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Antifibrotics and Reduced Mortality in Idiopathic Pulmonary Fibrosis: Immortal Time Bias

To the Editor:

Pirfenidone and nintedanib, antifibrotic medications approved for the treatment of patients with mild to moderate idiopathic pulmonary fibrosis (IPF), have been shown to slow the decline in lung function and are recommended by international treatment guidelines (1).

Meta-analyses of randomized trials of this treatment have investigated their effects on reducing mortality in patients with IPF, with rather divergent conclusions (2–6). Indeed, whereas a meta-analysis concluded that neither pirfenidone nor nintedanib is associated with lower mortality (2), others found reduced mortality only with nintedanib but not pirfenidone (3), or vice-versa (6). Meta-analyses conducted specifically among trials for only one of the antifibrotic drugs concluded a mortality benefit (4, 5).

On the other hand, observational studies have consistently reported remarkable reductions in mortality with antifibrotic medications (7). Such remarkable effects from observational studies are often the result of time-related biases, such as immortal time bias that tends to considerably exaggerate the benefit of drugs, including those used to treat respiratory diseases (8).

Given these inconsistencies, we reviewed the observational studies examining the effect of antifibrotics on mortality in IPF, focusing on time-related biases that could explain these discrepancies.

The Observational Studies

We searched the literature using MEDLINE and Embase for all observational studies of any antifibrotic reporting on mortality in patients with IPF (until January 24, 2022) and identified 14 studies reporting relative risks of death associated with antifibrotic use (9–22). The pooled relative risk of all-cause mortality with antifibrotic use was 0.62 (95% confidence interval [CI], 0.56–0.69) compared

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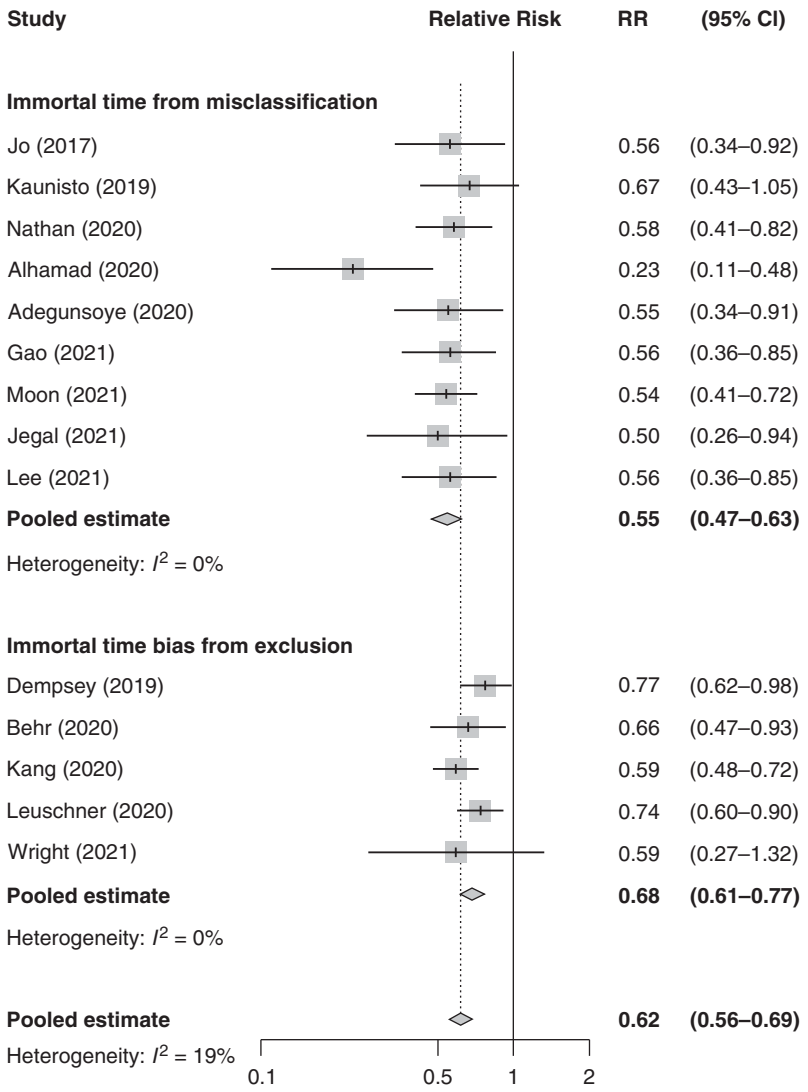

Figure 1. Forest plot of relative risks of mortality associated with antifibrotic use from the 14 observational studies, with pooled estimates by a random effects model, according to studies affected by immortal time bias from misclassification and from exclusion. CI = confidence interval; RR = relative risk.

with nonuse (Figure 1). We found that all 14 studies used definitions of exposure and follow-up that lead to immortal time bias.

Immortal time refers to a period of cohort follow-up during which the outcome under study cannot occur, usually because it involves the time from cohort entry to the start of the treatment under study (23). In essence, the patient necessarily must be alive at the time they initiate treatment and thus "immortal" during this period. Misclassifying or excluding this immortal time period in the design or analysis of an observational study when defining exposure will introduce immortal time bias (24).

For immortal time bias from misclassification, the immortal period is misclassified as exposed rather than unexposed (24). This bias is introduced in a cohort study by classifying patients as exposed to the antifibrotic treatment from the day of cohort entry, even if they only started their treatment later during follow-up. This bias is intensified if the definition of exposure also includes a minimum duration of antifibrotic use, which will increase the length of the immortal time, thus also augmenting the magnitude of the bias.

For immortal time bias by exclusion, the immortal period is differentially excluded from the treated and untreated groups (24). This occurs when the start of follow-up is defined as the initiation of treatment for the exposed group and the date of diagnosis or entry into the registry for the nonusers. Consequently, the immortal period from the date of diagnosis (or of registry entry) to the initiation of treatment is differentially excluded from the analysis in one group, which leads to a spurious protective effect.

Studies with Immortal Time Bias from Misclassification

Immortal time bias resulting from misclassification of the follow-up period from cohort entry to the initiation of antifibrotic treatment as "exposed" was noted in nine studies (9, 11, 13, 15, 16, 18, 20–22). The nine studies affected by this form of immortal time bias had a pooled

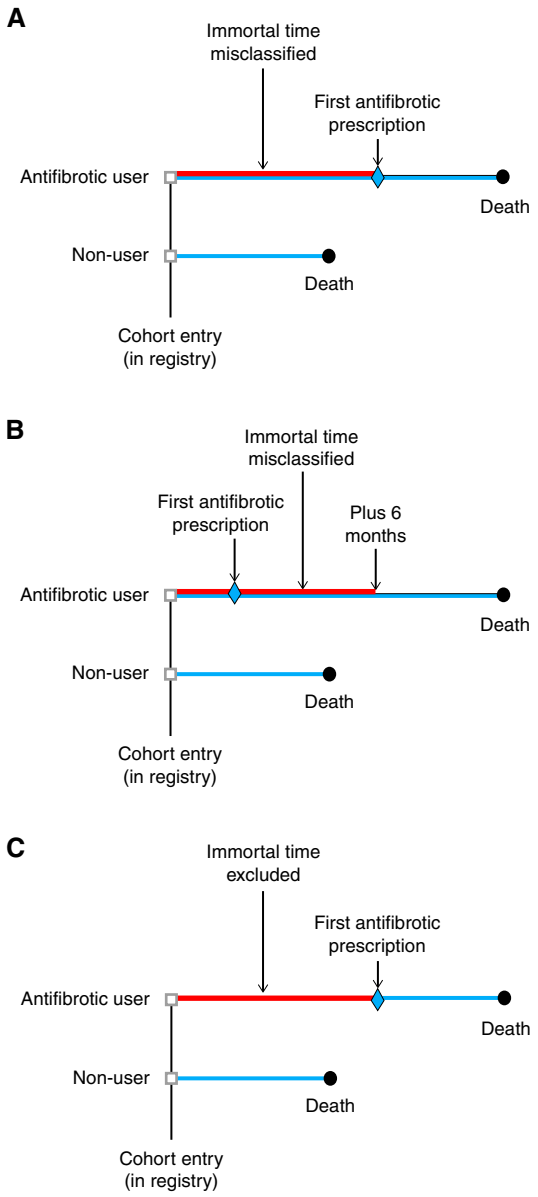

Figure 2. Illustration of immortal time bias from cohort studies, with the red line representing misclassified or excluded immortal time and the blue line indicating follow-up period for the outcome. (*A*) In the "users", the immortal time period between cohort entry and the first antifibrotic prescription is misclassified as "exposed to antifibrotic" when in fact, the patient is unexposed (9). (*B*) The immortal time period also includes the additional 6 months of required use to define exposure (16). (*C*) The immortal time bias from exclusion in cohort studies, which should not be excluded but included as unexposed, with the blue line starting at the first antifibrotic prescription.

relative risk of all-cause mortality with antifibrotic use of 0.55 (95% CI, 0.47–0.63) (Figure 1).

An example of immortal time misclassification is the study using the AIPFR (Australian IPF Registry), a national registry of 647 patients with IPF launched in 2012 (9). For the statistical analysis of mortality, a time to event approach was used, defined as the "time from AIPFR baseline until either death or censoring at last date the patient was known to be alive". Immortal time bias was introduced in this study by considering the patients as exposed to antifibrotics from the day of AIPFR enrollment, even if they only filled their first prescription afterward, so that the time between cohort entry and the first antifibrotic treatment during follow-up is immortal, as the patient must survive to receive this treatment. Figure 2A depicts this bias by comparing the survival times between two typical cohort patients in which the antifibrotics "users" will necessarily have longer survival, artificially created by this added immortal time. This bias is intensified if exposure is also defined by a minimum duration of antifibrotic use (Figure 2B), which will increase the length of the immortal time. Such immortal time bias from exposure misclassification, with or without an imposed minimum duration of treatment, will result in a biased and exaggerated "protective" effect of antifibrotics exposure.

Studies with Immortal Time Bias from Exclusion

Immortal time bias resulting from the exclusion of the time period from cohort entry to the initiation of antifibrotic treatment was noted in five studies (10, 12, 14, 17, 19). The five studies affected by this form of immortal time bias had a pooled relative risk of all-cause mortality with antifibrotic use of 0.68 (95% CI, 0.61–0.77) (Figure 1).

This form of immortal time bias, depicted in Figure 2C, was previously noted in the analysis of the Investigating Significant Health Trends in Idiopathic Pulmonary Fibrosis (INSIGHTS-IPF) registry of patients with IPF (12, 25). It reported a significantly lower risk of death (hazard ratio, 0.63; 95% CI, 0.45–0.87) in antifibrotic users compared with nonusers. The INSIGHTS-IPF cohort included 588 patients with IPF, of which 298 received an antifibrotic treatment at some time. Follow-up for mortality started at the treatment initiation for the antifibrotic users and at the registry enrollment date for the nonusers, so the time span between their registry enrollment and treatment initiation dates for the antifibrotic users was excluded from the analysis. This time span is immortal and should be included in the nonuser group up until the time "users" start their antifibrotic treatment; else, its omission introduces immortal time bias (24).

Conclusions

Observational studies are now widely used to evaluate the real-world effectiveness of drugs, especially to study major outcomes, such as mortality, which are rarely available in randomized controlled trials (26). We examined methodological aspects of 14 observational studies reporting a remarkable pooled 40% reduction in all-cause mortality with antifibrotics in the treatment of IPF. We showed that all were affected by immortal time bias, which systematically exaggerates the benefits of drugs.

Immortal time bias has been previously shown to affect many observational studies in the context of respiratory diseases (8), including those suggesting an important benefit of proton pump inhibitors on mortality in treating IPF (27). Observational studies that properly avoided this bias found no or little effect of these drugs on the major outcomes studied (28).

Although observational studies are important to assess the real-world effects of medications on major outcomes, proper design and analysis are essential to minimize bias. The observational studies reporting significantly decreased mortality with antifibrotic use cannot at this time be used as reliable evidence because all were

affected by immortal time bias. Indeed, studies with such "critical risk of bias" are too problematic to provide useful evidence and should be excluded from any synthesis (29).

However, immortal time bias, which tends to greatly exaggerate the benefit of drugs, is correctable with proper study design or data analysis. For example, immortal time bias can be avoided by using a time-dependent definition of exposure, such as with the Cox proportional hazards model with time-dependent exposure that allows a patient to move from a period of nonexposure to a period of exposure during the follow-up period (24). One could also use study design approaches such as the prevalent new-user design, which would match antifibrotic initiators with nonusers at the same time point in the disease course, thus avoiding immortal time bias (28, 30). The authors of these 14 publications are urged to repeat the analysis of their studies using such revised approaches that avoid immortal time bias. ■

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Mechanisms of Obesity-related Asthma: Is Insulin Getting on Your Nerves?

To the Editor:

Obesity increases both the incidence and the severity of asthma. Obese asthmatics experience more frequent exacerbations and often respond poorly to currently available asthma medications, which increases healthcare costs and leads to decreased quality of life. Prevention and management of this difficult disease are complicated by the lack of complete understanding of its underlying molecular mechanisms. Although systemic inflammatory mediators, including IL-1β, IL-4, IL-5, and TNF-α (tumor necrosis factor-α), are increased in obesity and metabolic syndrome, their causal role in obesity-related asthma in humans has not been demonstrated (1). Furthermore, increased bronchoconstriction is independent of airway inflammation in obese animals. Clearly, our existing inflammatory paradigms, which have produced significant therapeutic advances for other phenotypes and/or endotypes of asthma, require reexamination in the context of an obesity-related phenotype.

A recent study by Peters and colleagues (2) shows that insulin resistance is independently associated with airflow limitation, blunted treatment responses, and accelerated lung function decline over time in a SARP-3 (Severe Asthma Research Program–3) cohort. Their analysis demonstrates that effects of excess body mass on chest wall mechanics are unlikely to fully explain this association after correcting for body mass index in regression models. Their findings are consistent with those of previous studies, showing that insulin resistance is associated with increased asthma risk. The causal role of insulin resistance in asthma development is suggested by studies showing that insulin resistance frequently precedes the development of asthma symptoms and is associated with worse lung function in humans.

The authors, and an accompanying editorial (3), proposed several potential mechanisms to explain this relationship among insulin resistance, obesity, and asthma. Overlooked in this discussion, however, is the critical role of hyperinsulinemia in development of airway hyperresponsiveness due to nerve dysfunction. Airway parasympathetic nerves, which provide the dominant control of bronchoconstriction through the release of acetylcholine, become hyperresponsive to airway stimulation in the setting of hyperinsulinemia (4), which is usually a compensatory consequence of insulin resistance. Specifically, high concentrations of circulating insulin increase neuronal acetylcholine release by disrupting presynaptic, inhibitory M_2 muscarinic receptor function on parasympathetic nerves. Loss of M_2 receptor function and subsequent increased acetylcholine release increase bronchoconstriction (5). Experimentally, hyperinsulinemia's effects are attenuated by insulin-lowering agents such as metformin and pioglitazone (4, 6, 7).

Interestingly, in Peters and colleagues' study (2), the magnitude of insulin's effect on lung function decline over time in their longitudinal analyses may have been underrepresented because of their use of HOMA-IR (homeostatic model assessment for insulin resistance) only, which is calculated by multiplying fasting plasma glucose (mg/dl) by serum insulin (mIU/ml) and dividing by 405. On the basis of this formula, the main driver of increased HOMA-IR scores may be elevated insulin concentrations during insulin resistance, such as in the prediabetic or early stages of type 2 diabetes, or markedly elevated blood glucose concentrations due to decreased insulin secretion caused by pancreatic decline, as in the late stage of type 2 diabetes. Thus, using HOMA-IR alone in an analysis of the relationship between metabolic disorders and lung function may miss the opportunity to uncover the association between insulin and reduced lung function, which has been shown before in cross-sectional studies and clinical trials. Further exploration and corroboration of insulin concentration and decline of lung function in clinical trials should therefore be of great interest.

Overall, this study has important clinical implications regarding the independent role of insulin resistance in the decline of lung function in obese asthmatics. Results from Peters and colleagues (2) and other relevant investigations (4, 6, 7) provide a strong rationale for designing clinical trials to test whether inhibiting hyperinsulinemia, both alone and in combination with antagonists of nerve-mediated bronchoconstriction (e.g., tiotropium), is an effective treatment for obesity-related asthma. ■

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