Delay in Recognition of Pulmonary Arterial Hypertension

Factors Identified From the REVEAL Registry

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e-Appendix 1.

Background. The hemodynamic criteria necessary for enrollment into the REVEAL Registry differed from those conventionally required for a diagnosis of PAH.[1,2] A mean PAP >25 mm Hg (>30 mm Hg with exercise) and a PVR ≥3 Wood units were compulsory. However, the PCWP and LVEDP requirements were liberalized to include patients with values >15 to ≤18 mm Hg. This approach reflects current practice whereby clinicians treat some patients for PAH due to convincing clinical criteria despite a somewhat elevated PCWP or LVEDP. Here we present the analyses of the adult (age ≥19 years at diagnosis) REVEAL population including patients with PCWP >15 mm Hg.

References

1   Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary Arterial Hypertension: Baseline Characteristics From the REVEAL Registry. *Chest*. 2009

2   McGoon MD, Krichman A, Farber HW, et al. Design of the REVEAL registry for US patients with pulmonary arterial hypertension. *Mayo Clin Proc*. 2008;83(8):923-931.

e-Appendix 2.

REVEAL Sites – IRB/IRB #
University of Colorado HSC (Colorado Multiple IRB, 06-0235)
Columbia University (CUMC IRB, AAAC0789)
MAYO Clinic-Jackson (MAYO Clinic IRB, 06-002271 00)
Washington University (Washington University Human Research Protection Office (HRPO), 06-0753)
University of Minnesota Medical Center (University of Minnesota Research Subjects' Protection Programs IRB, 0607M89066)
Midwest Heart Foundation   (Western IRB, 20060231)
Children's Research Institute at Ohio State (Nationwide Children's IRB, 06-00411)
Ohio State University (Biomedical Institutional Review Board, 2006H0177)
Cleveland Clinic Foundation (Cleveland Clinic Foundation IRB, 06-259)
Intermountain Medical Center and the University of Utah (Intermountain Healthcare IRB, # 1009009)
Boston University School of Medicine (Western IRB, 1081775)
MAYO Clinic College of Medicine, Rochester (MAYO Clinic IRB, 06-00227100)
Baylor College of Medicine (Baylor College of Medicine IRB, H-19065)
University of Chicago Hospitals (The University of Chicago IRB, 14917B)
Georgia's Health Sciences University (Human Assurance Committee(HAC), 06-05-288)
Virginia Commonwealth University (Western IRB, 1090150)
University of Iowas Hospitals & Clinics (The University of Iowa IRB, #200603714)
Johns Hopkins Medical Center (Western IRB, 1078595)
Medical University of South Carolina (Office of Research Integrity (ORI) Medical University of South Carolina IRB, 16617)
Tufts-New England Medical Center   (Tufts Health Sciences Campus IRB, 7929)
Children's Hospital Department of Cardiology (Colorado Multiple IRB, 06-0500)
Rhode Island Hospital (Rhode Island Hospital IRB, 4075-06)
University Texas Health Science Center (University of Texas EIRB, HSC 20070383H)
Texas Children's Hospital   (Baylor College of Medicine IRB, H-19569)
Legacy Clinic Northwest (1. Oregon Health & Science University, 00002436; 2. Western IRB, 1099977)
University of Pittsburgh School of Medicine   (Western IRB, 1077291)
Kentuckiana Pulmonary Associates   (Western IRB, 1086454)
UCSF Medical Center (UCSF Committee on Human Research, H46460-29039-01)
Children's Hospital at Vanderbilt (Vanderbilt University IRB, 061152)
University of Florida (Western IRB, 1097909)
Allegheny General Hospital (Allegheny General Hospital IRB, RC -4088)
Inova Heart and Vascular Institute   (Western IRB, 1079519)
LA Biomedical Research Institute at Harbor-UCLA (LABioMed, 12722-01)
University of Maryland School of Medicine (University of Maryland For Human Subject Research IRB, H-28017)
Vanderbilt University Medical Center (Vanderbilt University IRB, 070020)
UCLA Medical Center (UCLA IRB, 06-06-118-02A)
Wayne University (Wayne State University Human Investigation Committee, 064606MP4E)
University Hospital of Cleveland (University Hospitals IRB, #07-06-28)
VA Greater Los Angeles Health System (Department of Veterans Affairs IRB, PCC2008-11178)
Beth Israel Medical Center (Beth Israel IRB, #013-08)

Penn Lung Center at Penn Presbyterian Medical Center (University of Pennsylvania IRB, 804760)

University of Alabama at Birmingham (Western IRB, 1078385)

North Shore University-LIJ Medical Center (BioMedical Research Alliance of New York, 06-02-83-03)

Duke University Medical Center (Duke University Health System IRB, 8650-06-6R0DB)

UCSD Medical Center (UCSD Human Research Protection Program, #060466)

St. Luke's Medical Center –Aurora (Aurora Health Care RSPP, L-06-74E)

Brigham and Women's Hospital Pulmonary Vascular Disease Program (Partners Human Research Committee, #2006P00088411)

Temple Lung Center (Temple Lung Center, #10127)

University Rochester Medical Center (Strong Health University of Rochester Research Subject Review Board, RSRB00014458)

Spectrum Health Hospitals   (Spectrum Health Research IRB, 2006-108)

Seattle Children's (Seattle Children's IRB, 12224)

Stanford University Medical Center (Stanford University, 96981 (eProtocol 5359)

e-Table 1. PAH Subgroup According to Time to Disease Recognition

PAH Subgroup	≤2 Years (n = 2037)	>2 Years (n = 553)	P Value[†]
Idiopathic PAH (IPAH)[*]	946 (46.4)	248 (44.8)	Reference
Associated with PAH (APAH)[*]			
Collagen vascular disease	498 (24.4)	157 (28.4)	0.11
Congenital heart disease	191 (9.4)	55 (9.9)	0.58
Portal hypertension	114 (5.6)	24 (4.3)	0.35
Drugs and toxins	108 (5.3)	27 (4.9)	0.83
HIV	46 (2.3)	3 (0.5)	0.010[‡]
Other APAH[§]	69 (3.4)	27 (4.9)	0.091
Familial PAH (FPAH)[*]	55 (2.7)	9 (1.6)	0.19
Pulmonary veno-occlusive disease[*]	8 (0.4)	3 (0.5)	0.71[‡]
Pulmonary capillary hemangiomatosis[*]	2 (0.1)	0 (0.0)	>0.99[‡]

Note: Of the final study population of 2733 patients, a total of 2590 had a PAH subgroup assigned at the time of diagnostic right-sided heart catheterization.

*Values are given as No. (%); †Unless otherwise stated, P values were obtained from χ^2 test evaluating the equality of proportions of the select category vs the IPAH reference group; ‡P value was obtained from Fisher's Exact Test evaluating the equality of the proportions of the select category vs the IPAH reference group; §Other APAH (2003 Venice classifications): thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, and splenectomy.

e-Table 2. Patient Demographic Characteristics According to Time to Disease Recognition

Characteristic	≤2 Years (n = 2149)	>2 Years (n = 584)	P Value[†]
Age at initial symptoms (y)*			
<36	457 (21.3)	174 (29.8)	<0.001
36 to <46	491 (22.8)	125 (21.4)	0.017
46 to <56	536 (24.9)	125 (21.4)	0.057
56 to <65	346 (16.1)	107 (18.3)	<0.001
≥65	319 (14.8)	53 (9.1)	Reference
Sex*			
Male	456 (21.2)	117 (20.0)	0.53[‡]
Female	1693 (78.8)	467 (80.0)	
Race/ethnicity*			
White	1564 (72.8)	435 (74.5)	Reference
Black	267 (12.4)	76 (13.0)	0.87
Hispanic	183 (8.5)	46 (7.9)	0.56
Asian or Pacific Islander	69 (3.2)	17 (2.9)	0.66
Native American or Native Alaskan	15 (0.7)	0 (0.0)	0.052[§]
Other	16 (0.7)	5 (0.9)	0.82
Unknown	35 (1.6)	5 (0.9)	0.16
Geographic region*			
Northeast	497 (23.1)	126 (21.6)	Reference
Midwest	491 (22.8)	119 (20.4)	0.75
South	617 (28.7)	175 (30.0)	0.39
West	544 (25.3)	164 (28.1)	0.19

Note: Numbers may not sum to the total number of patients within each variable due to missing data.
*Values are given as No. (%); †Unless otherwise stated, P values were obtained from χ^2 test evaluating the equality of proportions of the select category vs the reference group; ‡P value was obtained from overall χ^2 test; §P value was obtained from Fisher's Exact Test evaluating the equality of proportions of the select category vs the reference group.

e-Table 3. Patient Comorbid Conditions and Presenting Symptoms; Physician Specialty Consulted at Symptom Onset According to Time to Disease Recognition

Characteristic	≤2 Years (n = 2149)	>2 Years (n = 584)	P Value[†]
Comorbid conditions at diagnosis of PAH[*]			
History of obstructive airways disease[§]	408 (19.5)	170 (29.7)	<0.001
History of thromboembolic disease	194 (9.3)	71 (12.5)	0.022
Sleep apnea	428 (21.2)	161 (28.9)	<0.001
Obesity (BMI ≥30 kg/m^2)	594 (33.2)	187 (37.9)	0.052
Diabetes	257 (12.2)	85 (14.9)	0.089
Cancer (excluding skin cancer)	140 (6.7)	27 (4.7)	0.092
Presenting symptom(s) attributable to PAH[*]			
Abdominal distention	90 (4.2)	16 (2.7)	0.11
Chest pain/discomfort	467 (21.7)	119 (20.4)	0.48
Cough	296 (13.8)	88 (15.1)	0.42
Dizziness/lightheadedness	318 (14.8)	96 (16.4)	0.33
Dyspnea at rest	244 (11.4)	53 (9.1)	0.12
Dyspnea on exertion	1842 (85.7)	501 (85.8)	0.96
Edema	483 (22.5)	104 (17.8)	0.015
Fatigue	574 (26.7)	158 (27.1)	0.87
Presyncope/syncope	349 (16.2)	105 (18.0)	0.32
Raynaud's phenomenon	157 (7.3)	57 (9.8)	0.050
Palpitations	274 (12.8)	69 (11.8)	0.55
Physician specialty consulted at symptom onset[*]			
Cardiologist	606 (28.2)	140 (24.0)	0.36[‡]
Pulmonologist	493 (23.0)	129 (22.1)	Reference
Internist	287 (13.4)	81 (13.9)	0.64[‡]
Rheumatologist	73 (3.4)	30 (5.1)	0.057[‡]

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Other	271 (12.6)	68 (11.6)	0.80[‡]
Unknown	417 (19.4)	136 (23.3)	0.11[‡]

BMI, body mass index; PAH, pulmonary arterial hypertension.

Note: Numbers may not sum to the total number of patients within each variable due to missing data.
*Values are given as No. (%); †Unless otherwise stated, P values were obtained from overall χ^2 test; ‡P value was obtained from χ^2 test evaluating the equality of proportions of the select category vs the reference group; §History of obstructive airways disease was defined as having a history of obstructive lung disease and/or reactive airway disease.

e-Table 4. Patient Functional Classification, Exercise Tolerance, and RHC Variables According to Time to Disease Recognition

Characteristic	≤2 Years (n = 2149)	>2 Years (n = 584)	P Value[†]
NYHA/WHO functional class at PAH diagnosis[*‖]			
I	64 (4.1)	7 (1.7)	0.022
II	349 (22.2)	97 (23.5)	0.79
III	959 (61.1)	257 (62.4)	Reference
IV	197 (12.6)	51 (12.4)	0.84
6MWD at PAH diagnosis (meters)[*§‖]			
<250	155 (23.6)	52 (30.4)	0.012
250 to <410	341 (51.9)	68 (39.8)	Reference
≥410	161 (24.5)	51 (29.8)	0.026
mPAP (mm Hg)[*]			
<55	1362 (63.4)	385 (65.9)	0.26[‡]
≥55	787 (36.6)	199 (34.1)	
mRAP (mm Hg)[*]			
<10	1057 (54.1)	321 (61.0)	0.003
10 to <15	512 (26.2)	128 (24.3)	0.16
≥15	385 (19.7)	77 (14.6)	Reference
PCWP or LVEDP (mm Hg)[*]			
<12	1409 (65.6)	358 (61.4)	Reference
12 to <15	430 (20.0)	124 (21.3)	0.28
15 to ≤18	308 (14.3)	101 (17.3)	0.048
Cardiac index (L/min x m²)[*‖]			
<2	627 (39.1)	132 (32.0)	0.007[‡]
≥2	975 (60.9)	281 (68.0)	
PVR (Wood units)[*‖]			
<10	1072 (49.9)	328 (56.4)	0.006[‡]

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≥10	1075 (50.1)	254 (43.6)	
Vasoreactivity*¶			
Yes	107 (10.1)	30 (10.6)	0.84‡
No	948 (89.9)	254 (89.4)	

6MWD, 6-minute walking distance; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right-sided heart catheterization; WHO, World Health Organization.

Note: Numbers may not sum to the total number of patients within each variable due to missing data.

*Values are given as No. (%); †Unless otherwise stated, P values were obtained from χ^2 test evaluating the equality of proportions of the select category vs the reference group; ‡P value was obtained from overall χ^2 test; §Categorization was based on the quartiles of the distribution; the second and third quartiles were combined; ‖Missing data: functional classification of 752 patients; 6MWD of 1905 patients, cardiac index of 718 patients, and PVR of 4 patients; ¶Defined as patients with a decrease in mPAP ≥10 mm Hg to a level <40 mm Hg without a decrease in cardiac output.

e-Table 5. Unadjusted and Adjusted Logistic Regression of Factors Associated With a Time to Disease Recognition >2 Years

Risk Factor (units)	Unadjusted OR (95% CI)	Unadjusted P Value*	Adjusted OR (95% CI)†	Adjusted P Value*
Age at initial symptoms (y)				
<36	2.29 (1.63–3.22)	<0.001	3.15 (2.13–4.66)	<0.001
36 to <46	1.53 (1.08–2.18)	0.017	2.03 (1.36–3.03)	<0.001
46 to <56	1.40 (0.99–1.99)	0.058	1.63 (1.10–2.42)	0.016
56 to <65	1.86 (1.30–2.68)	<0.001	2.00 (1.34–3.05)	<0.001
≥65	Reference	Reference	Reference	Reference
Comorbid conditions				
History of obstructive airways disease‡	1.74 (1.41–2.15)	<0.001	1.83 (1.45–2.33)	<0.001
History of thromboembolic disease	1.40 (1.05–1.87)	0.022	1.45 (1.04–2.01)	0.027
Sleep apnea	1.51 (1.22–1.87)	<0.001	1.61 (1.26–2.05)	<0.001
Obesity	1.23 (1.00–1.51)	0.052		
Diabetes	1.26 (0.96–1.64)	0.090		
Cancer (non-cutaneous)	0.70 (0.46–1.06)	0.094		
6MWD at PAH diagnosis (meters)				
<250	1.68 (1.12–2.53)	0.012		
250 to < 410	Reference	Reference		
≥410	1.59 (1.06–2.39)	0.026		
Missing	1.39 (1.05–1.84)	0.023		
mRAP (mm Hg)				
<10	1.52 (1.15–2.00)	0.003	1.79 (1.30–2.46)	<0.001
10 to < 15	1.25 (0.91–1.71)	0.16	1.35 (0.96–1.88)	0.082
≥15	Reference	Reference	Reference	Reference
Cardiac index (L/min x m²)				
<2	Reference	Reference		
≥2	1.37 (1.09–1.72)	0.007		
Missing	1.48 (1.15–1.91)	0.002		

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PCWP or LVEDP (mm Hg)

<12	Reference	Reference	Reference	Reference
12 to <15	1.14 (0.90–1.43)	0.28	1.25 (0.96–1.64)	0.10
15 to ≤18	1.29 (1.00–1.66)	0.048	1.62 (1.19–2.20)	0.002

PVR (Wood units)

<10	1.29 (1.08–1.56)	0.006	1.26 (1.01–1.57)	0.039
≥10	Reference	Reference	Reference	Reference

6MWD; 6-minute walking distance; CI, confidence interval; LVEDP, left ventricular end-diastolic pressure; mRAP, mean right atrial pressure; OR, odds ratio; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

*P values from Wald χ^2 test; †Adjusted model contains the following covariates: age at initial symptoms attributable to PAH, history of obstructive airways disease, sleep apnea, history of deep vein thrombosis and pulmonary embolism, mRAP, PCWP or LVEDP, and PVR; ‡History of obstructive airways disease was defined as having a history of obstructive lung disease and/or reactive airway disease.