THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

The Consistent Effectiveness and Safety of Macitentan Therapies Across Idiopathic and Congenital Heart Disease-Associated Pulmonary Arterial Hypertension: A Single-Center Experience

ABSTRACT

Background: In this single-center study, we evaluated efficacy and safety issues and predictors of survival in patients with idiopathic and congenital heart disease-associated pulmonary arterial hypertension who were under macitentan therapies.

Method: Our study retrospectively evaluated 221 patients with pulmonary arterial hypertension enrolled in our single-center study, and mono, dual, and triple macitentan therapies were noted in 30, 115, and 76 patients, respectively. The longitudinal changes in clinical, neurohumoral, and echocardiographic measures of pulmonary arterial hypertension were evaluated. The Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management 2.0, and Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management Lite 2 scores at baseline, Swedish PAH Registry, Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension registry, and French Pulmonary Hypertension Network registry risk status both at baseline and first control were assessed.

Result: The median follow-up period was 1068 [415-2245] days. Macitentan was associated with significant improvements in functional class, 6-minute walk distance, N-terminal pro-brain natriuretic peptide (NT-proBNP), and echocardiographic measures without any deterioration of hemoglobin or hepatic enzymes. The low-risk scores with each model at baseline and/or first control are related to significantly better survival. Age, gender, and log-NT-proBNP in time-fixed and idiopathic pulmonary arterial hypertension, and log-NT-proBNP in time-dependent Cox proportional hazard regression analyses were independent predictors of mortality.

Conclusion: Mono- or sequential combination macitentan therapies were associated with sustained benefits in functional class, 6-minute walk distance, NT-proBNP, and echocardiographic measures in patients with idiopathic pulmonary arterial hypertension and congenital heart disease-associated pulmonary arterial hypertension, and low-risk scores at baseline and/or first controls can be translated to better survival.

Keywords: Macitentan, pulmonary arterial hypertension, Eisenmenger syndrome, REVEAL-Lite 2, COMPERA, SPAHR

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and eventually lethal disease caused by obliteration of pulmonary arterial vasculature by hypertrophied endothelial, smooth muscle, and adventitial cells, fibrous tissue overgrowth, and concentric remodeling that increase right ventricular afterload and result in right-sided heart failure.[1-3] Among the 3 signaling pathways that have been known to be involved in the pathogenesis of PAH, the role of the endothelin pathway with deleterious effects of endothelin-1 mediated by both the endothelin A and the endothelin B receptors has been well established.[1-3] Following the approval of bosentan and ambrisentandrugs for the treatment of idiopathic PAH (IPAH), hereditary or

ORIGINAL INVESTIGATION

Cihangir Kaymaz[1]
Seda Tanyeri[1]
Hacer Ceren Tokgöz[1]
Özgür Yaşar Akbal[1]
Ali Karagöz[1]
Berhan Keskin[1]
Barkın Kültürsay[1]
Aykun Hakgör[1]
Şeyhmus Külahçıoğlu[1]
Zübeyde Bayram[1]
Süleyman Çağan Efe[1]
İbrahim Halil Tanboğa[2]
Cem Doğan[1]
Mehmet Akbulut[3]
Nihal Özdemir[1]

[1]*Department of Cardiology, University of Health Sciences Turkey, Hamidiye Faculty of Medicine, Koşuyolu Heart Training and Research Hospital, İstanbul, Turkey*
[2]*Department of Cardiology, Faculty of Medicine, Nişantaşı University, İstanbul, Turkey*
[3]*Department of Cardiology, Faculty of Medicine, Fırat University, Elazığ, Turkey*

Corresponding author:
Cihangir Kaymaz
✉ cihangirkaymaz2002@yahoo.com

Received: March 22, 2022
Accepted: August 18, 2022
Available Online Date: September 24, 2022

Cite this article as: Kaymaz C, Tanyeri S, Tokgöz HC, et al. The consistent effectiveness and safety of macitentan therapies across idiopathic and congenital heart disease-associated pulmonary arterial hypertension: A single-center experience. *Anatol J Cardiol.* 2022;26(10):778-787.

DOI:10.5152/AnatolJCardiol.2022.1889

drug-associated PAH, PAH associated with congenital heart disease (CHD-APAH) or connective tissue diseases, and other PAH forms,[3-13] macitentan was developed as third endothelin receptor antagonist exhibiting a high and sustained binding affinity to both endothelin receptors with a deep tissue penetration, and long elimination half-life of the main drug and its metabolite provides once-daily dosing regimen.[14]

The Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN), a double-blind, event-driven, phase III, randomized clinical trial, demonstrated that macitentan versus placebo, either as monotherapy or as part of sequential combination therapy, was associated with significant and clinically relevant long-term improvements in combined morbidity/mortality end-point, hemodynamic and neurohumoral surrogates in patients with PAH.[15,16] Moreover, to describe the real-world efficacy and safety profile of macitentan in patients with PAH, 2 studies have been designed in the United States. The OPsumit® USers registry (OPUS) was a long-term, prospective, multicenter, and observational registry of patients newly treated with macitentan, while OPsumit® Historical USers cohort (OrPHeUS) study was a retrospective, multicenter, US medical chart review.[17,18] The combined OPUS and OrPHeUS data set comprising a large population of PH patients with a considerable exposure time provided important insights consistent with those observed in clinical trials.[17,18] However, the second randomized, double-blind, placebo-controlled, multicenter study Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity (MAESTRO) trial did not meet its primary endpoint of the change from baseline in 6-minute walk distance (6MWD) or many secondary endpoints and evoked a controversy regarding the efficacy of macitentan in Eisenmenger syndrome (ES) subset.[19,20]

In this retrospective observational study based on our single-center experience, we aimed to evaluate the effectiveness and safety of mono- or sequential combination therapies with macitentan in patients with different forms of PAH and to assess the reliability of currently available risk prediction models in this patient population.

HIGHLIGHTS

- An assessment of the reliability of currently available risk prediction models in the pulmonary hypertension patient population is needed.
- Regardless of the type of pulmonary hypertension, mono- or sequential combination macitentan therapies were associated with significant and sustained improvements in functional class, 6 minutes walking distance, NT-proBNP, echocardiographic measures of pulmonary hemodynamics, and right ventricular longitudinal function compared to baseline.
- The low-risk scores at baseline and/or first controls discriminated candidates for a better survival under macitentan therapies.

METHODS

Our study group comprised a subgroup of 221 patients (age: 46.7 + 17.9, female 162, 73.3%) with PAH who were under mono- or sequential combination therapies with macitentan extracted from 940 patients with pulmonary hypertension recruited in our single-center EvalUation of Pulmonary Hypertension Risk Factors AssociaTEd with Survival study.

The diagnostic algorithms, hemodynamic confirmation, clinical sub-classification of PH, and incident and prevalent PAH definitions have been based on the recommendations of the European Society of Cardiology/European Respiratory Society 2015 PH Guidelines.[1] For hemodynamic definitions of pulmonary hypertension on right heart catheterization, the cut-off value of mean pulmonary arterial pressure of ≥25 mm Hg has been adopted. For pre-capillary pulmonary hypertension diagnosis, pulmonary arterial wedge pressure (PAWP) ≤ 15 mm Hg and pulmonary vascular resistance (PVR) ≥ 3 Wood units criteria have also been included.[1]

According to the clinical etiologies of PAH, longitudinal changes in the World Health Organization functional class (FC), 6MWD, blood biochemistry, and cell counts, NT-proBNP, and echocardiographic and invasive hemodynamic measures of the pulmonary circulation and right heart functions, and Swedish PAH Registry (SPAHR),[21] Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry[22,23] and 4- and 3-component French Pulmonary Hypertension Network (FPHN) registry low-risk models[24] both at baseline and first control visit, and baseline risk scores as assessed by The Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), REVEAL 2.0, and its abridged version, 6-component REVEAL Lite 2 scores[25-29] were calculated.

All patients who were under regular follow-up have been informed, and a written informed consent was obtained from each patient, and the study protocol was reviewed and approved by the Institutional Ethics Committee (decision number of registry:2013.3/4). This study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

The normality of continuous variables was assessed using Shapiro–Wilk's test and histogram. Numerical variables were expressed as mean ± standard deviation or median and interquartile ranges (IQR: 25th-75th) according to distribution. Discrete data were shown as percentages and absolute numbers. For continuous data comparison according to survival status, we used the *t*-test or Mann–Whitney *U* test; for discrete data comparison according to survival status, we used the Pearson chi-square test. For longitudinal changes, continuous data comparison was made using the analysis of variance or Kruskal–Wallis's test according to normality of data, and pairwise comparison was made using Tukey HSD or Bonferroni multiple comparison test.

The main candidate predictor was age, gender, and clinical subgroups such as IPAH or CHD-APAH, while other candidate variables were chosen according to the literature.[1-3,21-30] Adjustment variables were determined as FC, 6MWD,

cardiac index, right atrial area, mono- or combination therapy, incident or prevalent PAH, NT-proBNP, and tricuspid annular plane systolic excursion (TAPSE).

To examine the relationship between all-cause mortality and measures of adjustment variables, Cox proportional hazard regression analyses with time-fixed and time-dependent models were used. First, the candidate variables known as prognostic according to expert opinion and literature were used in the model.[1-3,21-30] We used stepwise Cox proportional hazard regression analyses with an alpha value chosen as 0.25. The variables with an alpha value lower than 0.25 were included in time-fixed and time-dependent Cox regression analysis.

The cumulative risk of all-cause mortality was displayed using corresponding Kaplan–Meier plots. For all statistical analyses, we used R-software v. 4.02 with "survival," "survminer," "ggplot2," and "hmisc" packages (Vienna, Austria).

RESULTS

Baseline measures of patients including clinical subgroups of PAH, FC, 6MWD, NT-proBNP, baseline risk scores as assessed by REVEAL, REVEAL 2.0, REVEAL Lite 2, SPAHR, COMPERA, and 4- and 3-component FPHN low-risk models, and treatment patterns are presented in Table 1. Because invasive hemodynamic data were required for REVEAL, REVEAL-2.0 COMPERA, SWEDISH, and 4-component FPHN models, only patients who had catheter data of the last 1 month before the initiation of macitentan therapies were included, and 126 of the survivors and 31 of the deceased patients were analyzed. However, 3-component FPHN and REVEAL Lite 2 based on non-invasive measures were used in all patients.

Macitentan was noted to be used as monotherapy in 30 (13.6%) and as a part of dual and triple sequential combination therapies in 115 (52%) and 76 (34%) patients, respectively (Table 1). Switching from bosentan to macitentan was documented in 105 patients, and 6 (5.7%) of them remained on monotherapy, while 99 (94.3%) patients were on dual or triple combination therapies.

Follow-up duration from diagnosis was 35.5 (13.8-74.3, IQR 25th-75th) months, and time from initiation or switching to macitentan therapy was 17 (7.9-27.1, IQR 25th-75th) months. Longitudinal changes in risk scores, FC, 6MWD, NT-proBNP, blood biochemistry and cell counts, and echocardiographic and invasive hemodynamic measures of the pulmonary circulation and right heart functions across the periodical control examinations are presented in Table 2. The FC, 6MWD, NT-proBNP, pericardial effusion, right atrial area, TAPSE, annular systolic tissue velocity, pulmonary arterial systolic, and mean pressures estimated by Doppler showed significant improvements during the longitudinal follow-up period, whereas hemoglobin, alanine, and aspartate aminotransferase levels remained stable (Table 2).

Totally 43 (19.4%) patients died. Univariate time-fixed and time-dependent Cox proportional hazard regression analyses revealed that age, IPAH, FC, 6MWD, cardiac index, log-NT-proBNP, tricuspid annular-plane-systolic-excursi on, and right atrial area were associated with mortality (Table 3). Age, gender, and log-NT-proBNP were associated with mortality in multiple time-fixed Cox proportional hazard regression analyses, while IPAH and log-NTproBNP were associated with mortality in multiple time-dependent Cox proportional hazard regression analyses (Table 3). Kaplan–Meier survival estimates according to the baseline and control scores by SPAHR, COMPERA, and FPHN risk models showed that low-risk compared with moderate or high-risk status at baseline and at first control (3-6 months following the initiation of macitentan) was significantly associated with better survival (Figure 1a-f). The REVEAL, REVEAL 2.0, and REVEAL-Lite 2 scores showed comparable relationships with 1-year predicted survival probability (Figure 2a-c).

DISCUSSION

In this single-center study, regardless of the idiopathic PAH or CHD-APAH etiology, mono- or sequential combination macitentan therapies were associated with significant and sustained improvements in FC, 6MWD, NT-proBNP, echocardiographic measures of pulmonary hemodynamics, and right ventricular longitudinal function compared with baseline. Age, gender, and log-NT-proBNP in multiple time-fixed Cox proportional hazard regression analyses, and IPAH and log-NT-proBNP in multiple time-dependent Cox proportional hazard regression analyses predicted a higher risk of mortality. The low-risk scores according to the currently available multiparametric models at baseline and/or first 3- to 6-month controls discriminated against patients with better survival under macitentan therapies.

Following the SERAPHIN randomized clinical trial demonstrating the significant long-term improvements in combined morbidity/mortality end-point, hemodynamic and neurohumoral surrogates in patients with PAH with macitentan, either as monotherapy or part of sequential combination therapy,[15,16] OPUS prospective and OrPHeUS retrospective, multicenter registries have confirmed efficacy and safety of macitentan in a large population with PAH.[17,18] Macitentan and tadalafil combination was documented in 27.5% of the OPUS and OrPHeUS patients with PAH, and 30% of these were an upfront combination. Incident PAH was noted in 72.7%. The 12-month Kaplan–Meier estimates for freedom from hospitalization and overall survival rates were 63.3% (57-68.9) and 89% (84.4-92.3), respectively.[17,18] Although follow-up data remain limited, the low rates of double or triple combination therapies at 6 months after initiation of macitentan suggest the slow adoption of early combination therapy in their real-world practice.[17,18] This trend is markedly different from those in our series, in which dual and triple combination therapies were utilized in 54.6% and 32.3% of patients, respectively.

In the Right vEntricular remodeling in Pulmonary ArterIal hypeRtension (REPAIR) study evaluating the effects of macitentan on RV structure and function in PAH, macitentan treatment resulted in significant and clinically relevant

Table 1. Comparisons of Baseline Characteristics of Overall Patients, Survivors, and Non-survivors

	Overall Patients (n = 221)	Survivors (n = 178)	Non-survivors (n = 43)	*P*
Sex, female (%)	162 (73.3)	135 (75.8)	27 (62.8)	.083
Age (median [IQR])	42 (32; 63)	40.9 (28.8; 58.8)	58.0 (36.2; 70.7)	.012
Hgb (g/dL)	13.5 (11.9; 15.2)	13.6 (12; 15.3)	13.2 (10.6; 14.9)	.003
ALT (μ/L)	15.9 (10.1; 23.0)	16.0 (11; 23.0)	1508 (10.0; 21.0)	.435
AST (μ/L)	22.0 (18.0; 27.0)	21.0 (18.0; 27.0)	22.0 (17.0; 28.0)	.785
Follow-up 1 (median [IQR])	513 (237; 817	598 (284; 879)	280 (122; 446)	<.001
Follow-up 2 (median [IQR])	1068 (415; 2245)	1114 (476; 2482)	545 (215; 1770)	.011
Subgroup (%)				<.001
CHD-APAH	112 (48.9)	99 (53.8)	13 (28.9)	
IPAH	109 (47.5)	79 (42.9)	30 (66.7)	
Prevalent = 1 (%)	199 (90.0)	158 (88.8)	41 (95.3)	.192
Cath — PASP (mm Hg) (median [IQR])	92 (68; 116)	92.0 (67.0; 117.0)	93.0 (70.0; 112.0)	.944
Cath — PAMP (mm Hg (median [IQR])	56 (42; 75)	56.0 (42.0; 75.0)	55.0 (43.0; 75.0)	.854
Cardiac Index (l/min/m^2) (median [IQR])	2.3 (2.0; 3.0)	2.4 (2.1; 3.1)	2.2 (1.8; 2.6)	.053
PVR (Wood units) (median [IQR])	10.2 (5.0; 15.6)	11.0 (5.5; 15.0)	12.0 (7.5 ;20.0)	.102
PVR/SVR (median [IQR])	0.46 (0.28; 0.72)	0.5 (0.3; 0.7)	0.6 (0.4; 0.9)	.104
RAP (mm Hg) (median [IQR])	8.0 (5.0; 11.0)	8.0 (6.0; 11.0)	8 (5.0; 13.0)	.996
FC (median [IQR])	3.0 (3.0; 4.0)	3.0 (3.0;3.0)	4.0 (3.0;4.0)	<.001
6MWD (minutes) (median [IQR])	330 (135; 390)	345 (194; 393)	150 (35; 308)	<.001
Echo — PASP (mm Hg) (median [IQR])	85.0 (65.0; 108.0)	90 (65.0; 105.0)	106.0 (71.0; 125.0)	.122
Echo — PAMP (mm Hg) (median [IQR])	55.0 (44.0; 70.0)	55.0 (43.0; 68.0)	65.0 (47.0; 75.0)	.142
TAPSE (cm) (median [IQR])	2.0 (1.5; 2.3)	2.1 (1.6; 2.4)	1.4 (1.40; 2.0)	.023
St (cm/s) (median [IQR])	12 (9.9;14.2)	12.4 (9.6; 14.5)	10.8 (9.6; 11.7)	.183
RA area (cm^2) (median [IQR])	23.2 (18.0; 30.0)	22.0 (16.6; 29.7)	28.2 (21.5; 31.5)	.037
Pericardial effusion (%)	24 (10.5)	16 (9.0)	8 (18.6)	.077
NT-pro BNP (pg/mL) (median [IQR])	560 (200; 1667)	472.0 (179.0; 1397.0)	1486.0 (405.0; 2924.0)	.001
REVEAL (median [IQR])	8 (7.0; 10)	8 (7; 10.0)	10 (8.0; 11.0)	.023
REVEAL 2.0 (median [IQR])	8 (6; 11)	8 (5.0; 10.0)	11 (7; 13)	<.001
COMPERA (median [IQR])	1.8 (1.3; 2.3)	1.80 (1.31; 2.10)	2.0(1.4; 2.6)	.103
SWEDISH (median [IQR])	1.67 (1.29; 2.14)	1.6 (1.2; 2.0)	1.8 (1.4; 2.4)	.042
FPHN-invasive (median [IQR])	1.0 (0.0; 1.0)	1.0 (0.0; 1.0)	0.0 (0.0; 1.0)	.023
REVEAL-Lite 2 (median [IQR])	7 (6.0; 10.0)	7(6-9)	10 (8-12)	<.001
REVEAL (%)				.013
≤6	25 (15.9)	23 (18.3)	2 (6.5)	
7-8	57 (36.3)	50 (39.7)	7 (22.6)	
≥9	75 (47.7)	53(42.1)	22 (71)	
REVEAL 2.0 (%)				<.001
≤6	44 (28.0)	43 (34.1)	1 (3.2)	
7-8	9 (24.8)	32(25.4)	7(22.6)	
≥9	74 (47.1)	51 (40.5)	23 (74.2)	
COMPERA (%)				<.001
Low	19 (12.1)	19 (15.1)	0	
Moderate	88 (56.0)	75(59.5)	13 (41.9)	
High	50 (31.8)	32 (25.4)	18 (58.1)	
SWEDISH (%)				<.001
Low	13 (8.2)	13 (13.5)	0	
Moderate	97 (61.7)	83 (65.9)	14 (45.2)	
High	43 (27.3)	26 (20.6)	17 (54.8)	

(*Continued*)

Table 1. Comparisons of Baseline Characteristics of Overall Patients, Survivors, and Non-survivors (*Continued*)

	Overall Patients (n = 221)	Survivors (n = 178)	Non-survivors (n = 43)	*P*
REVEAL-Lite 2 (%)				<.001
Low	46 (20.0)	45 (24.5)	1 (2.2)	
Moderate	72 (31.4)	62(33.7)	10 (22.2)	
High	111 (48.4)	77(41.8)	34 (75.6)	
FPHN — 4-component low-risk criteria number (%)				.353
0	71 (45.2)	53 (42.1)	18 (58.1)	
1	53 (33.7)	45 (35.7)	8 (25.8)	
2	24 (15.2)	19(15.1)	5 (16.1)	
3	7 (4.4)	7 (5.6)	0 (0.0)	
4	2 (1.2)	2(1.6)	0 (0.0)	
FPHN — 3-component low-risk criteria number (%)				.005
0	151 (68.3)	111 (62.3)	38 (88.3)	
1	41 (18.5)	36 (20.2)	5 (11.7)	
2	14 (6.3)	14 (7.8)	0 (0.0)	
3	15 (6.8)	17 (9.5)	0 (0.0)	
Monotherapy (%)	30 (13.6)	25 (14)	5 (11.6)	.683
Dual combination (%)	115 (52.0)	95 (53.4)	20 (46.5)	.318
Macitentan + riociguat	2 (0.9)	1 (0.56)	1 (2.3)	
Macitentan + sildenafil	29 (13.1)	25 (14.0)	4 (9.3)	
Macitentan + tadalafil	85 (38.4)	71 (39.3)	14 (32.5)	
Macitentan + inhaled iloprost	2 (0.9)	1 (0.56)	1 (2.3)	
Triple combination (%)	76 (34.0)	58 (32.5)	18 (41.9)	.179
Macitentan + sildenafil + treprostinil	4 (1.8)	1 (0.56)	3 (7.0)	
Macitentan + sildenafil + inhaled iloprost	8 (3.6)	5 (2.8)	3 (7.0)	
Macitentan + tadalafil + epoprostenol	1 (0.4)	-	1 (2.3)	
Macitentan + tadalafil + treprostinil	9 (4.0)	5 (2.8)	4 (9.3)	
Macitentan + tadalafil + inhaled iloprost	35 (15.8)	29 (16.3)	6 (14.0)	
Macitentan + tadalafil + selexipag	13 (5.8)	12 (6.7)	1 (2.3)	
Macitentan + sildenafil + selexipag	2 (0.9)	2 (1.12)	-	
Macitentan + riociguat + selexipag	3 (1.3)	3 (1.7)	-	
Macitentan + riociguat + inhaled iloprost	1 (0.4)	1 (0.56)	-	

Continuous variables given as IQR (interquartile range) (25^{th}-75^{th}).
Because invasive hemodynamic data were required for REVEAL, REVEAL-2.0, COMPERA, SWEDISH, and 4-component FPHN models, only patients who had catheter data in the last 1 month before initiation of macitentan therapies were included, and 126 of the survivors and 31 of the deceased patients were analyzed. However, 3-component FPHN and REVEAL-Lite 2 based on non-invasive measures were used in all patients.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cath — PASP, catheter pulmonary artery systolic pressure; Cath — PAMP, catheter pulmonary artery mean pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; RAP, right atrial pressure; FC, functional class; 6MWD, 6 minute walking distance; Echo-PASP, echocardiographic pulmonary artery systolic pressure; Echo-PAMP, echocardiographic pulmonary artery mean pressure; TAPSE, tricuspid annular planar systolic excursion; St, right ventricular systolic velocity; RA area, right atrial area; NT-pro BNP, N-terminal peptide of brain natriuretic peptide.

improvements in both primary end-points of RV stroke volume [12 mL increase (96% confidence level: 8.4-15.6 mL; $P < .0001$)] with cardiac magnetic resonance (CMR) and PVR [decrease of 38% (99% confidence level: 31%-44%; $P < .0001$)] at week 26.[30] Significant, consistent, and sustainable improvements were also documented in secondary and exploratory CMR, hemodynamic, and functional measures at weeks 26 and 52.[30] Moreover, the upfront combination with macitentan and phosphodiesterase-5-inhibitors was found to provide highest improvements in RV stroke volume and PVR.[30]

On the other hand, cOmbination theraPy of maciTentan and tadalafIl in patients with newly diagnosed pulMonary Arterial Hypertension (OPTIMA), a prospective, single-arm, open-label, phase IV trial, in patients with newly diagnosed PAH, showed that upfront macitentan and tadalafil combination was related to significant improvements in PVR (47% reduction from baseline) and other measures of cardiopulmonary hemodynamics, FC, 6MWD, and NT-proBNP at week 16 without any unexpected safety concerns during long-term follow-up.[31] Upfront macitentan and riociguat combination therapy was also reported to improve clinical and functional

Table 2. Longitudinal Changes in the Measures Under Macitentan Therapies

Measures	0 Months	3 Months	6 Months	9 Months	12 Months	Final	*P*
FC (%)							<.001
1	2 (0.9)	2 (1.8)	1 (0.9)	1 (1.4)	3 (3.3)	2 (1.6)	
2	43 (19.4)	32 (29.3)	38 (36.1)	26 (37.1)	38 (41.8)	60 (48.0)	
3	116 (52.4)	56 (51.3)	55 (52.3)	35 (50.0)	42 (46.2)	49 (39.2)	
4	60 (27.1)	19 (17.4)	11 (10.4)	8 (11.4)	8 (8.8)	14 (11.2)	
6MWD (minute) (median [IQR])	330.0 (150; 390)	360 (250; 417.5)	375 (308.75; 420)	387.5 (286.25; 430)	382.5 (330;440)	395 (330;450)	<.001
Echo PASP (mm Hg) (median [IQR])	85 (62;107)	80 (60; 106.5)	69 (50; 100)	69.5 (55; 93.5)	70 (55; 101)	69 (49,5; 101.5)	.001
Echo PAMP (mm Hg) (median [IQR])	55 (43;70)	56 (41.75; 73.5)	47 (38.5; 71.5)	47.5 (42.75; 60.5)	51 (40; 68)	52 (38; 69)	.152
TAPSE (cm) (median [IQR])	2.0 (1.5; 2.3)	2.00 (1.65; 2.40)	2.1 (1.8; 2.4)	2.2 (1.8; 2.5)	2.2 (1.9; 2.55)	2.07 (1.6; 2.4)	.006
St (cm/s) (median [IQR])	12.0 (9.8; 14.2)	12.1 (10.85; 13.7)	12.0 (10.0; 14.0)	13.0 (11.0; 14.7)	12.8 (10.33; 14.0)	11.5 (10.0; 14.0)	.396
RA area (cm^2) (median [IQR])	23.4 (18.0; 30.0)	23.45 (15.85; 28.0)	20.7 (16.83; 25.3)	25.25 (20.0; 28.58)	20.40 (16.0; 25.0)	20.1 (16.8; 28.2)	.041
Pericardial effusion (%)	21 (9.3)	11 (9.9)	8 (7.5)	2 (2.9)	9 (9.8)	11 (8.9)	.594
Hemoglobin (g/dL) (median [IQR])	13.4 (11.8; 15.2)	13.0 (11.6; 15.0)	13.1 (12.05; 14.4)	12.9 (11.5; 15.6)	13.1 (12.28; 14.43)	13.6 (11.9; 15.47)	.332
ALT (μ/L) (median [IQR])	15.9 (10.0; 23.0)	14.35 (11.0; 20.0)	15.0 (11.0; 19.0)	14.0 (11.0; 18.0)	13.5 (10.0; 20.0)	13.0 (11.0; 18.5)	.242
AST (μ/L) (median [IQR])	21.7 (18.0; 27.0)	21.0 (17.0; 25.0)	21.0 (17.0; 25.0)	21.0 (18.0; 25.0)	19.5 (16.0; 23.0)	20.0 (16.65; 24.0)	.064
NT-proBNP (pg/mL) (median [IQR])	587 (200; 1626)	357.5 (145.65; 1114)	273.7 (127.1; 1019)	330.0 (96.36; 714.8)	181.9 (90.2; 544.2)	235.75 (83.14; 1006.75)	.004

FC, functional class; 6MWD, 6 minute walking distance; Echo PASP, echocardiographic pulmonary artery systolic pressure; Echo-PAMP, echocardiographic pulmonary artery mean pressure; TAPSE, tricuspid annular planar systolic excursion; St, right ventricular systolic velocity; RA area, right atrial area; NT-pro BNP, N-terminal pro-brain natriuretic peptide.

status, PVR, and other hemodynamic measures in patients with PAH, and was associated with an 85% transplant-free survival in the third year.[32] In the recently published TRITON trial comparing upfront macitentan and tadalafil double combination versus upfront macitentan, tadalafil and selexipag triple combination, a decrease in PVR at week 26 compared with baseline as the primary endpoint and changes in 6MWD and NT-proBNP as secondary exploratory endpoints were not different between treatment arms.[33] More importantly, the reduction in PVR with the double combination was 52% and was higher than previously reported PVR reductions ranging from 35% to 50% in various upfront or sequential combination series.[15,16,30-33] Moreover, this benefit seems to be higher than the critical threshold of 40% reduction in PVR which has been documented to be a novel prerequisite for a satisfactory right ventricular reverse remodeling.[34-36]

A recently published real-world prospective study evaluated the transition from ambrisentan to macitentan in patients with PAH. The IPAH or drug-associated PAH and CHD-APAH were noted in 25% and 60.7% of patients, respectively.[37] Switching to macitentan was found to be associated with progressive improvements in echocardiographic measures of right ventricular function and pulmonary arterial systolic pressure estimates, functional class, 6MWD, NT-proBNP, quality of life, and REVEAL scores over a 12-month period.[37] This study may provide important insights for into escalation strategies because of the similarity of PAH subgroup distributions as compared to those in our country.

In a retrospective study based on United States Centers for Medicare and Medicaid Services national Medicare database comparing the mortality among the macitentan, ambrisentan, and bosentan cohorts, macitentan was found to be associated with an 18% lower risk for mortality than ambrisentan (hazard ratio: 0.82, 95% CI: 0.72-0.93; $P = 0.0026$) and a 39% lower risk than bosentan (hazard ratio: 0.61, 95% CI: 0.53-0.71; $P < .0001$).[38] However, regardless of the ERA treatment index, a higher co-morbidity index, older age, and hospitalizations at baseline were found to be independent predictors of mortality in overall study group.[38]

Because longitudinal follow-up assessment has been based on non-invasive evaluation of patients, in the absence of clinical deterioration, the PVR reduction after initiation of macitentan therapies has not been addressed in our study. Furthermore, using a prospective design, a novel echocardiographic score proposed by Badagliacca et al[36] might provide further insights into the satisfaction level of right ventricular reverse remodeling in response to acceptable PVR reduction.

The first randomized, double-blind, placebo-controlled, multicenter study, Bosentan Randomized Trial of Endothelin

Table 3. Time-Fixed and Time-Dependent Univariable and Multivariable Cox Proportional Regression Analyses for Long-Term Mortality

	Univariate Analysis			
	Time-Fixed Cox Model		Time-Dependent Cox Model	
	HR, 95% CI	*P*	HR, 95% CI	*P*
Age (year)	1.03 (1.01-1.05)	<.001	1.02 (1.01-1.03)	<.001
Gender (reference, male)	0.54 (0.28-1.01)	.061	0.54 (0.27-1.01)	.062
Diagnosis				
IPAH vs. CHD-APAH	2.50 (1.28-4.84)	.004	2.50 (1.28-4.84)	.004
Incident vs. prevalent	0.75 (0.17-3.10)	.692	0.75 (0.17-3.10)	.698
FC	2.71 (1.68-4.38)	<.001	3.00 (2.22-4.06)	<.001
6MWD (minutes)	0.99 (0.99-0.99)	.001	0.99 (0.99-0.99)	.011
Cardiac index (L/min/m^2)	0.59 (0.36-0.98)	.042	0.59 (0.36-0.98)	.042
log-NT-proBNP (pg/mL)	1.80 (1.42-2.29)	<.001	1.77 (1.48-2.12)	<.001
TAPSE (cm)	0.42 (0.22-0.80)	.006	0.38 (0.25-0.56)	<.001
RA area (cm^2)	1.04 (1.02-1.07)	.001	1.03 (1.01-1.05)	.006
Mono versus dual/triple	1.14 (0.44-2.89)	.782	1.14 (0.44-2.89)	.783
	Multivariate analysis			
	Time-Fixed Cox Model		Time-Dependent Cox Model	
	HR, 95% CI	*P*	HR, 95% CI	*P*
Age	1.02 (1.00-1.04)	0.032	1.01 (0.99-1.03)	.133
Gender (reference, male)	0.42 (0.21-0.81)	0.013	0.85 (0.45-1.16)	.063
Diagnosis				
IPAH vs. CHD-APAH	1.71 (0.83-3.47)	0.126	2.78 (1.38-5.44)	.004
FC	1.31 (0.41-4.20)	0.645	1.73 (0.63-4.74)	.274
6MWD (minute)	0.99 (0.99-1.00)	0.653	1.00 (0.99-1.005)	.982
Cardiac index (L/min/m^2)	0.82 (0.48-1.41)	0.471	0.75 (0.46-1.22)	.269
Log pro-BNP (pg/mL)	1.44 (1.12-1.85)	0.003	1.37 (1.05-1.78)	.028
TAPSE (cm)	1.07 (0.70-1.62)	0.737	0.94 (0.65-1.35)	.736
RA area (cm^2)	1.01 (0.98-1.04)	0.245	0.99 (0.96-1.03)	.944

FC, functional class; 6MWD, 6 minute walking distance; TAPSE, tricuspid annular planar systolic excursion; RA area, right atrial area; NT-pro BNP, N-terminal pro-brain natriuretic peptide; IPAH, idiopathic pulmonary arterial hypertension; CHD-APAH, congenital heart disease-associated pulmonary arterial hypertension.

Antagonist Therapy-5 (BREATHE-5), showed that bosentan compared with placebo was associated with significant reductions in pulmonary vascular resistance index and mean pulmonary arterial pressure and improvement in exercise capacity in patients with ES for 16-week period.[4] The results of the subsequent observational research also suggested clinical benefits and improved survival with bosentan therapy in ES.[5-13] Following the BREATHE-5 study, disappointing results of the MAESTRO trial to meet its primary endpoint and many secondary endpoints remain a source of uncertainty regarding the efficacy of macitentan in patients with ES.[19,20] In comparison to the BREATHE-5 study in which only simple forms of ES, those in FC III, and those without Down syndrome or pre-existing treatment were enrolled, and the MAESTRO study included a more heterogeneous population such as more complex forms of ES, Down syndrome, broader FCs from II to IV, and a 27 % rate of background phosphodiesterase-5 inhibitor therapy.[4,19,20] Moreover, the endpoints in these 2 trials were different. An unexpected exaggerated placebo effect on 6MWD during a 16-week randomized period of MAESTRO with further improvement in 6MWD after cross-over from placebo to macitentan during the open-label extension phase raised questions about the reliability of the randomized period in this study.[19] The marked increases in the 6MWD following the cross-over to the active drug at 6th and 12th months in the open-label extension phase of MAESTRO study were comparable to those observed in placebo-bosentan cross-over cohort in the open-label extension phase of BREATHE-5.[4,19,20] In contrast to controversial results in 16-week randomized period of MAESTRO, our results confirmed the mid- to long-term efficacy and safety of mono- or combination macitentan therapies in patients with IPAH and CHD-APAH. The improvements in clinical, echocardiographic, and hemodynamic measures were consistent across the subgroups of PAH.

When REVEAL risk prediction model was applied to SERAPHIN data set, it was concluded that mortality risk in the placebo arm was underestimated, possibly due to cross-over to macitentan therapy.[39] Therefore, the mortality in the macitentan 10 mg arm compared with placebo was estimated to be 35 % lower than predicted, and this

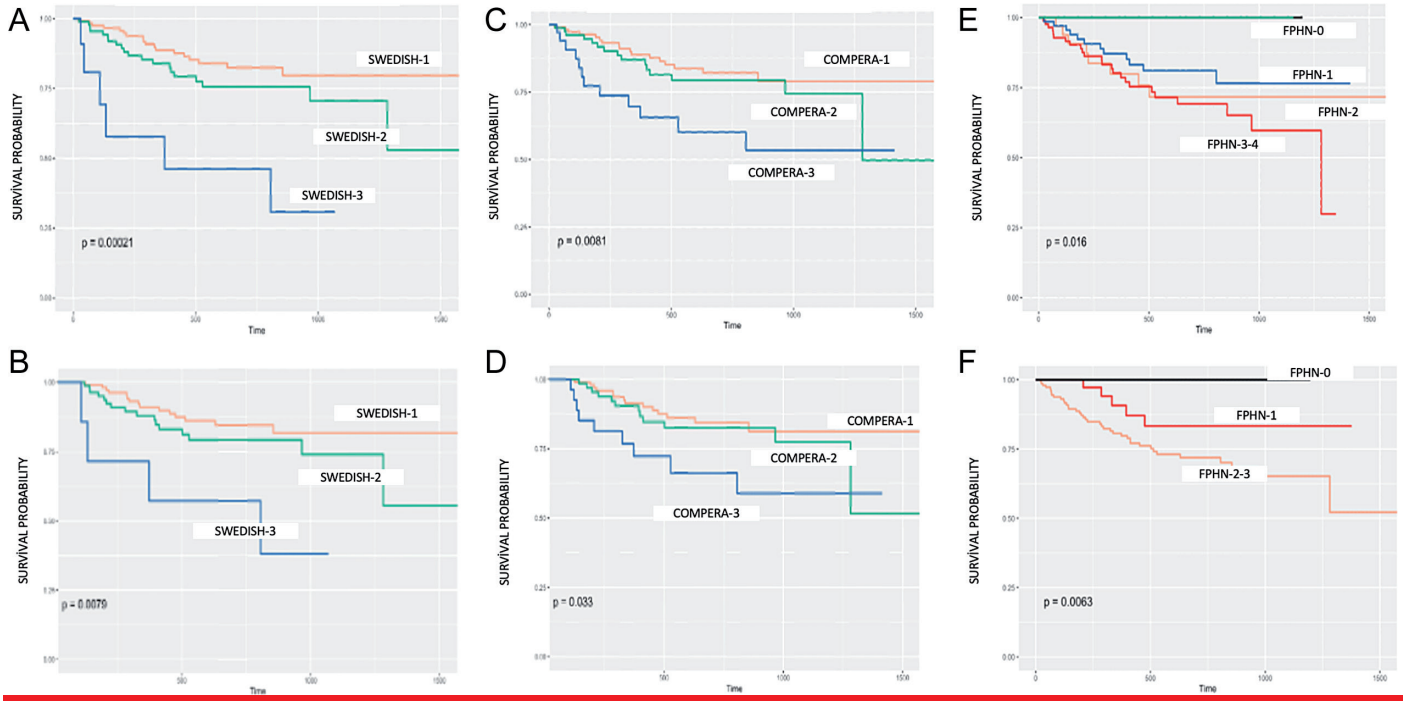

Figure 1. Kaplan–Meier survival estimates according to the baseline and first control scores after the initiation of macitentan by SPAHR (Figure 1A and 1B), COMPERA (Figure 1C and 1D), and FPHN (Figure 1E and 1F) models. SPAHR, Swedish Pulmonary Arterial Hypertension Registry; COMPERA, Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension registry; FPHN, French Pulmonary Hypertension Network.

might favor a potential survival benefit for macitentan.[39] In accordance with reported registries and series in which multiparametric risk models have been developed and/or validated or utilized,[21-29,39,40] low-risk versus moderate or high-risk with REVEAL, REVEAL 2.0, and abridged REVEAL Lite 2 scores at baseline and with SPAHR, COMPERA, and 2 FPHN risk scores at baseline and first control evaluation were associated with significantly better survival in our study. Age, gender, and log-NT-proBNP in time-fixed Cox proportional hazard regression analyses and IPAH and log-NT-proBNP in time-dependent Cox proportional hazard regression analyses were independent predictors of mortality. Hemoglobin and hepatic enzyme levels remained stable along with the macitentan therapies. Our results seem to provide important insights into management patterns in patients with CHD-PAH, which accounts for nearly half of the PAH population in our country.[9,41] The effect of the macitentan therapies on altered systemic arterial

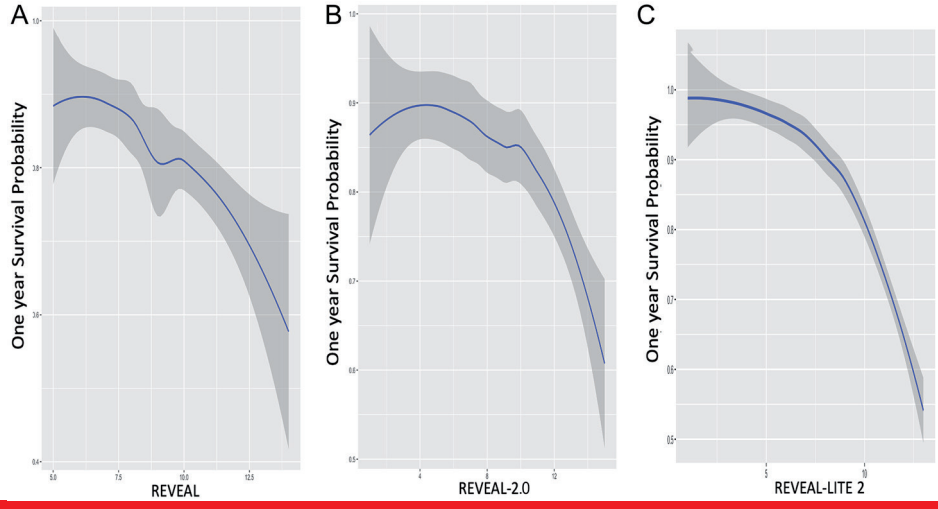

Figure 2. A, B, and C. The REVEAL, REVEAL 2.0, and REVEAL Lite 2 scores showed comparable relationship with 1-year predicted survival probability. REVEAL, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management.

vasodilatory reserves documented in these patients might offer further perspectives.[42]

Study Limitations

The retrospective nature of the analysis and absence of the randomization between macitentan and other endothelin receptor antagonist therapies might be considered the main limitations of this study. Moreover, our results represent longitudinal changes and risk prediction in patients under sequential combination therapies including macitentan but could not be regarded as a study designed to evaluate the treatment effect. Novel innovative randomized trial designs comparing upfront double and triple combinations versus sequential triple combinations including riociguat, selexipag, or parenteral prostanoids and utilizing the measures of right ventricle-pulmonary arterial coupling and adjudicated clinical worsening events as endpoints might provide new perspectives for PAH management.

CONCLUSIONS

In this single-center study, mono- or sequential combination macitentan therapies were associated with significant and sustained benefits in clinical, neurohumoral, and echocardiographic measures of pulmonary hemodynamics and right ventricular function without any signal suggesting the failure of macitentan therapies in CHD-APAH subgroup. The low-risk scores at baseline and/or first controls discriminated candidates for better survival under macitentan therapies.

Data availability: Raw data can be obtained from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethics committee decision date-Decision number: 20.10.2020 – 2020/10/376 Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Research Ethics Committee (2016-KAEK-112).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: CK, ST, HCT, OYA, AK, BKe, BKu, IHT, MA and NO conceived the study; CK drafted the article; all authors gave substantial contributions in the design of the research, data acquisition and interpretation and critical revision of the article.

Acknowledgments: None.

Declaration of Interests: The authors declare that there is no conflict of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Galiè N, Humbert M, Vachiery JL, et al. 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 Heart J* 2016;37(1):67-119. [CrossRef]
2. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913. [CrossRef]
3. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*. 2019;53(1):1801889. [CrossRef]
4. Galiè N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006; 114(1):48-54. [CrossRef]
5. Diller GP, Körten MA, Bauer UM, et al. Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects. *Eur Heart J*. 2016;37(18): 1449-1455. [CrossRef]
6. Duffels MG, Vis JC, Van Loon RL, et al. Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down's syndrome. *Am J Cardiol*. 2009; 103(9):1309-1315. [CrossRef]
7. Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. *Circulation*. 2010;121(1):20-25. [CrossRef]
8. Kermeen FD, Franks C, O'Brien K, et al. Endothelin receptor antagonists are an effective long-term treatment option in pulmonary arterial hypertension associated with congenital heart disease with or without trisomy 21. *Heart Lung Circ*. 2010; 19(10):595-600. [CrossRef]
9. Kücükoglu SM, Kaymaz C, Alehan D, et al. Pulmonary arterial hypertension associated with congenital heart disease: lessons learned from the large Turkish Nationwide Registry (Thales). *Pulm Circ*. 2021;11(3):1-10. [CrossRef]
10. Körten MA, Helm PC, Abdul-Khaliq H, et al. Eisenmenger syndrome and long-term survival in patients with Down syndrome and congenital heart disease. *Heart*. 2016;102(19):1552-1557. [CrossRef]
11. Crepaz R, Romeo C, Montanaro D, De Santis S. Long-term results of treatment with bosentan in adult Eisenmenger's syndrome patients with Down's syndrome related to congenital heart disease. *BMC Cardiovasc Disord*. 2013;13(1):74. [CrossRef]
12. D'Alto M, Romeo E, Argiento P, et al. Therapy for pulmonary arterial hypertension due to congenital heart disease and Down's syndrome. *Int J Cardiol*. 2013;164(3):323-326. [CrossRef]
13. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. *Am J Cardiol*. 2011;107(9):1381-1385. [CrossRef]
14. Gatfield J, Mueller Grandjean C, Sasse T, Clozel M, Nayler O. Slow receptor dissociation kinetics differentiate macitentan from other endothelin receptor antagonists in pulmonary arterial smooth muscle cells. *PLoS One*. 2012;7(10):e47662. [CrossRef]
15. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809-818. [CrossRef]
16. Galiè N, Jansa P, Pulido T, et al. SERAPHIN hemodynamic substudy: the effect of the dual endothelin receptor antagonist macitentan on hemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension. *Eur Heart J*. 2017;38(15): 1147-1155. [CrossRef]
17. Chin K, Channick R, Kim N, et al. Real-world evidence from the OPUS registry: an insight into pulmonary arterial hypertension

risk assessment parameters in clinical practice. *Am J Respir Crit Care Med*. 2019;199:A5079.
18. Kim N, Channick R, Chin K, et al. Macitentan in pulmonary hypertension (PH): data from OPUS and OrPHeUS real-world data sets. *Eur Respir J*. 2019;54:PA5458.
19. Gatzoulis MA, Landzberg M, Beghetti M, et al. Evaluation of macitentan in patients with Eisenmenger syndrome. *Circulation*. 2019;139(1):51-63. [CrossRef]
20. Ivy D, Wilson N. Correction to: a Tale of two endothelin receptor antagonists in Eisenmenger syndrome: it was the best of times, it was the worst of times. *Circulation*. 2019;139(6):e37. [CrossRef]
21. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2018;39(47): 4175-4181. [CrossRef]
22. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J*. 2017;50(2):1700740. [CrossRef]
23. Hoeper MM, Pittrow D, Opitz C, et al. Risk assessment in pulmonary arterial hypertension. *Eur Respir J*. 2018;51(3):1702606. [CrossRef]
24. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*. 2017;50(2):1700889. [CrossRef]
25. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). *Circulation*. 2010;122(2):164-172. [CrossRef]
26. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest*. 2012;141(2):354-362. [CrossRef]
27. Benza RL, Gomberg-Maitland M, Elliott CG, et al. 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(2):323-337. [CrossRef]
28. Benza RL, Kanwar M, Raina A, et al. Comparison of risk discrimination between the REVEAL 2.0 calculators, the French pulmonary registry algorithm and the Bologna method in patients with pulmonary arterial hypertension (PAH). *Am J Respir Crit Care Med*. 2019;199:A2512.
29. Benza RL, Kanwar MK, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL lite 2, for use in patients with pulmonary arterial hypertension. *Chest*. 2021;159(1):337-346. [CrossRef]
30. Vonk Noordegraaf AV, Channick R, Cottreel E, et al. The REPAIR study: effects of macitentan on RV structure and function in pulmonary arterial hypertension. *JACC Cardiovasc Imaging*. 2022;15(2):240-253. [CrossRef]
31. Sitbon O, Cottin V, Canuet M, et al. Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension. *Eur Respir J*. 2020;56(3):2000673. [CrossRef]
32. Sulica R, Sangli S, Chakravarti A , Steiger D. Clinical and hemodynamic benefit of macitentan and Riociguat upfront combination in patients with pulmonary arterial hypertension. *Pulm Circ*. 2019;9(1):2045894019826944. [CrossRef]
33. Chin KM, Sitbon O, Doelberg M, et al. Three- versus two-drug therapy for patients with newly diagnosed pulmonary arterial hypertension. *J Am Coll Cardiol*. 2021;78(14):1393-1403. [CrossRef]
34. D'Alto M, Badagliacca R, Lo Giudice F, et al. Hemodynamics and risk assessment 2 years after the initiation of upfront ambri sentan–tadalafil in pulmonary arterial hypertension. *J Heart Lung Transplant*. 2020;39(12):1389-1397. [CrossRef]
35. D'Alto M, Badagliacca R, Argiento P, et al. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. *Chest*. 2020;157(2):376-383. [CrossRef]
36. Badagliacca R, Poscia RR, Pezzuto B, et al. Prognostic relevance of right heart reverse remodeling in idiopathic pulmonary arterial hypertension. *J Heart Lung Transplant*. 2017;37:195-205. [CrossRef]
37. Chen Y, Luo J, Chen J , et al. The transition From ambrisentan to macitentan in patients with pulmonary arterial hypertension: a real-word prospective study. *Front Pharmacol*. 2021;12:811700. [CrossRef]
38. Benza RL, Lickert CA, Xie L, et al. Comparative effectiveness of endothelin receptor antagonists on mortality in patients with pulmonary arterial hypertension in a US Medicare population: a retrospective database analysis. *Pulm Circ*. 2020;10(4):1-11. [CrossRef]
39. Benza R, Torbicki A, Uno H, et al. Using controlled and real-world data in concert to assess survival benefits in pulmonary arterial hypertension: insights from SERAPHIN and REVEAL. *Eur Respir J*. 2017; 50:OA1986.
40. Kaymaz C, Akbal OY, Hakgor A, et al. Dart to the target: an alternative bull's eye parametric display for European Society of Cardiology / European Respiratory Society goal-orientated risk reduction strategy in pulmonary arterial hypertension. *Pulm Circ*. 2018;8:2045894018780522.
41. Kaymaz C, Mutlu B, Küçükoğlu MS, et al. Preliminary results from a nationwide adult cardiology perspective for pulmonary hypertension: RegiStry on cllnical outcoMe and sUrvival in pulmonaRy hypertension Groups (SIMURG). *Anatol J Cardiol*. 2017;18(4):242-250. [CrossRef]
42. Demirel M, Külahçıoğlu Ş, Tokgöz HC, et al. Impaired endotheliu m-dependent and endothelium-independent systemic vasodilatory reserve in pulmonary hypertension regardless the clinical group: a generalized dysfunction beyond the pulmonary arteries? *Anatol J Cardiol*. 2021;25(10):733-740. [CrossRef]