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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.

TABLE 1 Multivariate analyses of 1-year idiopathic pulmonary fibrosis-related mortality

	Hazard ratio (95% CI)	p-value
Bivariate		
Baseline anticoagulant use (yes <i>versus</i> no)	4.384 [1.667–11.534]	0.003
Multivariate		
Baseline anticoagulant use (yes <i>versus</i> no)	4.660 [1.123–19.347]	0.034
Age	0.978 [0.923–1.036]	0.445
Sex (male <i>versus</i> female)	1.273 [0.474–3.421]	0.633
Smoker (current/former <i>versus</i> never)	2.941 [1.064–8.131]	0.038
FVC	0.972 [0.935–1.010]	0.144
D _{LCO}	0.917 [0.858–0.980]	0.010
6MWD	0.996 [0.991–1.000]	0.078
SOBQ	0.991 [0.972–1.011]	0.382
Comorbidities		
CVD	0.898 [0.375–2.147]	0.808
CRF	2.124 [0.549–8.222]	0.275
COPD	0.894 [0.114–7.006]	0.915
Pulmonary hypertension	0.781 [0.093–6.538]	0.820
Atrial fibrillation	1.798 [0.419–7.711]	0.430
CVD risk factors		
Hypertension	1.276 [0.541–3.007]	0.577
Diabetes	0.963 [0.369–2.517]	0.939
Hypercholesterolaemia	1.076 [0.471–2.457]	0.863
Obesity	0.570 [0.237–1.372]	0.210

FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walking distance; SOBQ: Shortness of Breath Questionnaire; CVD: cardiovascular disease; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease.

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Comorbidities requiring anticoagulants may not explain unfavourable effects of these drugs on survival in IPF <http://ow.ly/tmglm302VEXz>

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Cardiac safety of extensively drug-resistant tuberculosis regimens including bedaquiline, delamanid and clofazimine

To the Editor:

I read with interest the recent article by TADOLINI *et al.* [1] describing QT (ECG Q-T wave interval) prolongation in a patient with extensively drug-resistant tuberculosis (XDR-TB) being treated with both bedaquiline and delamanid. QT prolongation is a recognised safety concern for both these drugs. In a placebo-controlled trial of delamanid in multidrug resistant-TB, QTcF intervals (using the correction for heart rate of FRIDERICIA [2]) increased 12.1 ms more from baseline in delamanid recipients over 6–10 weeks [3]. An increase of similar magnitude was observed in an open-label 24-week trial of bedaquiline, with most of the effect becoming apparent within the first 1–2 weeks [4]. The authors are correct that there is currently no clinical information regarding QT prolongation when these two drugs are co-administered.

However, readers may be less aware of QT prolongation due to clofazimine, which this patient also received as part of XDR-TB treatment. Clofazimine is a potent inhibitor of hERG potassium channel signalling, with essentially complete inhibition occurring *in vitro* at sub-therapeutic concentrations [4, 5]. hERG mutations can result in QT prolongation and potentially fatal arrhythmias, including ventricular tachycardia and torsade de pointe [6, 7]. *In vitro* measurement of hERG signalling effects is an important preclinical drug development tool to identify potential arrhythmia-inducing compounds [8], although recent studies indicate the modulating effects of other channels [9]. Testing for hERG signalling effects was not available at the time clofazimine was developed, some 50 years ago.

Two studies and one case report have confirmed the QT prolonging effects of clofazimine. In one study, 105 patients with newly diagnosed drug-sensitive TB were treated for 2 weeks with one of seven drugs or regimens (n=15 per arm), of which four included clofazimine 100 mg daily [10]. By day 14, QT intervals in patients receiving clofazimine alone increased from baseline by a mean of 17 ms. Patients receiving regimens containing both clofazimine and bedaquiline had increases of 20–21 ms. Patients receiving neither drug had no change in QT (–3 to 2 ms). Given the unusual pharmacokinetics of clofazimine, it is unlikely that this short treatment interval (14 days) was sufficient to reach steady state effects.

In a second study, 233 patients with drug-resistant TB were treated for 24 weeks with bedaquiline in an open label, single arm trial, in combination with an individualised background regimen [4]. 10 patients not receiving clofazimine at the time of enrolment were started on bedaquiline plus a background regimen including clofazimine. By week 24, their mean $\pm$ SE QTcF interval had increased 41.5 $\pm$ 8.4 ms from baseline. In contrast, in patients whose background regimen did not include clofazimine, the QTcF interval increased by only 12.9 $\pm$ 4.1 ms (p=0.009).

Finally, one case report describes ventricular tachycardia and torsade de pointe occurring in a 66 year-old man who had been treated for recurrent erythema nodosum leprosum with 300 mg of clofazimine per day for 11 months [11].

These findings indicate that clofazimine may indeed have been an important contributor to the QT prolongation in the patient reported by TADOLINI *et al.* [1]. Studies are needed to determine if clofazimine potentiates the combined QT prolonging effects of bedaquiline plus delamanid as it does with bedaquiline