

SUPPLEMENTAL MATERIAL

Appendix

List of SIOVAC Investigators

The following investigators, participated in the SIOVAC study:

Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid, and CIBERCV, Madrid. Spain: Javier Bermejo, Ana I Fernández, Francisco Fernández-Avilés, Teresa Mombiola, Ana González-Mansilla, Jaime Elízaga, José A García-Robles, Esther Pérez-David, Candelas Pérez del Villar, Ricardo Sanz, Enrique Gutierrez-Ibanes, María E Vázquez, Ana Mur, Yolanda Benito, Pablo Martínez-Legazpi, Alicia Barrio, and Alexandra Vázquez.

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.

Hospital Doce de Octubre and CIBERCV, Madrid. Spain: Pilar Escribano-Subias, Laura Domínguez, Rocío Tello de Meneses, M José Ruiz Cano and Carmen Jiménez López-Guarch.

Hospital Clínico de Valladolid and CIBERCV, Valladolid. Spain: J. Alberto San Román, Pedro Mota

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

Hospital Universitario de Araba-Txagorritxu, Vitoria. Spain: Angel Alonso-Gómez, M. Concepción Belló Mora, Dolores Mesa Rubio.

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 Sofia, 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.

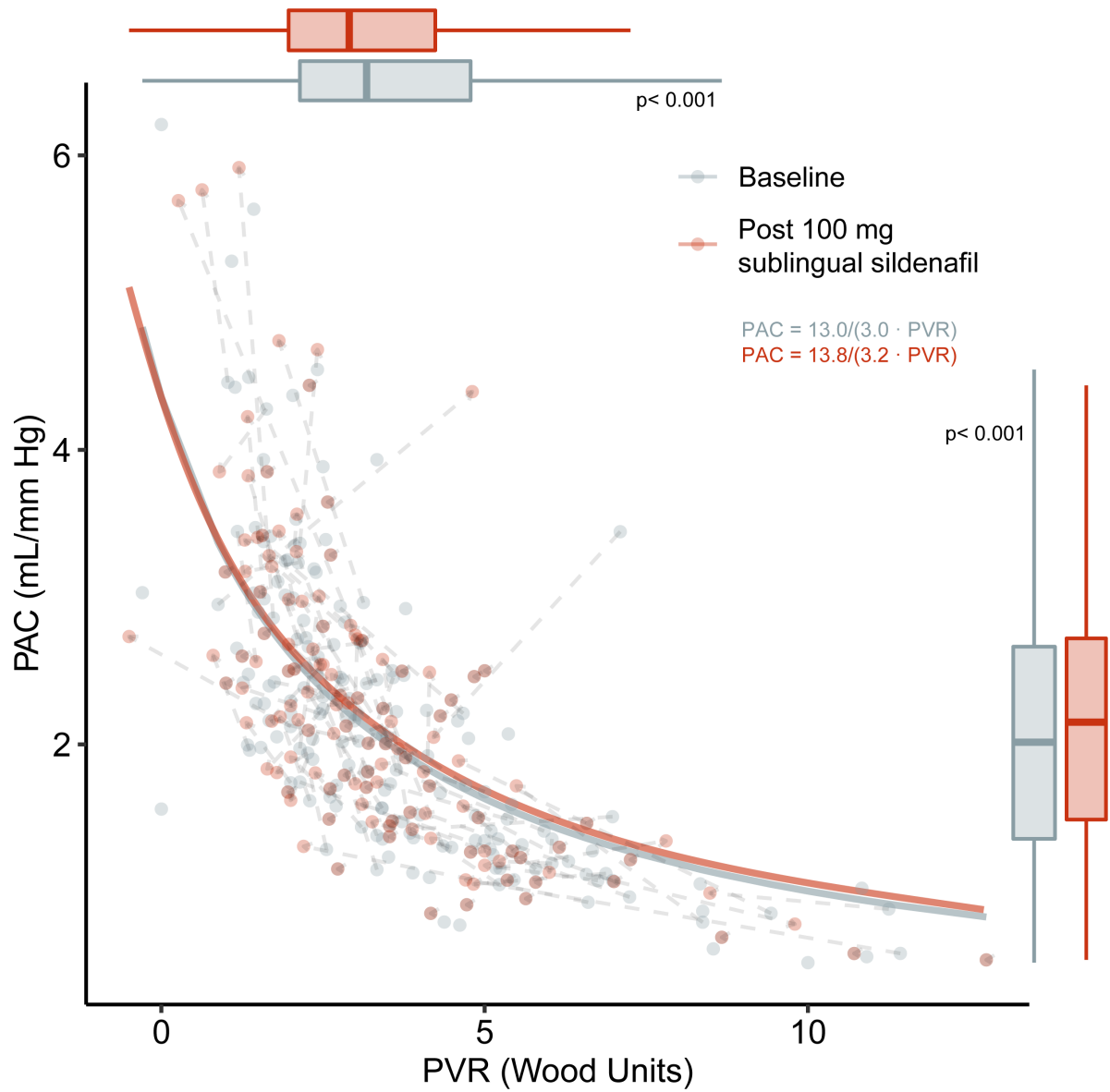
Supplemental Methods

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.