Unfavourable effects of medically indicated oral anticoagulants on survival in idiopathic pulmonary fibrosis: methodological concerns

To the Editor:

We read with great interest the article by KREUTER *et al.* [1] describing the unfavourable effects of anticoagulants in a pooled analysis of idiopathic pulmonary fibrosis (IPF) patients randomised to the placebo arm from the ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis) and CAPACITY (Clinical Studies Assessing Pirfenidone in Idiopathic Pulmonary Fibrosis: Research of Efficacy and Safety Outcomes) trials [2, 3]. In this pooled analysis, IPF anticoagulant users differed significantly from nonusers in almost every important baseline characteristic: anticoagulant users were older (age 71.1 ± 6.8 versus 66.9 ± 7.5 years, $p=0.0025$) and they also had a higher prevalence of cardiovascular disease (43.8% versus 25.8%, $p=0.0259$), chronic renal failure (9.4% versus 2.9%, $p=0.0419$), pulmonary embolism (15.6% versus 0.2%, $p<0.0001$), pulmonary hypertension (9.4% versus 2.7%, $p=0.0324$), atrial fibrillation (46.9% versus 2.4%, $p=0.0001$) and deep vein thrombosis (28.1% versus 1.4%, $p<0.0001$). Therefore, IPF anticoagulant users started off with an increased risk of death simply due to the higher prevalence of baseline cardiovascular comorbidities.

In the multivariate analyses adjusted for covariates (lung function parameters, comorbidities and cardiovascular risk factors), the use of anticoagulants was an independent predictor of IPF-related mortality (HR 4.7, 95% CI 1.1–19.3; $p=0.034$) but not of all-cause mortality. The authors did acknowledge that the underlying comorbidities for which anticoagulants were indicated in their analysis could have contributed to the observed increase in mortality among anticoagulant users. Nevertheless the conclusion was that “IPF-related mortality was statistically significant in the multivariate analysis of baseline anticoagulant use [...] the findings of our analysis suggest that anticoagulant use for medically indicated comorbidities may have unfavourable effects in IPF” [1].

Caution is advised when reaching such conclusion. The reasons are as follows. 1) The number of events was pretty small, especially in the group receiving anticoagulants at baseline: five and 23 IPF-related deaths among anticoagulant users and nonusers, respectively. This renders any estimate of effect very imprecise. For instance, in the anticoagulation group if only two IPF-related deaths were adjudicated as non-IPF-deaths that would make the crude association between anticoagulant use and IPF-related mortality nonsignificant, demonstrating a fragile statistical analysis. 2) The predictive performance of the Cox model is expected to be low in this context. The reasons are: there were only 28 IPF-related deaths (events) and 16 covariates included in the Cox model. Small data sets like that, with a few events per covariate (in this case 1.75 event per covariate), may lead to over fitted models with high optimism [4, 5]. Imprecision was also demonstrated for the effect of anticoagulant use on IPF-related mortality by the confidence interval obtained in the Cox model (95% CI 1.1–19.3): it was wide and had its lower limit close to no effect. For instance, only one IPF-related death needed to be ascertained as non IPF-related in the anticoagulant users group to make this adjusted estimate nonsignificant. 3) IPF-related death is a subjective end-point and that means it can be misclassified. Relatedness of death to IPF was not centrally confirmed in 75% of these deaths (CAPACITY trial was not centrally adjudicated and it contributed with 75% of the IPF-related deaths of this pooled analysis) [3]. If the deaths from the CAPACITY trials had been centrally confirmed, it is possible that the number of deaths classified as “IPF related” would have been smaller, which could have reduced the performance of the Cox model or even rendered the differences nonsignificant, as stated above.

In conclusion, we do acknowledge previous evidence suggesting harmful effects of anticoagulation in IPF patients [6]; however, we believe that the quality of evidence added by KREUTER *et al.* [1] on the association between anticoagulants and unfavourable outcomes in IPF patients should be regarded as very low [7].

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The question whether medically indicated anticoagulants are harmful to IPF patients still remains unanswered <http://ow.ly/KU3Y302SEMQ>

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From the authors:

We read the correspondence of L. Kawano-Dourado and colleagues related to our article “Unfavourable effects of medically indicated oral anticoagulants on survival in idiopathic pulmonary fibrosis” with great interest [1]. There is compelling evidence of an association between disturbances in the coagulation system and idiopathic pulmonary fibrosis (IPF); however, results from the ACE-IPF (anticoagulant effectiveness in idiopathic pulmonary fibrosis) randomised controlled trial of the vitamin K antagonist warfarin demonstrated deleterious effects of anticoagulation in IPF [2]. Based on these data, the recent update of the international guideline on IPF gave a strong recommendation against the use of anticoagulants [3]. Yet, the potential risks of medically indicated anticoagulation on mortality and other clinical outcomes in IPF remain unexplored. This is an important clinical question as almost one in every five patients with IPF receives anticoagulants for different indications [4]. In this regard, our *post hoc* analysis, which describes that patients in the placebo groups treated with anticoagulants in the CAPACITY and ASCEND trials had a higher rate of all-cause and IPF-related mortality compared with non-users, adds further insights in to the potential hazard of anticoagulant use in IPF [1]. We agree with Kawano-Dourado and colleagues that these data should be interpreted in light of the inherent limitations of a *post hoc* analysis based on a small number of events. However, these data represent, to our knowledge, the largest cohort of IPF subjects in whom this question has been addressed. Furthermore, our data are in line with two retrospective studies in IPF populations that also report a significantly higher risk of mortality in association with the use of anticoagulants for medical indications [5, 6] and this important clinical problem has recently also been highlighted by others [7].

While we agree with Kawano-Dourado and colleagues that, in general, comorbidities significantly affect prognosis in IPF [8], we disagree with their interpretation of the effects of cardiovascular comorbidities and their statement on the attribution to causes of death in our analyses. Given the *post hoc* nature of our analysis we cannot rule out the possibility of confounding due to differences in unobserved factors, however, on multivariate analysis we did not find an association between observed comorbidities necessitating anticoagulation and death (table 1). With regards attribution of death, this was adjudicated by a blinded clinical investigator in the CAPACITY studies and by a mortality assessment committee in ASCEND [9, 10].

In conclusion, despite the inherent limitations of *post hoc* analyses our data suggest that anticoagulant use for medically indicated comorbidities may contribute to respiratory worsening and death in IPF. Given that for many indications, *e.g.* atrial fibrillation, the choice to prescribe anticoagulation is based on an assessment of the balance between potential benefit and risk, and given also that almost 20% of patients with IPF have comorbid indications for anticoagulation further prospective research is urgently needed to elucidate the safest way of managing patients with IPF.