Mortality benefit with antifibrotics in idiopathic pulmonary fibrosis: real world evidence or bias?

To the Editor:

We read with interest the analysis conducted by Behr *et al.* [1] of the INSIGHTS-IPF registry of patients with idiopathic pulmonary fibrosis (IPF), particularly of the effectiveness of antifibrotic treatment on mortality. It showed that users of antifibrotics, namely pirfenidone and nintedanib, have a significantly lower risk of death (hazard ratio 0.63, 95% CI 0.45–0.87; p=0.005) compared with non-users. This 37% reduction in all-cause mortality is quite remarkable for an observational study in the context of regular clinical practice, despite the short mean duration of follow-up of 1.2 years and the expected confounding by indication inherent in such studies. We believe that this reported reduction in mortality with antifibrotic treatment is more likely the result of immortal time bias [2].

Immortal time bias is a time-related bias generally introduced in an observational cohort study by the definition of exposure [3]. It was recently described in the context of the effectiveness of anti-acid therapy on survival in IPF [4]. In the study by Behr *et al.* [1], antifibrotic treatment was not started systematically at the time of the registry enrolment visit, but at different visits during the registry observation period, at the discretion of the treating physician. Such time-dependency of the exposure can introduce this time-related bias if not considered accordingly in the study design or data analysis.

The INSIGHTS-IPF cohort included 588 patients with IPF, of which 298 received an antifibrotic treatment sometime during their enrolment in the registry and the remaining 290 patients did not. Importantly, time zero, the beginning of the follow-up period for mortality, differed for use or non-use of an antifibrotic. For the non-users, the follow-up period started at the "registry enrolment visit", while for the antifibrotic users, it started at the "initial treatment visit" [1]. This implies that, for the antifibrotic users, the time span between their "registry enrolment visit" and their "initial treatment visit" was excluded from the analysis. This time span is "immortal" since a patient had to remain alive to receive the treatment at their "initial treatment visit" (figure 1). Since such patients satisfied the definition of non-users at the time of their "registry enrolment visit" (they were not yet treated), they should be included in the non-user group up until the time they start their antifibrotic treatment. Omitting this time period from the analysis introduces immortal time bias [3].

An earlier description of the INSIGHTS-IPF registry shows that while 12% of the patients were using pirfenidone at their "registry enrolment visit", 44% were using it at the time of data analysis [5]. This suggests that a large majority of users initiated their antifibrotic treatment during cohort follow-up and thus contributed to immortal time bias. As a result, a substantial amount of immortal time was excluded from the analysis, likely impacting the impressive difference in mortality observed between the two study arms.

By discounting this key immortal time period, the authors are overestimating the rate of death in the non-users by removing "alive" person-time from the denominator of the rate. To illustrate, we approximated some values from the paper. Consider a crude rate ratio value of 0.63, computed as the rate of death in the exposed (61 deaths/209 person-years exposed to antifibrotics) divided by the rate of death in the unexposed (133 deaths/290 person-years unexposed). While the rate for the exposed is correct, the rate in the unexposed is missing portion of the denominator, namely the total immortal person-time. Thus, if for example the treated patients received antifibrotics on average 6 months after enrolment, this

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Study from the INSIGHTS-IPF registry is affected by immortal time bias, which greatly exaggerates the reported effectiveness of pirfenidone and nintedanib on lowering mortality by 37% in patients with IPF. https://bit.ly/2Xp7XTr

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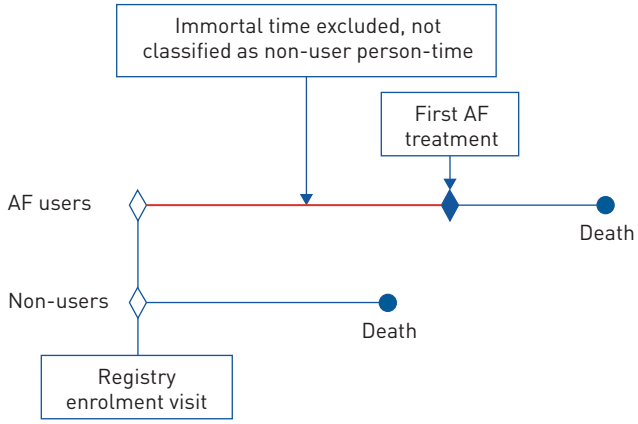

FIGURE 1 Pictorial representation of two typical patients of the INSIGHTS-IPF registry, with immortal time bias resulting from the exclusion of the time between enrolment in the registry and antifibrotic (AF) treatment initiation (red line) for the AF users, rather than including it as part of the non-users group.

would generate 149 person-years (298 users who were non-users for 6 months) of unexposed person-time which should be added to the 290 person-years of the non-users. Thus the rate in the unexposed would then be 133/439 and the corresponding rate ratio 0.96 instead of 0.63.

To avoid immortal time bias, one must use a time-dependent approach in either the data analysis or the study design [2, 3]. For example, data analysis could be based on a Cox model with time-dependent exposure, that classifies antifibrotic exposure as unexposed until the treatment is initiated and exposed thereafter, with proper consideration for informative censoring [3]. An alternative is to design the study, using for example the prevalent new-user design, that matches users and non-users at the same time point in the disease course [6]. Such an approach was recently used to assess the effectiveness of proton pump inhibitors in IPF on mortality [7]. In addition, different study designs that avoid this bias were also compared in this context [8].

In conclusion, immortal time bias has affected many observational studies in respiratory medicine, erroneously suggesting remarkable benefits for many drugs, which formed the basis for large randomised trials that did not confirm these reports [9, 10]. Careful use of proper time-dependent approaches to the data analysis or study design will avoid such inaccuracies in the important arena of real-world evidence research.

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References

1 Behr J, Prasse A, Wirtz H, *et al.* Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with idiopathic pulmonary fibrosis: long-term results of the INSIGHTS-IPF registry. *Eur Respir J* 2020; 56: 1902279.
2 Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf* 2007; 16: 241–249.
3 Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol* 2008; 167: 492–499.
4 Tran T, Suissa S. The effect of anti-acid therapy on survival in idiopathic pulmonary fibrosis: a methodological review of observational studies. *Eur Respir J* 2018; 51: 1800376.
5 Behr J, Kreuter M, Hoeper MM, *et al.* Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. *Eur Respir J* 2015; 46: 186–196.

6 Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiol Drug Saf* 2017; 26: 459–468.
7 Tran T, Assayag D, Ernst P, *et al.* Effectiveness of proton pump inhibitors in idiopathic pulmonary fibrosis: a population-based cohort study. *Chest* 2020; 159: 673–682.
8 Tran T, Suissa S. Comparing new-user cohort designs: the example of proton pump inhibitor effectiveness in idiopathic pulmonary fibrosis. *Am J Epidemiol* 2020; in press [https://doi.org/10.1093/aje/kwaa242].
9 Criner GJ, Connett JE, Aaron SD, *et al.* Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014; 370: 2201–2210.
10 Dransfield MT, Voelker H, Bhatt SP, *et al.* Metoprolol for the prevention of acute exacerbations of COPD. *N Engl J Med* 2019; 381: 2304–2314.