Risk Reduction and Hemodynamics with Initial Combination Therapy in Pulmonary Arterial Hypertension

Short title: Initial oral combination therapy in PAH

Roberto Badagliacca [a], Michele D'Alto [b], Stefano Ghio [c], Paola Argiento [b], Vincenzo Bellomo [d], Natale Daniele Brunetti [e], Gavino Casu [f], Marco Confalonieri [g], Marco Corda [h], Michele Correale [i], Carlo D'Agostino [l], Lucrezia De Michele [l], Giuseppe Galgano [d], Alessandra Greco [c], Carlo Lombardi [m], Giovanna Manzi [a], Valentina Mercurio [n], Massimiliano Mulè [o], Giuseppe Paciocco [p], Silvia Papa [a], Emanuele Romeo [b], Laura Scelsi [c], Davide Stolfo [q], Patrizio Vitulo [r], Robert Naeije [s], Carmine Dario Vizza [a]

[a] Dept. of Cardiovascular and Respiratory Sciences - Sapienza University of Rome, Italy

[b] Department of Cardiology, Monaldi Hospital – University "L. Vanvitelli", Naples, Italy

[c] Fondazione IRCCS Policlinico S Matteo, Pavia, Italy

[d] Department of Cardiology, "F.Miulli" Hospital, Acquaviva delle Fonti, Bari, Italy

[e] Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

[f] ATS Sardegna-ASSL Nuoro, San Francesco Hospital Nuoro, Italy

[g] Pulmonology Unit, Heart-Thorax-Vessels Dept., University Hospital of Cattinara, Trieste, Italy

[h] Azienda Ospedaliera "G. Brotzu" San Michele, Cagliari, Italy

[i] Cardiology Department, Ospedali Riuniti University Hospital, Foggia, Italy

[l] Cardiology Department – University Hospital Policlinico Consorziale Bari, Italy

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

[m] Cardiologia, Università degli studi di Brescia, Brescia, Italy

[n] Department of Translational Medical Sciences - Federico II University of Naples, Italy

[o] Ferrarotto Hospital, Catania, Italy

[p] Dipartimento Cardio-Toraco-Vascolare, Clinica Pneumologica, Azienda Ospedaliera San Gerardo, Monza, Italy

[q] Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy

[r] Pulmonology Unit, IRCCS - Istituto Mediterraneo Trapianti e Terapie ad Alta Specializzazione (ISMETT), Palermo, Italy

[s] Department of Pathophysiology, Free University of Brussels, Brussels, Belgium

C.D. Vizza and R. Naeije share the last authorship.

Address for correspondence:

Carmine Dario Vizza, MD

Dept. of Cardiovascular and Respiratory Sciences

I School of Medicine, Sapienza University of Rome

Policlinico Umberto I, Viale del Policlinico 155 - 00161 Rome, Italy

e-mail: dario.vizza@uniroma1.it Phone: +39 06 49979016

Authors contributions:

Contributions to the manuscript: (I) Conception and design of the study: R.Badagliacca, R. Naeije, C.D. Vizza; (II) Administrative support: all authors; (III) Data collection: all authors except R. Naeije; (IV) Data analysis: R. Badagliacca; (V) Data interpretation: R.Badagliacca, R. Naeije, C.D. Vizza; (VI) Drafting of the work: all authors; (VII) Critical revision for

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

important intellectual content: R.Badagliacca, M. D'Alto, R. Naeije, C.D. Vizza; (VIII) Final approval of manuscript: all authors.

Descriptor Number: 9.35 Pulmonary Hypertension: Clinical-Diagnosis/Pathogenesis/Outcome

Word count: 3152

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org**.**

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

At a Glance Commentary

What is the current scientific knowledge on this subject?

Initial combination of ERA and PDE-5i drugs in PAH improves functional class and exercise capacity and is associated with a decreased relative risk of clinical deterioration.

This is the current suggested approach for the naive patients who are not in the high risk status.

What does this study add to the field?

The present study shows that a low-risk status, as suggested by the current guideline, is achieved or maintained in a minority of patients with the initial ERA and PDE-5i combination therapy. This unsatisfactory treatment response appears related to a moderate treatment-induced decrease in PVR. The present study shows that either ERS/ESC or REVEAL 2.0 scores enriched by a PVR score at initial evaluation could predict the response to initial combination therapy. These results suggest that a subpopulation of naive patients currently candidate to initial oral combination therapy do not have a good treatment response and need a careful follow-up and escalation to parenteral prostanoid.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Abstract

Rationale: An initial oral combination of drugs is being recommended in pulmonary arterial hypertension (PAH), but the effects of this approach on risk reduction and pulmonary vascular resistance (PVR) are not known.

Objective: To test the hypothesis that a low-risk status would be determined by the reduction of PVR in PAH patients treated upfront with a combination of oral drugs.

Methods. The study enrolled 181 treatment-naive PAH patients (81 % idiopathic) with a follow-up right heart catheterization at 6 months (IQR 144-363 days) after initial combination of endothelin receptor antagonist + phosphodiesterase-5 inhibitor drugs and clinical evaluation and risk assessments by European guidelines and REVEAL scores.

Results. Initial combination therapy improved functional class and 6-min walk distance, and decreased PVR by an average of 35 % (median - 40 %). A third of the patients had a decrease in PVR < 25 %. This poor hemodynamic response was independently predicted by age, male sex, pulmonary artery pressure and cardiac index, and at echocardiography a right/left ventricular surface area ratio >1 associated with low tricuspid annular plane systolic excursion (TAPSE) < 18 mm. A low risk status at 6 months was achieved or maintained in only 34.8% (REVEAL score) to 43.1% (European score) of the patients. Adding criteria of poor hemodynamic response improved prediction of a low risk status.

Conclusion. A majority of PAH patients still insufficiently improved after 6 months of initial combinations of oral drugs is identifiable at initial evaluation by hemodynamic response criteria added to risk scores.

Keywords: pulmonary arterial hypertension, right heart remodeling, echocardiography, pulmonary vascular resistance, upfront therapy.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Introduction

In spite of considerable progress achieved with the introduction of endothelin receptor antagonists (ERA) and phosphodiesterase-5 inhibitors (PDE-5i), pulmonary arterial hypertension (PAH) remains a lethal disease (1). It was until recently recommended to start World Health Organisation (WHO) functional class II and III patients on one of these drugs with sequential addition of another one targeting a different pathway in case of clinical deterioration or insufficient improvement, with parenteral prostacyclins in patients with persistent deterioration or initial WHO functional class IV (1). The AMBITION (AMBrIsentan and Tadalafil in Patients with Pulmonary Arterial HypertensION) trial showed that a more aggressive strategy of initial combination of the ERA ambrisentan and the PDE-5i tadalafil vs either drug alone was associated with a decreased relative risk of clinical deterioration by 50% along with a 50% decrease in brain natriuretic peptide (BNP) and approximately a doubling of the increase in 6-min walk distance at 6 months (2). This study provided rationale for initial combination of oral therapies in PAH (3,4). However, the hemodynamic effects and risk status achieved with initial combination of oral therapies are not exactly known, so that clinicians remain with insufficient guidance as to whether more aggressive therapies with parenteral prostacyclins may be indicated.

Because most of symptomatology and outcome in PAH is determined by right ventricular (RV) function adaptation to increased afterload (5,6), we hypothesized that the efficacy of initial combination of an ERA and a PDE-5i would be related to decreased pulmonary vascular resistance (PVR). We assumed that a larger reduction in PVR would decrease afterload and thereby allow for improved RV structure and function, shift patients to lower risk status and better outcome. We therefore evaluated risk by the most recent version of United States Registry to Evaluate Early and Long-Term PAH Disease Management registry (REVEAL)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

score 2.0 (7) and by a validated simplified version of the European Respiratory and Cardiology Societes (ERS/ESC) guidelines-derived score (8) in a cohort of incident PAH patients put on initial combination of ERA+PDE-5i and who underwent an echocardiographic and right heart catheterization evaluation at baseline and at follow-up.

Methods

Population and study design

One hundred and eighty one treatment-naïve consecutive patients with idiopathic (I) PAH or PAH related to connective tissue disease (CTD) or congenital heart disease (CHD) with closed shunt, diagnosed between January 2013 and December 2018 in 11 centers of the Italian Pulmonary Hpertension NETwork (iPHNET) were retrospectively analyzed. The centers participating to the iPHNET share a common database for the prospective follow-up of PAH patients (9). The diagnosic work-up of PAH conformed to the European guidelines with the typical hemodynamic profile of precapillary pulmonary hypertension, defined by a mean pulmonary artery pressure-mPAP $\geq$ 25 mmHg, a pulmonary artery wedge pressure -PAWP <15 mmHg, and a PVR > 3 Wood Units, and the use of an algorithm including respiratory function tests (TLC >70%, FEV_1 >70%), perfusion lung scan, computer tomography scan and echocardiography. All patients were non-responders to acute vasodilator testing with nitric oxide at the time of diagnosis. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board for human studies of the Policlinico Umberto I - Sapienza University of Rome (Protocol n. 42412).

The data were collected retrospectively from the local databases which are used for the prospective follow-up of PAH patients in the centers. All the patients were followed by outpatient clinic visits every 3-6 months or when necessary. A complete assessment including clinical examination, 6-min walk tests, echocardiography, right heart catheterization, and the

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

ERS/ESC guidelines-derived risk assessment and the REVEAL 2.0 score, was collected from the patients' medical records at baseline and between 3 to 12 months of follow-up.

Measurements

Right heart catheterization was performed in accordance with the European guidelines (1), with zero reference levelled at mid chest in the supine position and cardiac output (CO) measured by thermodilution. PVR was calculated as (mPAP - PAWP) / CO. Baseline echocardiographic data were acquired using commercially available equipments and standard views, in accordance with international guidelines (10). To avoid missing data, only a limited number of simple parameters and derived measures were considered in the analysis: RV end-diastolic area to left ventricular end-diastolic area ratio (RVEDA/LVEDA) in the 4-chamber view (qualitative assessment), tricuspid annular plane systolic excursion (TAPSE) and presence of pericardial effusion. Tricuspid regurgitation was semi-quantitatively graded as mild, moderate or severe. We previously reported on inter-observer variabilities of these measurements among the Italian PH network (11,12): RVEDA intraobserver 0.18 ± 0.66 (95% confidence interval [CI]: -1.09 to 1.45), interobserver 0.15 ± 1.08 (95% CI: -2.07 to 2.37); LVEDA intraobserver 0.06 ± 0.79 (95% CI: -1.52 to 1.64), interobserver -0.07 ± 0.76 (95% CI: -1.63 to 1.49); TAPSE intraobserver 0.20 ± 0.63 (95% CI: -1.03 to 1.43), interobserver 0.00 ± 0.67 (95% CI: -1.06 to 1.06).

Risk assessment was based on a simplified version of the ERS/ESC guidelines score, with incorporation of WHO functional class, 6-min walk distance (6MWD), right atrial pressure (RAP) and cardiac index (CI) (8), and on the REVEAL score 2.0 which incorporates etiology, age, sex, WHO functional class, systolic blood pressure, heart rate, right atrial pressure, PVR, 6MWD, lung diffusing capacity for carbon monoxide (DL_{CO}), brain natriuretic peptide (BNP) levels, renal function, echocardiography of pericardial effusion, and previous hospitalization

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

(7).

Statistical analysis

Continuous data are expressed as mean ± standard deviation, and categorical data are expressed as counts and proportions. Two-group comparisons were done with paired, two-tailed t tests for means if the data were normally distributed or with Wilcoxon's rank-sum tests if the data were not normally distributed. Chi square or Fisher's exact tests were used to analyze the categorical data.

Univariate and multivariate logistic regression analysis were used to identify clinical and hemodynamic determinants of the lower tertile of PVR changes from baseline after treatment. ROC curves were used to identify the optimal age, RV/LV ratio and mPAP cut-points for PVR changes response. Based on the logistic ß coefficients, a PVR risk score was derived assigning weighted values to the four variables. The ß coefficient was rounded to the nearest integer to derive weights. The total sum based on the number of variables achieved was then used for each patient and included in the Cox multivariate analysis.

A sensitivity analysis was performed for patients treated with initial combination of ambrisentan-tadalafil.

Cox regression models were created with the ERS/ESC guidelines and the REVEAL 2.0 scores as categorical variables (low, intermediate, high risk)(Model-1 and Model-2). Then, all combinations of the logistic analysis-derived score values were added to the two models and computed/compared according to the models' Akaike Information Criterion (AIC) for prediction, optaining Model-3 and Model-4. Smaller AIC values indicated a better model fit. The proportional-hazards assumptions were assessed with the Log-minus-log plot.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Finally, internal validation of the Cox proportional hazard analysis models was based on bootstrapping, using 10.000 bootstrap samples and 95% percentile confidence intervals.

The c statistic was calculated for each model and the comparison of the values were tested by the method of DeLong et al. (13) to determine the incremental prognostic information. To make the results more robust, the Integrated Discrimination Improvement (IDI) was calculated for each model (14). The IDI determines whether adding a new risk factor improves the discrimination slope of a test. It calculates the average probability of an event for both event and nonevent groups and measures how much the average probability has increased with the addition of a new risk factor compared with the old model. An improved new model gives an increased predicted probability for events, compared with nonevents.

Regression analysis was performed to assess the relation between the absolute value of PVR and its changes during follow-up.

All statistical analyses were performed using SPSS software (version 25.0, IBM), Stata 13 (StataCorp, College Station, TX, USA).

Results

Patient population

There were 120 women and 61 men, aged 53±16 years, time from onset of symptoms to diagnosis 11±13 months, 146 idiopathic PAH (IPAH), 28 connective tissue disease (CTD) PAH and 7 corrected cardiac shunt-PAH, most of them in WHO class III with reduced exercise capacity (Table 1). The most frequent comorbidities were hyperlipidemia (11%), thyroid diseases (8%) and diabetes (4%). According to the ERS/ESC guidelines risk assessment, 27 (14.9%) patients were at low risk, 130 (71.8%) at intermediate risk, and 24 (13.3%) at high risk. According to the REVEAL 2.0 score, 19 (10.5%) patients were at low risk (score < 7),

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

100 (55.2%) at intermediate risk (score 7-8), and 62 (34.3%) at high risk (score > 8)(Table 2).

As shown in Table 1, the patients had severe PAH with markedly increased PVR and low CI. The echocardiography at baseline showed dilated RV, decreased TAPSE, tricuspid regurgitation and pericardial effusion (the latter in 38 patients).

The majority of patients were started on ambrisentan-tadalafil combination therapy (62%). All but 11/113 patients reached the full dose of ambrisentan and tadalafil (10 and 40 mg daily, respectively) within 2 months. Other initial PDE-5i and ERA combinations are shown in Table E1 in the online data supplement. None of the patients discontinued dual oral combination therapy due to severe side effects.

Clinical, hemodynamic and echocardiographic findings at follow-up

All the patients survived after a median of 180 days follow-up (IQR 144-363; minimum 79; maximum 394)(Figure E1 in the online data supplement). As shown in Table 1, the patients had significant improvements in WHO functional class, 6MWD, PVR, mPAP, RAP, CI, RVEDA/LVEDA<1, TAPSE, tricuspid regurgitation and pericardial effusion.

The median PVR reduction obtained with double oral initial therapy was -40.4% (IQR -25.8; -45.3)(-2.9 WU, IQR -4.8; -1.7 WU), resembling a normal distribution but with a long tail to the right (Figure 1). PVR decreased below 3 WU in 14 patients (7.7%). PVR increased in 19 patients (10.5%) in spite of initial combination therapy.

A sensitivity analysis focused on the subgroup of patients treated with the initial ambrisentan-tadalafil combination showed a median PVR reduction of – 38.0% (IQR -20.1;-45.0), not different from the overall population (p=ns).

Finally, we observed a median PVR reduction of 38% in the 28 CTD-PAH patients that was

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

not different from the overall population (p=ns).

Changes in ESC/ERS and REVEAL 2.0 scores

At second evaluation a low risk status was achieved in 78 of the patients (43.1 %) according to the ERS/ESC score or 63 patients (34.8%) according to the REVEAL 2.0 score (Figure 2). Patients at low risk at the time of diagnosis were more likely to remain in a low-risk status, while a significant proportion of those at intermediate risk were unable to improve. Notably, none of the patients at high risk at baseline improved to a low risk condition according to either score, and almost half of them remained in a high risk condition.

The sensitivity analysis for the subgroup of patients treated with initial ambrisentan-tadalafil combination showed a trend for a higher percentage of patients improving or remaining at a low-risk status compared with the overall population, but the difference was not statistically significant (Table E2 in the online data supplement).

The tight relationship between PVR reduction under initial oral therapy and the presence of a low-risk status at last observation is shown in figures 3-4. Indeed, the achievement of a low-risk status is clearly a function of PVR reduction, with a heterogeneous response within the low- and intermediate-risk patients, especially for the latter group.

Determinants of poor pulmonary vascular resistance reduction response

A multivariate logistic analysis was used to identify baseline variables that were associated with a PVR reduction of less than 25.8% (i.e. the lower tertile of PVR changes) defining a poor response. Age ≥ 60 years, male-sex, baseline mPAP ≥ 48 mmHg associated with low CI (< 2.5 l/min/m^2)(considered as an interaction term), and RV/LV ratio >1 associated with low TAPSE (< 18 mm)(considered as an interaction term) emerged as independent predictors of a poor PVR response (Table 3).

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

A "PVR score" was created deriving weighted integers from the beta coefficient of the 4 parameters. A weight of 1 was assigned for a ß coefficient of 0.51 and 0.62; a weight of 1.5 for a ß coefficient of 1.30 and 1.47. According to the total sum based on the number of variables for each patient, 17 (9.4%) had a score value between 0 and 1, 99 (54.7%) between 1.5 and 2.5, and 65 (35.9%) a score ≥ 3.

Figure 5 illustrates the tight relationship between PVR reduction and patient distribution based on the scoring system, showing the predicted probability of poor response in terms of PVR reduction after initial oral therapy. The specificity, sensitivity, positive predictive value, negative predictive value, and AUC for a score ≥ 3 were respectively, 89%, 68%, 83%, 78%, and 0.78 (95% C.I. 0.71-0.85, p=0.0001).

As shown in Table E3 (online supplement), patients older than 60 years compared to younger patients had a lower exercise capacity at baseline in spite of lower PVR, and a greater proportion of them were included in a high risk status. Furthermore, older patients had a more limited reduction in PVR after initial combination therapy.

As shown in Table E4 (online supplement), male patients compared to female patients had a lower PVR at baseline and a more limited decrease in PVR after initial combination therapy, yet RV function appeared to be worse as assessed by lower CI, lower TAPSE, and higher RV/LV ratio for similar PVR at second evaluation. Accordingly, a smaller number of male patients achieved a low-risk status after initial oral combination therapy.

Models prediction of treatment failure

At Cox multivariate analysis, Model-1 showed that the ERS/ESC risk assessment at baseline was able to predict the absence of a low risk condition after initial combination therapy (Model-1)(Table 4). The risk of not improving to a low risk condition for the intermediate and high

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

status was, respectively, 3.5 and 5.5 times higher than the low status to remain stable. Model-2 showed that the REVEAL 2.0 high risk status had a likelihood of not improving to a low risk condition of 4.4 times higher than the low status to remain stable, while the risk for the intermediate status was not significantly different from the low status.

Adding the weighted PVR prediction scoring system based on the determinants of poor PVR reduction, Model-3 and Model-4 were generated. A score ≥ 3 was able to increase the prognostic information of the models, as shown by the increased c-statistic, demonstrating the weight of RV afterload reduction in improving the power of the models based on the ERS/ESC and REVEAL 2.0 risk tools for predicting a poor response to initial combination therapy.

The internal validation of the Cox proportional hazard analysis models based on bootstrapping, using 10.000 bootstrap samples and 95% percentile confidence intervals, confirmed the main results, in terms of both statistical magnitude and direction (Table E5 in the online data supplement).

The incremental value of incorporating the weighted PVR prediction scoring system at the time of diagnosis is illustrated in figures 3-4. As the scoring system predicts a poor PVR reduction (figure 5), it becomes evident how a score ≥ 3 is able to improve patients discrimination within the low and intermediate risk profile. We further quantified the ability of the PVR prediction scoring system to account for differences in the distribution of risk across patients on top of the European and U.S. risk assessment tools by the IDI index and reclassified Model-3 and Model-4 incorporating the new predicitive variables, compared with Model-1 and Model-2. The discrimination slope of the updated models were, respectively, 63.2 percentage points higher than the original with an actual IDI index of 0.056 (Model-3 vs Model-1), and 36.8% with an actual IDI value of 0.080 (Model-4 vs Model-2), demonstrating the incremental prognostic power of Model-3 and Model-4 versus Model-1 and Model-2 for predicting poor

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

response to double oral treatment ($p<0.001$).

Discussion

The present results show that an initial combination of ERA and PDE-5i drugs in PAH markedly improves functional class and exercise capacity at 6 months of therapy, in agreement with the results of the AMBITION trial, and that these favorable effects are accompanied by improved risk scores and a reduction in PVR. However, the results also show that with the initial ERA-PDE-5i combination a low-risk status is achieved or maintained in a minority of patients, 35 % according to the REVEAL 2.0 score or 43 % according to the ERS/ESC score, with no high-risk patient achieving a low-risk status by either score. These disappointing treatment responses appear related to only moderate treatment-induced decrease in PVR, on average no more than 35 % (median - 40 %), and predicted by either ERS/ESC or REVEAL 2.0 scores enriched by a PVR score at initial evaluation.

The treatment algorithm for PAH was updated after the World Symposium of Pulmonary Hypertension (WSPH) held in Nice in 2018 with the prescription of targeted therapies according to ERS/ESC risk scores. Although some discussion still persists (4), experts agreed on initial combination of oral therapies in intermediate risk patients and initial parenteral prostacyclin therapy in high risk patients, with triple combination of these drugs in patients still in intermediate or high risk states at 3 to 6 month reevaluation (3). The present results show that initial combination of oral drugs does not sufficiently improve risk in at least half of PAH patients, and that this can only to some extent be predicted at baseline by use of currently available scores.

Since PAH is a RV afterload mismatch syndrome (5,6), we reasoned that treatment failure would be related to insufficient decrease in PVR. It has been recently shown that triple initial combination of PAH drugs with inclusion of a parenteral prostacyclin decreases PVR by an

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

average of 65 %, and that this more favorable hemodynamic effect results is persistent clinical improvement, low risk status and reverse remodeling of the RV (15,16). Even though this was demonstrated in only limited number but high risk patient populations, these observations mirrored those reported in acutely reversible IPAH (17) and support the notion that more decrease in PVR, preferably > 50-60 % allows for an improved right heart function and a better clinical response (6).

The present results bring in a prediction score for PVR reduction weighted for the independent effects of age, sex, hemodynamic severity of pulmonary hypertension and echocardiography of RV failure. Prediction of insufficient decrease in PVR by less than 25 %, as recorded in one third of the patients and which corresponds approximately to the maximum error on the measurement (18) allowed for an improvement of risk scores' prediction of insufficient therapeutic responses after several months of combination therapy. The PVR score requires addition of echocardiography to right heart catheterization, but with simple daily routine measurements of RV structure and systolic function added to tricuspid regurgitation and detection of pericardial effusion. It would not therefore much add to the workload of initial evaluation of a PAH patient.

A high-risk profile at diagnosis (whether by European or REVEAL 2.0 scoring system) was associated with a high likelihood of treatment failure, defined by persistence of high or intermediate risk status after several months of initial combination therapy (3). These patients should probably be treated upfront with addition of a parenteral prostacyclin, but this will have to be established in a properly designed randomized controlled trial. On the other hand, patients at intermediate ESC/ERS (not REVEAL 2.0) risk status were at higher risk of treatment failure after initial combination therapy compared with the low-risk patients. This uncertainty concerns a large proportion of incident PAH patients (19) who may indeed benefit from a better

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

stratification with addition of a PVR score as designed in the present study. Of note, because of the non-modifiable but important risk factors included in the Reveal 2.0 score, this score potentially predicted more high-risk patients at baseline and at follow-up than the ESC/ERS score, which only includes treatment responsive variables. Other causes of differences in risk assessment between the scores may be the lesser impact of WHO functional class II and greater impact of previous hospitalizations in the REVEAL 2.0 score. As recently discussed, both these tools may be used to define treatment objectives with the ideal goal of obtaining a "low-risk" profile, but one does not know which one is preferable (19).

A pooled weighted analysis of 16 randomized controlled trials of mostly monotherapies targeting the pulmonary circulation including a total of 2.353 PAH patients revealed a mean decrease of 25 ± 8% for PVR at 4 months of follow-up (20). Subsequent initial double combinations of targeted oral therapies were associated with more important reductions of PVR ranging on average from - 28 % to 55 % (21). Evidence is accumulating that a decrease in PVR of > 50 to 60 % is needed to induce a return to normal of RV dimensions and function (6,11,15-17,21,22). Since the likelihood of RV reverse remodeling is related to the decrease in PVR in a sigmoid relationship (6,23), it appears that in the range of > 40 % decrease of PVR the improvement in RV structure and function may be huge for little additional fall in PVR. This argues in favor of PVR- and/or imaging-directed therapeutic strategies. We therefore believe that adding a PVR score to current risk scores may help clinicians in selecting the best therapeutic regimen for PAH patients.

The median decrease in PVR of only 40 % (mean decrease 35 %) after 6 months of initial combination therapy in the present study is smaller than a mean 45 % decrease in 97 PAH patients reevaluated after 4 months reported by Sitbon et al (24). In that study, the majority of the patients was treated with bosentan combined to sildenafil, in contrast with the present study

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

in which the majority of the patients were treated with the ambrisentan-tadalafil combination. However, the difference is not explained by different potencies of drugs, as in the sudy by Sitbon et al the combination of an ERA with tadalafil appeared to be superior. There is also data suggesting higher clinical efficacy of the initial ambrisentan-tadalafil combination in CTD (mostly SSc)-PAH (25, 26) with a median PVR decrease of 55 % after 9 months treatment reported by Hassoun et al. However, in the present study we observed a median PVR reduction of 38% in the 28 CTD-PAH patients that was not different from the decrease in PVR observed in the IPAH patients.

In the present study, male patients had a lower PVR at baseline compared to female patients, yet their RV adaptation to afterload appeared worse as assessed by lower CI, TAPSE and higher RV/LV ratio for similar PVR at second evaluation. As a consequence, a smaller proportion of male patients achieved a low-risk status after initial oral combination therapy. This data is in keeping with previous magnetic resonance imaging of higher RV ejection fraction at the same PVR (27) and invasive demonstration of higher gold standard RV ratio of end-systolic to arterial elastances in female compared to male PAH patients (28).

On the other hand, patients older than 60 years compared with younger patients had a lower exercise capacity at baseline despite lower PVR, and a greater proportion qualified for a high risk status. This is in accordance with recent report of a different phenotype in older PAH patients having lower functional capacity for the same level of RV afterload compared to younger patients (29).

This study has limitations as being retrospective and limited in imaging. However, we believe that its results are convincing as the study was multi-centric with original hemodynamic and echocardiography data, results analysed with rigorous statistics and demonstration with updated risk scores what the clinicians and their patients can expect from initial double

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

combination of oral drugs in PAH.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

REFERENCES

1. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46:903-975.

2. Galie` N, Barbera` JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JH, Langley J, Rubin LJ; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015; 373:834-844.

3. Galiè N, Channick RN, Frantz RP Grünig E, Jing ZC, Moiseeva O, Preston IR, Pulido T, Safdar Z, Tamura Y, McLaughlin VV. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019; 53:1801889.

4. Humbert M, Lau EMT. Should initial combination therapy be the standard of care in pulmonary arterial hypertension? Yes. Chest 2019; 156:1039-1042.

5. Lahm T, Douglas IS, Archer SL, Bogaard HJ, Chesler NC, Haddad F, Hemnes AR, Kawut SM, Kline JA, Kolb TM, Mathai SC, Mercier O, Michelakis ED, Naeije R, Tuder RM, Ventetuolo CE, Vieillard-Baron A, Voelkel NF, Vonk-Noordegraaf A,

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Hassoun PM; American Thoracic Society Assembly on Pulmonary Circulation. Assessment of Right Ventricular Function in the Research Setting: Knowledge Gaps and Pathways Forward. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med. 2018; 198(4):e15-e43. doi: 10.1164/rccm.201806-1160ST.

6. Sanz J, Sánchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, Function, and Dysfunction of the Right Ventricle: State-of-the-Art Review. J Am Coll Cardiol 2019; 73:1463-1482.

7. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, McGoon MD, Pasta DJ, Selej M, Burger CD, Frantz RP.. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL Risk Score Calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest 2019; 156:323-337.

8. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, Picard F, de Groote P, Jevnikar M, Bergot E, Chaouat A, Chabanne C, Bourdin A, Parent F, Montani D, Simonneau G, Humbert M, Sitbon O. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J 2017; 50:1700889

9. Poscia R, Ghio S, D'Alto M, Vitulo P, Mulè M, Albera C, Parisi F, Badagliacca R, Fedele F, Vizza CD. 'Real-life' information on pulmonary arterial hypertension: the iPHnet Project. Curr Med Res Opin. 2014; 30: 2409-2414.

10. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. Endorsed by the European Association of Echocardiography, a registered branch of the

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23: 685-713

11. Badagliacca R, Raina A, Ghio S, D'Alto M, Confalonieri M, Correale M, Corda M, Paciocco G, Lombardi C, Mulè M, Poscia R, Scelsi L, Argiento P, Sciomer S, Benza RL, Vizza CD. Influence of various therapeutic strategies on right ventricular morphology, function and hemodynamics in pulmonary arterial hypertension. J Heart Lung Transplant 2018; 37: 365-375

12. Badagliacca R, Papa S, Valli G, et al. Echocardiography Combined With Cardiopulmonary Exercise Testing for the Prediction of Outcome in Idiopathic Pulmonary Arterial Hypertension. Chest 2016; 150: 1313-1322.

13. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837-845

14. Hlatky MA, Greenland P, Arnett DK, Ballantyne CM, Criqui MH, Elkind MS, Go AS, Harrell FE Jr, Hong Y, Howard BV, Howard VJ, Hsue PY, Kramer CM, McConnell JP, Normand SL, O'Donnell CJ, Smith SC Jr, Wilson PW; American Heart Association Expert Panel on Subclinical Atherosclerotic Diseases and Emerging Risk Factors and the Stroke Council. Criteria for evaluation of novel markers of cardiovas- cular risk: a scientific statement from the American Heart Association. Circulation. 2009; 119: 2408-2416

15. Sitbon O, Jais X, Savale L, Bergot E, Bergot E, Macari EA, Bouvaist H, Dauphin C, Picard F, Bulifon S, Montani D, Humbert M, Simonneau G. Upfront triple combination

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J 2014; 43:1691-1697.

16. D'Alto M, Badagliacca R, Argiento P, Romeo E, Farro A, Papa S, Sarubbi B, Russo MG, Vizza CD, Golino P, Naeije R. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. Chest 2020; 157: 376-383.

17. Badagliacca R, Poscia R, Pezzuto B, Papa S, Reali M, Pesce F, Manzi G, Gianfrilli D, Ciciarello F, Sciomer S, Biondi-Zoccai G, Torre R, Fedele F, Vizza CD. Prognostic relevance of right heart reverse remodeling in idiopathic pulmonary arterial hypertension. J Heart Lung Transplant 2017 Oct 2:S1053-2498(17)32041-7. doi: 10.1016/j.healun.2017.09.026.

18. Naeije R, D'Alto M, Forfia PR. Clinical and research measurement techniques of the pulmonary circulation: the present and the future. Progr Cardiovasc Dis. 2015; 57: 463-72

19. Weatherald J, Boucly A, Sahay S, Humbert M, Sitbon O. The low risk profile in pulmonary arterial hypertension. Time for a paradigm shift to goal-oriented clinical endpoints? Am J Respir Crit Care med 2018; 197: 860-868

20. Savarese G, Musella F, D'Amore C, Losco T, Marciano C, Gargiulo P, Rengo G, Dellegrottaglie S, Bossone E, Leosco D, Perrone-Filardi P. Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. Eur Respir J. 2013;42:414–424.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

21. Badagliacca R, Papa S, Matsubara H, Lang IM, Poscia R, Manzi G, Vizza CD. The importance of right ventricular evaluation in risk assessment and therapeutic strategies: raising the bar in pulmonary arterial hypertension. Int J Cardiol 2020; 301: 183-189

22. Van de Veerdonk MC, Huis In T Veld AE, Marcus JT, Westerhof N, Heymans MW, Bogaard HJ, Vonk-Noordegraaf A. Upfront combination therapy reduces right ventricular volumes in pulmonary arterial hypertension. Eur Respir J 2017; 49:1700007.

23. Badagliacca R, Papa S, Manzi G, Miotti C, Luongo F, Sciomer S, Cedrone N, Fedele F, Naeije R and Vizza CD. Usefulness of Adding Echocardiography of the Right Heart to Risk Assessment Scores in Prostanoid-Treated Pulmonary Arterial Hypertension. JACC Cardiovasc Imaging. 2020. https:/doi.org/10.1016/j.jcmg.2020.04.005

24. Sitbon O, Sattler C, Bertoletti L, Savale L, Cottin V, Jaïs X, De Groote P, Chaouat A, Chabannes C, Bergot E, Bouvaist H, Dauphin C, Bourdin A, Bauer F, Montani D, Humbert M, Simonneau G. Initial dual oral combination therapy in pulmonary arterial hypertension. Eur Respir J 2016; 47: 1627-1634

25. Hassoun PM, Zamanian RT, Damico R, Lechtzin N, Khair R, Kolb TM, Tedford RJ, Hulme OL, Housten T, Pisanello C, Sato T, Pullins EH, Corona-Villalobos CP, Zimmerman SL, Gashouta MA, Minai OA, Torres F, Girgis RE, Chin K, Mathai SC. Ambrisentan and tadalafil upfront combination therapy in scleroderma-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2015; 192: 1102-1110

26. Coghlan JG, Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, Kuwana M, McLaughlin VV, Peacock AJ, Simonneau G, Vachiéry JL, Blair C, Gillies H, Miller KL, Harris JHN, Langley J, Rubin LJ; AMBITION investigators. Initial combination

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. Ann Rheuma Dis 2017; 76: 1219- 1227.

27. Jacobs W, Van de Veerdonk MC, Trip P, De Man F, Heymans MW, Marcus JT, Kawut SM, Bogaard HJ, Boonstra A, Vonk Noordegraaf A. The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension. Chest 2014; 145: 1230-1236

28. Tello K, Richter MJ, Yogeswaran A, Ghofrani HA, Naeije R, Vanderpool R, Gall H, Tedford RJ, Seeger W, Lahm T. Sex differences in right ventricular arterial coupling in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2020 Jun 5. doi: 10.1164/rccm.202003-0807LE

29. Badagliacca R, Rischard F, Papa S, Kubba S, Vanderpool R, Yuan JX, Garcia JGN, Airhart S, Poscia R, Pezzuto B, Manzi G, Miotti C, Luongo F, Scoccia G, Sciomer S, Torre R, Fedele F, Vizza CD. Clinical implications of idiopathic pulmonary arterial hypertension phenotypes defined by cluster analysis. J Heart Lung Transplant 2020; 39: 310-320

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Figure Legends

Figure 1. Distribution of decreases in pulmonary vascular resistance after 6 months of initial double combination therapy.

There was a wide range of PVR responses centered on a 40 % decrease. PVR decreased by less than 25 % in one third of the patients. PVR was increased 19 patients, but fell below 3 Wood units in 16 patients.

Abbreviation: PVR: pulmonary vascular resistance

Figure 2. A. Histogram reporting percent changes in ESC/ERS score from diagnosis to last observation. B. Histogram reporting percent changes in REVEAL 2.0 score from diagnosis to last observation.

Abbreviations: ESC: European Society of Cardiology; ERS: European Respiratory Society, REVEAL: United States Registry to Evaluate Early and Long-Term PAH Disease Management registry.

Figure 3. A. Boxplots of PVR reduction (%) versus ESC/ERS risk-score at diagnosis, with in patients who achieved or not a low-risk status (green vs red boxes respectively. Box edges represent the 25th (Q1) and 75th (Q3) quantiles, respectively. The whiskers extend to the minimum and maximum distribution. Outliers, defined as values more than 1.5 times the interquartile range above Q3 or below Q1, are reported as black stars. A low risk status was achieved only by patients with initial low or intermediate risk status, and was related to the decrease in PVR.

Abbreviations: ESC: European Society of Cardiology; ERS: European Respiratory Society; PVR: pulmonary vascular resistance

Figure 4. A. Boxplot reporting PVR reduction (%) versus REVEAL 2.0 risk-score at diagnosis (low: < 7; intermediate: 7-8; high: > 8), based on the presence of a low-risk status at last

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

observation (green boxes). Box edges represent the 25th (Q1) and 75th (Q3) quantiles, respectively. The whiskers extend to the minimum and maximum distribution. Outliers, defined as values more than 1.5 times the interquartile range above Q3 or below Q1, are reported as black stars. A low risk status was achieved only by patients with initial low or intermediate risk status, and was related to the decrease in PVR.

Abbreviations: PVR: pulmonary vascular resistance; REVEAL: United States Registry to Evaluate Early and Long-Term PAH Disease Management registry.

Figure 5. Predicted probability of poor PVR reduction response to therapy (defined as the lower tertile of PVR reduction), based on the weighted PVR prediction score value at baseline. Age ≥ 60 years, male-sex, baseline mPAP ≥ 48 mmHg associated with low CI (< 2.5 l/min/m^2), and RV/LV ratio >1 associated with low TAPSE (< 18 mm) were independent predictors of poor PVR reduction and have been included in the score (weighted value, respectively: 1.5, 1.5, 1.0, and 1.0). The specificity, sensitivity, positive predictive value, negative predictive value, and AUC for a score ≥ 3 were respectively, 89%, 68%, 83%, 78%, and 0.78 (95% C.I. 0.71-0.85, p=0.0001).

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table 1. Clinical, hemodynamic and echocardiographic characteristics of the study population

	BASELINE	**FOLLOW UP**	**Δ**	**p**
Age, years	53±16			
Sex, M:F	61:120			
Race (caucasian)	100%			
BMI	26.1±5.6			
WHO class	2.8±0.4	2.4±0.6	-0.4±0.6	0.001
I-II	37 (20.4%)	107 (59.1%)		
III	127 (70.2%)	65 (35.9%)		
IV	17 (9.4%)	9 (5.0%)		
6MWT, m	331±99	384±108	52±84	0.001
HEMODYNAMICS				
RAP, mmHg	9±5	7±4	-2±4	0.001
mPAP, mmHg	50±12	44±14	-7±12	0.001
CI, l/min/m2	2.4±0.8	3.0±0.9	0.6±0.8	0.001
PVR, UW	11±6	7±4	-4±5	0.001
PAWP, mmHg	10±3	9±4	-0.5±4	0.209
HR, beat/min	79±16	73±15.	-6±18	0.001
ECHOCARDIOGRAPHY				
TAPSE, mm	16±4	19±4	2±4	0.001
RV/LV ratio	<0.001			
< 1	6(3%)	34(19%)		
1	27(15%)	31(17%)		
> 1	148(82%)	116(64%)		

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Tricuspid regurgitation, grade	<0.001		
mild	85(47%)	99(55%)	
moderate	61(34%)	65(36%)	
severe	35(19%)	17(9%)	
Pericardial effusion, yes	38(21%)	19(10%)	<0.001

Results are expressed as means ± SD. *BMI:* body mass index; *WHO*: World Health Organization; *6MWT*: non-encouraged 6-minute walk test; *RAP*: mean right atrial pressure; *mPAP*: mean pulmonary arterial pressure; *CI*: cardiac index; *PVR*: pulmonary vascular resistance; PA*WP*: wedge pressure; *RV*: right ventricular end-diastolic area; *LV*: left ventricular end-diastolic area; *TAPSE*: tricupid anular plane systolic excursion.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table 2. Changes in risk assessment according to the European and REVEAL scoring systems.

	Diagnosis	**Follow-up**	*Low*	*Intermediate*	*High*
European score					
Low	27 (14.9%)		19 (10.5%)	8 (4.4%)	-
Intermediate	130 (71.8%)		59 (32.6%)	69 (38.1%)	2 (1.1%)
High	24 (13.3%)			15 (8.3%)	9 (5.0%)
REVEAL score					
Low (< 7)	19 (10.5%)		11 (6.1%)	8 (4.4%)	
Intermediate (7-8)	100 (55.2%)		52 (28.7%)	40 (22.1%)	8 (4.4%)
High (> 8)	62 (34.3%)		-	33 (18.2%)	29 (16.0%)

PVR: pulmonary vascular resistance; *REVEAL: United States Registry to Evaluate Early and Long-Term PAH Disease Management registry.*

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table 3. Determinants of the lower tertile of PVR reduction (< 25.8%).

	B	OR	(95% CI)	p	n. (%) patients
Age ≥ 60, years	1.47	4.3	(1.8-10.3)	0.001	82 (45.3)
Male-sex	1.30	3.7	(1.5-7.2)	0.007	61 (33.7)
mPAP ≥ 48 mmHg (CI < 2.5 l/min/m^2)	0.51	1.7	(1.1-4.0)	0.02	73 (40.3)
RV/LV >1 (TAPSE < 18 mm)	0.62	1.8	(1.1-4.2)	0.02	85 (46.9)

mPAP: mean pulmonary arterial pressure; *RV*: right ventricular end-diastolic area; *LV*: left ventricular end-diastolic area; *TAPSE*: tricupid anular plane systolic excursion.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table 4. Cox modeling for prediction of treatment failure. Model-1 refers to the ERS/ESC risk assessment; Model-2 refers to the REVEAL 2.0 risk assessment; Model-3 refers to the ERS/ESC risk assessment associated with the weighted PVR prediction score; Model-4 refers to the REVEAL 2.0 risk assessment associated with the weighted PVR prediction score. For each model the c-statistic value has been reported.

	HR	**(95% CI)**	**p**	***c*-statistic (95% CI)**
Model-1				0.60 (0.52-0.68)
Euro-low status	*Ref.*			
Euro-intermediate status	3.55	(1.70-7.41)	0.001	
Euro-high status	5.47	(2.45-12.2)	0.0001	
Model-2				0.69 (0.62-0.77)
REVEAL < 7	*Ref*			
REVEAL 7-8	1.49	(0.65-3.40)	0.33	
REVEAL > 8	4.43	(2.02-9.68)	0.0001	
Model-3				0.70 (0.62-0.78)
Euro-low status	*Ref.*			
Euro-intermediate status	3.54	(1.70-7.41)	0.001	
Euro-high status	5.00	(2.23-11.1)	0.0001	
PVR prediction score ≥ 3	1.79	(1.21-2.64)	0.004	
Model-4				0.73 (0.66-0.81)
REVEAL < 7	*Ref.*			
REVEAL 7-8	1.53	(0.67-3.50)	0.30	
REVEAL > 8	3.97	(1.81-8.71)	0.001	
PVR prediction score ≥ 3	1.76	(1.18-2.63)	0.006	

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

PVR: pulmonary vascular resistance; *REVEAL: United States Registry to Evaluate Early and Long-Term PAH Disease Management registry.*

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

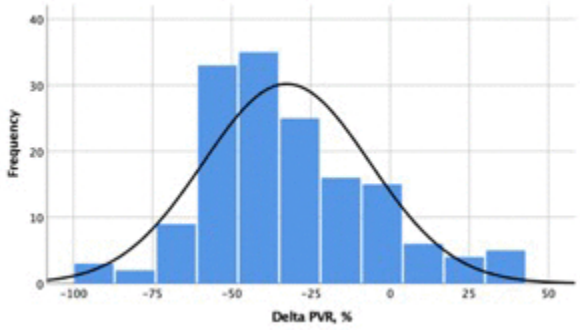

Figure 1. Distribution of decreases in pulmonary vascular resistance after 6 months of initial double combination therapy.
There was a wide range of PVR responses centered on a 40 % decrease. PVR decreased by less than 25 % in one third of the patients. PVR was increased 19 patients, but fell below 3 Wood units in 16 patients.
Abbreviation: PVR: pulmonary vascular resistance

104x61mm (72 x 72 DPI)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

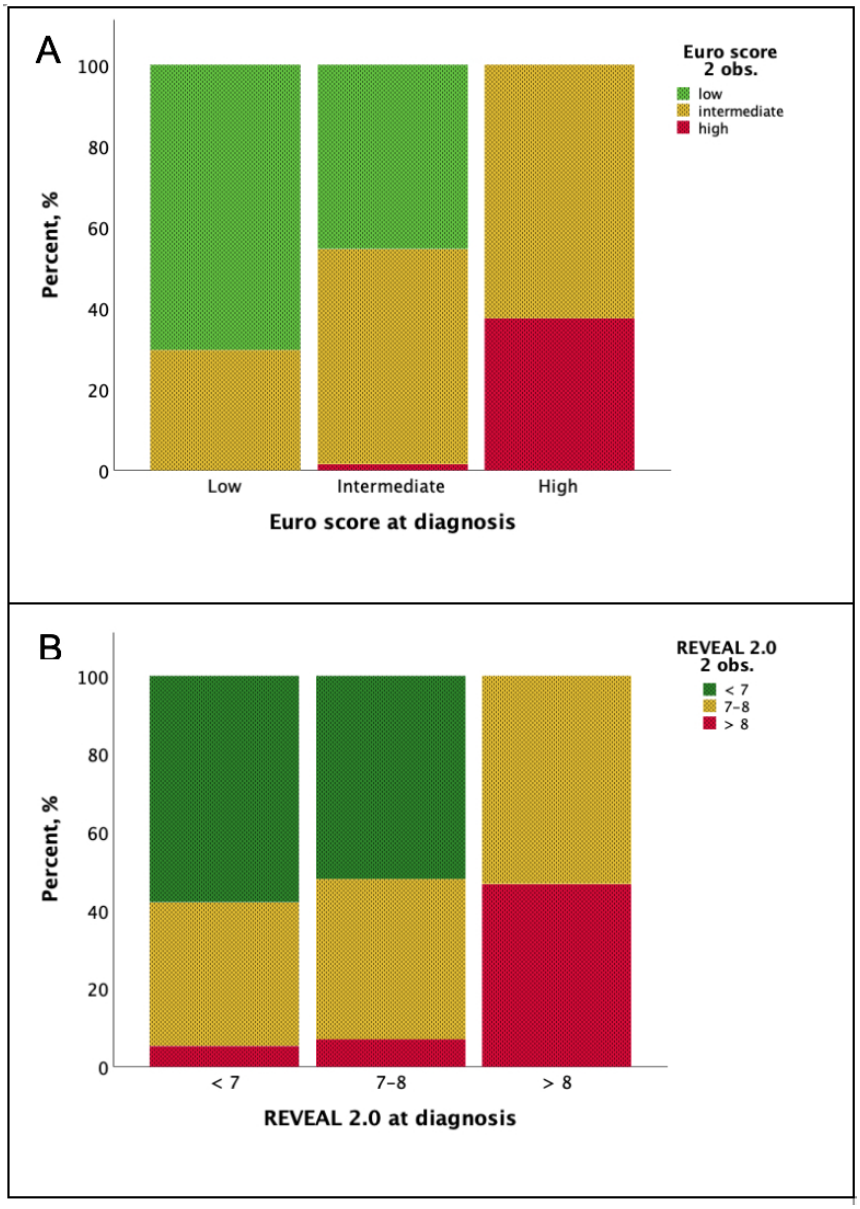

Figure 2. A. Histogram reporting percent changes in ESC/ERS score from diagnosis to last observation. B. Histogram reporting percent changes in REVEAL 2.0 score from diagnosis to last observation.
Abbreviations: ESC: European Society of Cardiology; ERS: European Respiratory Society, REVEAL: United States Registry to Evaluate Early and Long-Term PAH Disease Management registry.

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

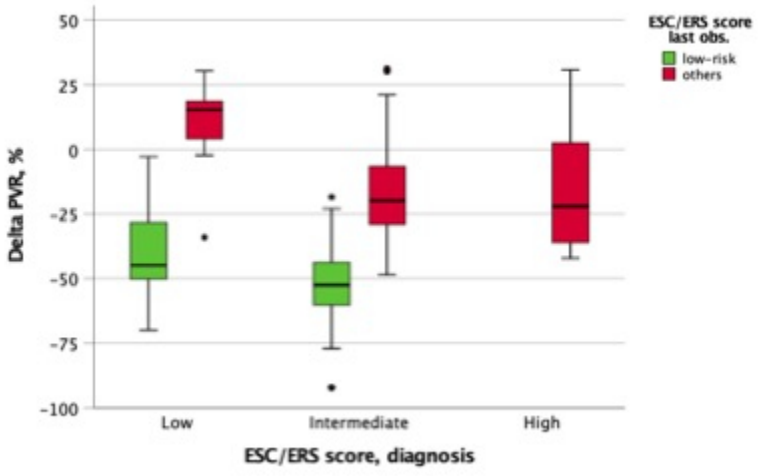

Figure 3. A. Boxplots of PVR reduction (%) versus ESC/ERS risk-score at diagnosis, with in patients who achieved or not a low-risk status (green vs red boxes respectively. Box edges represent the 25th (Q1) and 75th (Q3) quantiles, respectively. The whiskers extend to the minimum and maximum distribution. Outliers, defined as values more than 1.5 times the interquartile range above Q3 or below Q1, are reported as black stars. A low risk status was achieved only by patients with initial low or intermediate risk status, and was related to the decrease in PVR.
Abbreviations: ESC: European Society of Cardiology; ERS: European Respiratory Society; PVR: pulmonary vascular resistance

139x88mm (72 x 72 DPI)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

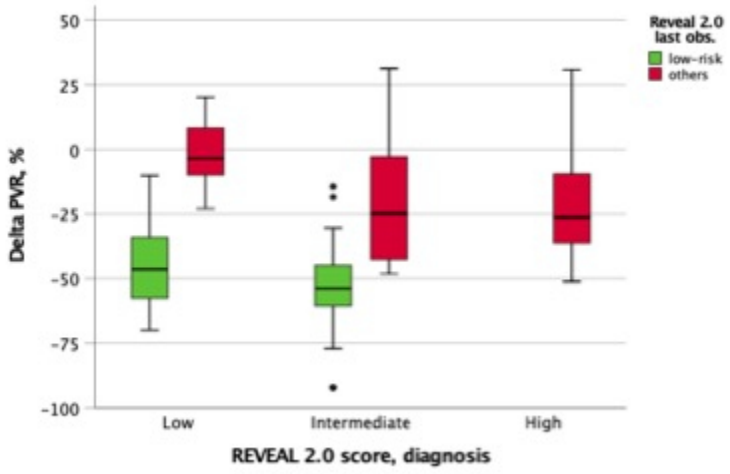

Figure 4. A. Boxplot reporting PVR reduction (%) versus REVEAL 2.0 risk-score at diagnosis (low: < 7; intermediate: 7-8; high: > 8), based on the presence of a low-risk status at last observation (green boxes). Box edges represent the 25th (Q1) and 75th (Q3) quantiles, respectively. The whiskers extend to the minimum and maximum distribution. Outliers, defined as values more than 1.5 times the interquartile range above Q3 or below Q1, are reported as black stars. A low risk status was achieved only by patients with initial low or intermediate risk status, and was related to the decrease in PVR.
Abbreviations: PVR: pulmonary vascular resistance; REVEAL: United States Registry to Evaluate Early and Long-Term PAH Disease Management registry.

136x88mm (72 x 72 DPI)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

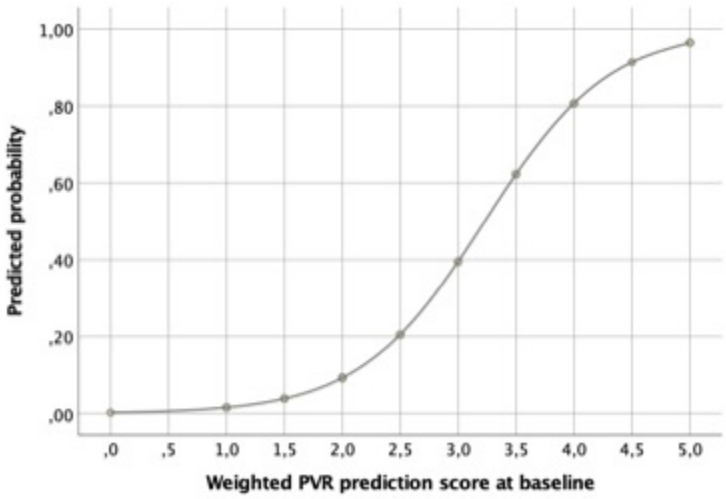

Figure 5. Predicted probability of poor PVR reduction response to therapy (defined as the lower tertile of PVR reduction), based on the weighted PVR prediction score value at baseline. Age > 60 years, male-sex, baseline mPAP > 48 mmHg associated with low CI (< 2.5 l/min/m2), and RV/LV ratio >1 associated with low TAPSE (< 18 mm) were independent predictors of poor PVR reduction and have been included in the score (weighted value, respectively: 1.5, 1.5, 1.0, and 1.0). The specificity, sensitivity, positive predictive value, negative predictive value, and AUC for a score > 3 were respectively, 89%, 68%, 83%, 78%, and 0.78 (95% C.I. 0.71-0.85, p=0.0001).

130x88mm (72 x 72 DPI)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

ONLINE DATA SUPPLEMENT

Risk Reduction and Hemodynamics with Initial Combination Therapy in Pulmonary Arterial Hypertension

Roberto Badagliacca, Michele D'Alto, Stefano Ghio, Paola Argiento, Vincenzo Bellomo, Natale Daniele Brunetti, Gavino Casu, Marco Confalonieri, Marco Corda, Michele Correale, Carlo D'Agostino, Lucrezia De Michele, Giuseppe Galgano, Alessandra Greco, Carlo Lombardi, Giovanna Manzi, Valentina Mercurio, Massimiliano Mulè, Giuseppe Paciocco, Silvia Papa, Emanuele Romeo, Laura Scelsi, Davide Stolfo, Patrizio Vitulo, Robert Naeije, Carmine Dario Vizza

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Figure E1. Frequency distribution plot of time from diagnosis to second right heart catheterization (RHC).

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table E1. Initial combination therapy distribution.

	n. (%)
Ambrisentan-Tadalafil	113 (62.4)
Ambrisentan-Sildenafil	11 (6.1)
Bosentan-Sildenafil	22 (12.2)
Bosentan-Tadalafil	13 (7.2)
Macitentan-Sildenafil	10 (5.5)
Macitentan-Tadalafil	12 (6.6)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table E2. Changes in risk assessment according to the European and REVEAL scoring systems. Sensitivity analysis for patients with initial combination Ambrisentan-Tadalafil.

	Diagnosis	**Follow-up**	*Low*	*Intermediate*	*High*
European score					
Low	14 (12.4%)		11 (9.7%)	3 (2.7%)	-
Intermediate	83 (73.4%)		41 (36.3%)	41 (36.3%)	1 (0.9%)
High	16 (14.2%)			9 (7.9%)	7 (6.2%)
REVEAL score					
Low (< 7)	9 (8.0%)		7 (6.2%)	2 (1.8%)	-
Intermediate (7-8)	57 (50.4%)		35 (31.0%)	18 (16.0%)	4 (3.5%)
High (> 8)	47 (41.6%)		-	33 (29.2%)	14 (12.4%)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table E3. Baseline and follow-up characteristics of patients based on age.

	< 60 years old	**≥ 60 years old**	**p**
N.	99	82	
BASELINE			
WHO class	2.7±0.4	2.8±0.3	ns
6MWT, m	349±77	305±113	0.006
HEMODINAMYCS			
RAP, mmHg	8.6±4.2	8.6±5.2	ns
mPAP, mmHg	53.3±13	46.8±10	0.0001
CI, l/min/m2	2.3±0.8	2.3±0.6	ns
PVR, UW	12.7±6.4	9.9±4.3	0.001
ECOCARDIOGRAPHY			
TAPSE	16.5±4.2	16.7±3.7	ns
RV/LV ratio			
< 1	3(3.0%)	3(3.7%)	ns
1	12(12.1%)	15(18.3%)	ns
> 1	84(84.9%)	64(78%)	ns
EUROPEAN SCORE			0.02
Low	16 (16.2%)	11 (13.4%)	
Intermediate	76 (76.8%)	54 (65.9%)	
High	7 (7.0%)	17 (20.7%)	
REVEAL SCORE			0.0001
Low (< 7)	9 (9.1%)	10 (12.2%)	
Intermediate (7-8)	70 (70.7%)	30 (36.6%)	
High (> 8)	20 (20.2%)	42 (51.2%)	

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

FOLLOW-UP			
WHO class	2.2±0.6	2.5±0.6	0.0001
6MWT, m	420±82	327±126	0.0001
HEMODINAMYCS			
RAP, mmHg	7.0±3.9	6.8±4.2	ns
mPAP, mmHg	44.7±15	42.5±11	ns
CI, l/min/m2	3.1±0.8	2.7±0.7	0.007
PVR, UW	7.4±3.7	7.7±3.9	ns
ECOCARDIOGRAPHY			
TAPSE	19.2±3.4	17.9±5.0	0.052
RV/LV ratio			0.02
< 1	24(24.2%)	10(12.2%)	
1	14(14.1%)	17(20.7%)	
> 1	61(61.7%)	55(67.1%)	
EUROPEAN SCORE			0.0001
Low	53 (53.5%)	25 (30.5%)	
Intermediate	45 (45.5%)	47 (57.3%)	
High	1 (1.0%)	10 (12.2%)	
REVEAL SCORE			0.0001
Low (< 7)	45 (45.5%)	18 (22.0%)	
Intermediate (7-8)	50 (50.5%)	31 (37.8%)	
High (> 8)	4 (4.0%)	33 (40.2%)	

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table E4. Baseline and follow-up characteristics of patients based on gender.

	Male	Female	p
N.	61	120	
BASELINE			
WHO class	2.8±0.4	2.7±0.4	ns
6MWT, m	336±93	325±100	ns
HEMODINAMYCS			
RAP, mmHg	9.5±5.3	8.1±4.3	ns
mPAP, mmHg	49.6±10	50.8±13	ns
CI, l/min/m2	2.3±0.7	2.4±0.8	ns
PVR, UW	10.0±4.1	12.3±6.3	0.009
ECOCARDIOGRAPHY			
TAPSE	16.6±4.0	16.6±3.9	ns
RV/LV ratio			
< 1	1(1.6%)	5(4.1%)	ns
1	7(11.5%)	20(16.7%)	ns
> 1	53(86.9%)	95(79.2%)	ns
EUROPEAN SCORE			ns
Low	11(18.0%)	16(13.3%)	
Intermediate	43(70.5%)	87(72.5%)	
High	7(11.5%)	17(14.2%)	
REVEAL SCORE			ns
Low (< 7)	5(8.2%)	14(11.7%)	
Intermediate (7-8)	32(52.5%)	68(56.7%)	
High (> 8)	24(39.3%)	38(31.6%)	

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

FOLLOW-UP			
WHO class	2.3±0.6	2.3±0.6	ns
6MWT, m	378±120	381±108	ns
HEMODINAMYCS			
RAP, mmHg	7.7±3.8	6.4±4.1	ns
mPAP, mmHg	43.7±10	43.7±15	ns
CI, l/min/m2	2.7±0.7	3.0±0.8	0.01
PVR, UW	7.4±3.0	7.6±4.2	ns
ECOCARDIOGRAPHY			
TAPSE	17.6±4.4	19.2±4.1	0.01
RV/LV ratio			0.01
< 1	8(13.1%)	26(21.7%)	
1	8(13.1%)	23(19.2%)	
> 1	45(73.8%)	71(59.1%)	
EUROPEAN SCORE			0.001
Low	24(39.3%)	54(45.0%)	
Intermediate	34(55.7%)	58(48.3%)	
High	3(5.0%)	8(6.7%)	
REVEAL SCORE			0.001
Low (< 7)	17(27.9%)	46(38.3%)	
Intermediate (7-8)	27(44.2%)	54(45.0%)	
High (> 8)	17(27.9%)	20(16.7%)	

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

Table E5. Bootstrap estimates of Cox proportional hazard analysis for prediction of treatment failure.

	B	HR	95% CI	p
Model-1				
Euro-low status	*Ref.*			
Euro-intermediate status	1.26	3.55	1.99-8.58	0.0001
Euro-high status	1.69	5.47	2.97-13.7	0.0001
Model-2				
REVEAL < 7	*Ref.*			
REVEAL 7-8	0.40	1.49	0.88-3.78	0.09
REVEAL > 8	1.48	4.43	2.50-10.4	0.0001
Model-3				
Euro-low status	*Ref.*			
Euro-intermediate status	1.26	3.54	2.07-8.16	0.0001
Euro-high status	1.61	5.00	2.74-12.5	0.0001
PVR prediction score ≥ 3	0.58	1.79	1.28-2.56	0.001
Model-4				
REVEAL < 7	*Ref.*			
REVEAL 7-8	0.43	1.53	0.72-3.44	0.1
REVEAL > 8	1.37	3.97	1.94-9.52	0.001
PVR prediction score ≥ 3	0.56	1.76	1.19-2.51	0.002

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC

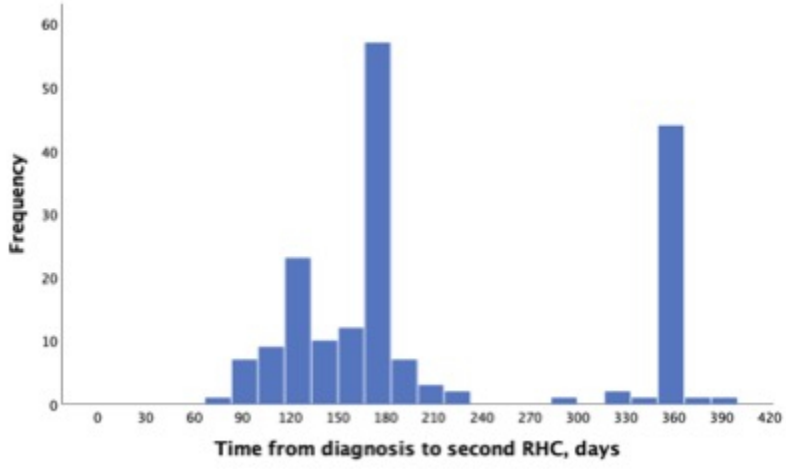

Figure E1. Frequency distribution plot of time from diagnosis to second right heart catheterization (RHC).

141x88mm (72 x 72 DPI)

AJRCCM Articles in Press. Published August 28, 2020 as 10.1164/rccm.202004-1006OC