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ORIGINAL RESEARCH

Persistent Pulmonary Hypertension in Corrected Valvular Heart Disease: Hemodynamic Insights and Long-Term Survival

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BACKGROUND: The determinants and consequences of pulmonary hypertension after successfully corrected valvular heart disease remain poorly understood. We aim to clarify the hemodynamic bases and risk factors for mortality in patients with this condition.

METHODS AND RESULTS: We analyzed long-term follow-up data of 222 patients with pulmonary hypertension and valvular heart disease successfully corrected at least 1 year before enrollment who had undergone comprehensive hemodynamic and imaging characterization as per the SIOVAC (Sildenafil for Improving Outcomes After Valvular Correction) clinical trial. Median (interquartile range) mean pulmonary pressure was 37 mm Hg (32–44 mm Hg) and pulmonary artery wedge pressure was 23 mm Hg (18–26 mm Hg). Most patients were classified either as having combined precapillary and postcapillary or isolated postcapillary pulmonary hypertension. After a median follow-up of 4.5 years, 91 deaths accounted for 4.21 higher-than-expected mortality in the age-matched population. Risk factors for mortality were male sex, older age, diabetes mellitus, World Health Organization functional class III and higher pulmonary vascular resistance—either measured by catheterization or approximated from ultrasound data. Higher pulmonary vascular resistance was related to diabetes mellitus and smaller residual aortic and mitral valve areas. In turn, the latter correlated with prosthetic nominal size. Six-month changes in the composite clinical score and in the 6-minute walk test distance were related to survival.

CONCLUSIONS: Persistent valvular heart disease–pulmonary hypertension is an ominous disease that is almost universally associated with elevated pulmonary artery wedge pressure. Pulmonary vascular resistance is a major determinant of mortality in this condition and is related to diabetes mellitus and the residual effective area of the corrected valve. These findings have important implications for individualizing valve correction procedures.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT00862043.

Key Words: heart failure ■ pulmonary hypertension ■ valvular heart disease

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CLINICAL PERSPECTIVE

What Is New?

- Mortality of patients with persistent pulmonary hypertension in successfully corrected valvular heart disease is high.
- Major risk factors are age, male sex, diabetes mellitus, advanced functional class, and high pulmonary vascular resistance.

What Are the Clinical Implications?

- Chronically elevated left-sided heart pressures play a major role in the development and perpetuation of persistent valvular heart disease–pulmonary hypertension.
- Small valve prostheses, particularly in the mitral position, show the highest-risk hemodynamic profile.
- Thus, preventing the consequences of persistent valvular heart disease–pulmonary hypertension should rely not only on an adequate timing of the valve interventions but also on avoiding small residual valve areas, particularly in men and patients with diabetes mellitus.

Nonstandard Abbreviations and Acronyms

6MWT	6-minute walk test
LHD	left-sided heart disease
mPAP	mean pulmonary arterial pressure
PAWP	pulmonary artery wedge pressure
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
PSAP	pulmonary artery systolic pressure
SIOVAC	Sildenafil for Improving Outcomes After Valvular Correction
VHD	valvular heart disease

The most common cause of pulmonary hypertension (PH) worldwide is left-sided heart disease (LHD),[1,2] and valvular heart disease (VHD) is a significant cause of this type of PH.[3,4] Despite important improvements in the timing of valve interventions, long-standing PH after surgery is still frequent.[5] Furthermore, as a result of nonestablished mechanisms, PH may eventually develop in patients with corrected VHD who did not show PH before surgery.[6] Understanding the physiological bases of persistent VHD-PH would benefit of a comprehensive hemodynamic profiling of patients with this condition.

Signs of PH by Doppler echocardiography after correction of VHD are associated with long-term mortality and disability.[6–10] Selecting therapeutic strategies in group 2 PH requires counterbalancing their risks against robust survival indicators of the underlying disease. However, to our knowledge, there are no prospective series of patients with unequivocal persistent VHD-PH studied at late stages after the valve correction. Extrapolating outcomes from other causes of LHD-PH such as heart failure may be misleading because additional risk factors that impact pulmonary pressures such as left ventricular (LV) systolic and diastolic dysfunction[11] may be absent in corrected VHD.

The present study was designed to assess the hemodynamic bases of persistent VHD-PH and to identify catheterization and imaging predictors of survival of patients with this condition, studied at least 1 year after the primary valvular lesion was successfully corrected. For this purpose, we related long-term survival with baseline variables of the SIOVAC (Sildenafil for Improving Outcomes After Valvular Correction) trial cohort.[12] Additionally, we aimed to validate 6-month surrogate end points typically used in prospective clinical trials in the field.

METHODS

The data that support this study are available from the corresponding author on reasonable request.

Patients and Study Design

SIOVAC was an investigator-driven, multicenter, academically sponsored, randomized, double-blind, placebo-controlled, parallel clinical trial testing the efficacy of sildenafil on 6-month outcomes of patients with persistent VHD-PH.[12] The study was performed in 18 academic hospitals in Spain and the Fundación de Investigación Biomédica Hospital Gregorio Marañón served as the coordinating center. The main results showed that sildenafil was related to worse clinical outcomes than placebo at 6 months.[12] Patients were enrolled between May 2008 to December 2015, and on September 2019 the survival status was updated from the electronic records or telephonic interview. The investigator drug was interrupted at the end of the 6-month randomization period. The study was authorized by the Spanish Agency of Medicinal Products and Medical Devices and approved by the reference ethic committee and the local ethic committees of all participant institutions. All patients provided written informed consent. A second approval by the ethics committees was obtained for the purpose of extending follow-up, which waived the need for signing a new informed consent. The SIOVAC trial is registered with ClinicalTrials.gov NCT00862043 and EudraCT 2007-007033-40.

Patients were screened in outpatient clinics and imaging laboratories of participating institutions.[12] In summary, enrollment criteria included echocardiographic signs of PH (systolic pulmonary artery pressure ≥50 mm Hg as measured by Doppler echocardiography), a successful surgical or percutaneous valvular replacement or repair procedure with complete correction of the left-sided heart valve disease performed at least 1 year before inclusion, and a stable clinical condition. Major exclusion criteria included any significant residual prosthesis or native left-sided heart valvular dysfunction and a life expectancy <2 years. Only patients with a mean pulmonary arterial pressure (mPAP) ≥30 mm Hg by right-sided heart catheterization were randomized and received the investigation drug. However, nonrandomized patients with PH (mPAP between 20 and 30 mm Hg) underwent an identical follow-up protocol and are also included in the present report.

Procedures

All patients underwent clinical, imaging, and catheterization procedures at enrollment. Hemodynamic measures during right-sided heart cardiac catheterization were obtained at baseline and after an acute vasoreactivity test with 100 mg of sublingual sildenafil.[12,13] The diastolic pressure gradient and (mean) transpulmonary pressure gradient were calculated subtracting the mean pulmonary artery wedge pressure (PAWP) from the diastolic and mean pulmonary artery pressures, respectively. Pulmonary vascular resistance (PVR) and pulmonary arterial compliance were calculated as transpulmonary pressure gradient/cardiac output and stroke volume/pulse pressure, respectively. Pulmonary arterial elastance was calculated as systolic pulmonary artery pressure/stroke volume.

We used current definitions of PH (mPAP ≥20 mm Hg) as well as hemodynamic classification criteria for defining precapillary PH (PAWP ≤15 mm Hg), isolated postcapillary PH (PAWP >15 mm Hg and PVR <3 Wood units [WU]), and combined precapillary and postcapillary PH (PAWP >15 mm Hg and PVR ≥3 WU).[14] Patients with a PAWP ≤15 mm Hg but PVR <3 WU were designated as having "high-output" PH. All patients underwent clinical assessment, 6-minute walk test (6MWT), and Doppler echocardiography examinations at baseline and at 3 and 6 months.

A blinded core laboratory analyzed cardiac images.[12] Mitral and aortic effective valve areas were determined by the continuity equation using stroke volume values obtained by cardiac catheterization divided by their respective valvular Doppler time-velocity integrals. Mitral valve mismatch was defined for repaired mitral valves or prostheses in the mitral position as an effective valve area index ≤1.2 cm^2/m^2 of body surface area, whereas aortic valve mismatch was defined as a prosthetic effective valve area index ≤0.65 cm^2/m^2. Blood sampling was performed at baseline and 6 months for brain natriuretic peptide measurements. All randomized patients stopped the investigation product after the 6-month period and underwent medical management as per criteria of their referring physicians.

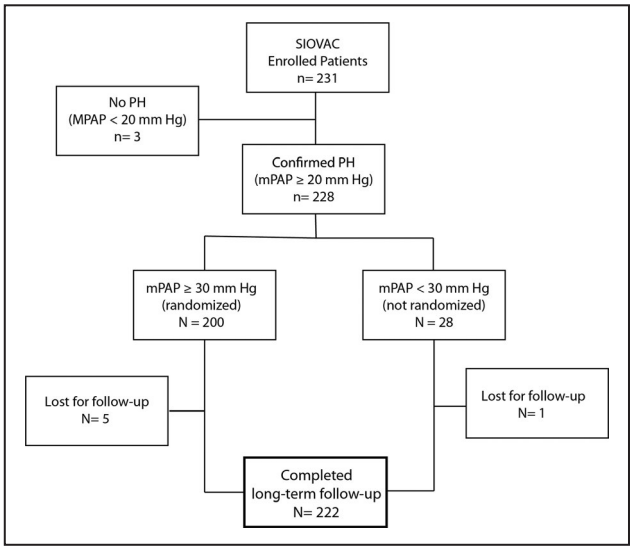

Figure 1. Enrollment of the study cohort.
The confirmatory catheterization procedure excluded pulmonary hypertension (PH) (mean pulmonary arterial pressure [mPAP] <20 mm Hg) in 3 patients, and 6 were lost to follow-up. Consequently, 222 patients with catheterization-confirmed PH and complete follow-up data are the basis of this report. SIOVAC indicates Sildenafil for Improving Outcomes After Valvular Correction.

End Points

For the extended follow-up period, the primary end point of the present investigation was all-cause mortality and the secondary end point was cardiovascular mortality, which included all cardiac causes, stroke, and fatal hemorrhagic complications. The primary end point of the SIOVAC randomized clinical trial was change (improved, unchanged, or worsened) in the clinical composite score, in terms of: (1) death or hospital admission for heart failure, (2) change in functional class, and (3) patient global self-assessment at 6 months.[12,15] Secondary end points of the clinical trial were 6-month changes in the 6MWT distance, brain natriuretic peptide levels, and Doppler-derived systolic pulmonary artery pressure. The primary and secondary end points of the randomized clinical trial were validated against the primary end point of the present long-term study.

Table 1. Baseline Characteristics of the Study Cohort

	Not Randomized	Randomized	Full Cohort
	n= 27	n= 195	N= 222
Age, y	71 (66–76)	72 (66–77)	72 (66–77)
Women, n (%)	20 (74)	149 (76)	169 (76)
Weight, kg	68 (68–71)	67 (58–80)	67 (58–78)
Systolic BP, mm Hg	129 (120–138)	136 (122–150)	135 (121–149)
Diastolic BP, mm Hg	67 (61–72)	70 (64–80)	70 (63–79)
Heart rate, beats per min^{-1}	68 (60–77)	70 (62–78)	70 (61–79)
Atrial fibrillation, n (%)	20 (74)	138 (71)	158 (71)
Hypertension, n (%)	19 (70)	126 (65)	145 (65)
Hyperlipidemia, n (%)	12 (44)	84 (43)	96 (43)
Diabetes mellitus, n (%)	7 (26)	57 (29)	64 (29)
Smoking, n (%)	3 (11)	13 (7)	16 (7)
Heart valve procedures			
Mitral valve repair, n (%)	5 (18)	21 (11)	26 (12)
Mitral valve replacement, n (%)	15 (56)	156 (80)	171 (77)
Aortic valve replacement, n (%)	14 (52)	90 (46)	104 (47)
Tricuspid valve surgery, n (%)	8 (30)	75 (39)	83 (37)
Mitral and aortic valve surgery, n (%)	7 (26)	72 (37)	79 (36)
Patients with reinterventions, n (%)	5 (19)	61 (31)	66 (30)
Time since last valvular surgery, y	9 (4–15)	7 (3–13)	7 (3–13)
Type of valve prosthesis, n (%)			
Mechanical	22 (82)	153 (79)	175 (79)
Biological	3 (11)	36 (19)	39 (18)
Nominal size of prostheses, median (IQR)			
Mitral	29 (27–29)	27 (25–29)	27 (25–29)
Aortic	21 (21–25)	21 (19–23)	21 (20–23)
Coronary artery revascularization			
Coronary artery bypass graft, n (%)	0 (0)	13 (7)	13 (6)
Percutaneous coronary intervention, n (%)	0 (0)	12 (6)	12 (5)
Functional status			
WHO functional classification, n (%)			
I or II	22 (81)	111 (57)	133 (60)
III	5 (19)	84 (43)	89 (40)
6-min walk test distance, m	366 (318–410)	356 (270–408)	358 (272–408)
Concomitant mediations			
Acenocoumarol or warfarin, n (%)	26 (96)	180 (92)	206 (93)
Aspirin, n (%)	1 (4)	19 (10)	20 (9)
Diuretics, n (%)	20 (80)	167 (86)	187 (84)
Aldosterone receptor antagonist, n (%)	11 (41)	83 (43)	94 (42)
ACE inhibitors, n (%)	11 (41)	77 (40)	88 (40)
Angiotensin II receptor blocker, n (%)	4 (18)	41 (21)	45 (20)
Laboratory			
BNP, pg mL^{-1}	40 (21–68)	59 (25–153)	55 (24–135)
Cardiac catheterization data			
Right atrial pressure, mm Hg	10 (8–14)	12 (9–17)	12 (9–16)
Pulmonary artery oxygen saturation, %	66 (61–72)	64 (59–70)	64 (59–70)
Mean pulmonary artery pressure, mm Hg	25 (23–28)	39 (34–44)	37 (32–44)

(*Continued*)

Table 1. Continued

	Not Randomized	Randomized	Full Cohort
	n= 27	n= 195	N= 222
Mean PAWP, mm Hg	17 (12–23)	22 (20–26)	22 (18–26)
Cardiac index, L min^{-1}/m^{-2}	2.7 (2.3–3.1)	2.8 (2.4–3.3)	2.8 (2.4–3.3)
Transpulmonary pressure gradient, mm Hg	9 (6–11)	16 (12–22)	15 (11–21)
Diastolic pressure gradient, mm Hg	1 (–2–4)	3 (0–7)	2 (0–6)
Pulmonary vascular resistance, WU	1.9 (1.3–2.7)	3.4 (2.3–5.0)	3.2 (2.1–4.8)
Pulmonary arterial compliance, mL/mm Hg^{-1}	2.5 (2.1–3.1)	1.9 (1.3–2.5)	2.0 (1.4–2.7)
Pulmonary arterial elastance, mm Hg/mL	0.6 (0.5–0.8)	0.9 (0.7–1.2)	0.9 (0.7–1.2)
PH classification, n (%)			
Precapillary PH	2 (7)	7 (4)	9 (4)
Isolated postcapillary PH	14 (52)	80 (41)	94 (42)
Combined postcapillary PH	2 (7)	108 (55)	110 (50)

All values are described as median (interquartile range) unless otherwise indicated. ACE indicates angiotensin-converting enzyme; BNP, brain natriuretic peptide; BP, blood pressure; IQR, interquartile range; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; WHO, World Health Organization; and WU, Wood units.

Statistical Analysis

All data are presented as median (interquartile range) except when otherwise indicated. We used multivariable imputation by chained equations for relevant missing data. We used the Pearson linear correlation coefficient (*r*) to assess the relationship between quantitative variables, and paired *t* tests to analyze the pre-/post-effects of the acute vasodilator test. We used multivariable linear regression to address predictors of PVR. Survival data were right-censored at 84 months and Kaplan-Meier plots and log-rank differences were calculated. The best cutoff values were obtained using maximally selected rank statistics implemented for survival analyses.[16] The standardized mortality ratio (and its 95% CI) was calculated comparing the cohort against the sex- and age-matched Spanish population for the studied period.[17] We used univariable and multivariable Cox proportional hazards models to analyze survival. For multivariable models, we selected predictors based on the results of univariate analyses and then underwent backwards stepwise selection using cross-validation of 1000 replicates; only variables entered >50% of the replicates were retained. Identical variables were chosen in a sensitivity analysis performed using a purposeful selection strategy. For variable reduction of Doppler echocardiography data, we fitted a multivariable least-squares linear regression model using measured PVR as the dependent variable (Data S1 and Figure S1). The noninvasive surrogate of PVR was then entered in the Cox models instead of measured PVR. Bias-adjusted metrics of overall performance of multivariable models was assessed calculating the R^2 and the C-statistic by bootstrapping 1000 replicates. Proportional hazards assumptions were addressed by analysis of Schoenfeld residuals of each covariable and the global model. A cluster (random) effect of the recruiting center was excluded by mixed-effects Cox regression. For the validation analyses of 6-month end points, we also used the Kaplan-Meier method, log-rank tests and calculated their hazard ratios (HRs). We used R (version 4.0; The R Foundation) for all analyses and plots, and statistical significance was established at $P<0.05$.

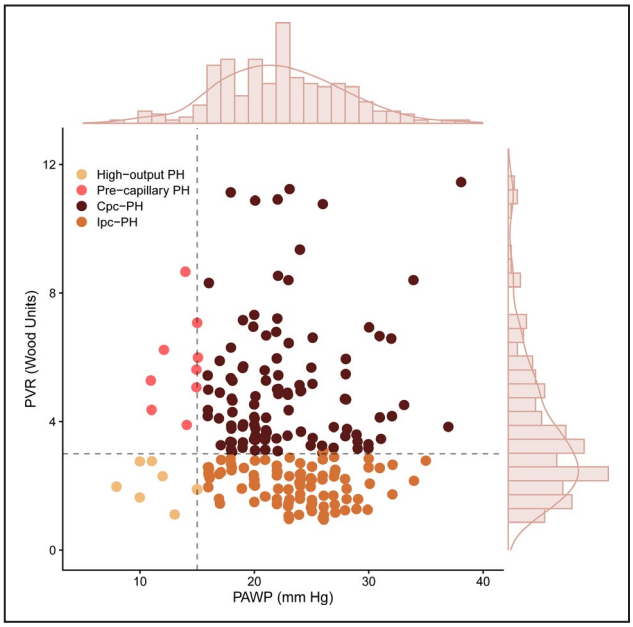

Figure 2. Hemodynamic characterization at enrollment. CpcPH indicates combined postcapillary pulmonary hypertension; IpcPH, isolated postcapillary pulmonary hypertension; PAWP, pulmonary capillary pressure; PH, pulmonary hypertension; and PVR, pulmonary vascular resistance

Table 2. Echocardiographic Data

	Not Randomized	Randomized	Full Cohort
Total Population	**n=27**	**n=195**	**N=222**
Available Data	**n=20**	**n=187**	**N=207**
LV end-diastolic volume index, mL/m^2	58 (42–68)	54 (44–64)	52 (43–63)
LV end-systolic volume index, mL/m^2	22 (17–28)	22 (16–29)	21 (16–26)
LV ejection fraction, %	61 (54–62)	59 (54–64)	60 (55–63)
LV end-diastolic dimension, cm	49 (44–55)	50 (46–53)	50 (45–53)
Interventricular septum diastolic thickness, cm	1.0 (0.9–1.1)	1.1 (1.0–1.2)	1.0 (0.9–1.2)
RV end-diastolic area, cm^2	20.9 (16.0–24.3)	19.9 (17.5–23.4)	19.8 (17.5–24.0)
RV end-systolic area, cm^2	12.0 (9.2–13.4)	13.0 (10.7–14.9)	13.1 (11.1–15.5)
RV fractional area shortening, %	40 (40–50)	40 (30–40)	40 (30–40)
Right atrial area, cm^2	23.1 (19.8–33.2)	22.7 (19.0–28.2)	23.1 (18.9–28.6)
Left atrial diameter, cm	5.2 (4.7–5.8)	5.0 (4.6–5.5)	5.1 (4.6–5.6)
Left atrial volume index, mL·m^{-2}	89 (65–104)	91 (71–116)	90 (71–115)
Peak aortic jet velocity (native valve), m/s	1.8 (1.6–2.1)	1.9 (1.7–2.4)	1.9 (1.7–2.4)
Peak aortic jet velocity (prostheses), m/s	2.5 (1.9–3.2)	2.7 (2.3–3.1)	2.7 (2.3–3.1)
Effective aortic valve area index (prostheses), cm^2/m^2	0.96 (0.70–1.28)	0.88 (0.69–1.12)	0.88 (0.70–1.13)
Aortic valve patient-prosthesis mismatch (prostheses), n (%)	2 (18)	20 (24)	22 (23)
Aortic regurgitation, n (%)			
0	11 (55)	94 (52)	105 (53)
I	8 (40)	67 (37)	75 (37)
II	1 (5)	19 (11)	20 (10)
Peak E wave velocity (native valve), m/s	1.6 (1.3–1.7)	1.6 (1.4–1.8)	1.6 (1.4–1.8)
Peak E wave velocity (surgical valve), m/s	1.9 (1.7–2.3)	2.0 (1.8–2.1)	2.0 (1.8–2.1)
Diastolic transmitral pressure gradient (surgical valve), mm Hg	5.0 (4.1–6.0)	4.9 (4.0–6.3)	4.9 (4.0–6.3)
E wave deceleration time (native valve), ms	301 (211–373)	179 (160–247)	205 (163–290)
E wave deceleration time (prostheses or repaired valve), ms	321 (224–354)	219 (186–287)	221 (188–299)
Effective mitral valve area index (prostheses or repaired), cm^2·m^{-2}	0.92 (0.86–1.14)	1.05 (0.83–1.18)	1.04 (0.83–1.18)
Mitral valve patient-prosthesis mismatch (prostheses or repaired), n (%)	8 (66)	126 (79)	134 (78)
Mitral regurgitation, n (%)			
0	14 (70)	106 (59)	120 (60)
I	5 (25)	48 (27)	53 (27)
II	1 (5)	26 (14)	27 (13)
Tricuspid annular plane systolic excursion, cm	1.7 (1.5–2.0)	1.5 (1.2–1.7)	1.5 (1.3–1.8)
Tricuspid regurgitation, n (%)			
0	0 (0)	1 (1)	1 (1)
I	5 (25)	18 (10)	23 (12)
II	8 (40)	99 (56)	107 (54)
III	7 (35)	50 (28)	57 (29)
IV	0 (0)	9 (5)	9 (5)
Pulmonary flow acceleration time, ms	96 (81–112)	69 (60–83)	69 (60–83)
Tricuspid jet peak regurgitant velocity, m/s	3.0 (2.7–3.2)	3.5 (3.2–3.9)	3.5 (3.2–4.0)
Estimated pulmonary systolic arterial pressure, mm Hg	46 (38–53)	61 (53–72)	61 (53–76)

All values are described as median (interquartile range) unless otherwise indicated. LV indicates left ventricular; and RV, right ventricular.

RESULTS

Study Population

The present report is based on 222 patients of the 231 initially entering the SIOVAC cohort (Figure 1). The median (interquartile range) age was 72 years (66–77 years), 169 patients (76%) were women, and 64 patients (29%) had diabetes mellitus. The most frequent valvular surgery was mitral valve replacement (n=171, 77%), and roughly one third of patients had undergone

Table 3. Correlation Analyses of Factors Related to PAWP and PVR

	PAWP	PVR
Mitral mean transvalvular pressure gradient[§]	0.21*	−0.05
Mitral valve area index[§]	−0.05	−0.28*
Mitral prosthesis-patient mismatch (no vs yes)[§]	22 vs 22 mm Hg	2.8 vs 3.9 WU*
Aortic mean transprosthetic pressure gradient	0.20*	−0.10
Aortic prosthetic valve area index	−0.26*	0.03
Aortic prosthesis-patient mismatch (no vs yes)[†]	22 vs 23 mm Hg	3.1 vs 3.9 WU

Values represent Pearson correlation coefficient (*r*), except [†], which shows mean values for either group. PAWP indicates pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; and WU, Wood units.

*$P<0.05$.

[§]Patients with mitral valve repair or mitral valve replacement.

more than 1 valve procedure (Table 1). Most patients (n=214, 93%) had mechanical prostheses. Among these, 85% were of bileaflet design.

Catheterization and Echocardiographic Profiling

Baseline hemodynamic results showed significant elevation in mPAP and PAWP (37 mm Hg [32–44 mm Hg] and 23 mm Hg [18–26 mm Hg], respectively), whereas cardiac index was in the low-normal range (Table 1, Figure 2). Median PVR was 3.2 WU (2.1–4.8 WU). One half of the study population (n=110) experienced combined postcapillary PH, whereas 94 patients (42%) experienced isolated postcapillary PH. Of the remaining 18 patients showing a PAWP <15 mm Hg, precapillary PH was present in 9 (4%). Results of acute vasodilator tests are summarized in Data S1.

Median LV ejection fraction was 60% (55%–63%) and only 34 patients (15%) showed values <50% (Table 2). Almost all patients had mild or moderate degrees of tricuspid regurgitation and tricuspid annular plane systolic excursion was in the low limits. Mitral prosthesis mismatch was found in 78% of patients with previous mitral surgery and available ultrasound data. These patients showed higher values of PVR, as PVR inversely correlated with effective mitral valve area index ($r=-0.28$, $P=0.0002$; Table 3). Multivariable regression showed that PVR was directly related to the presence of diabetes mellitus (β=0.9 WU, $P=0.005$) and inversely related to mitral and aortic valve area indices (β=−1.5 WU and 0.8 WU per cm^2/m^2 [$P=0.003$ and $P=0.048$], respectively). In turn, valve area index correlated with nominal size, both of mitral ($r=0.30$, $P=0.001$) and aortic ($r=0.32$, $P=0.005$) prostheses.

Survival

During the follow-up period (median 4.5 years [3.3–6.4 years]), 91 deaths were recorded (41%). Causes of death were cardiovascular in 70 (78%), noncardiovascular in 15 (16%), and undetermined in 6 (7%) patients. Cardiovascular deaths were of cardiac origin in 52 patients (end-stage heart failure in 42, sudden cardiac death in 5, acute myocardial infarction in 2, and other events in 3), fatal hemorrhagic events in 15, and ischemic stroke in 3. Median overall survival rates at 12, 24, and 60 months were 0.95 (95% CI, 0.92–0.98), 0.86 (95% CI, 0.81–0.90), and 0.62 (95% CI, 0.55–0.69), respectively (Figure 3A). Compared with the Spanish age-matched population, the standardized mortality ratio was 4.21 (95% CI, 3.43–5.17; $P<0.0001$). Kaplan-Meier curves for cardiovascular mortality and stratification according to the enrollment group are shown in Figure 3B and 3C. In randomized patients, 6-month exposure to the investigation drug was unrelated to long-term survival (HR, 0.81; 95% CI, 0.52–1.25 [$P=0.34$], sildenafil versus placebo).

Survival Predictors

Demographic, clinical, catheterization, and echocardiographic factors were related to all-cause mortality (Table 4). Multivariable analyses (Table 5) showed that the most determinant risk factor for mortality was male sex (HR, 1.92; 95% CI, 1.20–3.08). Age, diabetes mellitus, and functional class were related to mortality. Among catheterization variables, mPAP, transpulmonary pressure gradient, pulmonary arterial elastance, and PVR were all related to survival (Table 4; Figure 4). However, the latter was the only catheterization variable entering multivariable prediction models (HR, 1.10; 95% CI, 1.01–1.19 per WU [$P=0.04$]). Neither the hemodynamic PH classification nor the response to the acute vasodilator test predicted survival (Table 4, Figure 3D). Among echocardiographic variables, the estimated PSAP, tricuspid annular plane systolic excursion, and transmitral pressure gradient were all related to survival (Table 4), but no echocardiographic variable alone added predictive value to clinical factors in multivariable models. Echocardiographic data yielded a relatively accurate estimate of PVR by multivariable linear regression (Figure 5). This noninvasive estimate of PVR was the most powerful predictor of all-cause mortality in the multivariable model (HR, 1.25; 95% CI, 1.06–1.42 per 1 noninvasive WU). Optimal thresholds of PVR and noninvasive PVR to predict all-cause mortality were identical: 4.3 WU. Performance of the 3 multivariable models (clinical, clinical+catheterization, and clinical+ultrasound) to predict survival was nearly identical (bootstrapped C-index: 0.67 to 0.68, Table 5). Survival curves for the most relevant predictors of all-cause mortality are shown in Figure 6. Demographic, clinical, catheterization, and ultrasound predictors

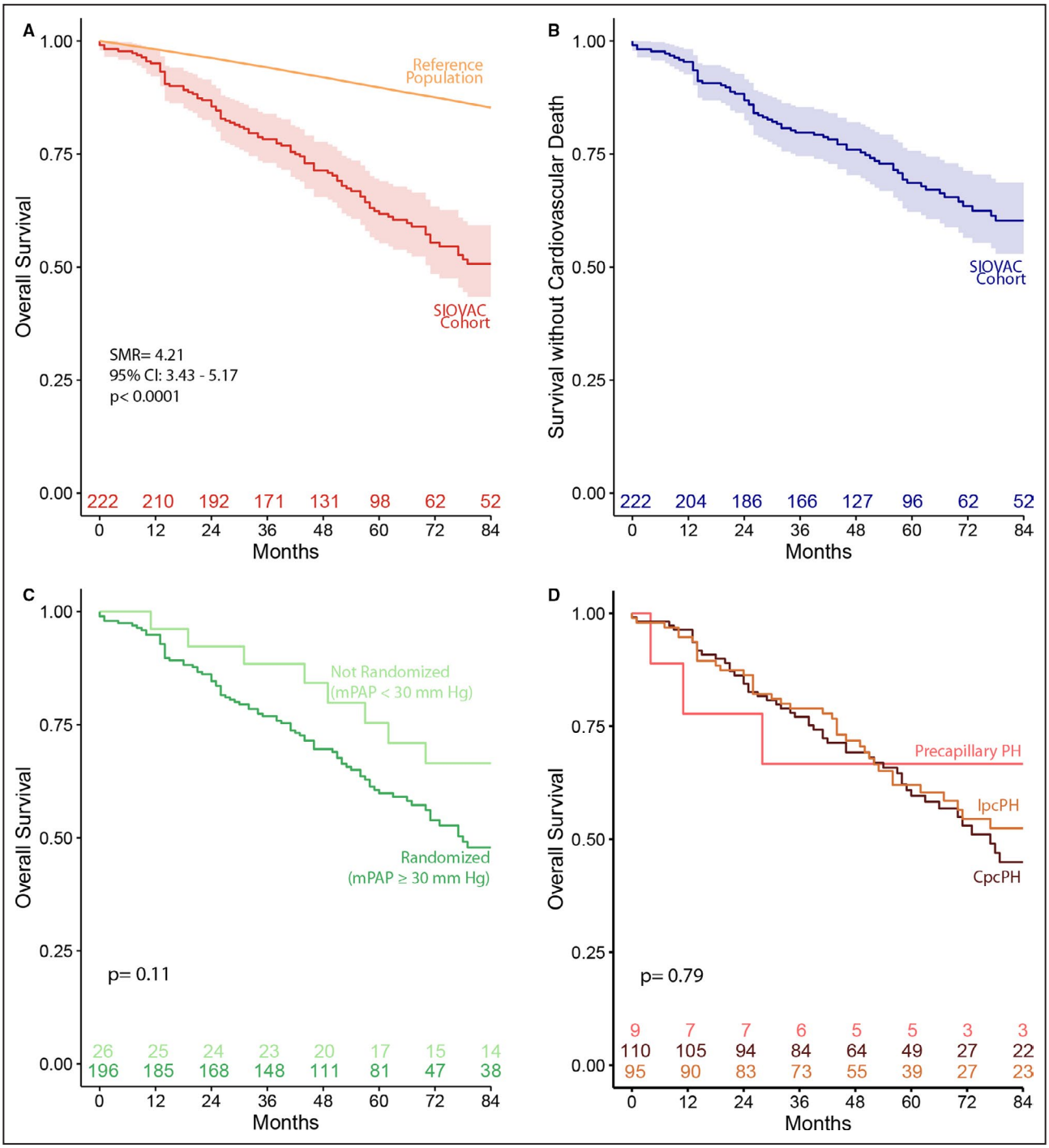

Figure 3. Survival curves of the study cohort.
(**A**) Global survival of the full cohort compared with the Spanish age-matched control population. (**B**) Survival without cardiovascular mortality. (**C, D**) Stratification based on the role in the clinical trial and pulmonary hypertension (PH) classification group, respectively. CpcPH indicates combined postcapillary pulmonary hypertension; IpcPH, isolated postcapillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; SIOVAC Sildenafil for Improving Outcomes After Valvular Correction; and SMR, standard mortality ratio.

related to cardiovascular mortality were similar to those related to all-cause mortality (Table 6).

The composite clinical score and changes in 6MWT distance evaluated at 6 months performed relatively well to predict survival, whereas the change in brain natriuretic peptide levels performed worse (Figure 7; bootstrapped C-indices: 0.62, 0.57, and 0.52, respectively).

Table 4. Univariate Predictors of Mortality

	HR	95% CI	*P* Value
Clinical			
Age (per 10 y)	1.65	1.24–2.19	0.0006
Men	1.72	1.09–2.70	0.018
Diabetes mellitus	2.10	1.39–3.18	0.0005
WHO functional class III vs I or II	2.08	1.38–3.14	0.0005
Time from last surgery (per y)	1.00	0.98–1.03	0.57
6MWT distance (per 50 m)	0.83	0.75–0.93	0.0008
BNP (per 1 log pg mL^{-1})	1.27	1.05–1.53	0.01
Catheterization			
mPAP (per 10 mm Hg)	1.34	1.08–1.65	0.007
PAWP (per 10 mm Hg)	1.21	0.82–1.77	0.34
TPG (per 1 mm Hg)	1.04	1.01–1.06	0.009
DPG (per 1 mm Hg)	1.02	0.99–1.06	0.25
TPG >12 mm Hg (binary)	1.38	0.87–2.18	0.17
PVR (per 1 WU)	1.12	1.03–1.22	0.007
PVR >3 WU (binary)	1.19	0.79–1.81	0.40
PAC (per 1 mL/mm Hg)	1.00	0.87–1.17	0.96
Pulmonary arterial elastance (per 1 mm Hg/mL)	1.70	1.10–2.63	0.016
Acute vasoreactivity test			
Delta CO (per increase 0.5 mL/min)	1.04	0.89–1.22	0.58
Delta PVR (per decrease 0.5 WU)	1.00	0.90–1.11	0.98
Delta PAC (per increase 0.5 mL/mm Hg)	1.08	0.89–1.31	0.41
Echocardiography			
LV ejection fraction (per 10%)	0.95	0.74–1.21	0.65
RV fractional area change (per 10%)	0.87	0.70–1.09	0.22
RV end-diastolic area (per 5 cm^2)	1.05	0.85–1.29	0.65
RV end-systolic area (per 5 cm^2)	1.18	0.87–1.59	0.29
Right atrial area (per 5 cm^2)	1.03	0.92–1.16	0.62
Tricuspid annular plane systolic excursion (per 0.5 cm)	0.71	0.53–0.97	0.031
Mean diastolic transmitral pressure gradient (per 1 mm Hg)	1.10	1.01–1.19	0.025
Transmitral velocity deceleration time (per 100 ms)	0.89	0.69–1.16	0.38
Prosthetic/repaired mitral valve area index (per 0.5 cm^2/m^{-2})	1.08	0.76–1.53	0.66
Prosthetic aortic valve area index (per 0.5 cm^2/m^{-2})	0.97	0.71–1.32	0.87
Pulmonary acceleration time (per 10 ms)	0.93	0.84–1.03	0.16
Tricuspid regurgitation (per 1 degree)	0.92	0.68–1.25	0.60
Peak TR jet velocity (per 1 m/s)	1.31	1.08–1.59	0.005
Estimated PSAP (per 10 mm Hg)	1.17	1.04–1.33	0.01
Estimated PVR (per 1 WU)	1.23	1.06–1.42	0.007

6MWT indicates 6-minute walk test; BNP, brain natriuretic peptide; CO, cardiac output; DPG, diastolic pulmonary gradient; HR, hazard ratio; LV, left ventricular; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PAWP, pulmonary artery wedge pressure; PSAP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RV, right ventricular; TPG, transpulmonary pressure gradient; TR, tricuspid regurgitation; WHO, World Health Organization; and WU, Wood units.

DISCUSSION

In the largest prospective cohort of patients with invasively documented persistent VHD-PH reported so far, we demonstrate that the long-term survival of this condition is poor. In most cases, this complication is related to a chronic elevation of left-sided heart pressures, with only 4% of patients showing precapillary PH according to current definitions. Men with diabetes mellitus in World Health Organization (WHO) functional class III and a PVR >4.3 WU—either measured by catheterization or estimated using echocardiography—are patients at highest risk for dying. These findings have important implications for understanding

Table 5. Multivariable Models of Any-Cause Mortality

Model	Variable	HR	95% CI	X^2	*P* Value
Clinical					
	Sex (male vs female)	1.92	1.20–3.08	7.42	0.006
	Age (per 10 y)	1.49	1.11–2.01	7.04	0.008
	Diabetes mellitus	1.69	1.10–2.59	5.68	0.01
	WHO functional class III vs I or II	1.62	1.05–2.53	4.64	0.03
	6MWT distance (per 50 m)	0.92	0.82–1.04	2.65	0.10
Bootstrapped R2=0.13; C-index=0.67					
Clinical+catheterization					
	Age (per 10 y)	1.56	1.17–2.09	8.96	0.011
	WHO functional class III vs I or II	1.76	1.15–2.68	6.87	0.008
	Sex (male vs female)	1.82	1.15–2.87	6.50	0.011
	Diabetes mellitus	1.70	1.11–2.61	5.97	0.014
	PVR (per 1 WU)	1.10	1.01–1.19	4.02	0.04
Bootstrapped R^2=0.13; C-index=0.67					
Clinical+echocardiography					
	Predicted PVR (per 1 WU)	1.25	1.06–1.46	7.52	<0.001
	WHO functional class III vs I or II	1.82	1.14–2.92	6.33	0.011
	Age (per 10 y)	1.44	1.05–1.98	5.17	0.02
	Sex (male vs female)	1.73	1.03–2.92	4.26	0.04
	Diabetes mellitus	1.47	0.91–2.37	2.53	0.11
Bootstrapped R^2=0.14; C-index=0.68					

For each model, predictors are sorted by their statistical relevance. 6MWT indicates 6-minute walk test; HR, hazard ratio; PVR, pulmonary vascular resistance; WHO, World Health Organization; and WU, Wood units.

the foundations of persistent VDH-PH as well as for its potential prevention.

Understanding Persistent VHD-PH

Unlike in other causes of LHD-PH, the causative left-sided heart lesion is usually corrected in persistent VHD-PH, and only in 15% of patients showed LV systolic dysfunction in our series. It is classically believed that valvular hemodynamics return to normal after correction of the valvular lesion and that LV systolic dysfunction is prevented when valvular interventions are accurately timed. Because patients with preoperative PH frequently do not have normalized pulmonary pressure after surgery, the focus has been usually placed on preoperative vascular damage.[5,8,18] Therefore, PH in operated valvular patients is frequently designated "residual PH," attributing PH to irreversible changes in arterial and arteriolar pulmonary vessels caused by delayed surgery.[19,20]

Our finding of almost universal PAWP elevation in most patients with VHD-PH challenges this interpretation. The foundations of a chronic elevation of PAWP remain unknown, but factors such as functionally restrictive valves (see below),[5] LV diastolic dysfunction, and progressive vascular remodeling at the arteriolar, undetermined, and venular vessels[21] may be involved. In addition, the high prevalence of atrial fibrillation and the large atrial volumes observed in our cohort support a potential role of atrial dysfunction.[22] Some authors have suggested the early role of reactive increase in pulmonary arterial tone related to neurohormonal (eg, endothelin-mediated) and neurogenic mechanisms.[23] This functional impairment could be unmasked by the response to acute vasodilation tests, which, in theory, would be able to discriminate (early) "reversible" from (late) "fixed" mechanisms of precapillary and combined postcapillary PH. However, the results of our study show no long-term prognostic value of acute or chronic use of sildenafil.[12] These findings further advise against the indiscriminate use of vasoreactivity tests in fields other than specific causes of group 1 PH.[1]

Survival of Patients With Persistent VHD-PH

Survival in patients with persistent VHD-PH was 62% at 5 years, and all-cause mortality was 4.2 times

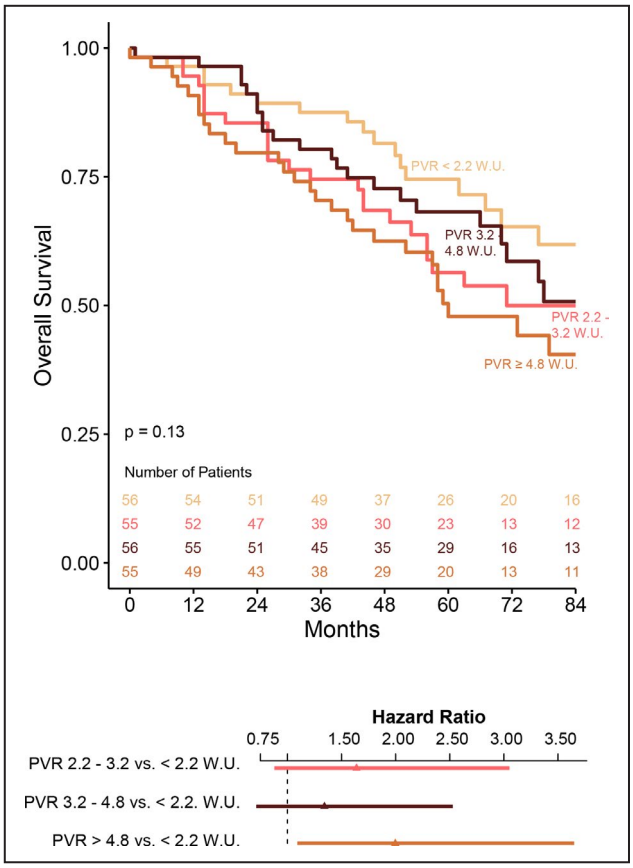

Figure 4. The relationship between pulmonary vascular resistance (PVR) and outcomes.
(**A**) Kaplan-Meir survival curves based on the PVR quartile distribution. (**B**) Per-quartile hazard ratio (HR) analysis. When analyzed by quantiles of the distribution, only quartile 4 vs quartile 1 was significant (HR not including 1), without significant differences in the intermediate categories.

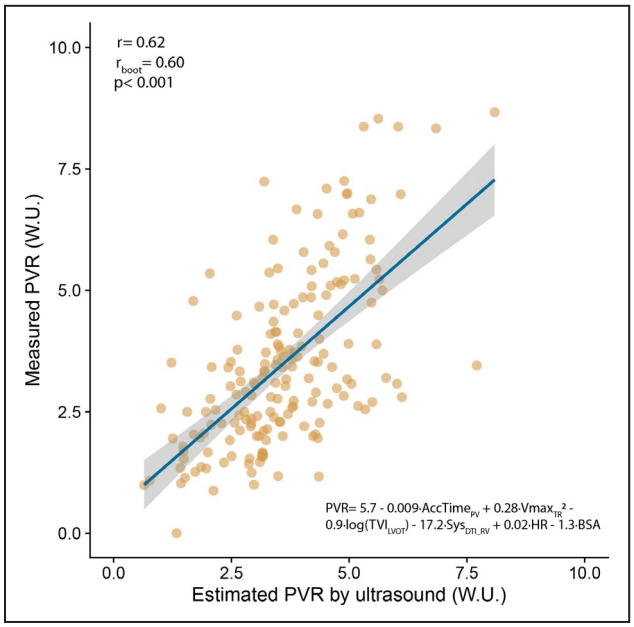

Figure 5. Results of the multivariable regression fitting for predicting pulmonary vascular resistance (PVR) from ultrasound data.
AccTimePV indicates Doppler acceleration time as measured by pulsed-wave Doppler at the level of the pulmonary valve (ms); BSA, body surface area (m^2); HR, heart rate (min^{-1}); PVR, pulmonary vascular resistance (Wood units [WU]); SysDTI_RV, peak systolic myocardial velocity as measured by Doppler tissue imaging of the right ventricular free wall (cm/s); TVI_{LVOT}, left ventricular outflow-tract pulsed-wave Doppler time velocity integral (cm); and VmaxTR, peak jet velocity of the tricuspid regurgitation jet (m/s).

higher than in the matched population. Compared with global cohorts of group 2 PH, this survival rate is close to rates previously reported in some groups[4] but markedly lower than the standard mortality ratio 7.1 value reported by others.[2] It is also similar to the mortality rate of patients with heart failure,[24,25] but it doubles the mortality rate of unselected carriers of mechanical valve prostheses (standard mortality ratio, 1.74–1.99).[26] More than two thirds of our cohort were women, and female sex was associated with a better prognosis, 2 typical findings of other causes of PH,[27] and persistent VHD-PH.[5] The high prognostic value we observed for WHO functional class III and 6MWT distance underscores the role of functional characterization of patients with PH. Importantly, clinical variables yielded the most useful prognostic information.

A unique characteristic of our cohort is its exhaustive characterization by right-sided cardiac catheterization. Inconsistent with other LHD-PH reports,[28,29] neither PAWP nor the PH group classification were related to mortality. This lack of association may be attributable to the fact that elevated PAWP in VHD is not an indicator of advanced LV systolic or diastolic dysfunction.[29] In our cohort, the PVR cutoff value for predicting survival was 4.3 WU, slightly higher than the 3.0 WU threshold that defines combined postcapillary PH in current guidelines.[14] This higher cutoff explains why PH classification was not related to outcomes in our series, and, again, emphasizes the singularity of this condition. As in other cohorts, we found no relationship between the diastolic pressure gradient and outcomes.[28,30]

Among the Doppler echocardiographic variables, tricuspid annular plane systolic excursion, the transprosthetic mitral pressure gradient, and peak tricuspid regurgitation jet velocity correlated with survival. Remarkably, tricuspid regurgitation was not related to mortality, in concordance with recent observations.[31] Echocardiographic variables added no prognostic information to clinical and demographic data in univariable modeles. Instead, clustered as estimated PVR, they were significantly related to global and cardiovascular survival.

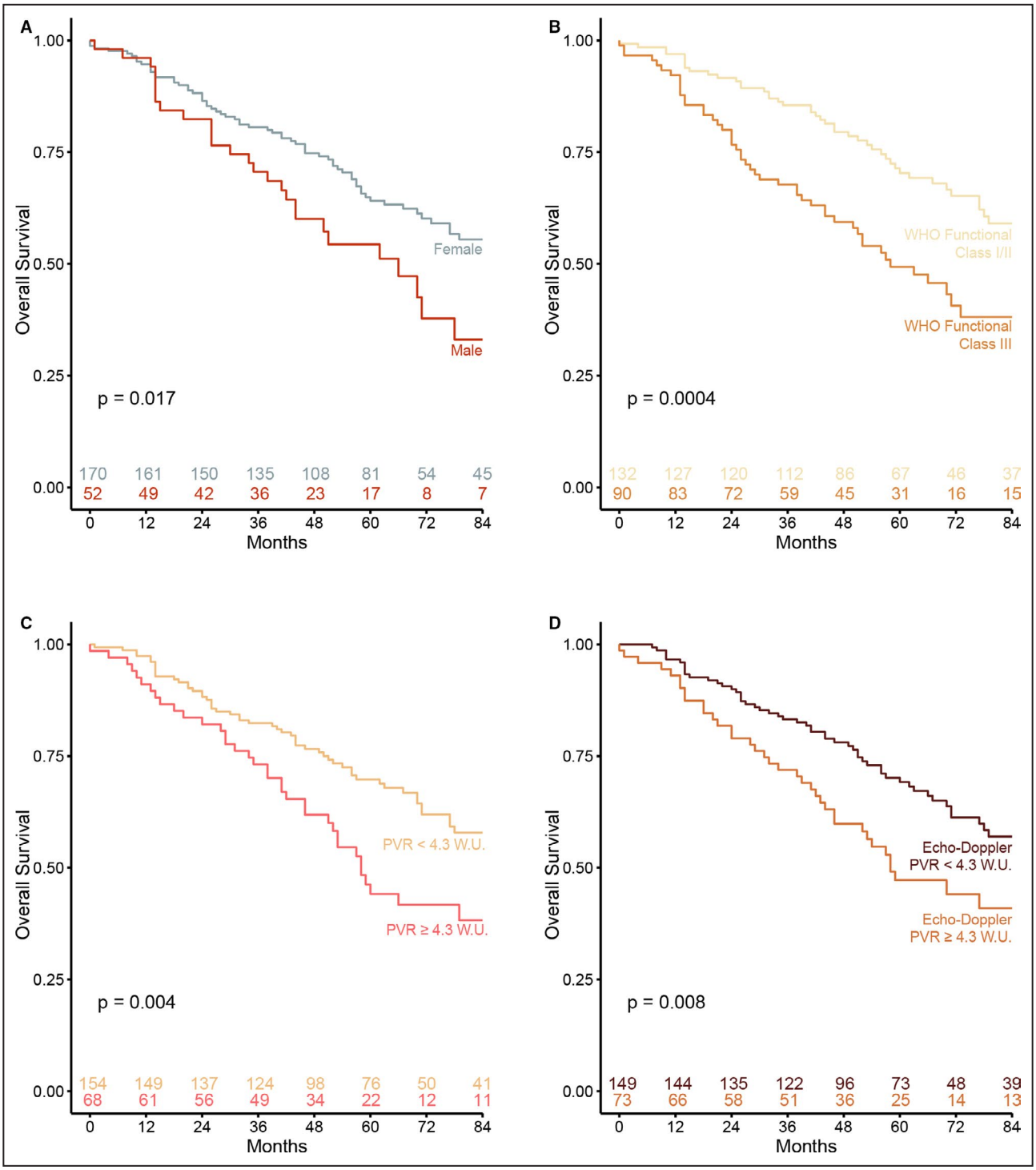

Figure 6. Kaplan-Meier overall-survival curves based on most relevant predictors.
Stratification based on sex (**A**), World Health Organization (WHO) functional class (**B**), and pulmonary vascular resistance (PVR), either measured (**C**) or estimated by ultrasound (**D**).

Clinical Implications for Preventing PH and its Consequences

In the present article, we identified procedural issues that have a direct impact on outcomes. Diabetes mellitus was particularly deleterious, not only because of its direct impact on survival but also because it showed an additive effect on PVR. Although the interaction between diabetes mellitus and LHD-PH is not a novel finding,[32–35] its potential implications in VHD-PH had not been reported. A significant number of patients in our cohort met the criterion of patient-valve

Table 6. Multivariable Models of Cardiovascular Mortality

Model	Variable	HR	95% CI	X^2	*P* Value
Clinical					
	Sex (male vs female)	2.43	1.45–4.08	11.45	0.0007
	Age (per 10 y)	1.47	1.05–2.05	5.02	0.025
	6MWT distance (per 50 m)	0.86	0.75–0.98	4.91	0.03
	WHO functional class III vs I or II	1.57	0.94–2.60	3.03	0.08
	Diabetes Mellitus	1.31	0.79–2.16	1.09	0.30
Bootstrapped R^2=0.11; Dxy=0.36; C-index=0.68					
Clinical+catheterization					
	Sex (male vs female)	2.16	1.31–3.59	8.98	0.003
	Age (per 10 y)	1.58	1.14–2.19	7.41	0.007
	WHO functional class III vs I or II	1.81	1.12–2.93	5.90	0.02
	PVR (per 1 WU)	1.10	1.01–1.19	3.90	0.05
	Diabetes mellitus	1.93	0.85–2.30	1.71	0.19
Bootstrapped R^2=0.10; D_{xy}=0.34; C-index=0.67					
Clinical+echocardiography					
	Sex (male vs female)	2.17	1.20–3.92	6.59	0.01
	WHO functional class III vs I or II	1.87	1.08–3.25	4.98	0.03
	Predicted PVR (per 1 WU)	1.24	1.02–1.50	4.81	0.03
	Age (per 10 y)	1.45	1.00–2.08	3.95	0.05
	Diabetes mellitus	1.09	0.60–1.96	0.08	0.78
Bootstrapped R^2=0.08; D_{xy}=0.27; C-index=0.64					

For each model, predictors are sorted by their statistical relevance. 6MWT indicates six-minute walk test; HR, hazard ratio; PVR, pulmonary vascular resistance; WHO, World Health Organization; and WU, Wood units.

mismatch (>79% of patients with mitral disease), and effective residual valve area was inversely related with PVR. These observations constitute an invasive and long-term confirmation of prior Doppler-based reports relating prosthesis-patient mismatch and restrictive annuloplasties to persistent VHD-PH.[5,7,36] As expected, effective valve area was, in turn, related to prosthetic nominal size. In consequence, whenever possible, mitral valve repair should be preferred over replacement, but restrictive annuloplasties should be avoided. Prostheses with sizes and designs showing the largest functional areas are preferable but may require more complex surgical techniques. Thus, procedural risks must be carefully balanced, keeping in mind that based on the results of our study, elderly patients and those with diabetes mellitus are at the highest risk of the consequences of persistent PH. Furthermore, adequate sizing of prostheses should not be overlooked in men, despite their larger body surface area. For aortic valve procedures, transcatheter aortic valves yield larger effective area than their surgical sutural equivalents.

If PH is suspected at least 1 year after the primary valvular lesion has been corrected, patients should undergo a comprehensive workup. Valvular dysfunction must be ruled out in the first place. Noninvasive estimates of PVR and pulmonary pressures should be obtained, but a right-sided catheterization procedure ought to characterize the hemodynamic substrate. Patients should be closely followed, and aggressive therapeutic interventions may occasionally be considered, particularly in men with diabetes mellitus, as well as in patients with functional class III or PVR values >4.3 WU. The observation of a direct relationship between walking distance and survival suggests a potential benefit of cardiac rehabilitation.[37] Treatment options for these patients must be further studied, and the survival rates described herein are a suitable reference to balance their risks. For future clinical trials in the field, our results support 6-month changes in the composite clinical score and in 6MWT distance as valid end points. However, longer-term studies with clinical end points continue to be preferred for phase 3 studies.

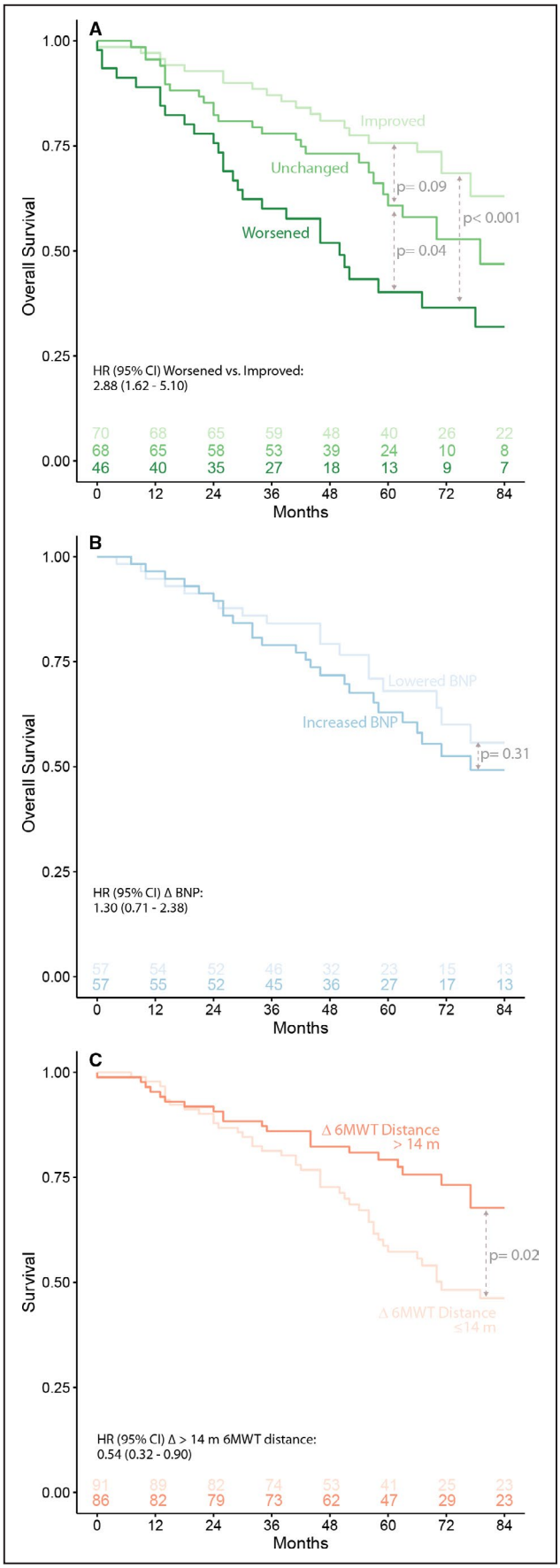

Figure 7. Survival curves of the 6-month end points of the SIOVAC (Sildenafil for Improving Outcomes After Valvular Correction) clinical trial.

(**A, B, C**) Split survival curves based on the clinical composite score, median change in brain natriuretic peptide (BNP) levels, and median change in the 6-minute walk test (6MWT) distance, respectively. HR indicates hazard ratio.

Study Limitations

Data on the primary valvular lesions and hemodynamic profiles immediately before and after surgery were unavailable, precluding a longitudinal picture of PH in these patients. However, the period elapsed from the last surgery to recruitment was long (median 7 years), almost one third of the cohort had undergone prior reinterventions, and the finding of high PAWPs was almost universal. These issues suggest that postcorrection factors are the major determinants of outcomes in patients with persistent VHD-PH. Because the SIOVAC cohort was recruited for participating in a clinical trial, we cannot exclude certain selection bias toward more severe disease. Median mPAP of the full study cohort was 37 mmHg, far above the cutoff of 20 mm Hg now established as PH diagnostic criterion.[14] Therefore, results should be extrapolated with caution to milder degrees of PH. The multivariable ultrasound PVR model was calculated and validated in the same sample. Even though bootstrapping was used to palliate overfitting, future studies are needed. Finally, pulmonary functional tests were not performed and, therefore, a combination of group 2 and group 3 PH causes cannot be excluded in some patients. However, the infrequent usage of bronchodilator medications suggests a low prevalence of pulmonary disease in the cohort.

CONCLUSIONS

Elevated left-sided heart pressures play a major role in persistent VHD-PH. Mortality of patients with persistent VHD-PH is more than 4 times higher than in the age- and sex-matched general population. Risk factors for mortality in patients with this condition are age, male sex, diabetes mellitus, advanced functional class, and high PVR—measured by cardiac catheterization or approximated using ultrasound. Patients with diabetes mellitus and those with small valve prostheses show the worst hemodynamic profiles. These findings present an opportunity for preventing this complication.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Appendix: List of SIOVAC Investigators
Data S1
FIGURE S1

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SUPPLEMENTAL MATERIAL

Appendix

List of SIOVAC Investigators

The following investigators, participated in the SIOVAC study:

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Instituto de Salud Carlos III: Raquel Yotti.

Hospital Virgen de las Nieves, Granada. Spain: Rocío García-Orta, Inés Uribe, and Mercedes González.

Hospital Clínico Universitario de Salamanca, and CIBERCV Salamanca. Spain: Pedro Luis Sánchez, José M González-Santos, Javier Martín-Moreiras, Antonio Arribas, M. Milagros Clemente Lorenzo and Alejandro Diego Nieto.

Hospital Universitario de León, León, Spain: Mario Castaño, Armando Pérez de Prado and David Alonso.

Hospital Puerta de Hierro Majadahonda and CIBERCV, Majadahonda, Madrid. Spain: Javier Segovia-Cubero, Manuel Gómez-Bueno, Inés Sayago Silva and Miguel Ángel Cavero.

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Hospital Santa Creu i San Pau and CIBERCV, Barcelona. Spain: Xavier Borrás, Carmen Amorós Galitó.

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Complejo Universitario Fundación Alcorcón, Alcorcón. Spain: Javier Botas, Raquel Campuzano.

Complejo Hospitalario Universitario de A Coruña and CIBERCV, A Coruña. Spain: María G Crespo-Leiro, Raquel Marzoa, José Cuenca.

Hospital de Galdakao-Usansolo, Usansolo. Spain: Sonia Velasco.

Hospital Infanta Leonor, Madrid. Spain: Roberto Muñoz, Verónica Suberviola, Cristina Beltrán Herrera, Laura Mora, M. Mar Sarrión and David Vaqueriza.

Hospital Universitari Germans Trias i Pujol and CIBERCV, Badalona. Spain: Antoni Bayes-Genís, Elena Ferrer.

Hospital Clínico de Santiago de Compostela and CIBERCV, Santiago de Compostela. Spain: José R. González-Juanatey, Belén Cid and Amparo Martínez Monzonís.

Hospital Universitario Reina Sofía, Córdoba. Spain: Amador López, José M. Arizón de Prado, Marta Santisteban and Dolores Mesa Rubio.

Hospital Universitario de la Vall d'Hebron and CIBERCV, Barcelona. Spain: Arturo Evangelista and David García-Dorado.

Hospital Virgen de la Victoria and CIBERCV, Málaga, Spain: Eduardo de Teresa, Manuel Jiménez-Navarro and Fernando Carrasco Chinchilla.

Hospital Universitario San Cecilio, Granada. Spain: Eduardo Moreno-Escobar.

Hospital Universitario de Getafe, Madrid. Spain: Joaquín Alonso.

Data S1.

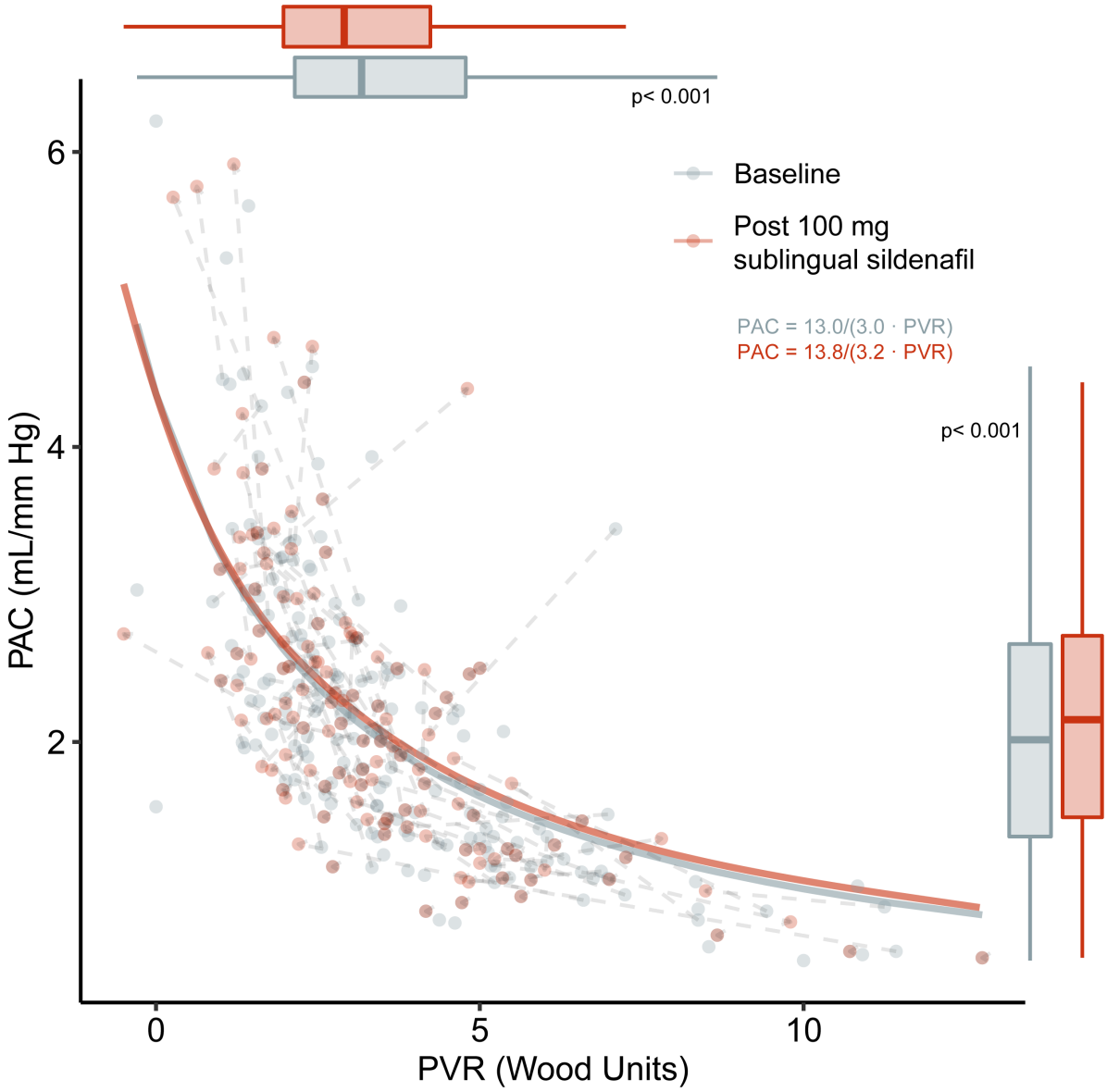
Supplemental Methods

Because no single echocardiographic variable was related to survival in the multivariable model, we underwent a variable-reduction strategy to cluster Doppler-echocardiographic variables into a single metric. For this purpose, we underwent a multivariable linear regression model to predict PVR, as measured by cardiac catheterization. Combining ultrasound variables shown in **Table 2** with other relevant noninvasive information we underwent automatic variable selection by cross-validation backwards selection algorithm using 1,000 replicates. Predicted values of PVR estimated noninvasively were then entered in the uni and multivariable Cox proportional-hazard models to predict survival.

Supplemental Results

The acute vasoreactivity test (n= 140) induced significant reductions in PAWP (mean decrease -1.1 mm Hg, p= 0.003), mPAP (-3.3 mm Hg, p< 0.0001), and PVR (-0.6 W.U, p< 0.0001), without significantly changing cardiac output (-0.46 l/min, p= 0.22), and significantly increasing PAC (+0.46 mL/mm Hg; **Figure S1**). Despite these changes, the impact of sildenafil on the PAC-PVR nonlinear relationship was negligible (**Figure S1**).

Figure S1. Acute Vasoreactivity Test.



Values for each patient with available data are shown for baseline (red) and post-sildenafil (100 mg, sublingual) connected by a dotted line. Global effects for the full cohort are shown in the marginal boxplots.