What's the (end) point?

To the Editor:

Clinicians caring for children or adults with pulmonary arterial hypertension (PAH) face a number of challenges, not the least of which is determining whether a patient has met treatment targets based on changes in a given test (such as the 6-min walk distance (6MWD)) and whether these changes translate to meaningful improvements in that patient's quality of life or survival. While several treatment benchmarks (such as achieving a 6MWD >380–440 m) have been put forth in recent consensus guidelines, none of the proposed intermediates has been established as a true surrogate for disease outcomes in PAH [1, 2]. A correlate does not a surrogate make; a given end point needs to be validated before being used to inform treatment or prove therapeutic efficacy [3]. A number of criteria are necessary to establish surrogacy [3–5]. A valid surrogate should be reliable, preferably integral to the disease causal pathway, targeted by treatment, and should track with "hard" outcomes (such as survival) across multiple studies. Finally, therapy-induced changes in the end point should explain a significant proportion of the treatment effect (50–75%) in terms of the outcome of interest.

Ploegstra *et al.* [6] recently published a study in the *European Respiratory Journal* that showed that changes in functional class, *N*-terminal pro-brain natriuretic peptide, and tricuspid annular plane systolic excursion in patients receiving PAH treatment predicted transplant-free survival in a paediatric cohort. The authors propose that these measures be used as treatment goals in children with PAH. While we appreciate this important addition to the understudied area of paediatric PAH, the recommendation that these markers should serve as guideposts for goal-directed PAH therapy may be premature.

Justification for this caution is evidenced by recent studies of the 6MWD and haemodynamics in adults, which have been shown in multiple observational studies to be associated with survival both at baseline and after therapy [7–10]. We and others have found that while changes in these measures were associated with outcomes in PAH clinical trials (as in prior observational studies), the drug-induced changes (compared with placebo) explained very little of the variances in outcomes [11–14]. At most, the changes in 6MWD and pulmonary vascular resistance respectively explained only 22% and 14% of the effect of treatment on clinical events at 12 weeks, falling short of the desired 50% mark and suggesting that they are not valid surrogates for short-term outcomes.

These recent observations regarding some of the strongest predictors of outcome in adult PAH challenge us to rethink our approach. Simply stated, even established risk factors for clinical events cannot be assumed to function well as surrogate end points or treatment targets. In fact, most of the children in this cohort had no change in their functional class (mean±SD −0.3±0.66) and, even among non-survivors, functional class appeared to be static or improve after several months of treatment, making it difficult to conclude that this end point could be applied with precision as a surrogate in paediatric PAH [6]. Treatment targets should be studied prospectively and validated against outcomes important to clinicians and patients before being set forth as standards for care. What we have learned only recently in adult PAH may serve as a valuable lesson for the future in all PAH patients.

@ERSpublications
Well-established disease correlates may be inadequate surrogate end-points for outcomes in paediatric and adult PAH http://ow.ly/EUYOQ

Corey E. Ventetuolo[1,2] and Steven M. Kawut[3,4]
[1]Dept of Medicine, Alpert Medical School of Brown University, Providence, RI, USA. [2]Dept of Health Services, Policy and Practice, Alpert Medical School of Brown University, Providence, RI, USA. [3]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA. [4]Dept of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.

Received: Oct 14 2014 | Accepted: Nov 19 2014

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

References

1 McLaughlin VV, Gaine SP, Howard LS, *et al.* Treatment goals of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D73–D81.

2 Hoeper MM, Markevych I, Spiekerkoetter E, *et al.* Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 858–863.
3 Fleming TR, DeMets DL. Surrogate end points in clinical trials: Are we being misled? *Ann Intern Med* 1996; 125: 605–613.
4 Buyse M, Molenberghs G. Criteria for the validation of surrogate endpoints in randomized experiments. *Biometrics* 1998; 54: 1014–1029.
5 Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. *Stat Med* 1992; 11: 167–178.
6 Ploegstra M-J, Douwes JM, Roofthooft MTR, *et al.* Identification of treatment goals in paediatric pulmonary arterial hypertension. *Eur Respir J* 2014; 44: 1616–1626.
7 McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106: 1477–1482.
8 Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.
9 Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 487–492.
10 Provencher S, Sitbon O, Humbert M, *et al.* Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 589–595.
11 Ventetuolo CE, Gabler NB, Fritz JS, *et al.* Are hemodynamics surrogate end points in pulmonary arterial hypertension? *Circulation* 2014; 130: 768–775.
12 Gabler NB, French B, Strom BL, *et al.* Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. *Circulation* 2012; 126: 349–356.
13 Savarese G, Musella F, D'Amore C, *et al.* Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. *Eur Respir J* 2013; 42: 414–424.
14 Savarese G, Paolillo S, Costanzo P, *et al.* Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012; 60: 1192–1201.

Eur Respir J 2015; 45: 853–854 | DOI: 10.1183/09031936.00191314 | Copyright ©ERS 2015

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.