anorexigen-associated PAH. We would explain this observation by the substantial delay in the start of targeted PAH therapy in the prevalent cohort. This is confirmed by the prevalent patients showing more advanced disease as measured by invasive haemodynamics at the time of inclusion, as well as a trend towards reduced peak oxygen uptake. This observation is in agreement with data suggesting that patients suffer irreversible progression of disease if targeted therapy is delayed [2, 3]. Our data on the prognosis of incident patients also confirms previous survival data reported by HOEPER *et al.* [4] from a single centre cohort treated with contemporary targeted PAH therapy.

Even with cautious interpretation of our data, they strongly contrast with the generalised conclusions drawn by HUMBERT *et al.* [1] from their data. Although self-selection of sicker patients during the pre-inclusion phase in prevalent patients should result in a relative survival advantage of the remaining patients compared with incident patients [5], our data suggest that this can be offset by the beneficial effect of early institution of targeted therapy. Although comparing our data with those from HUMBERT *et al.* [1] is carrying some limitations, it illustrates the problem of generalising prognostic data even when obtained from a large multicentre registry.

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From the authors:

We thank R. Wensel and colleagues for their comments on our recent article highlighting survivor bias in prevalent cohorts of pulmonary arterial hypertension (PAH) patients [1]. In this rebuttal, we provide information indicating that their analysis of our data and their own retrospective cohort probably suffer from misinterpretation and biases.

R. Wensel and colleagues report that a retrospective analysis from seven German pulmonary hypertension centres during 1996–2008 showed better survival in incident patients with idiopathic, familial or anorexigen-associated PAH patients compared to prevalent cases. This statement probably arises due to a misunderstanding of the definition of incident and prevalent cases. As stated in our recently published manuscripts [1–3], incident cases were defined as patients diagnosed with PAH using right-heart catheterisation during the recruitment phase of our registry. By contrast, prevalent cases were defined as patients in whom the diagnosis was made prior to the start of the registry. By definition, the date of diagnosis corresponded to the date of confirmatory right-heart catheterisation. We understand that R. Wensel and colleagues employed a different approach, defining so-called prevalent patients as subjects with a prior diagnosis of PAH in whom initiation of PAH-targeted therapy was delayed. This definition of prevalent patients erroneously leads the authors to state that ''prevalent patients have the disadvantage of potentially more advanced disease and, because of that, delayed start of targeted therapy''. Indeed, the distinction between incident and prevalent cases in our series by no means distinguishes a group of patients in whom initiation of treatment was delayed, as this would clearly be an unacceptable approach [4]. As stated in our articles, use of targeted therapies, including prostacyclin derivatives, endothelin receptor antagonists and phosphodiesterase 5 inhibitors was at the discretion of treating clinicians at each centre, according to current guidelines and availability of treatments [1, 3]. Conventional therapy alone was used in a similar proportion of incident and prevalent cases on PAH diagnosis (corresponding mostly to acute vasodilator responders who benefited from first-line calcium channel blocker therapy, patients in New York Heart Association functional class (NYHAFC) II or patients who died prematurely before any specific therapy could be proposed). In contrast, 70% of patients were treated with initial targeted therapy with a prostacyclin derivative (including intravenous epoprostenol), endothelin receptor antagonist or phosphodiesterase 5 inhibitors [2, 3].

In the letter of R. Wensel and colleagues, the authors refer to a retrospective analysis of 250 patients in seven German PAH centres over a 12-yr period. This relatively low number might reflect selection bias, as it is unlikely that expert centres treat, on average, only three incident and prevalent patients with idiopathic, familial or anorexigen-associated PAH annually. Recent European guidelines have attempted to define what would be the optimal characteristics of a pulmonary hypertension referral centre, and the proposed numbers were much higher than figures presented by R. Wensel and colleagues [4]. In the 2009 European Society of Cardiology/European Respiratory Society guidelines, it was stated that referral centres should follow $\geqslant$50 patients with PAH or chronic thromboembolic pulmonary hypertension and should receive at least two new referrals per month [4]. In agreement with this recommendation, the French PAH Network (17 centres) recruited 674 PAH patients (356 idiopathic, familial and anorexigen-associated PAH) over a 1-yr period (October 2002–October 2003).

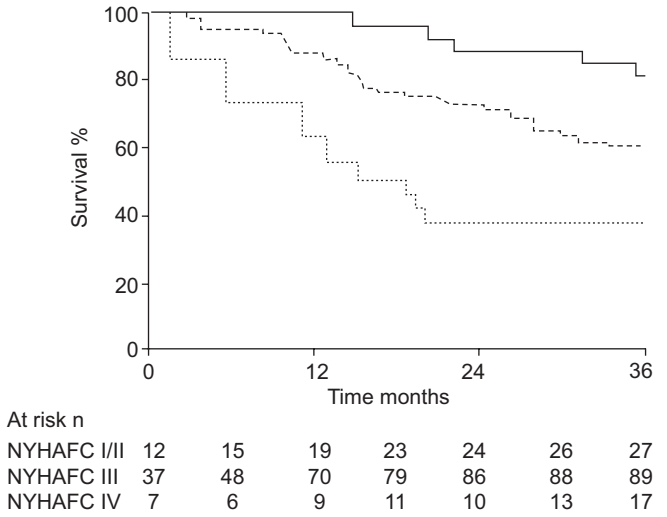

FIGURE 1. Kaplan–Meier estimates of survival among the combined population of patients with idiopathic, familial and anorexigen-associated pulmonary arterial hypertension stratified according to baseline New York Heart Association Functional Class (NYHAFC) (———: I/II; -------: III; ·····: IV). Reproduced from [3] with permission from the publisher.

In addition, the retrospective description of the patient population described by R. Wensel and colleagues requires re-evaluation, as it would seem unlikely that no NYHAFC IV incident patients were identified during a 12-yr experience. Indeed, ~10–15% of incident PAH patients have presented with NYHAFC IV symptoms in most reported registries to date, emphasising the reality of late diagnosis in this condition [1–3].

As shown in our article, selection of the sickest patients accounted for a high mortality rate, as demonstrated by steeper slopes of the mortality curves in the incident population compared to the prevalent one [1]. When figure 4 of our article is analysed, the higher mortality rate of incident patients clearly reflects worst outcomes in this population [1]. In addition, the 95% confidence intervals (CI) are consistent with worst outcomes in incident *versus* prevalent PAH patients, arguing in favour of a sicker incident population. In the prevalent cohort, the 1-, 2- and 3-yr survival rates were 88% (95% CI 85–91%), 79% (95% CI 75–82) and 71% (95% CI 67–74%) as compared with 88% (95% CI 80–93%), 65% (95% CI 56–74%) and 51% (95% CI 42–60%) in the incident cohort, respectively ($p<0.0001$). Therefore, the incident population clearly exhibited worse outcomes. Lastly, we agree that selection of the sickest patients would lead to a high early mortality rate, which might then stabilise over time, as the sickest patients would have died. This is shown in our previous report in *Circulation* showing marked early mortality in incident NYHAFC IV patients *versus* NYHAFC II and III patients (fig. 1) [3].

In conclusion, we would like to take this opportunity to reinforce our view that retrospective analysis of biased populations may lead to major misinterpretation. It is thus timely to focus future epidemiological PAH research on properly designed prospective incident PAH patient cohorts in order to provide novel and unbiased information [5–7]. Description of such cohorts should help define priorities for future clinical research.

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