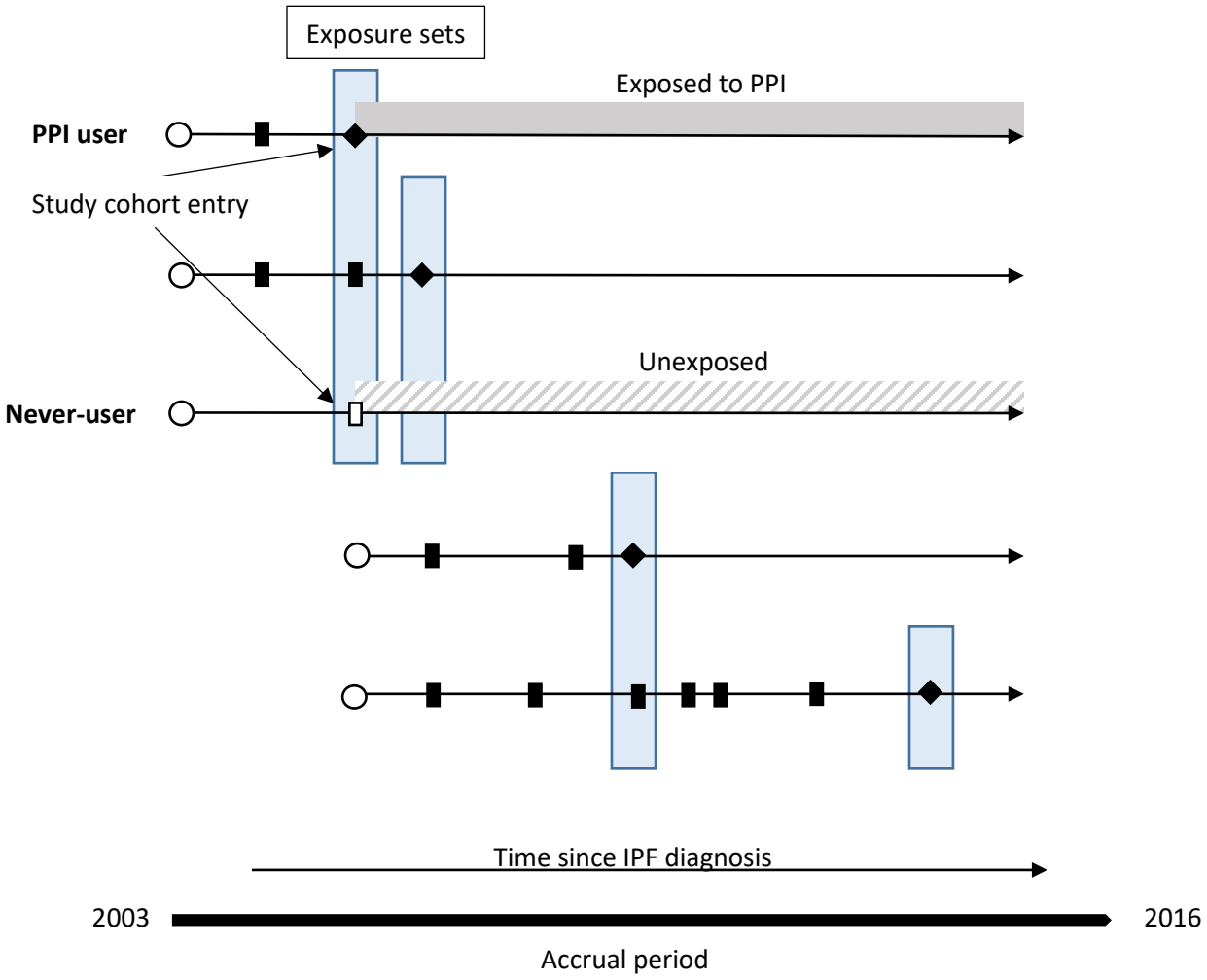


Abbreviations: IPF, idiopathic pulmonary fibrosis; PPI, proton pump inhibitor.

3.2.6 Variant of the prevalent new-user cohort design

Due to the exposure definition in manuscript 2, which censored non-users at the time of their first PPI prescription and the large number of patients who received a PPI prescription after their IPF diagnosis, it was necessary to account for potential informative censoring in the analyses. Manuscript 3 explored alternative approaches to address informative censoring. I applied a variant of the prevalent new-user cohort design by only allowing uncensored non-users, i.e. never-users, of PPIs, to be potential matches. This approach ignores censored observations and only uses uncensored observations in the analysis (73), i.e. patients who would never be censored due to a PPI prescription during follow-up. However, this approach may considerably reduce sample size, particularly if the censoring event, i.e. a PPI prescription, is common. In addition, it may also introduce selection bias by excluding all subject who eventually are exposed to PPIs. In Figure 3.2 the base cohort consists of five patients with IPF, only one patient was a never-user. Thus, this study cohort only included one PPI user and one TCPS-matched never-user, leaving three patients unmatched.

Figure 3.2 Illustration of the prevalent new-user cohort design variant: one PPI user is matched 1:1 to one never-user based on exposure sets and time-conditional propensity scores



○ = IPF diagnosis
◆ = first PPI prescription
▮ = physician visit without a PPI prescription
▯ = matched physician visit based on time-conditional propensity score

Abbreviations: IPF, idiopathic pulmonary fibrosis; PPI, proton pump inhibitor.

Table 3.1 READ codes used to identify IPF diagnoses in the CPRD

READ Code	Read Term
H563.00	Idiopathic fibrosing alveolitis
H563z00	Idiopathic fibrosing alveolitis NOS
H563.11	Hamman-Rich syndrome
H563.12	Cryptogenic fibrosing alveolitis
H563.13	Idiopathic pulmonary fibrosis
H563100	Diffuse pulmonary fibrosis
H563200	Pulmonary fibrosis
H563300	Usual interstitial pneumonitis
Hyu5000	[X] Other interstitial pulmonary diseases

Abbreviations: NOS, not otherwise specified; [X], terms that have been added to the Read Codes to ensure that every ICD-10 code is cross-mapped to a Read Code.

Table 3.2 Variables included in the time-conditional propensity score model based on patient characteristics measured prior to the first PPI prescription or corresponding physician visits within a given exposure set

Variable	Description	Look-back period*	Values#	Sources
Age at IPF diagnosis	Year of IPF diagnosis minus year of birth	At IPF diagnosis	Continuous; unit: years	CPRD
Sex	Male or female	Anytime	Binary: male/female(reference)	CPRD
Body mass index	BMI=weight/(height)^2	5 years	Categorical: <25 kg/m^2 (reference) 25-30 kg/m^2 ≥30 kg/m^2 unknown	CPRD
Smoking status	Smoking status at IPF diagnosis: past smoker (medical codes for past smoker, or smoking cessation >1 year prior to IPF diagnosis), current smoker (medical codes for smoker or smoking cessation in the year prior to IPF diagnosis), non-smoker (medical code for non-smoker)	Anytime	Categorical: ex-smoker, non-smoker (reference), current smoker, unknown	CPRD
Excessive alcohol use	Medical code for alcohol-related diseases, symptoms, or stages of alcoholism	Anytime	Binary: yes/no	CRPD
Ethnicity	Ethnicity	Anytime	Categorical: White (reference), Other, unknown	CPRD
Hospitalization	Presence of a hospitalization admission in the year prior to cohort entry	1 year	Binary: yes/no	HES
Asthma	Most recent medical code for asthma	Anytime	Binary: yes/no	CPRD, HES
COPD	Medical code for COPD	Anytime	Binary: yes/no	CPRD, HES
GERD	Medical code for GERD	Anytime	Binary: yes/no	CPRD, HES
Nissen fundoplication	Medical code for Nissen fundoplication	Anytime	Binary: yes/no	CPRD, HES
Arrhythmia	Medical code for arrhythmia	Anytime	Binary: yes/no	CPRD, HES
Heart failure	Medical code for heart failure	Anytime	Binary: yes/no	CPRD, HES
Hypertension	Medical code for hypertension	Anytime	Binary: yes/no	CPRD, HES
Myocardial infarction	Medical code for myocardial infarction	Anytime	Binary: yes/no	CPRD, HES
Stroke	Medical code for stroke	Anytime	Binary: yes/no	CPRD, HES
Diabetes Mellitus	Presence of prescriptions for diabetes mellitus medications	Anytime	Binary: yes/no	CPRD
Cancer	Most recent medical code for cancer	5 years	Binary: yes/no	CPRD, HES
Lung cancer	Most recent medical code for lung cancer	5 years	Binary: yes/no	CPRD, HES

Variable	Description	Look-back period*	Values#	Sources
Renal disease	Medical code for renal disease	Anytime	Binary: yes/no	CPRD, HES
Depression	Medical code for depression	Anytime	Binary: yes/no	CPRD, HES
PPI use prior to IPF diagnosis	PPI prescriptions in the year prior to IPF diagnosis	1 year	Binary: yes/no	CPRD
H2-Blockers	Presence of most recent H2-blocker prescription	1 year	Binary: yes/no	CPRD
Inhaled corticosteroids	Presence of most recent inhaled corticosteroid prescription	1 year	Binary: yes/no	CPRD
Oral corticosteroids	Presence of most recent oral corticosteroid prescription	1 year	Binary: yes/no	CPRD
Azathioprine	Presence of most recent azathioprine prescription	1 year	Binary: yes/no	CPRD
ACE inhibitors	Presence of most recent ACE inhibitor prescription	1 year	Binary: yes/no	CPRD
ARBs	Presence of most recent ARB prescription	1 year	Binary: yes/no	CPRD
Beta blockers	Presence of most recent beta blocker prescription	1 year	Binary: yes/no	CPRD
Diuretics	Presence of most recent diuretic prescription	1 year	Binary: yes/no	CPRD
Anticoagulants	Presence of most recent anticoagulant prescription	1 year	Binary: yes/no	CPRD
Antiplatelets	Presence of most recent antiplatelet prescription	1 year	Binary: yes/no	CPRD
Statins	Presence of most recent statin prescription	1 year	Binary: yes/no	CPRD
NSAID	Presence of most recent NSAID prescription	1 year	Binary: yes/no	CPRD

*Lookback period starts from the date of study cohort entry.

#Binary variables used 'no' as the referent.

Abbreviations: ACE inhibitor, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; BMI, body mass index; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; IPF, idiopathic pulmonary fibrosis; NSAID, non-steroidal anti-inflammatory drug, PPI, proton pump inhibitor.

4 The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis: a methodological review of observational studies

4.1 Preamble: Manuscript 1

While researching the literature on the effectiveness of PPIs in IPF, there was no synthesis of the studies available on this topic, despite the conditional recommendation for anti-acid therapy in IPF treatment guidelines. It also became quickly apparent that the results regarding the effectiveness of anti-acid therapy on mortality were quite uneven, with risk reductions ranging from 50% to no effect, which highlighted the necessity of an in-depth review. In particular, with regard to biases in pharmacoepidemiology, such as immortal time bias, which has shown to produce effect estimates of apparent large risk reductions, even when there is no effect (61, 62). The manuscript presented in this section fills this gap and summarizes the existing evidence on observational studies assessing the effectiveness of anti-acid treatment in IPF.

While the literature search and data extraction of this review was done systematically, available quality assessment tools used in systematic reviews, such as the ROBINS-I, do not adequately address pharmacoepidemiology biases. After an in-depth review of the Methods section of each article, I therefore grouped studies according to the presence of immortal time bias and described how this bias was introduced.

This manuscript is entitled “The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis: a methodological review of observational studies” was published in the *European Respiratory Journal* (94).

4.2 Title page

Title: The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis: a methodological review of observational studies

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4.3 Abstract

Background: International treatment guidelines for idiopathic pulmonary fibrosis (IPF) give a conditional recommendation for anti-acid therapy. As some observational studies reported discrepant findings on the effectiveness of anti-acid therapy on mortality in IPF, we reviewed all studies to evaluate whether immortal time bias explains these discrepancies.

Methods: We searched the EMBASE AND MEDLINE databases until July 2017 for observational studies assessing the effectiveness of anti-acid therapy on mortality in IPF. Hazard ratios of mortality with anti-acid therapy were pooled across studies using random-effect models, stratified by the presence of immortal time bias.

Results: We identified 10 observational studies. Four of the five studies reporting beneficial effects of anti-acid therapy use on mortality were affected by immortal time bias (pooled hazard ratio 0.46; 95% CI 0.30-0.69), while the fifth was unclear. The five studies that avoided immortal time bias reported no effect of anti-acid therapy on mortality (pooled hazard ratio 0.99; 95% CI 0.81-1.22).

Conclusion: The apparent beneficial effects of anti-acid therapy on mortality in patients with IPF result from observational studies affected by immortal time bias. The effectiveness of anti-acid therapy in IPF thus remains uncertain and needs to be reassessed with more accurate observational study methods and randomized trials.

4.4 Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare and irreversible fibrotic lung disorder of unknown cause. It is characterised by a progressive decline of lung function and is associated with poor prognosis (5, 31). Median survival after diagnosis is estimated to be 2-5 years (2, 3). Between 2011 and 2015, two anti-fibrotic medications were approved for the treatment of patients with mild to moderate IPF in the US, Canada, and Europe: pirfenidone and nintedanib (7, 95, 96). These two medications slow the decline in lung function but have not shown to reduce all-cause mortality in sufficiently powered studies (96). Pirfenidone and nintedanib are now conditionally recommended by international IPF treatment guidelines (6).

Another conditionally recommended treatment for IPF is anti-acid therapy, which is normally indicated for gastroesophageal reflux disease (GERD), a common comorbidity in patients with IPF (50, 97). However, the evidence supporting this recommendation, regardless of the presence of GERD, is generally weak with very low confidence in effect estimates (6, 12-14, 16). Thus, newer national guidelines (Germany, Switzerland and Sweden) recommend anti-acid therapy only as treatment for GERD in IPF (98-100). After the latest update of the treatment guidelines in 2015, observational studies investigating the effectiveness of anti-acid therapy, including proton pump inhibitors (PPIs), continued to report conflicting results on all-cause mortality (17-23). Results ranged from large reductions in mortality associated with use of anti-acid therapy to no association. The highly beneficial findings are of such remarkable magnitude that they are likely a result of biases, in particular time-related biases such as immortal time bias, that have been shown to affect observational studies of drug effects in various therapeutic areas (61, 62, 101, 102).

Immortal time is a period during follow-up in which, by design, the study outcome cannot occur (103). Immortal time is typically introduced when the individual's exposure/treatment status is

determined after the start of follow-up. Individuals who are classified as exposed have to be alive and event-free until the exposure definition is met. Misclassification or exclusion of the immortal time period leads to immortal time bias. This type of bias is often introduced in cohort studies of drug effects and artificially reduces the rate of events occurring in the treated group, which biases the estimate downward and often leads to the erroneous conclusion that exposure to the treatment is protective, even when there is no treatment effect (61, 62). It may also underestimate or mask increased risks.

To date, immortal time bias has not been described in the field of IPF. In this methodological appraisal, we review observational studies evaluating the association between anti-acid therapy and mortality in IPF, particularly to identify those affected by immortal time bias. For the sake of brevity, our review focuses solely on mortality as the outcome of interest and not on other outcomes of interest in IPF such as lung function decline and quality of life. We also discuss other methodological issues that led to the discrepant findings among the observational drug effectiveness studies (104).

4.5 Methods

We identified publications and abstracts in EMBASE and MEDLINE (from the earliest available online year until July 2017) using a search strategy based on a combination of concepts addressing the study population, the exposure, and the outcome of interest: IPF AND anti-acid therapy AND mortality. We used keywords and derivations thereof for “idiopathic pulmonary fibrosis”, “anti-acid therapy”, “GERD treatment” or “proton pump inhibitors”, “mortality” and “survival” (Supplement 1). Titles and abstracts were screened for eligibility, with full texts of eligible studies carefully reviewed. We also examined the references of included articles and those in previous

reviews. Studies had to provide information on mortality. We only included studies with a comparison group that reported hazard ratios (HR) or other estimates, which allowed us to approximate the HR and its corresponding 95% confidence interval (CI) if no HR was reported. The Methods section of each included study was reviewed in depth for various sources of bias including time-related biases, particularly immortal time bias, by assessing the available information on study design, exposure definition, and statistical analysis (103). Study-specific HRs were then pooled using random-effect models, stratified by studies with or without immortal time bias. Subgroup differences were tested using Q test. The amount of between-study heterogeneity was estimated by the I^2 statistic (105). Data analyses were performed using the 'meta' package from R version 3.4.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2017).

4.6 Results

Overall, we identified 10 relevant studies published from 2011 to 2017 (Supplement 2): seven cohort studies and three retrospective observational studies using pooled data from randomised controlled trials (RCTs) of other treatments for IPF (14-23). The pooled HR of all-cause mortality associated with anti-acid therapy use over all 10 studies was 0.63 (95% CI 0.45-0.90).

Five of the cohort studies associated use of anti-acid therapy with a reduced risk in mortality in IPF (Table 4.1) (14, 15, 17, 21, 23). Four of these cohort studies clearly introduced immortal time bias in their study design and analysis, as described in an example below. In contrast, the studies using methods to avoid immortal time bias, such as a time-dependent data analysis, did not find an association between anti-acid therapy use and mortality (Table 4.2) (16, 18-20, 22). Figure 4.1 displays the forest plot of the results for the four studies clearly demonstrating immortal time bias

(pooled HR 0.46, 95% CI 0.30-0.69; I^2 = 51%) in contrast with the five studies that avoided this bias (pooled HR 0.99, 95% CI 0.81-1.22; I^2 = 0%), with the difference between the two HRs being statistically significant (p <0.01).

Description and example of immortal time bias

An example of a study affected by immortal time bias in evaluating the effectiveness of PPIs in IPF was a retrospective cohort of 215 IPF patients who entered the cohort at the time of their initial clinic visit (17). Exclusion criteria included loss to follow-up before 12 months and PPI therapy duration of less than 12 months for reasons other than death or lung transplantation. Patients were categorised in PPI users (PPI use ≥ 12 months, n=130) and non-users (no PPI prescription, n=85) and followed until lung transplantation or death, which occurred in 77 PPI users and 63 non-users. Cox proportional hazards models were used to estimate the crude and adjusted HRs. Use of PPIs was associated with a significant protective effect (adjusted HR=0.58, 95% CI 0.39-0.87) and an increase in survival time (median survival of 3.4 vs. 2 years).

In this study, immortal time bias was introduced by the definition of exposure: IPF patients were classified as exposed if they used PPIs for at least 12 months during follow-up. The period from the start of follow-up until the 12-month exposure definition was fulfilled is immortal (Figure 4.2). Indeed, while the 85 non-users were at risk of death immediately after cohort entry, the 130 PPI users had to survive at least 12 months after cohort entry. This immortal period led to a survival advantage among PPI users, resulting in the inaccurate conclusion that PPI users lived 1.4 years longer than non-users. Another limitation of the study was the exclusion of patients who used PPIs for less than 12 months, who should be included and considered as unexposed. These patients should contribute to the person-time and events necessary to estimate death rates among unexposed patients with IPF.

To illustrate how immortal time bias may affect effect estimates, we used crude data from the study conducted by Ghebremariam et al. As the data necessary to quantify the bias are not provided in the article, for the purpose of illustration, we approximated hazard rates based on the reported median survival, which generated a total follow-up of 377 person-years for PPI-use and 182 person-years for non-use. Furthermore, we assumed that all 130 PPI users had the minimum period of 1 year of immortal time due to the exposure definition. This would amount to 130 immortal person-years in which PPI users were not at risk of death and which should have been classified as unexposed person-time. Thus, 35% (130/377 person years) of total follow-up time among PPI users were immortal. Based on the median survival time and the number of deaths in each group the rates of death are 20.4 per 100 person-years for PPI use and 34.7 per 100 person years for non-use, resulting in a crude HR of 0.59, which is very similar to the reported crude HR of 0.60. Accounting for the immortal person-time by adding this immortal person-time to person-time at risk in non-users, produced a corrected crude HR of 1.55 (Table 4.3), which is likely overestimated as the number of deaths among unexposed patients who used PPIs for less than 12 months is unknown. This simple illustration shows how incorrectly classified person-time at risk due to immortal time can lead to beneficial effect estimates and that person-time rather than patients should be analysed. There are more sophisticated approaches to estimate adjusted HRs that appropriately account for time-varying exposures, such as extended Cox models (106).

Other studies with immortal time bias

Other cohort studies also introduced immortal time bias by using an exposure definition that required a minimum duration of PPI use after cohort entry to define exposure. The Stanford study included 132 patients with IPF. Patients were categorised in PPI users (PPI use ≥ 12 months, n=87)

and non-users (no PPI prescription) and followed until lung transplantation or death. Mean survival in the PPI group was 3.4 years compared to 1.9 years in non-users, leading to the conclusion that PPIs improve survival in patients with IPF (adjusted HR=0.56, approximated 95% CI 0.34-92) (15).

The South Korean study (n=786) introduced immortal time bias by using different cut-off durations to categorise exposure to PPIs. Cox proportional hazards models were used to evaluate whether PPIs were associated with IPF-related mortality. The authors concluded that using PPIs for more than four months may have a protective effect (adjusted HR=0.51, 95% CI 0.21-1.22) (21). However, patients were by definition immortal during the four months after the first prescription. Corresponding Kaplan-Meier curves showed that there were no events in the exposed group in the first four months. If the cut-off duration was set at two or three months, there were no differences in mortality (two months: crude HR=0.87, 95% CI 0.54-1.41). This demonstrates how immortal time bias was introduced by exposure categories based on the prolonged duration of PPI use.

Finally, the Chinese cohort study identified 69 patients with IPF and compared 34 anti-acid therapy users (≥ 6 months) to 35 non-users (<6 months or none). Median survival in anti-acid therapy users was 31 months compared to 23 months in non-users (adjusted HR=0.23, 95% CI 0.12-0.44) (23). Again, immortal time bias was introduced by the exposure definition requiring a minimum duration of anti-acid therapy use. In addition to immortal time bias, the adjusted Cox model using stepwise regression led to an even more biased estimate as this method selected variables that may not have been adequate for confounder adjustment (107).

Studies with no time-related bias

Five observational studies of the association between anti-acid therapy and mortality did not use exposure definitions or analyses that introduced immortal time bias (Table 4.2). These included two cohort studies and three studies that analysed secondary data from RCTs. The Swedish cohort study (n=462) used a time-dependent exposure definition allowing patients to move from an unexposed to an exposed status, thus avoiding immortal time bias. Drug exposure was assessed during each quarter based on dispensed prescriptions, and drug effects on mortality were estimated in patients with IPF who initiated long-term oxygen therapy. During the follow-up period (median survival 6.7 months), 329 (71%) IPF patients died. This study found no association between use of anti-acid treatment and death (HR=1.12, 95% CI 0.87-1.42) (18).

The second cohort study from Germany (n=272, 2004-2012) assessed use of PPIs only once at baseline (first clinic visit) using an intention-to-treat approach. 171 (63%) patients died during follow-up. Use of PPIs at baseline did not show any differences in median survival (48 months in users vs. 42 months in non-users, approximated HR=0.88, 95% CI 0.42-1.83) (19).

Lee et al. retrospectively analysed data from 242 IPF patients randomised to placebo groups of three RCTs of other treatments for IPF. Using an intention-to-treat approach, patients were categorised into anti-acid therapy users (n=124) or non-users (n=118) based on reported use at baseline visit before randomisation. Data on self-reported anti-acid therapy use was recorded at each follow-up visit but not included in the mortality analysis. All-cause mortality was assessed at 30 weeks. Time to all-cause mortality, did not differ significantly between the two groups (approximated HR=0.61, 95% CI 0.33-1.14) (16).

Another post-hoc analysis was conducted by Kreuter et al. This study included 624 patients with IPF from the placebo arms of three RCTs evaluating pirfenidone. The authors assessed the effect

of anti-acid therapy use on all-cause mortality at 52 weeks using an intention-to-treat approach. 291 patients received anti-acid therapy at baseline. Drug use was documented subsequently during the trials (25% patients started anti-acid therapy after baseline) but was not implemented in the mortality analyses. After confounder adjustment, use of anti-acid therapy at baseline did not improve all-cause mortality (HR=0.80, 95% CI 0.30-1.70) (20). The authors repeated the analysis with patients randomised to the pirfenidone treatment arms (n=623) and again did not find an association between all-cause mortality in anti-acid therapy use (HR=0.80, 95% CI 0.30–2.50) (22).

Unclassifiable Study

In 2011, the first published study on the effectiveness of anti-acid therapy involved a retrospective cohort of 204 patients with IPF, with cohort entry taken as the date of the first clinic visit, defined as the date of diagnosis (14). Patients were followed until lung transplantation or death, which occurred in 97 (48%) patients. Information on treatment was collected in a "prospective" manner, though the authors state that exposure was classified into anti-acid therapy users (n=96, 47%) and non-users at the time of diagnosis. The median survival time for those using anti-acid therapy was 65.5 months compared with 29.9 months for non-users. The resulting adjusted HR comparing anti-acid therapy use to non-use at IPF diagnosis was 0.47 (95% CI 0.24-0.93), suggesting a highly protective effect of anti-acid therapy. However, the paper also reported that the median follow-up time between the two groups was similar (around 22 months). This discrepancy between the median follow-up time (22 months) and median survival time (36 months) of the cohort is unexpected and raises the question of whether immortal time was not introduced by classifying patients ever using anti-acid therapy during follow-up as exposed (Figure 4.3). Based on the

available information and inconsistencies in the reported data, it is unclear whether the protective effect is due to immortal time bias, rendering this study inconclusive.

4.7 Discussion

Between 2011 and 2017, ten observational studies evaluated the effectiveness of anti-acid therapies among patients with IPF on mortality. Our review did not assess other outcomes and excluded studies that evaluated outcomes such as lung function decline but did not report mortality data (108). Five studies, including the first published in 2011, reported highly beneficial effects of anti-acid therapies in IPF, with significant reductions in mortality, whereas the remaining studies did not find an association. Pooling the effect estimates of all included studies produced a HR of 0.63 (95% CI 0.45-0.90). However, when we stratified the analyses by the presence of immortal time bias, we found that the direction of the overall pooled HR was driven by the studies with immortal time bias. This highlights the need to identify and exclude studies affected by immortal time bias from such pooled analyses to avoid biased results.

We showed that four of the cohort studies reporting significant reductions in mortality associated with anti-acid therapy were affected by immortal time bias. This bias was introduced by a required minimum duration of anti-acid therapy use to define exposure status. The exposed group, by design, had to survive that period and was, thus, immortal, whereas the unexposed group was at risk of death immediately after cohort entry. The immortal-biased cohort studies led to exaggerated results with a highly significant 54% reduction in all-cause mortality (95% CI 31%-70%), which likely motivated the initiation of a pilot RCT that currently investigates the effectiveness of the PPI omeprazole in patients with IPF in the UK (NCT02085018) (109). Immortal time bias can be avoided using appropriate study designs and analyses (61, 62).

Five studies, including three retrospective analyses using data from RCTs, did not find any association between anti-acid therapy use and mortality. One of these studies used a time-dependent analysis to avoid immortal time bias, whereas the other studies used an intention-to-treat approach from cohort entry on. Even though free from immortal time bias, these studies have several other limitations, including residual confounding due to the observational nature of the studies. First, the Swedish cohort study using an appropriate statistical analysis only enrolled IPF patients with advanced disease who required supplemental oxygen, thus not generalizable to the general IPF population. Second, patient populations enrolled in RCTs represent a homogenous patient population which is different from the heterogeneous 'real-world' IPF population. Third, the RCTs were not designed to investigate mortality as the primary outcome. Thus, with an estimated median survival of 2-5 years after diagnosis, one-year RCTs are likely too short to observe any differences in mortality associated with use of anti-acid therapy. Fourth, the intention-to-treat approach uses only one single exposure measurement and assumes that patients adhere to treatment until the end of follow-up. If anti-acid information on treatment was recorded during follow-up but not analysed, this likely led to exposure misclassification. To better understand treatment patterns and effects it is necessary to additionally assess anti-acid therapy use in a time-dependent manner during a sufficient period of follow-up (110, 111).

4.8 Conclusions

Immortal time bias is evident in the four cohort studies that suggested that anti-acid therapy in IPF is highly effective at reducing mortality. Since the studies unaffected by this bias did not find that anti-acid therapy is effective, it would be imperative to reanalyse the data from the four studies affected by immortal time bias using proper methods that avoid this bias. In addition to ongoing

randomised trials, new observational studies that use proper methods of design and analysis to avoid such time-related biases are now needed to assess the effectiveness of PPIs in IPF in the real world setting of clinical practice. Until such further work is undertaken, the scientific evidence of the potential beneficial effects of anti-acid therapy on survival remains uncertain.

4.9 Tables

Table 4.1 Immortal time bias in cohort studies investigating the effects of anti-acid therapy on all-cause mortality in idiopathic pulmonary fibrosis

Study {author year (reference)}	Sample size	Data source	Exposure [a]	Adjusted hazard ratio (95% CI)	Duration of follow-up
Lee JS et al. [§] 2011 **(14)**	204	Two study centres	Anti-acid therapy vs. non-use at diagnosis	0.47 (0.24–0.93)	6 years
Ho et al. 2013 **(15)**	132	Single centre	PPIs ≥ 12 months vs. non-use	0.56 (0.34-0.92)*	5 years
Ghebremariam et al. 2015 **(17)**	215	Two study centres	PPIs ≥ 12 months vs. non-use	0.58 (0.39-0.87)	5 years
Lee CM et al. [#] 2016 **(21)**	786	Single centre	PPIs ≥ 4 months vs. < 4 months	0.51 (0.21-1.22)	5 years
Liu et al. 2017 **(23)**	69	Single centre	Anti-acid therapy ≥ 6 months vs. < 6 months	0.23 (0.12-0.44)	5 years

[a] Exposure to anti-acid therapy included proton pump inhibitors and H2 blockers.
[§] Suspected immortal time bias.
[#] Outcome defined as IPF-related mortality.
*We calculated approximations of hazard ratios and/or 95% confidence intervals based on reported median survival times and p-values.
Abbreviations: CI, confidence interval; IPF, idiopathic pulmonary fibrosis; PPIs, proton pump inhibitors.

Table 4.2 Observational studies investigating the effects of anti-acid therapy on all-cause mortality in idiopathic pulmonary fibrosis, avoiding immortal time bias

Study {author, year (reference)}	Sample size	Data source	Exposure [a]	Adjusted hazard ratio (95% CI)	Duration of follow-up
Lee JS et al. 2013 **(16)**	242	RCTs, placebo arms	Time-fixed at enrolment: Anti-acid therapy vs. non-use	0.61 (0.33-1.14)*	30 weeks
Ekstrom et al. 2016 **(18)**	462	Cohort study: population-based, oxygen-dependent IPF	Time-dependent: Anti-acid therapy vs. non-use	1.12 (0.87-1.42)	4 years
Kreuter et al. 2016 **(19)**	272	Cohort study: single centre	Time-fixed at baseline: PPI use vs. non-use	0.88 (0.42-1.83)*	8 years
Kreuter et al. 2016 **(20)**	624	RCTs, placebo arms	Time-fixed at enrolment: Anti-acid therapy vs. non-use	0.80 (0.30-1.70)	1 year
Kreuter et al. 2017 **(22)**	623	RCTs, treatment arms	Time-fixed at enrolment: Anti-acid therapy vs. non-use	0.80 (0.30-2.50)	1 year

[a] Exposure to anti-acid therapy included proton pump inhibitors and H2 blockers.
*We calculated approximations of hazard ratios and/or 95% confidence intervals based on reported median survival times and p-values.
Abbreviations: CI, confidence interval; IPF, idiopathic pulmonary fibrosis; RCT, randomised controlled trial.

Table 4.3 An illustration of crude hazard ratios for death associated with proton pump inhibitor (PPI) use before and after correcting for immortal time bias

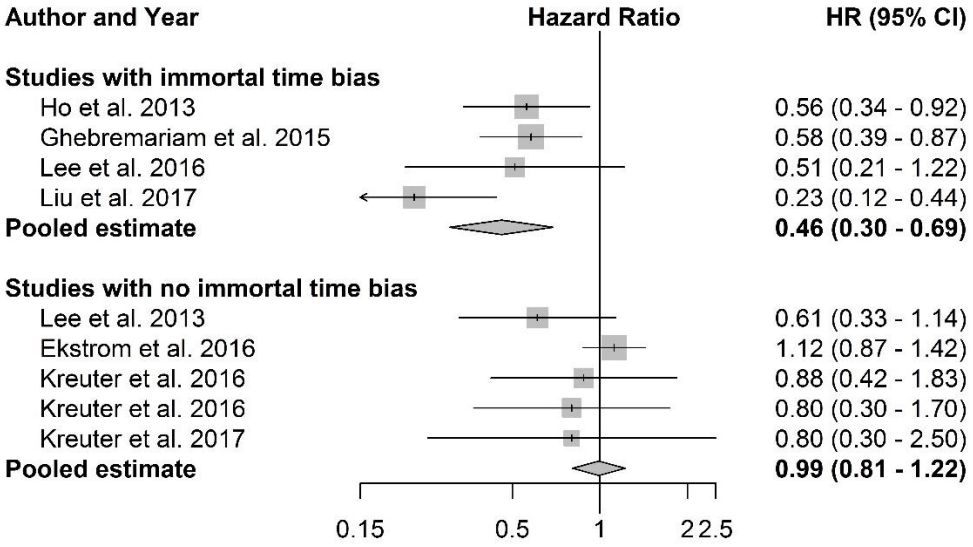
	PPI users			Non-users			
	Person years of follow-up	**No. of events**	**Hazard rate (95% CI)**	**Person years of follow-up**	**No. of events**	**Hazard rate (95% CI)**	**Crude hazard ratio (95% CI)**
Biased analysis							
Immortal person-time[#]	130	0		0	0		
At risk person-time	247	77		182	63		
Total	377	77	0.20[*] (0.16-0.25)	182	63	0.35[*] (0.26-0.43)	0.59 (0.42-0.82)
Corrected analysis							
Immortal person-time	0	0		130	0		
At risk person-time	247	77		182	63		
Total	247	77	0.31 (0.24-0.38)	312	63	0.20 (0.15-0.25)	1.55 (1.11-2.16)

[#] Time from cohort entry until the end of the 12th month of follow-up.

* Hazard rates and 95% confidence intervals (CI) were approximated from median survival times: 3.4 years (PPI users), 2.0 years (non-users) (17).

4.10 Figures

Figure 4.1 Forest plot of the association between the use of anti-acid therapy and all-cause mortality in studies with immortal time bias and with no time-related bias. Pooled estimates were computed using the random effects model.



Abbreviations: CI, confidence interval; HR, hazard ratio.

Figure 4.2 Illustration of immortal time bias using the proton pump inhibitor (PPI) exposure definition in the cohort study by Ghebremariam et al. (17). Idiopathic pulmonary fibrosis (IPF) patients classified as exposed had to receive PPIs for at least 12 months during follow-up (thick black line). The time between cohort entry (time 0) until the definition of exposure was met is immortal because the patient had to survive this period to be classified as exposed. For example, the top PPI user initiated PPIs during follow-up. The span between time 0 until the initiation of PPIs (thick grey line) is immortal but then the patient also had to survive the 12 months of PPI use (thick black line) before an event could occur, introducing two types of misclassified immortal time.

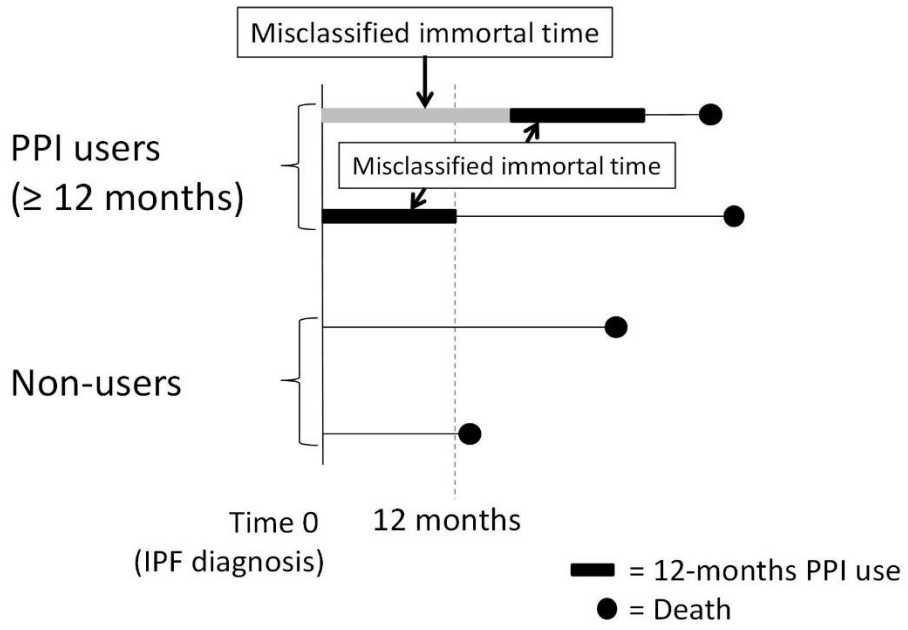
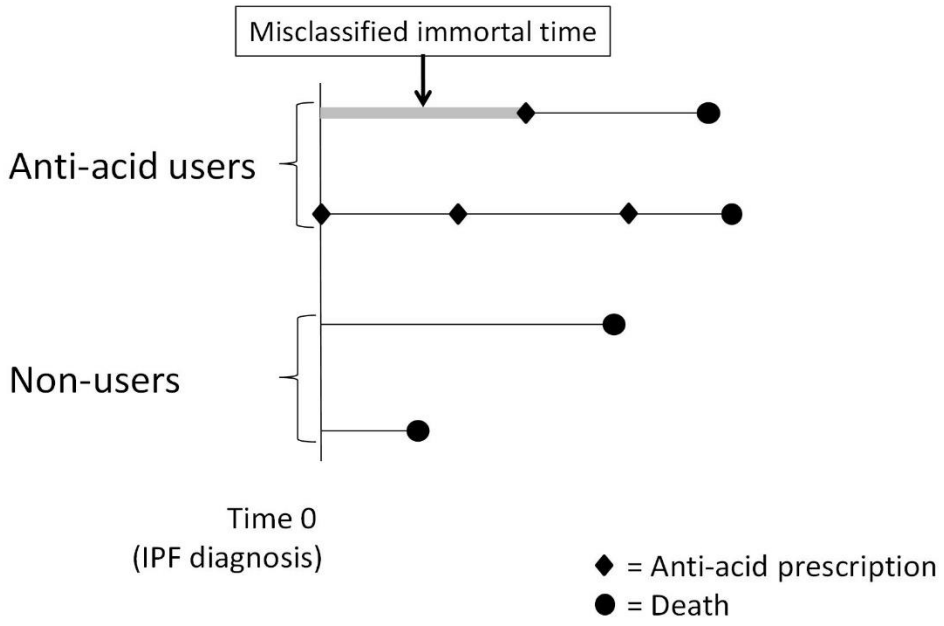


Figure 4.3 Example of immortal time bias in patients with idiopathic pulmonary fibrosis (IPF) exposed to anti-acid therapy who died from any cause. Anti-acid therapy users were ever users, i.e. they used anti-acid therapy at diagnosis throughout follow-up (top patients) or they were non-users at IPF diagnosis and initiated anti-acid therapy during follow-up (second patient). The time between cohort entry and the first anti-acid prescription is immortal (thick grey line) because the subject must survive to receive this first anti-acid prescription. Additionally, this time is misclassified as exposed to anti-acid therapy when it is in fact unexposed, leading to immortal time bias.



4.11 Appendix

Supplement 1. EMBASE Search Strategy (July 3, 2017)

Database: Embase Classic+Embase <1947 to 2017 July 03>

Search Strategy:

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1 idiopathic pulmonary fibrosis.mp. or exp fibrosing alveolitis/

2 cryptogenic fibrosing alveolitis.mp.

3 idiopathic interstitial pneumonia.mp. or exp interstitial pneumonia/

4 idiopathic fibrosing alveolitis.mp.

5 pantoprazole/ or omeprazole/ or esomeprazole/ or exp proton pump inhibitor/ or rabeprazole/ or histamine H2 receptor antagonist/ or proton pump inhibitor*.mp. or lansoprazole/ or gastroesophageal reflux/ or gerd* treatment.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

6 anti-acid*.mp. or exp antacid agent/

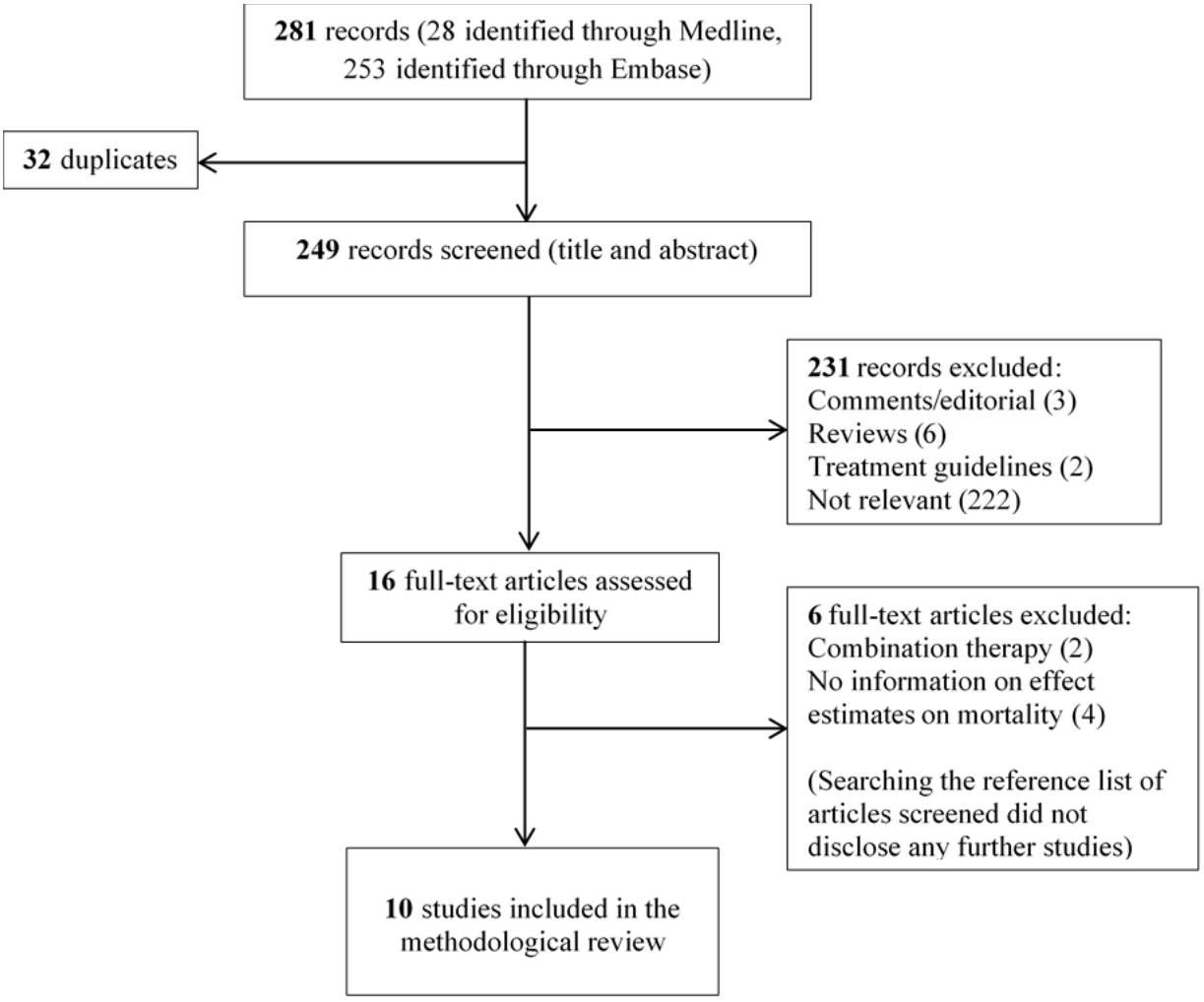
7 ppi*.mp.

8 antiacid*.mp.

9 (mortality or survival or survive or death or die*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

10 (1 or 2 or 3 or 4) and (5 or 6 or 7 or 8) and 9

Supplement 2. Flow chart of the study selection for the methodological review



5 Effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis: a population-based cohort study

5.1 Preamble: Manuscript 2

The methodological review presented in the last chapter illustrated that almost all of the highly beneficial effects of PPIs on survival in IPF were a result of immortal time bias. The studies without immortal time bias were affected by other limitations, including small sample size, short follow-up, selective patient populations, that may have affected the results. For example, the one-year follow-up in RCTs was likely too short to assess mortality in patients with IPF. Moreover, patients with IPF enrolled in RCTs are likely not generalizable to the overall IPF population.

Given the limitations of previous studies, of which some were used as evidence supporting the treatment recommendation for IPF, the aim of this manuscript was therefore to conduct an observational comparative effectiveness study to assess the effectiveness of PPIs in IPF regarding all-cause mortality, respiratory-related mortality, and respiratory-related hospitalizations using a large population-based database. This allowed to assess the effect of PPIs in IPF using real-world data with a long-term study follow-up.

This manuscript, entitled “Effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis: a population-based cohort study” has been submitted to *CHEST*.

5.2 Title page

Title: Effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis: a population-based cohort study

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5.3 Abstract

Background: Gastroesophageal reflux disease is a common co-morbidity in idiopathic pulmonary fibrosis (IPF) and may contribute to its progression. Anti-acid therapy, such as proton pump inhibitors (PPIs), has been considered as a potential treatment option for IPF. The evidence for this treatment comes from several observational studies affected by time-related bias. We assessed the association between use of PPIs and all-cause mortality, respiratory-related mortality, and respiratory-related hospitalization in patients with IPF using a large population-based cohort, designed to avoid this bias.

Methods: We used the UK Clinical Practice Research Datalink to identify a cohort of patients diagnosed with IPF between 2003 and 2016. The prevalent new-user cohort design was used to match patients initiating PPIs with non-users using time-conditional propensity scores, with follow-up until death or end of observation. Cox models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) of death and of a respiratory-related hospitalization, correcting for informative censoring by weighted inverse probability.

Results: There were 1852 PPI users who were matched to 1852 non-users identified among the cohort of patients with IPF, with 2.8 years median survival (mortality rate 26.7 per 100 per year). The HR of all-cause mortality with PPI use was 1.07 (95% CI 0.94-1.22), relative to non-use. For respiratory-related mortality the HR was 1.10 (95% CI 0.94-1.28) and 1.0 (95% CI 0.86-1.16) for respiratory-related hospitalizations.

Conclusion: PPI use was not associated with lower mortality or hospitalization incidence in this large study conducted among patients with IPF within a real world setting of clinical practice and designed to avoid biases affecting previous studies, PPIs may not be as beneficial in treating IPF as suggested by some studies and conditionally recommended in treatment guidelines.

5.4 Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare, chronic, and irreversible fibrotic lung disorder characterized by progressive scarring of the lung parenchyma and worsening of lung function, and is associated with poor prognosis despite recent advances in IPF treatment (5, 19, 31, 112, 113). Median survival after diagnosis is estimated to be 2-5 years (2, 3).

Gastroesophageal reflux disease (GERD) is a common co-morbidity in IPF. Microaspiration due to GERD is hypothesized to contribute to the progression of IPF (114, 115). This led to the exploration of treatments for GERD, including anti-acid therapy such as proton pump inhibitors (PPIs), as a potential treatment option for IPF. Health outcomes in previous studies included cough frequency, pulmonary function, and mortality (14, 20, 71). Notably, observational studies assessing the association between anti-acid therapy and mortality in IPF have shown inconsistent results, ranging from risk reductions of 50% to no association (14, 20). Despite these discrepant results, the current international IPF treatment guidelines conditionally recommend anti-acid therapy for all patients with IPF regardless of the presence of GERD (5). Some limitations of previous studies included small sample size, short follow-up, and immortal time bias, which highlights the need for a larger, more accurate observational study to assess the role of anti-acid therapy in IPF in a real-world setting (94, 114).

As PPIs are the most commonly used anti-acid treatment, the aim of this study was to assess the association between use of PPIs and all-cause mortality, respiratory-related mortality, and respiratory-related hospitalizations in patients with IPF using a large population-based cohort design that avoided some of the methodological limitations in previous studies.

5.5 Methods

Data sources

We used the UK's Clinical Practice Research Datalink (CPRD) GOLD linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases. The CPRD is a large primary care database which contains electronic medical record for more than 17 million people from more than 680 general practices. Participating general practitioners have been trained to record medical information, such as demographic data, lifestyle factors, including smoking and alcohol use, and medical diagnoses, using the Read code classification. Drugs prescribed by general practitioners are coded based on the UK Prescription Pricing Authority dictionary. CPRD data have been previously validated and shown to be of high quality (77). The HES database records all inpatient and outpatient hospital admission information, including primary and secondary diagnoses using ICD-10 (International Classification of Diseases, Tenth Revision) codes and hospital procedures using OPCS-4 (Office of Population Censuses and Surveys classification of interventions and procedures, 4th version). ONS contains electronic death certificates, including the underlying cause of death using ICD-10 codes. HES and ONS can only be linked to general practices in England, which represent approximately 75% of all practices (77).

Base cohort

The base cohort included patients with a first diagnosis of IPF between 1 January 2003 and 31 December 2016, who had at least one year of medical history prior to diagnosis and were older than 40 years at diagnosis. IPF diagnosis was based on Read codes: H563.00 (idiopathic fibrosing alveolitis), H563z00 (idiopathic fibrosing alveolitis NOS), H563.11 (Hamman-Rich syndrome), H563.12 (cryptogenic fibrosing alveolitis), H563.13 (idiopathic pulmonary fibrosis), H563100

(diffuse pulmonary fibrosis), H563200 (pulmonary fibrosis). Patients with connective tissue disease, hypersensitivity pneumonitis, sarcoidosis, pneumoconiosis, or asbestosis prior to IPF diagnosis were excluded. Patients were only included into the base cohort if their medical record was linked to HES and ONS. Base cohort entry was defined as the first date of IPF diagnosis.

Study cohort

The study cohort, formed using the prevalent new-user design, first identified all patients from the base cohort who had a PPI prescription after IPF diagnosis.(93) Thus, chronologically for each patient who was prescribed a PPI, we identified a matched reference patient with IPF who did not use a PPI based on time-based exposure sets. Time-based exposure sets were defined as time intervals (± 1 month) around the date of the first PPI prescription from time since IPF diagnosis (base cohort entry). Potential reference patients had a record of a physician visit within the corresponding exposure set, with no prescription for PPI. The requirement for a physician visit implies that the patient had the opportunity to become a PPI user at that time. Exposed and reference patients were matched 1:1 on time-conditional propensity scores (116) using conditional logistic regression to estimate the propensity to receive a PPI after IPF diagnosis. Matched reference patients could be prescribed a PPI later during follow-up. In this case, the follow-up for the unexposed patient was artificially censored and the patient could be included as a PPI user from that point onward if matched to an unexposed IPF patient at that time. Thus, this study cohort provides a comparison of PPI users to time- and propensity score-matched non-users. Study cohort entry is the date of the first PPI prescription or the corresponding matched physician visit within the same exposure set. Patients meeting the study inclusion criteria were followed until the earliest of the following events: occurrence of one of the study outcomes, lung transplant, first PPI

prescription for reference subjects, end of registration with the general practice, or end of the study period (May 2017).

Study outcomes

The primary outcome was all-cause mortality. Secondary outcomes included respiratory-related mortality and respiratory-related hospitalizations. Death from any cause was identified using the CPRD and ONS. Respiratory-related death was identified in ONS, respiratory-related hospital admissions were identified in HES (ICD-10 codes for any respiratory condition: J00-J99).

Covariates

Baseline covariates were identified in the time-dependent baseline period which was defined as the year prior to study cohort entry, namely the date of the first PPI prescription or the corresponding matched date for non-users. Variables included in the time-conditional propensity score model were age, sex, body mass index, smoking history, excessive alcohol use, ethnicity, prior hospitalizations, co-morbidities and medications. Co-morbidities included asthma, chronic obstructive pulmonary disease, GERD, a history of Nissen fundoplication, cardiovascular disease, diabetes, cancer, renal disease, as well as depression. Medications included oral and inhaled corticosteroids, ACE-inhibitors, beta-blockers, anticoagulants, diuretics, statins, nonsteroidal anti-inflammatory drugs, H2-blockers, and previous PPI use prior to IPF diagnosis. As the amount for missing data was small, e.g. less than 1% for smoking history, it was treated as a separate category in the analyses.

Statistical analyses

Descriptive statistics were used to summarize the characteristics of the patients in the matched groups. The accuracy of matching among covariates was assessed using standardized mean differences. Kaplan–Meier technique was used to estimate the survival function of time to death from cohort entry. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and the 95% confidence interval (CI) of each outcome associated with PPI use compared to no use, using a modified intention-to-treat approach. As the number of non-users who were censored because of starting PPIs was high, we additionally accounted for informative censoring due to a first PPI prescription for matched non-users using inverse probability censoring weights (117). For respiratory hospitalizations, we accounted for death as a competing risk (118). To maximize the comparability between the two groups, the models were additionally adjusted for age, sex, history of smoking, prior hospitalization, and concomitant cardiovascular disease.

Several sensitivity analyses were conducted to verify the robustness of our results. First, we restricted the follow-up period to one year to minimize exposure misclassification. Second, as the CPRD does not include standardized diagnostic criteria for diagnosing IPF, we performed a sensitivity analysis on a subset of patients to ensure more accurate IPF diagnosis by requiring additional information on IPF using the hospital database HES. These patients had to have additional concurrent IPF-related diagnostic tests (lung biopsy or chest imaging) recorded in the CPRD or HES databases or a concurrent additional ICD-10 code for IPF (J84.1) recorded in the HES database within one month of IPF diagnosis. Third, we performed stratified analyses by PPI use prior to IPF diagnosis to assess the association between PPI initiation after IPF diagnosis and all-cause mortality.

All statistical analyses were performed using SAS (Version 9.4). The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (Protocol 17_143) and the Ethics Committee of the Jewish General Hospital (JGH Protocol #2018-769, 17-110), Montreal, Quebec, Canada.

5.6 Results

Figure 5.1 shows that the base cohort included 2944 patients diagnosed with IPF between 1 January 2002 and 31 December 2016. A total of 1916 (65%) patients received a PPI prescription after IPF diagnosis (mean 7.8 months, range 0-136.9 months). After propensity score matching, the study cohort included 1852 patients who used PPIs after IPF diagnosis and 1852 matched patients who had not used PPIs by the time of study cohort entry (matching date). Table 5.1 shows that patient characteristics were well balanced with standardized differences below 0.10 (e.g. azathioprine use was similar in both groups) except for co-existing GERD, an indication for PPI use, and PPI use before IPF diagnosis which were more prevalent in PPI users. There were 62% of PPI users who had a history of PPI use prior to their IPF diagnosis compared with 45% among the matched non-users. On average, PPI users received eight (interquartile range 3-12) prescriptions in the first year.

In the overall study cohort, there were 1703 deaths from any cause (incidence rate (IR) 26.7 per 100 per year, 95% confidence interval (CI) 25.5-28.0). There were 1125 (66%) deaths related to respiratory diseases. Median survival was 2.8 years (range 0-13 years) and 70% of the patients had died within 5 years of IPF diagnosis. The mean follow-up for PPI users was 2.4 years (median 1.7 years) and 1.1 (median 0.3 years) for non-users.

There were 1221 deaths (821 (67%) related to respiratory causes) among PPI users and 482 deaths (304 (63%) related to respiratory causes) among non-users (Table 5.2). Among the patients who used PPIs, the IR of death from any cause was 27.8 per 100 per year (95% CI 26.2-29.4). Among the matched patients the IR was 24.3 per 100 per year (95% CI 22.2-26.5). The corresponding weighted Kaplan-Meier curves were similar when comparing both groups (Figure 5.2).

As 1090 (59%) of the matched non-users started using PPIs during follow-up, inverse probability censoring weights were used to address informative censoring. The most important predictors of censoring were age, concomitant GERD, and previous PPI use prior to IPF diagnosis. After inverse probability censoring weighting, the overall adjusted HR of all-cause mortality was 1.07 (95% CI 0.94-1.22) with PPI use compared to no use, while for respiratory-related mortality it was 1.10 (95% CI 0.94-1.28). After accounting for death as a competing risk, the HR of respiratory related hospitalization associated with PPI use was 1.00 (95% CI 0.86-1.16), compared to no use.

Table 5.3 shows the results of the sensitivity analyses which globally showed consistent results with main analysis, with the exception of the stratification by history of PPI use prior to IPF diagnosis. Seven hundred and forty-eight patients died during the first year of follow-up. The HR of all-cause mortality in the first year associated with PPIs was 0.89 (95% CI 0.75-1.07), compared to no use. When the analysis was restricted to the subset of patients with more accurate diagnosis, there was no difference in mortality among PPI users and non-users (HR=0.99; 95% CI 0.75-1.30). On the other hand, the stratified analysis by prior PPI use showed that among patients who did not use PPIs before IPF diagnosis, the HR of death associated with initiating PPIs was 1.45 (95% CI 1.11-1.90), while for those who were previously on PPIs, the HR was 0.97 (95% CI 0.74-1.26).

5.7 Discussion

This first large observational study of patients with IPF conducted in a real-world primary care setting found that the use of PPIs is not associated with an improved survival compared to non-use. The rate of respiratory-related deaths and hospitalizations was also similar between PPI users and non-users and results remained consistent in sensitivity analyses.

The debate on the potential effectiveness of anti-acid therapy as a treatment for IPF is still ongoing. The evidence supporting anti-acid therapy in the international IPF treatment guidelines is uncertain, with many researchers calling for a robust randomized controlled trial. A recent pilot trial in the UK studying the cough frequency in 45 patients with IPF found that omeprazole was well tolerated (71). Previous observational studies had reported survival benefits of up to 50% associated with PPI use in patients with IPF (15, 17, 21, 23) to no association between PPI use and survival (18, 20, 22, 25, 119). An explanation for the beneficial findings was that anti-acid treatment such as PPIs reduces acid microaspiration, which may contribute to the progression of IPF (114, 115). However, a review showed that the studies showing important mortality reduction were affected by immortal time bias, which led to the highly beneficial results (94).

To date, six studies that avoided immortal time bias reported no association between PPI use and survival, although some uncertainty remained because of certain design limitations. Indeed, three secondary analyses of data from randomized controlled trials of other IPF therapies had a maximum follow-up of 12 months, which is likely too short to assess the effect of PPIs on an outcome such as mortality and represent a selected homogeneous patient population limiting generalizability (20, 22, 119). One population-based study assessed the effectiveness of PPIs in patients with advanced IPF who were on long-term oxygen therapy, results are thus not generalizable to the general IPF population (18, 19). A study using data on close to 600 patients

from the Australian IPF registry did not account for left truncation in their analyses which creates uncertainty regarding potential survival bias (25). Compared to previous studies, our large cohort study of over 3000 patients newly diagnosed with IPF avoided immortal time bias and had sufficiently long follow-up to assess mortality in a real-world setting. Our study found no difference in mortality between PPI users and non-users, after accounting for informative censoring. There was also no difference in respiratory-related hospitalizations between PPI users and non-users.

The data analysis used in our study accounted for an important source of bias. As almost 60% of the matched non-users started PPIs during follow-up, it was necessary to correct for artificial censoring due to a PPI initiation in our analyses (120). This censoring mechanism led to a differential study follow-up among PPI users and non-users (2.4 years vs. 1.1 years) and also introduced informative censoring. I.e. non-users who were censored due to PPI initiation could not have died as non-users and could have only experienced the outcome as a PPI user. This would lead to a higher event rate in PPI users and therefore to a higher HR, when comparing PPI users to non-users. Indeed, the analysis that did not account for informative censoring resulted in a HR of all-cause mortality of 1.18 (95% CI 1.06-1.31), comparing PPI use to non-use, while it was 1.07 (95% CI 0.94-1.22) with the more accurate analysis that corrected for informative censoring using inverse probability censoring weighting. In the setting of non-differential censoring, this differential follow-up is also inherently adjusted for by the Cox proportional hazards model which takes duration of follow-up into account when analysing time-to-event data, comparing the outcome for PPI users with non-users at the same time of follow-up.

The analysis stratified by prior PPI use resulted in a modification of the hazard ratios. Among patients with no prior PPI use, the initiation of PPIs after IPF diagnosis was associated with higher

mortality compared with non-users (HR=1.45; 95% CI 1.11-1.90), while it was 0.97 (95% CI 0.74-1.26) among those with previous use. This latter estimate is susceptible to greater bias than the former as it was derived from a cohort of patients who were diagnosed IPF while they were using PPIs. Such cohorts can be subject to biases, such as the healthy user effect (121): Patients who continued to use PPIs after the IPF diagnosis tolerated the drug well and were less likely to die shortly after their IPF diagnosis. Restricting the study to patients who did not use PPIs prior to their IPF diagnosis avoids this source of bias (121, 122). Nonetheless, the estimate based on this stratum of patients who did not use PPIs prior to their IPF diagnosis may be affected by residual confounding, despite matching on time-conditional propensity scores.

One of the strengths of this study is the use of the prevalent new-user design (93) which allowed us to identify a comparable time of cohort entry for matched PPI users and non-users to avoid immortal time bias (61, 62). Matched patients have the same duration of IPF and similar other patient characteristics which minimizes confounding. PPI users started to use PPIs at the time of matching whereas non-users did not but had the opportunity to obtain a PPI prescription at the matched physician visit. This design can therefore be used when there is no active comparator. Using data from a large population-based primary care database allowed to identify a large number of IPF patients with sufficient follow-up, allowing for precise estimates.

As this observational study analyses data from a population-based primary care database and IPF is typically diagnosed by a specialist, there may be misclassification of IPF in our study. However, it does also reflect how IPF may be managed in primary care. Some diagnostic misclassification may also have occurred due to the diagnostic guidelines that have changed over the 15 years spanning the study. However, other diagnostic aetiologies were excluded to minimize this problem and we expect that the majority of patients in our cohort have IPF or a fibrotic interstitial lung

disease behaving like IPF. By restricting our study cohort to patients who had an IPF-related diagnostic test, such as lung biopsy or chest imaging, or an additional diagnostic code for IPF recorded in the HES, we created a subset of patients that was more likely to have an accurate IPF diagnosis. In this subset, there was no difference in mortality among PPI users and non-users (HR=0.99, 95% CI 0.75-1.30). Another limitation that comes with the use of a population-based database is the lack of information on disease severity or laboratory tests related to pulmonary function to explore the potential of effect modification. The reasons for PPI prescriptions are also not available in this database. The main indication for the use of PPIs is GERD, which was more prevalent in PPI users even after matching (26.0% vs 18.8%). PPIs should be considered when treating GERD in patients with IPF. However, our study aimed to assess the effectiveness of PPIs as a treatment in IPF regardless of the presence of GERD. A further limitation is the potential for exposure misclassification in the modified intention-to-treat analysis. In our study, patients received on average eight PPI prescriptions in the first year of follow-up and 21 PPI prescriptions during their overall follow-up. This usage pattern shows that patients were generally adherent in our study, making exposure misclassification less likely. We also assessed the association between PPI use and 1-year mortality and results were in accordance with the main analysis (HR=0.89; 95% CI 0.75-1.07). Due to the observational nature of this study there is potential for residual confounding. We tried to minimize this bias by matching on time since IPF diagnosis and on time-conditional propensity scores.

In all, this large population-based study conducted in a real world setting of clinical practice found that PPI use is not associated with improved survival or reduced incidence of respiratory-related hospitalization in patients with IPF compared to non-use. This study suggests that PPIs may not

be as beneficial in treating IPF as suggested by some studies and conditionally recommended in treatment guidelines.

5.8 Tables

Table 5.1 Patient characteristics of patients with IPF who used PPIs and propensity score-matched non-users at cohort entry.

	PPI use (n=1852)	No PPI use (n=1852)	Standardized difference
Mean (SD) age at diagnosis [years]	75.4 (9.4)	75.6 (9.5)	-0.02
Men	1150 (62.1)	1209 (65.3)	-0.07
Mean (SD) IPF duration [years]	0.5 (0.9)	0.5 (0.9)	0.02
BMI [kg/m^2]			0.05
<25	549 (29.6)	531 (28.7)	
25-30	663 (35.8)	692 (37.4)	
≥30	466 (25.2)	439 (23.7)	
Unknown	174 (9.4)	190 (10.3)	
Smoking status			0.03
Ex-smoker	866 (46.8)	873 (47.1)	
Non-smoker	674 (36.4)	657 (35.5)	
Smoker	299 (16.1)	309 (16.7)	
Unknown	13 (0.7)	13 (0.7)	
Alcohol-related disorders	537 (29.0)	551 (29.8)	0.05
Ethnicity			0.08
White	1715 (92.6)	1698 (91.7)	
Other	59 (3.2)	52 (2.8)	
Unknown	78 (4.2)	102 (5.5)	
Medical history prior to cohort entry			
Hospitalization in the year before cohort entry	1066 (57.6)	982 (53.0)	0.09
Asthma	410 (22.1)	379 (20.5)	0.04
COPD	595 (32.1)	576 (31.1)	0.02
GERD	481 (26.0)	348 (18.8)	0.17
Nissen Fundoplication	6 (0.3)	5 (0.3)	0.01
Arrhythmia	297 (16.0)	300 (16.2)	0.00
Heart failure	410 (22.1)	398 (21.5)	0.02
Hypertension	1076 (58.1)	1042 (56.3)	0.04
Pulmonary hypertension	50 (2.7)	44 (2.4)	0.02
Myocardial infarction	277 (15.0)	239 (12.9)	0.06
Stroke	149 (8.1)	144 (7.8)	0.01
Diabetes Mellitus	286 (15.4)	255 (13.8)	0.05
Cancer	341 (18.4)	322 (17.4)	0.03
Lung cancer	31 (1.7)	23 (1.2)	0.04
Renal disease	511 (27.6)	493 (26.6)	0.02
Depression	305 (16.5)	281 (15.2)	0.04
Medications prescribed in the year prior to cohort entry			
Inhaled corticosteroids	240 (13.0)	230 (12.4)	0.02
Oral corticosteroids	675 (36.5)	587 (31.7)	0.10
Azathioprine	66 (3.6)	53 (2.9)	0.04

	PPI use (n=1852)	No PPI use (n=1852)	Standardized difference
Angiotensin converting enzyme inhibitors	575 (31.1)	556 (30.0)	0.02
Angiotensin II receptor blockers	8 (0.4)	7 (0.4)	0.01
Beta blockers	533 (28.8)	481 (26.0)	0.06
Diuretics	863 (46.6)	826 (44.6)	0.04
Anticoagulants	199 (10.8)	218 (11.8)	-0.03
Antiplatelet	859 (46.4)	790 (42.7)	0.08
Statins	914 (49.4)	853 (46.1)	0.07
Non-steroidal anti-inflammatory drugs	241 (13.0)	214 (11.6)	0.04
H2-Blockers	117 (6.3)	111 (6.0)	0.01
PPIs in the year prior IPF diagnosis	1153 (62.3)	840 (45.4)	0.34

Data are n (%), unless otherwise specified.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IPF, idiopathic pulmonary fibrosis; SD, standard deviation; PPI, proton pump inhibitor.

Table 5.2 Crude and adjusted hazard ratios for the association between the use of PPIs after IPF diagnosis and the risk of the study outcomes compared to no use, using a modified intention-to-treat analysis

Exposure	Number of patients	Number of events	Person-years	Incidence rate (95% CI) per 100 person years	Crude HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR (95% CI) with IPCW*§
All-cause mortality							
PPI use	1852	1221	4390	27.8 (26.2-29.4)	1.20 (1.08-1.33)	1.18 (1.06-1.31)	1.07 (0.94-1.22)
No use	1852	482	1978	24.3 (22.2-26.5)	1.00	1.00	1.00
Respiratory-related death							
PPI use	1852	821	4390	18.7 (17.4-20.0)	1.28 (1.12-1.47)	1.23 (1.05-1.43)	1.10 (0.94-1.28)
No use	1852	304	1978	15.4 (13.6-17.1)	1.00	1.00	1.00
Respiratory-related hospitalizations #							
PPI use	1852	849	3532	24.0 (22.4-25.7)	1.13 (0.93-1.31)	1.12 (0.97-1.30)	1.00 (0.86-1.16)
No use	1852	403	1713	23.5 (21.2-25.8)	1.00	1.00	1.00

*After matching on propensity score, further adjusted for age, sex, smoking, history of hospitalization in the year prior to cohort entry, and concomitant cardiovascular disease.
§ 95% CIs were calculated based on robust standard errors.
#Accounted for competing risk of death.
Abbreviations: CI, confidence interval; HR, hazard ratio; IPCW, inverse probability of censoring weighting; PPI, proton pump inhibitor.

Table 5.3 Sensitivity analyses for the crude and adjusted hazard ratios of all-cause mortality associated with PPI use compared to no use

All-cause mortality	Crude HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR (95% CI) with IPCW*§
1-year mortality #			
PPI use (n=1852)	1.25 (1.07-1.45)	1.23 (1.05-1.43)	0.89 (0.75-1.07)
No use (n=1852)	1.00	1.00	1.00
With IPF code in HES (n=869)			
PPI use (n=440)	1.08 (0.88 -1.32)	1.07 (0.85-1.35)	0.99 (0.75-1.30)
No use (n=429)	1.00	1.00	1.00
With history of PPI use (n=1702) #			
PPI use (n=851)	1.18 (0.93-1.49)	1.08 (0.86-1.36)	0.97 (0.74-1.26)
No use (n=851)	1.00	1.00	1.00
Without history of PPI use (n=1414) #			
PPI use (n=707)	1.42 (1.23-1.64)	1.51 (1.30-1.75)	1.45 (1.11-1.90)
No use (n=707)	1.00	1.00	1.00

*Adjusted for age, sex, smoking, history of hospitalization, and concomitant cardiovascular disease if not already used as the stratifying variable. The subset analysis was further adjusted for propensity score deciles and duration of disease.

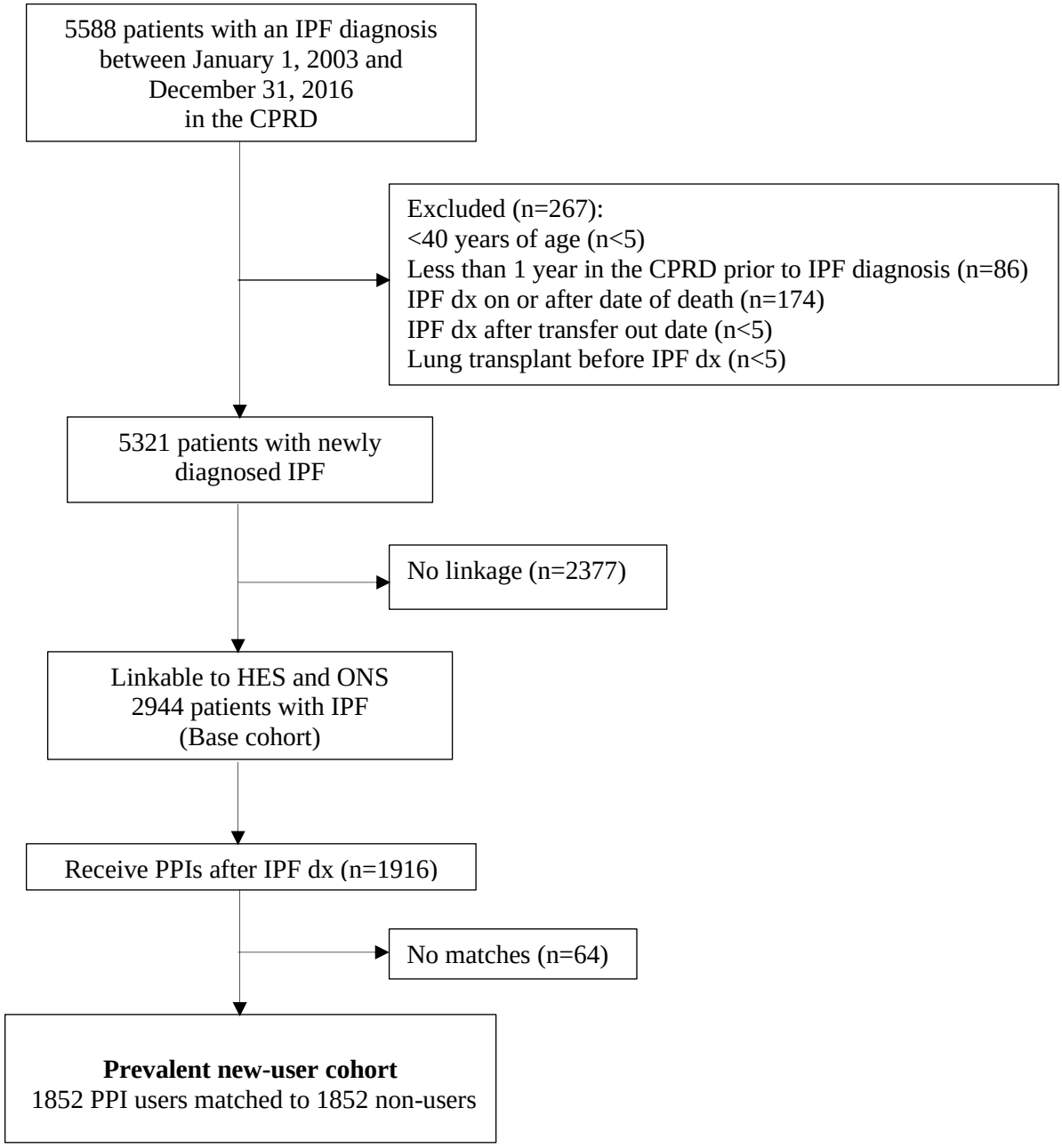
§ 95% CIs were calculated based on robust standard errors.

#Propensity score-matched.

Abbreviations: CI, confidence interval; HES, Hospital Episode Statistics; HR, hazard ratio; IPCW, inverse probability of censoring weighting; PPI, proton pump inhibitor.

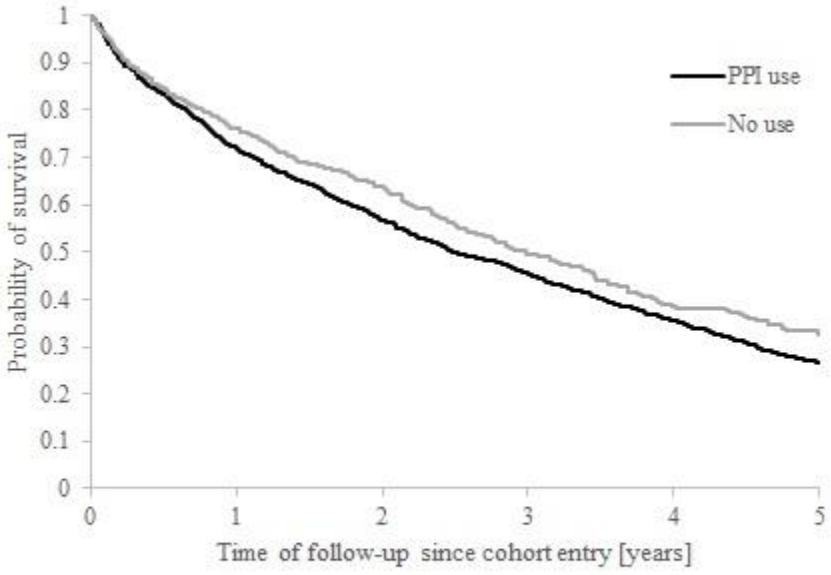
5.9 Figures

Figure 5.1 Flowchart showing the selection of the study cohort



Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; IPF, idiopathic pulmonary fibrosis; ONS, Office for National Statistics; PPI, proton pump inhibitor.

Figure 5.2 Kaplan-Meier curves of survival, comparing proton pump inhibitor (PPI) use (black line) to no use (grey line), after matching on propensity scores and weighted by informative censoring weights



Number at risk						
PPI use	1852	1191	816	563	375	232
No use	1852	585	339	195	116	75

6 Comparing new-user cohort designs: the example of proton pump inhibitor effectiveness idiopathic pulmonary fibrosis

6.1 Preamble: Manuscript 3

The observational study presented in manuscript 2 revealed that informative censoring due to a PPI initiation among non-users needed to be addressed in the evaluation of PPI effectiveness in IPF. Methods to account for informative censoring, such as inverse probability of censoring weights, have not been discussed or validated within the novel prevalent new-user cohort design before. I therefore explored two alternative approaches in comparative effectiveness research, when there is no active comparator and informative censoring is present and compared them to the original prevalent new-user cohort design, using PPI effectiveness in IPF as an illustration. The first approach used a different sampling strategy when selecting the comparison group using the prevalent new-user design. To avoid informative censoring due to a PPI initiation, only uncensored non-users, i.e. never-users, were eligible to be matched to PPI users. The second approach used a marginal structural Cox model and included the full base cohort in the analysis to create comparable treatment groups, similarly to the time- and propensity score matching in the prevalent new-user cohort design, that were balanced with regards to time-dependent confounding and differential censoring (111).

The manuscript, entitled "Comparing new-user cohort designs: the example of proton pump inhibitor effectiveness in idiopathic pulmonary fibrosis", is being prepared for submission to the *American Journal of Epidemiology*.

6.2 Title page

Title: Comparing new-user cohort designs: the example of proton pump inhibitor effectiveness idiopathic pulmonary fibrosis

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6.3 Abstract

The prevalent new-user cohort design is useful in pharmacoepidemiology to assess the effectiveness of a drug in the absence of an active comparator. Alternative approaches, particularly in the presence of significant informative censoring, include a variant of this design based on never-users of the study drug and the marginal structural Cox model (MSCM) approach. These were compared in assessing the effectiveness of proton pump inhibitors (PPI) on mortality in idiopathic pulmonary fibrosis (IPF) using a cohort of patients with IPF identified in the UK's Clinical Practice Research Datalink. The cohort included 2944 patients, with 1916 initiating PPIs during follow-up and 2136 deaths (rate 25.8 per 100 person-years). The conventional prevalent new-user design found a hazard ratio (HR) of death associated with PPI use compared with non-use of 1.07 (95% confidence interval (CI) 0.94-1.22). The variant to the prevalent new-user design comparing with never-users found a HR of 0.82 (95% CI 0.73-0.91) while the MSCM found a HR of 1.08 (95% CI 0.85-1.38). In conclusion, the marginal structural model and the conventional prevalent new-user design, both accounting for informative censoring, produced similar results. However, the prevalent new-user cohort design variant based on never-users introduces selection bias and should be avoided.

6.4 Background

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease associated with poor prognosis, with a median survival of 2-5 years after diagnosis (1-3). Because of a potential effect of acid reflux on the progression of IPF, proton pump inhibitors (PPI) are used to treat this disease and have been given conditional recommendations in international IPF treatment guidelines (6). These recommendations were based on several observational studies that assessed the effectiveness of PPIs in IPF, with particular interest in survival (14, 16). Subsequent studies continued to evaluate the effectiveness of PPIs in IPF (17, 18, 20-23, 25). However, several of these studies were affected by immortal time bias or presented other limitations, such as small sample size or a short study period (94).

A recent study used a large population-based database and a prevalent new-user cohort design specifically to circumvent these limitations, while allowing to assess the effectiveness of a drug in the absence of an active comparator (93, 123) . This design paired each new-user of PPI with a time-matched non-user who had a physician visit without a PPI at that time and who had a similar value of the time-conditional propensity score (TCPS) (93). The non-user can receive a PPI prescription later during follow-up, at which point they are censored. However, with high incidence of PPI use during follow-up (65%), the non-user comparison group introduces a significant amount of potential informative censoring which can be corrected by inverse probability of censoring weighting. This conventional approach has yet to be compared with other methods.

In this paper, we compare the conventional prevalent new-user approach with alternative approaches in the context of estimating the effect of PPIs on mortality and hospitalization in patients with IPF. It was first compared with a variation of this design that would select

comparators only among never-users of PPIs to avoid censoring among non-users due to PPI initiation. Second, it was compared with the marginal structural model approach, which uses the entire cohort to create comparable treatment groups at different time points in follow-up, balanced with respect to time-dependent confounders and differential censoring (111, 124).

6.5 Methods

Study population

This study used data from the United Kingdom's Clinical Practice Data Research Datalink (CPRD) GOLD linked the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases. The CPRD GOLD is a large primary care database which contains electronic medical record for more than 17 million people from more than 680 general practices. Participating general practitioners have been trained to record medical information, such as demographic data, lifestyle factors, including smoking and alcohol use, and medical diagnoses, using the Read code classification. Drugs prescribed by general practitioners are coded based on the UK Prescription Pricing Authority dictionary. CPRD data have been previously validated and shown to be of high quality (77). The HES database records all inpatient and outpatient hospital admission information, including primary and secondary diagnoses using ICD-10 (International Classification of Diseases, Tenth Revision) codes and hospital procedures using OPCS-4 (Office of Population Censuses and Surveys classification of interventions and procedures, 4th version). ONS contains electronic death certificates, including the underlying cause of death using ICD-10 codes. HES and ONS can only be linked to general practices in England, which represent approximately 75% of all practices in England (77).

Base cohort

The base cohort included patients with a first diagnosis of IPF between 1 January 2003 and 31 December 2016, who had at least one year of medical history prior to diagnosis and were older than 40 years at diagnosis (123). Patients were only included into the base cohort if their medical record was linked to HES and ONS. Base cohort entry was defined as the date of IPF diagnosis.

Conventional prevalent new-user cohort design with non-users

The formation of the study cohort for this design has been described previously (123). In brief, within the base cohort all patients with a first PPI prescription after IPF diagnosis were identified (PPI new-user). All first prescriptions were chronologically ordered, and time-based exposure sets were created (±1 month). Potential reference patients had a record of a physician visit within the corresponding exposure set, with no prescription for PPIs. PPI users and reference patients were matched 1:1 without replacement on (TCPS) (116) using conditional logistic regression to estimate the propensity to receive a PPI after IPF diagnosis. Matched reference patients could be prescribed a PPI later during follow-up and were censored at this point. This introduced the potential for informative censoring and was addressed by using inverse probability of censoring weighting in the analysis. Study cohort entry was the date of the first PPI prescription for PPI users and the corresponding physician visit for non-users.

Prevalent new-user cohort design variant with never-users

We used the prevalent new-user cohort design within the base cohort of newly diagnosed IPF patients, only allowing never-users of PPIs to be selected as potential matches to PPI users to avoid the issue of informative censoring by only analysing uncensored non-users (73). Never-users were

matched 1:1 without replacement based on time-based exposure sets and TCPS estimated using conditional logistic regression (93, 116). Cohort entry was the day of the first PPI prescription for PPI new-users and the date of the corresponding physician visit for never-users.

Marginal structural Cox model

This approach included all patients from the base cohort. Patients entered the study cohort on the day of their IPF diagnosis. Follow-up was measured in monthly time units, allowing time-varying covariates to be updated at each person-month. Patients who were exposed to PPIs during follow-up were considered unexposed until their first PPI prescription and exposed from then on. Stabilized inverse probability treatment and censoring weights (IPTW and IPCW) were applied to create a pseudo-population that was balanced with regard to measured treatment selection and censoring selection factors that affect the outcome (time-dependent confounders and differential censoring). To obtain IPTWs for each person-months in which a patient had not started using PPIs yet, we estimated the probabilities that a patient received his own observed PPI prescription in a certain month, given the patient's past medical history up to that month. This approach using time-updated information until PPI initiation is similar to the TCPS used in the prevalent new-user design, where the probability to initiate a PPI is calculated based on information prior to each exposure set defined by a PPI prescription. The probability of censoring in each person-month was similarly estimated. Two mechanisms for censoring were considered in the calculation of the IPCW. First, the probability of administrative censoring due to end of study or loss to follow-up in the CPRD. For the analysis with respiratory-related hospitalization as the outcome, deaths were also considered as a censoring event to account for competing risk (118). Second, we also estimated the probability of censoring due to a PPI initiation to account for informative censoring.

The resulting weight from this estimation is comparable to the IPCW to account for informative censoring due to PPI initiation among non-users in the conventional prevalent new-user cohort design.

Outcome

The primary study outcome was death from any cause identified in the CRPD or ONS. Other outcomes of interest were respiratory-related deaths identified in ONS and respiratory related-hospitalization identified in HES. Patients were followed until the earliest of the following events: occurrence of one of the study outcomes, death, lung transplant, end of registration with the general practice, or end of the study period (May 2017).

Covariates

Baseline covariates were identified in the year prior to study cohort entry. Time-varying covariates were identified at each person-month during follow-up in the MSCM. The same covariates were included in the TCPS model of the prevalent new-user cohort design and the model to calculate the IPTW in the MSCM. These variables were age, sex, body mass index, smoking history, excessive alcohol use, ethnicity, prior hospitalizations, co-morbidities and medications. Co-morbidities included asthma, chronic obstructive pulmonary disease, GERD, a history of Nissen fundoplication, cardiovascular disease, diabetes, cancer, renal disease, as well as depression. Medications included oral and inhaled corticosteroids, ACE-inhibitors, beta-blockers, anticoagulants, diuretics, statins, nonsteroidal anti-inflammatory drugs, H2-blockers, and previous PPI use prior to IPF diagnosis. The models to estimate the probability of censoring due to PPI initiation in the conventional prevalent new-user cohort design and the MSCM included the same

covariates. As the amount for missing data was small, e.g. less than 1% for smoking history, it was treated as a separate category in the analyses.

Statistical analyses

Prevalent new-user cohort design

The statistical analyses for both sampling strategies using the prevalent new-user cohort design were the same. However, the conventional prevalent new-user design with non-users additionally accounted for informative censoring due to PPI initiation among non-users by using IPCW, estimated using logistic regression (72). The Cox proportional hazards model was used to estimate the unadjusted and adjusted HR and the 95% CI of all-cause mortality, respiratory-related mortality and respiratory-related hospitalizations associated with PPI use compared to either no user or never use, using a modified intention-to-treat approach. Models were adjusted for potential confounders measured at cohort entry, including age, sex, smoking history, cardiovascular disease, and previous hospitalization. We additionally accounted for competing risk of death for the outcome respiratory-related hospitalizations using IPCW (118). In the weighted analyses in order to take within-subject correlation into account, we calculated 95% CIs for the marginal HRs based on robust standard errors (125).

Marginal structural Cox model

We used pooled logistic regression models to estimate stabilized inverse probability weights (IPTW and IPCW) (124). We fitted the models for the numerator of the weights using baseline covariates only and the models for the denominator of the weights using fixed and time-updated covariates. A time-dependent Cox model weighted by the resulting stabilized weights was then

used to estimate the marginal HR adjusted for potential confounders measured at cohort entry, including age, sex, smoking history, cardiovascular disease, and previous hospitalization. In order to take within-subject correlation into account, we calculated 95% CIs for the marginal HRs based on robust standard errors (125).

All analyses were conducted using SAS (Version 9.4). The study was approved by the Independent Scientific Advisory Committee of the CPRD (Protocol 17_143) and the Ethics Committee of the Jewish General Hospital (JGH Protocol # 2018-769, 17-110), Montreal, Quebec, Canada.

6.6 Results

The base cohort included 2944 patients newly diagnosed with IPF from 2003-2016, with a mean follow-up of 2.1 years (interquartile range 0.8-4.0, maximum 13.6 years). Overall, 1916 (65%) patients were prescribed a PPI at some point after their IPF diagnosis (mean time to PPI initiation was 7.8 months, range 0-136.9 months) (Appendix 1). In total, there were 8277 person-years of follow-up of which 4685 person-years were exposed to PPIs. There were 2136 (73%) deaths from any cause during follow-up. The overall all-cause mortality rate was 25.8 (95% CI 24.7-26.9) per 100 person-years. Median survival was 2.8 years in the full cohort.

Figure 6.1 shows the formation of the base cohort, which was the study cohort for the MSCM, and the matched cohort based on the prevalent new-user cohort design with never-users. Table 6.1 gives an overview of the baseline characteristics in the base cohort, the matched cohort sampling from never-users only, and the matched cohort sampling from all non-users.

Conventional prevalent new-user cohort design with non-users

The study cohort included 1852 PPI users matched to 1852 non-users. Overall, there was no association between all-cause mortality (HR=1.07, 95% CI 0.94-1.22), respiratory-related mortality (HR=1.10, 95% CI 0.94-1.28), or respiratory-related hospitalization (HR=1.00, 95% CI 0.86-1.16) and PPI use compared to no use (Table 6.2). The Kaplan-Meier curve of all-cause mortality among PPI users compared to non-users is displayed in Figure 6.2A.

Prevalent new-user cohort design variant with never-users

There were 1028 never-users and 1916 PPI users in the base cohort of 2944 patients diagnosed with IPF. After time- and TCPS-matching, the study cohort included 1017 PPI users matched to 1017 never-users. The mean follow-up was 1.6 years (median 0.9 years) for never-users and 2.2 years (median 1.4 years) for PPI users. After matching, PPI users were more likely to be female, to have a history of GERD, and to be on more co-medications compared to never-users (Table 6.1). There were 1353 (67%) deaths from any cause during follow-up (range 0-13.4 years). The overall all-cause mortality rate was 34.9 (95% CI 33.0-36.7) per 100 person- years. Median survival was 1.9 years in this cohort. Median survival was 2.2 years in PPI users and 1.6 years in never-users. Among the patients who used PPIs, the incidence rate of death from any cause was 30.7 per 100 per year (95% CI 28.4-33.0). Among matched never-users the incidence rate was 40.6 per 100 per year (95% CI 37.5-43.7). Figure 6.2B shows the Kaplan-Meier curve of all-cause mortality among PPI users compared to never-users.

PPI users had lower risk of all-cause mortality (HR=0.82, 95% CI 0.73-0.91) and respiratory related death (HR=0.85, 95% CI 0.74-0.98) compared to never use (Table 6.2). The HR of

respiratory-related hospitalization associated with PPI use was 0.91 (95% CI 0.76-1.08) compared to never use.

Marginal structural Cox model

This cohort study included all 2944 patients diagnosed with IPF, including 1916 who were prescribed a PPI at some point. There were 1376 deaths out of 2136 that occurred in PPI users. The mortality rate among exposed follow-up was 29.4 (95% CI 27.8-30.7) per 100 person-years. Among unexposed follow-up it was 21.2 (95% CI 19.7-22.7) per 100 person-years. The median survival from IPF diagnosis was 2.2 years in the PPI user group and 3.5 years in the non-user group. Figure 6.2C displays the weighted Kaplan-Meier curves by treatment group.

Using the MSCM approach and after adjustment for potential confounders, the HR of all-cause mortality associated with PPI use was 1.08 (95% CI 0.85-1.38) compared with non-use (Table 6.2). The HR for respiratory-related mortality was 1.00 (95% CI 0.73-1.36) and for respiratory-related hospitalizations it was 1.16 (95% CI 0.98-1.37). Figure 6.3 shows that HRs for the three outcomes estimated under the three approaches.

6.7 Discussion

We explored alternative approaches to assess the effectiveness of treating IPF with PPIs, compared with non-use. The unique methodological challenge in this study was the large proportion of the cohort (65%) exposed to PPIs at some point during follow-up, which introduced censoring. Consequently, the conventional prevalent new-user cohort design with non-users as the comparison group had to account for informative censoring and found no association between PPI

use and mortality (HR=1.07). In contrast, a variant of the prevalent new-user cohort design that avoided censoring by sampling the comparison group exclusively from the never-users resulted in a significantly lower risk of mortality with PPIs (HR=0.82). In comparison, the marginal structural Cox model approach yielded a similar estimate to the conventional prevalent new-user cohort design (HR=1.08). We discuss how the approaches led to different results and consider their feasibility in addressing informative censoring.

The variant to the prevalent new-user cohort design based on sampling exclusively from never-users of PPIs as the comparator group resulted in a HR of 0.82 (95% CI 0.73-0.91) of all-cause mortality associated with PPI use. While this unexposed comparator group avoided the issue of informative censoring, which had to be adjusted for in the conventional prevalent new-user cohort design, it introduced selection bias by conditioning on future exposure information (126, 127). These never-users likely included either patients who were healthy survivors and did not ever require a prescription for PPIs or patients who were too sick to receive a prescription and died early. The latter patient group can explain why PPI use seemed to be even already effective at six months with regard to mortality (HR=0.73, 95% CI 0.60-0.88) (Appendix 2). Never-users were more likely to die shortly after their IPF diagnosis compared to PPI users (Appendix 3). This led to a higher mortality rate and shorter follow-up among never-users. Indeed, the mortality rate among never-users in this cohort was 40.6 (95% CI 37.5-43.7) per 100 person-years compared to 24.3 (95% CI 22.2-26.5) per 100 person-years among non-users in the conventional prevalent new-user cohort design with non-users. We also found that 79 (89%) of 89 patients who received their IPF diagnosis during a hospital stay or at discharge were never-users which shows that these patients were more likely to have more severe disease. Another indication for poorer health could also be the overall lower use of other medications in the never-user group, where physicians did

not prescribe unnecessary medications. Therefore, by choosing never use as the comparator group and thus primarily selecting patients with poor health, the mortality rate in the comparator group was inflated, and PPI use appeared to be beneficial. Even though choosing never use as the comparison group seems to be a quick fix to avoid informative censoring, it will introduce selection bias at the study design level, which cannot be corrected using data analytical methods.

The marginal structural Cox model approach is useful in the presence of time-varying confounding due to the time-varying nature of exposure and the absence of an active comparator in this study (111). For example, patients who receive a PPI prescription are likely to be different to a non-user with regard to their health status at the same point during follow-up, which may also affect their likelihood of death. The MSCM creates a re-weighted pseudo patient population that would lead to balanced treatment groups of PPI new-users and non-users with regard to time-varying predictors of treatment and includes inverse probability of censoring weights to account for informative censoring due to a PPI initiation (111).

This analysis showed the similarity between the MSCM approach and the conventional prevalent new-user cohort design. Indeed, both approaches estimate the probability to initiate treatment based on time-varying patient characteristics up until the first PPI prescription and account for informative censoring using IPCW. It is thus not surprising that the resulting HRs of all-cause mortality associated with PPI use were similar between the MSCM (1.08; 95% CI 0.85-1.38) and the prevalent new-user approach (1.07; 95% CI 0.94-1.22). However, while the point estimates were similar, the confidence interval for the MSCM was wider. Although both methods adjusted for informative censoring, this 91% wider confidence interval on the log scale may be due to the use of inverse probability weighting by the MSCM to adjust for confounding compared with the 1:1 matching used in conventional prevalent new-user approach. Such weighting for confounding

can decrease the precision in the presence of extreme weights. Truncation of these weights could lead to more precise effect estimates but could also affect the control of confounding (Appendix 4) (124, 128). More research is needed to evaluate the impact of these approaches on the precision of these estimates.

Despite the similar findings, there may be some advantages of one approach over the other. The cohort formation in the MSCM is less complex than in the prevalent new-user cohort design, but the data analytical techniques are more challenging. However, for the typical consumer of clinical research, the prevalent new-user cohort design may be simpler because of its resemblance to the randomized controlled trial in terms of data presentation, which is not the case for the MSCM. Indeed, for example, Table 6.1 presents the exposed and unexposed group at cohort entry, making these two groups directly comparable with respect to the time-dependent covariates. Outcome events are also directly attributed to the comparison groups, rather than to exposed and unexposed person-time. In addition, this analysis suggests that it may also result in increased precision, though this needs further research for confirmation.

This study has several strengths. This study provided alternative strategies for comparative effectiveness studies in the absence of an active comparator and a high degree of informative censoring using real-world data. We used approaches, such as the prevalent new-user cohort design and marginal structural models, to minimize confounding. Moreover, we accounted for informative censoring due to the high frequency of PPI initiation in the unexposed group, which had not been an issue in prior applications of the prevalent new-user design where exposure was relatively infrequent. There are also limitations. First, using inverse probability weighting in the MSCM may be more similar to sampling with replacement. In the prevalent new-user cohort design, the matches were sampled without replacement. Future research studies need to evaluate

sampling with replacement in the prevalent new-user cohort design. Second, inverse probability weights, as applied in the MSCM and as control for informative censoring, are only valid if the measured covariates are sufficient to adjust for both confounding and selection bias due to loss of follow-up (110). It also assumes that the models for initiation of PPIs and censoring, given the past, are correctly specified. Thus, residual confounding and differential censoring may still be present in the re-weighted study populations.

In summary, the prevalent new-user cohort design variant that only selected never-users to circumvent informative censoring introduced selection bias by conditioning on future exposure and should be avoided when choosing the comparator group in the prevalent new-user cohort design. The MSCM and the conventional prevalent new-user cohort design produced similar results and can both be used in the absence of an active comparator and when informative censoring is present. The prevalent new-user cohort design may be favoured by some because of its simplicity and familiarity in data presentation and improved precision.

6.8 Tables

Table 6.1 Baseline characteristics of patients with IPF at diagnosis (base cohort) and according to exposure at study cohort entry, United Kingdom, 2003-2016

	Study cohort						
	Base cohort	Sampling from non-users			Sampling from never-users		
Covariates		PPI use	No use of PPIs	Stand. diff.	PPI use	Never use of PPIs	Stand. diff.
Number of patients with IPF	2944	1852	1852		1017	1017	
Mean (SD) age at diagnosis [years]	75.8 (9.5)	75.4 (9.4)	75.6 (9.5)	-0.02	76.2 (9.5)	76.7 (9.6)	-0.06
Men	1884 (64.0)	1150 (62.1)	1209 (65.3)	-0.07	636 (62.5)	685 (67.4)	-0.10
Mean (SD) IPF duration [years]	-	0.5 (0.9)	0.5 (0.9)	0.02	0.5 (0.9)	0.5 (0.9)	0.02
BMI [kg/m^2]				0.05			0.13
<25	832 (28.3)	549 (29.6)	531 (28.7)		310 (30.5)	326 (32.1)	
25-30	1060 (36.0)	663 (35.8)	692 (37.4)		341 (33.5)	357 (35.1)	
≥30	702 (23.9)	466 (25.2)	439 (23.7)		257 (25.3)	201 (19.8)	
Unknown	350 (11.9)	174 (9.4)	190 (10.3)		109 (10.7)	133 (13.1)	
Smoking status				0.03			0.06
Ex-smoker	1403 (47.7)	866 (46.8)	873 (47.1)		466 (45.8)	466 (45.8)	
Non-smoker	1049 (35.6)	674 (36.4)	657 (35.5)		369 (36.3)	347 (34.1)	
Smoker	453 (15.4)	299 (16.1)	309 (16.7)		174 (17.1)	191 (18.8)	
Unknown	39 (1.3)	13 (0.7)	13 (0.7)		8 (0.8)	13 (1.3)	
Alcohol-related disorders	831 (28.3)	537 (29.0)	551 (29.8)	0.05	290 (28.5)	290 (28.5)	0.00
Ethnicity				0.08			0.11
White	2683 (91.1)	1715 (92.6)	1698 (91.7)		932 (91.6)	904 (88.9)	
Other	83 (2.8)	59 (3.2)	52 (2.8)		28 (2.8)	19 (1.9)	
Unknown	178 (6.1)	78 (4.2)	102 (5.5)		57 (5.6)	94 (9.2)	
Medical history prior to cohort entry							
Hospitalization[a]	1424 (48.4)	1066 (57.6)	982 (53.0)	0.09	547 (53.8)	508 (50.0)	0.08
Asthma	586 (19.9)	410 (22.1)	379 (20.5)	0.04	196 (19.3)	147 (18.0)	0.03
COPD	707 (27.1)	595 (32.1)	576 (31.1)	0.02	310 (30.5)	308 (30.3)	0.00
GERD	551 (18.7)	481 (26.0)	348 (18.8)	0.17	117 (11.5)	86 (8.5)	0.10
Arrhythmia	421 (14.3)	297 (16.0)	300 (16.2)	0.01	159 (15.6)	147 (14.5)	0.03
Heart failure	586 (19.9)	410 (22.1)	398 (21.5)	0.00	233 (22.9)	224 (22.0)	0.02
Hypertension	1594 (54.1)	1076 (58.1)	1042 (56.3)	0.02	575 (56.5)	530 (52.1)	0.09
Pulmonary hypertension	54 (1.8)	50 (2.7)	44 (2.4)	0.04	33 (3.2)	25 (2.5)	0.05
Myocardial infarction	370 (12.6)	277 (15.0)	239 (12.9)	0.02	126 (12.4)	114 (11.2)	0.09
Stroke	229 (7.8)	149 (8.1)	144 (7.8)	0.06	91 (9.0)	99 (9.7)	-0.03
Diabetes Mellitus	430 (14.6)	286 (15.4)	255 (13.8)	0.01	136 (13.4)	139 (13.7)	-0.01
Cancer	471 (16.0)	341 (18.4)	322 (17.4)	0.05	210 (20.7)	170 (16.7)	0.10
Lung cancer	25 (0.9)	31 (1.7)	23 (1.2)	0.03	16 (1.6)	15 (1.5)	0.01

Covariates	Study cohort						
	Base cohort	Sampling from non-users			Sampling from never-users		
		PPI use	No use of PPIs	Stand. diff.	PPI use	Never use of PPIs	Stand. diff.
Renal disease	717 (24.4)	511 (27.6)	493 (26.6)	0.04	276 (27.1)	260 (25.6)	0.04
Depression	429 (14.6)	305 (16.5)	281 (15.2)	0.02	140 (13.8)	124 (12.2)	0.05
Medications prescribed in the year prior to cohort entry							
Inhaled corticosteroids	368 (12.5)	240 (13.0)	230 (12.4)	0.02	133 (13.1)	120 (11.8)	0.04
Oral corticosteroids	645 (21.9)	675 (36.5)	587 (31.7)	0.10	535	293	0.12
Azathioprine	61 (2.1)	66 (3.6)	53 (2.9)	0.04	33(3.2)	28 (2.8)	0.03
Angiotensin converting enzyme inhibitors	895 (30.4)	575 (31.1)	556 (30.0)	0.02	299 (29.4)	310 (30.5)	-0.02
Angiotensin II receptor blockers	12 (0.4)	8 (0.4)	7 (0.4)	0.01	<5	<5	0.00
Beta blockers	760 (25.8)	533 (28.8)	481 (26.0)	0.06	280 (27.5)	235 (23.1)	0.10
Diuretics	1334 (45.3)	863 (46.6)	826 (44.6)	0.04	474 (46.6)	462 (45.4)	0.02
Anticoagulants	302 (10.3)	199 (10.8)	218 (11.8)	-0.03	117 (11.5)	126 (12.4)	-0.03
Antiplatelet	1202 (40.8)	859 (46.4)	790 (42.7)	0.08	420 (41.3)	353 (34.7)	0.14
Statins	1275 (43.3)	914 (49.4)	853 (46.1)	0.07	426 (41.9)	379 (37.3)	0.09
NSAIDs	366 (12.4)	241 (13.0)	214 (11.6)	0.04	119 (11.7)	72 (7.1)	0.16
H2-Blockers	166 (5.6)	117 (6.3)	111 (6.0)	0.01	84 (8.3)	60 (5.9)	0.09
PPIs in the year prior IPF diagnosis	1318 (44.8)	1153 (62.3)	840 (45.4)	0.34	442 (43.5)	148 (14.6)	0.67

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IPF, idiopathic pulmonary fibrosis; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SD, standard deviation.

[a] in the year prior to cohort entry

Table 6.2 Comparison of crude and adjusted hazard ratios for the association between the use of PPIs after IPF diagnosis and study outcomes compared to no use, obtained from three different study designs (United Kingdom, 2003-2016): the conventional prevalent new-user cohort design with sampling from all non-users, the prevalent new-user cohort design variant with sampling from never-users only, and the marginal structural Cox model.

a) Study outcome all-cause mortality

Exposure	N	Number of events	Person-years	Incidence rate (95% CI) per 100 person-years	Crude HR	Adjusted HR (95% CI)
Conventional prevalent new-user cohort design						
PPI use	1852	1221	4390	27.8 (26.2-29.4)	1.20	1.07 (0.94-1.22)*
No use	1852	482	1978	24.3 (22.2-26.5)	1.00	1.00
Prevalent new-user cohort design variant with never-users						
PPI use	1017	684	2231	30.7 (28.4-33.0)	0.79	0.82 (0.73-0.91)**
Never use	1017	669	1647	40.6 (37.5-43.7)	1.00	1.00
Marginal structural Cox model						
PPI use	1916[a]	1376	4685	29.4 (27.9-31.0)	1.37	1.08 (0.85-1.38)***
No use	2821[a]	760	3592	21.2 (19.7-22.7)	1.00	1.00

b) Study outcome respiratory-related mortality

Exposure	N	Number of events	Person-years	Incidence rate (95% CI) per 100 person-years	Crude HR	Adjusted HR (95% CI)
Conventional prevalent new-user cohort design						
PPI use	1852	821	4390	18.7 (17.4-20.0)	1.28	1.10 (0.94-1.28)[b]
No use	1852	304	1978	15.4 (13.6-17.1)	1.00	1.00
Prevalent new-user cohort design variant with never-users						
PPI use	1017	461	2231	20.7 (18.8-22.6)	0.82	0.85 (0.74-0.98)[c]
Never use	1017	436	1647	26.5 (24.0-29.0)	1.00	1.00
Marginal structural Cox model						
PPI use	1916[a]	932	4685	19.9 (18.6-21.2)	1.44	1.00 (0.73-1.36)[d]
No use	2821[a]	491	3592	13.7 (12.5-14.9)	1.00	1.00

c) Study outcome respiratory-related hospitalization

Exposure	N	Number of events	Person-years	Incidence rate (95% CI) per 100 person-years	Crude HR	Adjusted HR (95% CI)
Conventional prevalent new-user cohort design						
PPI use	1852	849	3532	24.0 (22.4-25.7)	1.13	1.00 (0.86-1.16)[b]
No use	1852	403	1713	23.5 (21.2-25.8)	1.00	1·00
Prevalent new-user cohort design variant with never-users						
PPI use	1017	441	1807	24.4 (22.1-26.7)	0.90	0.91 (0.76-1.08)[c]
Never use	1017	399	1385	28.8 (26.0-31.6)	1.00	1.00
Marginal structural Cox model						
PPI use	1916[a]	792	3479	22.8 (22.2-24.4)	1.22	1.16 (0.98-1.37)[d]
No use	2821[a]	659	3055	21.6 (19.9-23.2)	1.00	1.00

Abbreviations: CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor.

[a] Number of patients who were PPI-users or non-users at some point during follow-up. Patients in the marginal structural model could contribute person-time to both comparison groups.

[b] After matching on time-conditional propensity score, further adjusted for age, sex, smoking, history of hospitalization in the year prior to cohort entry, and concomitant cardiovascular disease, and weighted by inverse probability of censoring weights. 95% CIs were calculated based on robust standard errors.

[c] After matching on time-conditional propensity score, further adjusted for age, sex, smoking, history of hospitalization in the year prior to cohort entry, and concomitant cardiovascular disease.

[d] Weighted by inverse probability of treatment and censoring weights and adjusted for age at IPF diagnosis, sex, history of smoking, history of hospitalization in the year prior to IPF diagnosis, and cardiovascular disease at the time of IPF diagnosis. 95% CIs were calculated based on robust standard errors.

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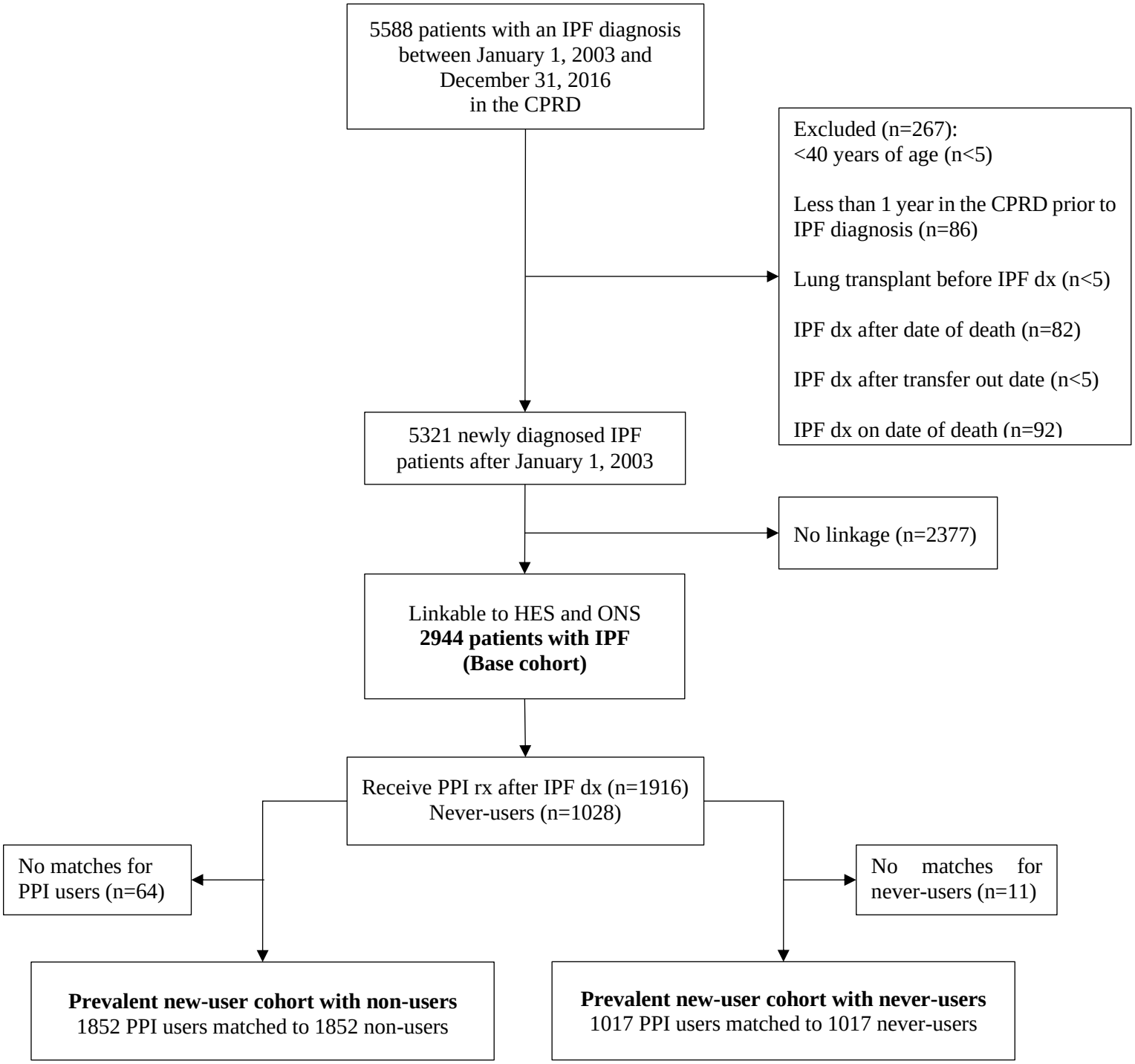
6.9 Figures

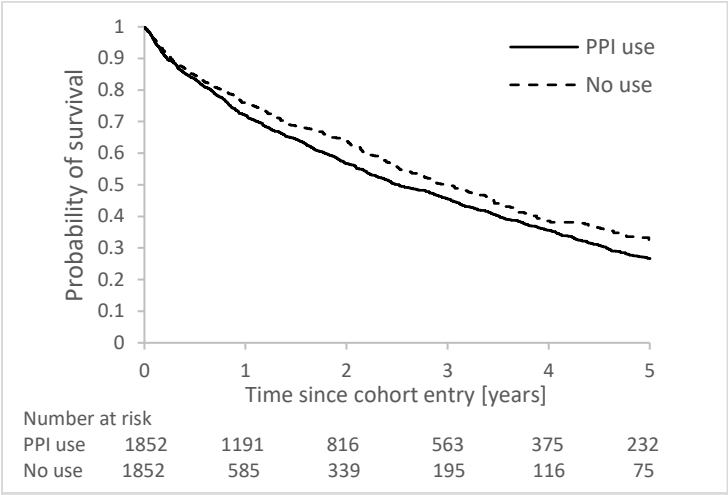
Figure 6.1 Flowchart describing the selection of the study cohorts of patients with IPF in the United Kingdom Clinical Practice Research Datalink between 2003 and 2016.



Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; IPF, idiopathic pulmonary fibrosis; ONS, Office for National Statistics; PPI, proton pump inhibitor.

Figure 6.2 Kaplan-Meier curves of all-cause mortality comparing proton pump inhibitor (PPI) use (solid line) to the comparison group (dashed line) in patients diagnosed with IPF in the United Kingdom (2003-2016) based on the A) conventional prevalent new-user cohort design (weighted by inverse probability of censoring weights), B) the prevalent new-user cohort design with never-users, and C) the marginal structural Cox model (weighted by inverse probability of treatment and censoring weights).

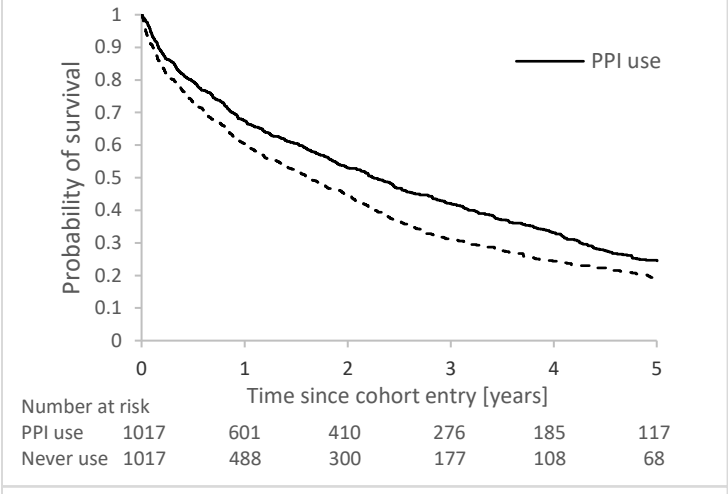
A)



Number at risk

PPI use	1852	1191	816	563	375	232
No use	1852	585	339	195	116	75

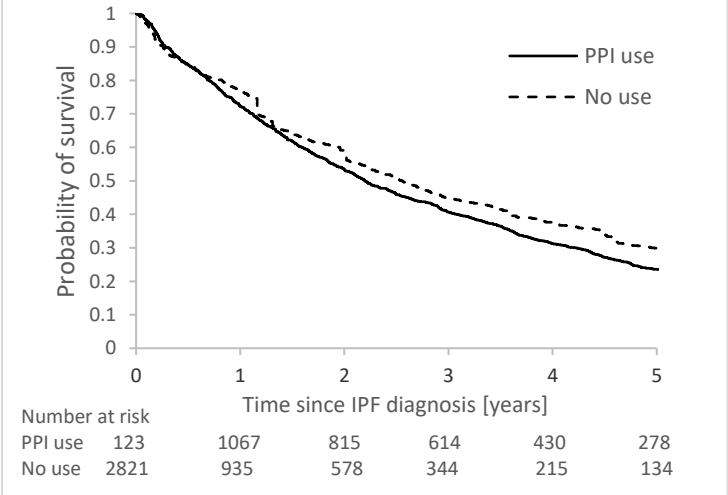
B)



Number at risk

PPI use	1017	601	410	276	185	117
Never use	1017	488	300	177	108	68

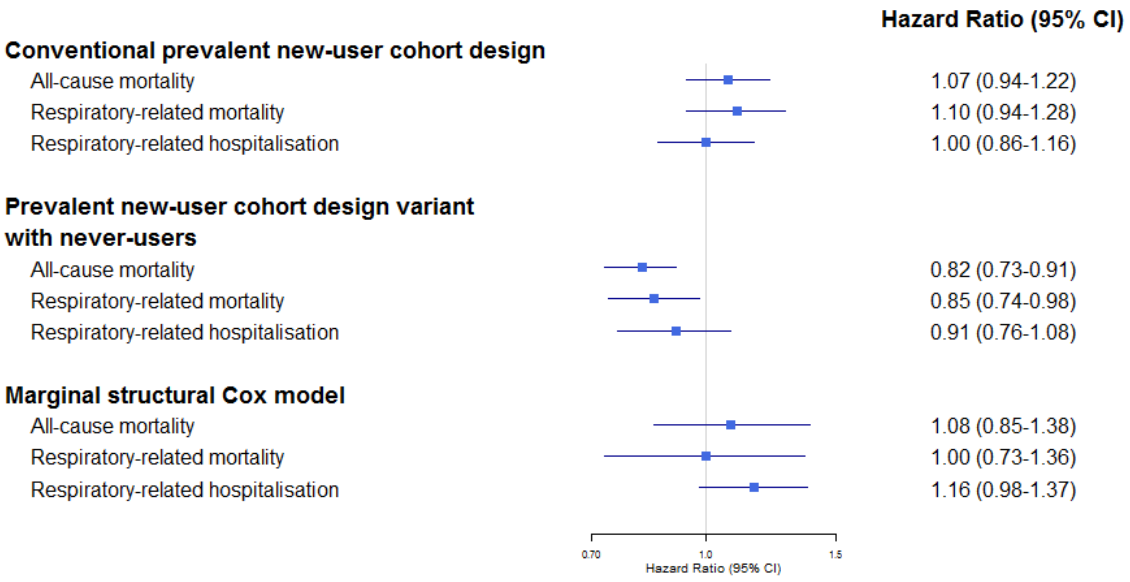
C)



Number at risk

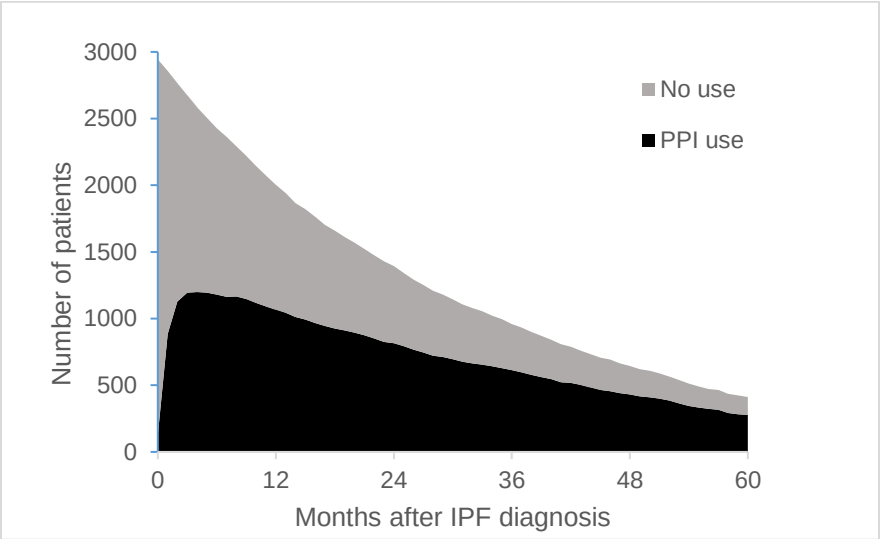
PPI use	123	1067	815	614	430	278
No use	2821	935	578	344	215	134

Figure 6.3 Forest plot of the hazard ratios and 95% confidence intervals (CI) of each outcome associated with proton pump inhibitor use compared to no use in each study design in a cohort of patients with IPF, United Kingdom, 2003-2016.



6.10 Appendix

Appendix 6.1 Number of patients at risk who were exposed and not exposed to proton pump inhibitors (PPIs) according to months after IPF diagnosis, United Kingdom, 2003-2016. The figure demonstrates that the number of PPI users among the patients with IPF at risk increased over time.

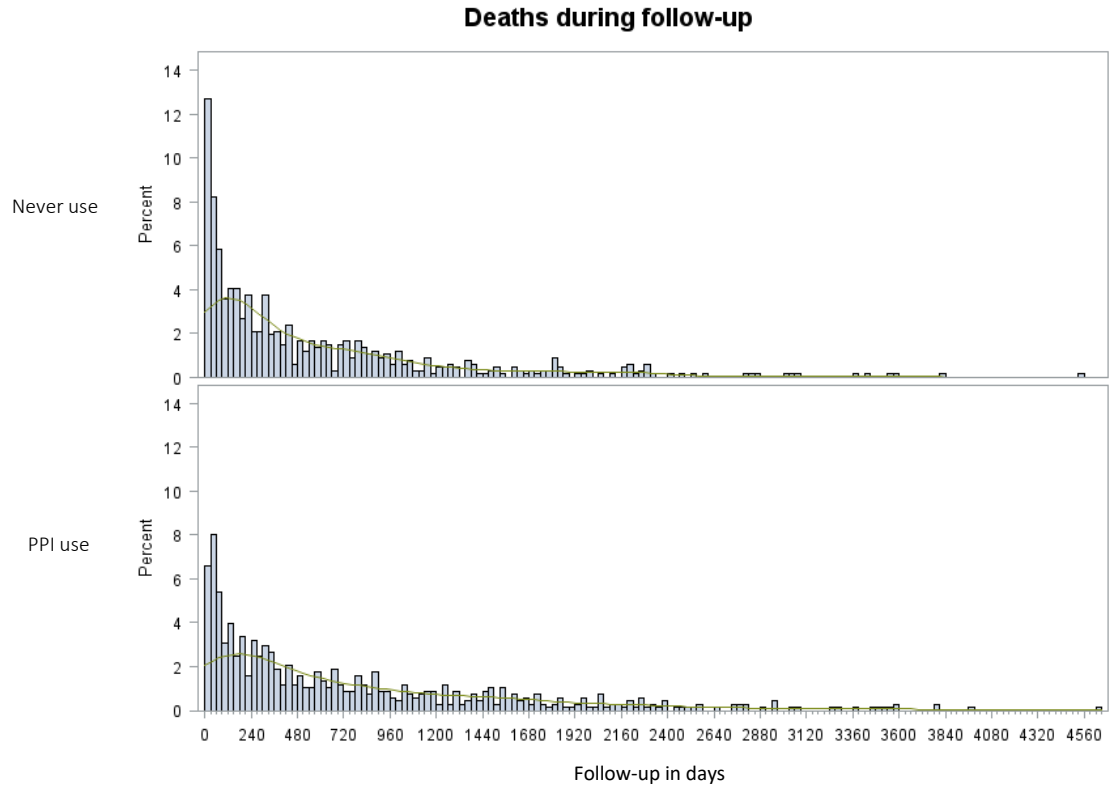


Appendix 6.2 Crude and adjusted hazard ratios (HR) of all-cause mortality at 6 months after IPF diagnosis associated with PPI use compared to never use.

Exposure	N	Number of events	Person-years	Incidence rate (95% CI) per 100 person-years	Crude HR	Adjusted HR (95% CI)*
PPI use	1017	204	434	47.0 (40.5-53.4)	0.73	0.73 (0.60-0.88)
Never use	1017	262	399	65.7 (57.8-73.7)	1.00	1.00

* After matching on time-conditional propensity score, further adjusted for age, sex, smoking, history of hospitalization in the year prior to cohort entry, and concomitant cardiovascular disease.

Appendix 6.3 Distribution of timing of death after IPF diagnosis during follow-up in never-users compared to PPI users. Never-users (upper graph) died earlier during follow-up compared to PPI users (lower graph).



Appendix 6.4 Impact of truncation of the stabilized weights on the estimated association between PPI use and all-cause mortality. No truncation of weights corresponds to the marginal structural model used in this study. The analysis with truncated weights decreases the control of bias but increases the precision of the effect estimate.

Truncation	**Estimated weight**		**Treatment association estimate**	
	Mean (SD)	**Range**	**HR (95% CI)***	**Standard error**
None	1.11 (3.9)	0.02-676.73	1.08 (0.85-1.38)	0.12
1^{st} and 99^{th} percentile	1.05 (0.6)	0.21-7.34	1.22 (1.09-1.35)	0.05

*Weighted by inverse probability of treatment and censoring weights and adjusted for age at IPF diagnosis, sex, history of smoking, history of hospitalization in the year prior to IPF diagnosis, and cardiovascular disease at the time of IPF diagnosis. 95% CIs were calculated based on robust standard errors.

7 Discussion

7.1 Summary of findings

The work presented in this thesis offers a detailed picture of the effectiveness of PPIs on survival in IPF which had remained unclear despite a conditional recommendation for anti-acid therapy in IPF treatment guidelines (6, 114). First, given the inconsistent results of anti-acid therapy on mortality reported in the 2015 IPF treatment guidelines, we conducted a methodological review to examine observational studies on the association between anti-acid therapy and mortality, with a particular focus on immortal time bias in these studies. Manuscript 1 found that the highly beneficial findings associating anti-acid therapy with improved survival in previous observational studies were a result of immortal time bias in 4 out of 5 studies (Chapter 4), a bias that had not been discussed in the field of IPF before. Studies without immortal time bias consistently found no association between anti-acid treatment and mortality. This review also revealed several shortcomings in studies without immortal time bias, which highlighted the necessity for a well-designed large longitudinal observational study to evaluate the effectiveness of PPIs in IPF on all-cause mortality, respiratory-related mortality, and the incidence of respiratory-related hospitalizations. Second, using a large longitudinal population-based database and applying the novel prevalent new-user cohort design to reduce confounding in comparative effectiveness research in the absence of an active comparator, we found that PPI use did not lead to reduced mortality or incidence of hospitalization compared to no use in patients with IPF (Chapter 5). Manuscript 2 furthermore showed that informative censoring needs to be considered in the estimation of PPI effectiveness in IPF due to the high incidence of PPI prescriptions. We accounted for informative censoring in this study using inverse probability of censoring weights. Finally, as the prevalent new-user cohort design with weighted analysis had not been used before, we applied

two alternative approaches to address confounding and informative censoring in studies of PPI effectiveness in IPF and compared these to the original effectiveness study. The first approach was a variant of the prevalent new-user design comparing PPI use to never use to avoid informative censoring. The second approach used a marginal structural model with inverse probability weights to address time-varying confounding and differential censoring. Manuscript 3 found that the first approach led to selection bias and should be avoided. The marginal structural model produced similar results as estimated in the conventional prevalent new-use design (Chapter 6), with no association between PPI use and mortality or incidence of hospitalization in patients with IPF. These results affirm that PPIs may not be as beneficial in treating PPIs as initially suggested.

7.2 Research implications

The results in this dissertation show that PPIs are not as beneficial in treating IPF as suggested in some previous observational studies and international IPF treatment guidelines (6). Survival benefits were a result of immortal time bias, which continues to occur in observational drug effectiveness studies, either due to selection bias or exposure misclassification (61, 101). Quality assessment tools in systematic reviews on observational studies in pharmacoepidemiology should specifically address pharmacoepidemiology biases to prevent biased pooled estimates that included biased studies in the meta-analysis. Around the same time of the publication of our methodological review, a systematic review with meta-analysis was published on the treatment of gastroesophageal reflux in patients with IPF (63). However, this study did not assess any pharmacoepidemiology biases and concluded that low-quality evidence had shown that treatment of gastroesophageal reflux was associated with a reduction in IPF-related mortality but not all-cause mortality when compared to no use. The importance of critical appraisal in the field of IPF

was highlighted in an editorial written on manuscript 1 in the European Respiratory Journal (70). Particularly in the field of IPF, where only pirfenidone and nintedanib have shown to reduce the rate of decline in lung function and slow disease progression but no or small survival benefits (7, 129), researchers and clinicians should be suspicious if a treatment not directly related to IPF suddenly improves survival by 50%.

While some studies have suggested that PPIs may have a pleiotropic effect that goes beyond acid suppression in IPF (17), these *in vitro* and *in vivo* findings should be replicated before a trial on PPIs on disease progression in IPF is carried out. Furthermore, the biological mechanism through which GERD or microaspiration may contribute to disease progression in IPF is still not well understood. As GERD is a prevalent co-morbidity in IPF (50), many patients with IPF will receive PPIs to treat their acid reflux. However, the few studies that indicated a potential benefit of PPIs in IPF raised more questions than answers, resulting in publications titled "Idiopathic Pulmonary Fibrosis: Increased Survival with "Gastroesophageal Reflux Therapy" Fact or Fallacy?" (130) or "Antacid therapy in idiopathic pulmonary fibrosis: more questions than answers?" (114). It is still unclear if and how GERD may affect IPF, whether PPIs could be effective in patients without GERD, which clinical outcomes would be most relevant to assess whether PPIs could be effective in IPF in patients without GERD, and whether there are potential risks related with long-term use of PPIs. Thus, the discussion regarding the relationship between GERD and IPF and consequently anti-acid therapy with or without GERD in IPF continues, with several experts highlighting the need for more robust evidence, including RCTs (70, 114, 130, 131). Based on the available evidence, certain national guidelines have altered their treatment recommendations, and no longer recommend anti-acid treatment for IPF regardless of the presence of GERD but note that GERD or reflux symptoms in patients with IPF should be treated with anti-acids (130, 132). My findings

fit with the emerging literature, that questions the effectiveness of PPIs in IPF, and the changes made in certain national IPF treatment guidelines. My thesis contributes to the evidence that anti-acid treatment and PPIs should not be recommended to treat IPF regardless of the presence of GERD based on the previously suggested potential survival benefit.

When conducting comparative effectiveness research, one concern in observational studies is confounding by indication, which is not present in RCTs due to randomization (133). Using an active comparator and new-user for the same indication at the same stage of disease can reduce this bias (134). However, in the absence of an active comparator, finding an appropriate comparison group is more challenging. Manuscripts 2 and 3 in this dissertation used data from a large population-based primary care database and showed that the novel prevalent new-user cohort design with matching on time and TCPS can be used when there is no active comparator and when the exposure of interest is common. As non-users were censored at the time of their first PPI prescription, the high incidence of PPIs during follow-up led to a significant amount of potential informative censoring. We addressed this by using IPCW, a technique based on weighted analysis (72). However, as this approach to account for dependent censoring has not been applied in the prevalent new-user cohort design before, it was necessary to compare this design to other methods, such as the marginal structural model, which uses inverse probability weights to create comparable treatment groups with regard to time-varying confounding and differential censoring. The results in both approaches were similar, demonstrating that matching on time and TCPS in the prevalent new-user approach is similar to the IPTW in the marginal structural model. The prevalent new-user cohort design additionally increased the precision of the effect estimate, resulting in narrower confidence intervals. This thesis demonstrated a novel feasible approach to conduct comparative

effectiveness research using real-world data in the absence of an active comparator and when informative censoring is present.

7.3 Limitations

One of the strengths of the observational studies in this thesis was the population-based data that it used. This allowed us to capture a large cohort of patients with IPF and follow their management in primary care. We noted several specific strengths and limitations throughout the three manuscripts presented in this thesis. However, there were also overarching limitations and research challenges in this thesis that I will further elaborate.

The CPRD is a primary care database, whereas IPF is diagnosed by a specialist. Thus, there is potential for misclassification of IPF diagnoses, including a delay in diagnosis which could explain the mean age of 75 years at diagnosis in our cohort. However, as GPs function as gate-keepers in the UK, diagnostic codes for IPF recorded in the CPRD will likely be accurate and reflect disease management in primary care. Furthermore, diagnostic guidelines for IPF have changed over time (5, 31-33) leading to another potential source of diagnostic misclassification. We attempted to reduce misclassification in several ways: we only included IPF diagnoses after 2003, one year after the consensus statement on the definition of IPF (32) and we excluded other known causes of ILD. We therefore expect that the majority of patients in our cohort have IPF or a fibrotic interstitial lung disease behaving like IPF. Additionally, by further restricting our study cohort to patients who had a record of a diagnostic test, such as lung biopsy or chest imaging, or an additional diagnostic code for IPF recorded in the HES, we created a subset of patients that was more likely to have an accurate IPF diagnosis. Estimates in this subset were similar to estimates obtained in the study cohort overall, which was reassuring.

Another limitation is the potential for exposure misclassification. Even though prescription data in the CPRD are well documented, there is no data available on PPI prescriptions written in hospital, by specialists, or on over-the-counter use leading to potential exposure misclassification. However, secondary care-initiated PPI treatment is usually continued by GPs (90, 91). Furthermore, most specialized clinics for interstitial lung diseases operate under a "shared-care" model where GP and specialists follow and monitor the patient longitudinally to provide regular, easy to access support to patients with IPF (135-137). Despite the over-the-counter availability of PPIs, uptake is reported to be low and the number of PPI prescriptions continues to rise in the UK (91, 138). Additionally, prescription medications are free without any co-payment at dispensation for patients older than 60 years, making over-the-counter use less likely in this population. In manuscript 2 and 3, we defined patients as being exposed to PPIs based on one prescription. We could have potentially misclassified exposure status if patients with IPF did not adhere to or discontinued the prescribed PPI during follow-up. By using a modified intention-to-treat approach in our analysis, non-adherence or discontinuation was also not accounted for among PPI users. Given that our analysis compared PPI use to no use, it is possible that the effect estimates were thus slightly overestimated. Still, misclassification due to lack of adherence is less likely among long-term PPI recipients who receive monthly PPI prescriptions over a long period of time. When we restricted the follow-up to one year to reduce exposure misclassification in manuscript 2, results were in accordance with the findings in the primary analysis.

Pharmacoepidemiology studies often distinguish between new and prevalent drug users (139). While the analyses in manuscript 2 and 3 studies new-users of PPIs after IPF diagnosis, these patients could have used PPIs prior to their IPF diagnosis and were technically not truly new-users. However, the underlying research question was whether patients diagnosed with IPF should start

treatment with PPIs regardless of whether they had used PPIs before their IPF diagnosis, i.e. whether they had GERD, which is in accordance with the IPF treatment recommendation that suggests routine treatment with anti-acid therapy among all patients with IPF. This was reflected in the primary analysis in manuscript 2. I conducted sensitivity analyses to separately assess the effect of PPIs among patients who used PPIs prior to their IPF diagnosis and who did not and found that results differed in these two subgroups. While the analyses indicated that the subpopulations – with and without a history of PPI use before IPF diagnosis - were likely different, restricting the analyses to either one of these two subgroups significantly reduced the sample size and the generalizability of the findings.

Another limitation is that we were not able to control directly for disease severity in this work, which is used to guide treatment choices in IPF and assess prognosis (140). Even though the CPRD contains information on laboratory results, including lung function tests, these data are not routinely recorded for patients with IPF. Nevertheless, by matching on disease duration and time-conditional propensity scores that were based on the medical history of patients, and adjusting for potential confounders in the analyses, confounding due to disease severity is less likely to be differential with regards to the exposed and unexposed groups.

7.4 Conclusions and opportunities for future research

The discussion of treatment for GERD as a potential treatment option for IPF that started more than a decade ago is still ongoing. Even though the effectiveness of anti-acid therapy in IPF has been questioned by many researchers and clinicians, the current IPF treatment guidelines still conditionally recommend treatment for GERD to treat IPF. This thesis provides evidence showing that anti-acid therapy, including PPIs, should not be recommended as a treatment option based on

the potential survival benefit that has been observed in some previous observational studies. Further research to gain a better insight into the potential biological mechanism between PPIs and IPF is needed before large scale RCTs are conducted to assess the effectiveness of PPIs on other outcomes in IPF. The work in my thesis also introduced a novel approach that can be used in comparative effectiveness research using real-world healthcare data, when there is no active comparator and informative censoring is present. Future pharmacoepidemiology research affected by these two shortcomings can use this approach to overcome these limitations. While the prevalent new-user cohort and marginal structural model approaches produced the same point estimates, the confidence limits of the former were tighter which may be beneficial when greater precision is required. Further research comparing the accuracy and precision of these two alternative techniques would be valuable.

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