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From the authors:

We thank C.E. Ventetuolo and S.M. Kawut for their interest in our study and for calling attention to the important issue of the validation of surrogate end points and treatment targets in the field of pulmonary arterial hypertension (PAH) [1]. We sincerely agree with the author's words of caution that "a correlate does not a surrogate make" [2], and that none of the currently proposed clinical endpoints in PAH has yet been established as the ideal true surrogate for clinical disease outcome.

However, what exactly is the point here? To answer this question, several aspects need to be addressed. First of all, the highest treatment priority in PAH is not to reach a given surrogate end point, but to improve the patient's quality of life and survival. Measurements can be identified that directly measure how a patient feels (symptoms) or functions (the ability to perform activities in daily life) and such measurements are clinically meaningful for the patient, even if they are not associated with survival [3]. Such measurements are valid outcome parameters in themselves, instead of indirect surrogates for another outcome measure, for instance survival. World Health Organization functional class, 6-min walk distance and also relief of symptoms, can be regarded as such types of outcome measures and therefore can serve as justified and valid treatment goals.

With the currently available treatment modalities, we now strive for improving another clinically meaningful outcome: survival. Mortality is a "hard" outcome measure, but obviously not very useful in guiding treatment of the individual patient due to its irreversible nature. Also, it is not a practical outcome measure in clinical trials due to the required patient numbers and prolonged study duration. Therefore, surrogate measures come into place. Ventetuolo and Kawut correctly emphasise that adequate validation of surrogate measures is crucial and they have demonstrated that this has not been done properly for many of the clinical endpoints or treatment targets that have been proposed for adult patients with PAH [4–7]. In our study in children with PAH, we identified three intermediates in which therapy-induced changes predicted comparable directional changes in the ultimate outcome: survival [1, 8]. Ventetuolo and Kawut describe the ideal single true surrogate endpoint that would preferably be part of the causal pathway of the disease and would account for most of the impact of a therapy on the ultimate clinical outcome [2, 8]. Indeed, in our paediatric study, we did not undeniably demonstrate these latter two properties for the three identified intermediates.

However, at this point, it is important to understand the difference between a clinical end point and a treatment goal. A clinical end point is used in (interventional) trials. To prove efficacy of the intervention, it is relevant that the intervention-induced change in the clinical end point indeed explains a substantial proportion of the change in outcome. In contrast, a treatment goal is a measurement that can guide management in the individual patient, in order to reach a condition that is associated with improved outcome. For a patient, it is important that treatment goal is reached because it is associated with improved outcome, leaving aside the question of whether it is reached through a specific intervention. Moreover, in the clinical practice of PAH, a single surrogate outcome that explains at least 50–70% of the effect on survival is not known, whereas independent treatment goals, that individually explain a change in outcome less than 50–70%, may sum up when applied in combination.

Furthermore, the evidence with which C.E. Ventetuolo and S.M. Kawut depreciate the value of clinical end points in adults with PAH, requires some considerations. Recent surrogate end point validation studies in adults [4–7] evaluated therapy-induced changes in relation to composites of "soft" clinical events (including hospitalisation, clinical worsening and escalation of therapy) that have not undeniably demonstrated a correlation with the hard outcome, survival. Furthermore, analyses had to be restricted to the short duration of clinical trials (mostly 12 weeks). Thus, relations to hard outcomes in the long term could not be assessed and one should therefore be careful to reject potential treatment targets prematurely [4–7]. In this respect, the current paediatric study is unique in allowing the evaluation of therapy-induced changes in relation to hard outcomes (transplant-free survival) during a median follow up of >3 years.

In PAH, clinical reality and the ideal world do not yet line up. We agree that surrogate markers in PAH need to be scrutinised and validated and that the search for ideal surrogates must continue. During this challenging quest, one should certainly throw out the bathwater, but be sure to take care of the baby.

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Potential treatment targets should not be rejected in the search for surrogate end points in paediatric PAH http://ow.ly/EYF6A

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