JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
AND EUROPEAN SOCIETY OF CARDIOLOGY.

VOL. 69, NO. 16, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.02.038

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis

An Expert Statement

Carlos E. Ruiz, MD, PhD,[a] Rebecca T. Hahn, MD,[b] Alain Berrebi, MD,[c] Jeffrey S. Borer, MD,[d] Donald E. Cutlip, MD,[e] Greg Fontana, MD,[f] Gino Gerosa, MD,[g] Reda Ibrahim, MD,[h] Vladimir Jelnin, MD,[a] Hasan Jilaihawi, MD,[i] E. Marc Jolicoeur, MD,[h] Chad Kliger, MD,[j] Itzhak Kronzon, MD,[j] Jonathon Leipsic, MD,[k] Francesco Maisano, MD,[l] Xavier Millan, MD,[m] Patrick Nataf, MD,[n] Patrick T. O'Gara, MD,[o] Philippe Pibarot, DVM,[p] Stephen R. Ramee, MD,[q] Charanjit S. Rihal, MD,[r] Josep Rodes-Cabau, MD,[p] Paul Sorajja, MD,[s] Rakesh Suri, MD,[t] Julie A. Swain, MD,[u] Zoltan G. Turi, MD,[v] E. Murat Tuzcu, MD,[t] Neil J. Weissman, MD,[w] Jose L. Zamorano, MD,[x] Patrick W. Serruys, MD, PhD,[y] Martin B. Leon, MD,[b] of the Paravalvular Leak Academic Research Consortium

ABSTRACT

The VARC (Valve Academic Research Consortium) for transcatheter aortic valve replacement set the standard for selecting appropriate clinical endpoints reflecting safety and effectiveness of transcatheter devices, and defining single and composite clinical endpoints for clinical trials. No such standardization exists for circumferentially sutured surgical valve paravalvular leak (PVL) closure. This document seeks to provide core principles, appropriate clinical endpoints, and endpoint definitions to be used in clinical trials of PVL closure devices. The PVL Academic Research Consortium met to review evidence and make recommendations for assessment of disease severity, data collection, and updated endpoint definitions. A 5-class grading scheme to evaluate PVL was developed in concordance with VARC recommendations. Unresolved issues in the field are outlined. The current PVL Academic Research Consortium provides recommendations for assessment of disease severity, data collection, and endpoint definitions. Future research in the field is warranted. (J Am Coll Cardiol 2017;69:2067–87) © 2017 American College of Cardiology Foundation and European Society of Cardiology.

This article is being published concurrently in *European Heart Journal*. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.

From the [a]Hackensack University Medical Center, Structural and Congenital Heart Center, Hackensack, New Jersey; [b]Columbia University Medical Center and Cardiovascular Research Foundation, New York, New York; [c]Hôpital Européen Georges Pompidou, Paris, France; [d]State University of New York Downstate Medical Center and College of Medicine, New York, New York; [e]Baim Institute for Clinical Research, Boston, Massachusetts; [f]Cedars Sinai Medical Center, Los Angeles, California; [g]Padua University Hospital, Padua, Italy; [h]Montreal Heart Institute, Montreal, Quebec, Canada; [i]NYU Langone Medical Center, New York, New York; [j]Lenox Hill Heart and Vascular Institute-North Shore LIJ Health System, New York, New York; [k]St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [l]University Hospital Zurich, Zurich, Switzerland; [m]Hospital Santa Creu i Sant Pau, Barcelona, Spain; [n]AP-HP Hôpital Bichat Service de Cardiologie, Paris, France; [o]Brigham & Women's Hospital, Boston, Massachusetts; [p]Québec Heart & Lung Institute, Quebec City, Quebec, Canada; [q]Ochsner Clinic, New Orleans, Louisiana; [r]Mayo Clinic, Rochester, Minnesota; [s]Minneapolis Heart Institute and Abbott Northwestern Hospital, Minneapolis, Minnesota; [t]Clevelend Clinic, Cleveland, Ohio; [u]Mount Sinai School of Medicine, New York, New York; [v]Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey; [w]MedStar Health Research Institute, Washington, DC; [x]Hospital Clínico San Carlos, Madrid, Spain; and the [y]Imperial College London, London, United Kingdom. Dr. Ruiz has received institutional educational grants from Medtronic, St. Jude Medical, and Philips Healthcare; and is a consultant for St. Jude Medical. Dr. Hahn is a consultant for St. Jude Medical; and is a speaker for GE Medical, Abbott Vascular, and Boston Scientific. Dr. Berrebi is a speaker for Philips Healthcare. Dr. Borer is on the data safety monitoring board for Cardiorentis, Novartis, Celladon, GlaxoSmithKline, and Pfizer; is a

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

AE = adverse event

CMR = cardiac magnetic resonance

CT = computed tomography

LA = left atrial/atrium

LV = left ventricle/ventricular

PVL = paravalvular leak

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

The clinical effect of paravalvular leak (PVL) following circumferentially sutured surgical cardiac valve replacement varies significantly depending on the type of valve prosthesis and the implant location. Because the long-term outcomes of this complication, as well as surgical or transcatheter interventions for PVL, are largely unknown, there is a fundamental need for these studies. The absence of comprehensive retrospective or prospective data arises from the lack of uniform definitions to establish disease severity, clinical endpoints to assess safety and efficacy, and appropriate single and composite endpoints to assess outcomes. In addition, cohort/statistical considerations may be specific to this disease process.

Following publication of the first standardized definitions and endpoints associated with cardiac valvular operations (1,2), the Valve Academic Research Consortium (VARC) has collaborated with the U.S. Food and Drug Administration and device manufacturers to periodically update consensus definitions for clinical endpoints in valve implantation. Accordingly, the Paravalvular Leak Academic Research Consortium (PVLARC) working group harnessed Academic Research Consortium (ARC) methodologies and assembled to discuss current knowledge and evidence concerning clinical studies of PVL therapies. Representatives from the U.S. Food and Drug Administration, device manufacturers, and academic research organizations in the United States and Europe joined a panel of clinical cardiologists, interventional cardiovascular specialists, imaging experts, cardiovascular surgeons, and regulatory and clinical trial experts at the American College of Cardiology Heart House in February 2015 to review and summarize the current state of knowledge on surgical PVL. As a result of this effort, this document provides consensus expert opinion on core principles and endpoint definitions for clinical studies of PVL (**Central Illustration**). This document focuses exclusively on PVL following valve replacement with circumferentially sutured surgical prosthetic valves, defined as an abnormal communication between the sewing ring of a surgical prosthesis and the native annulus. PVL related to transcatheter valve prostheses is comprehensively discussed in the VARC-2, Mitral Valve Academic Research Consortium, and various reviews (3,4). The Online Appendix discusses unanswered questions related to this intervention, which could form the basis for clinical studies.

consultant for Boehringer Ingelheim, Abbott, Sarepa, Amgen, and Gilead; serves on the events adjudication committee for AstraZeneca, Takeda USA, and Biotronik; serves on the advisory board of ARMGO; and owns stock in Biomarin. Dr. Cutlip receives institutional research support from Medtronic and Boston Scientific. Dr. Fontana is national principal investigator (PI) for Abbott; is a consultant for Medtronic; is a consultant and PI for LivaNova; is on the speakers bureau for Peerbridge Health; and has equity in Entourage Medical. Dr. Gersa receives meeting attendance sponsorship from Edwards Lifesciences, Medtronic, Sorin, Neochord, Artech, St. Jude Medical, and Aptiva Medica; receives speakers bureau fees from St. Jude Medical; and receives research grants sponsorship from Gada Group. Dr. Ibrahim is a consultant and proctor for St. Jude Medical, Gore, and Boston Scientific; and has received honoraria from AstraZeneca, Bayer, Boston Scientific, and St. Jude Medical. Dr. Jelnin is a consultant for Cardiac Implants; has received an institutional grant from Philips Healthcare; and has received educational grants from St. Jude Medical and Medtronic. Dr. Jilaihawi is a consultant to Edwards Lifesciences and St. Jude Medical; and his institution receives a research grant from Medtronic. Dr. Kliger has received speaking honoraria from St. Jude Medical and Philips Healthcare. Dr. Kronzon is a consultant for Philips Healthcare, CRF Clinical Trials Center, Cardiovascular Research Foundation, and Cardiac Implants, LLC. Dr. Leipsic has institutional core laboratory contracts for Edwards, Medtronic, Neovasc, Tendyne, and Ancora; and serves as a consultant for Edwards, Valcare, Valtech, Heartflow, and Circle Cardiovascular Imaging. Dr. Maisano is a consultant for St. Jude Medical; and has received grants from St. Jude Medical and Philips. Dr. Pibarot has core laboratory contracts with Edwards Lifesciences, for which he receives no direct compensation. Dr. Sorajja has served as a speaker, consultant, and on the advisory board for Abbott Vascular, Medtronic, and Boston Scientific; and has served as a consultant for Intervalve and Lake Regions Medical. Dr. Suri is co-PI of the COAPT trial; is on the Steering Committee for PORTICO valve St. Jude Medical; is national PI for Perceval-LivaNova; and receives research grants from Edwards, Abbott, St. Jude Medical, and LivaNova. Dr. Turi is on the clinical events committee for Mitralign; and receives educational grants from Medtronic and St. Jude Medical. Dr. Tuzcu is on the clinical events committee for Mitralign; has received 2 grants from Medtronic and St. Jude; and taught in the St. Jude Interventional Fellows Course, but waived the honoraria. Dr. Weissman's organization has received research grant support from Abbott, Boston Scientific, Direct Flow, Edwards, Medtronic, and St. Jude Medical. Dr. Serruys has received personal fees from Abbott Vascular, AstraZeneca, Biotronik, Cardialysis, GLG Research, Medtronic, SinoMedical Sciences Technology, Société Europa Digital Publishing, Stentys France, Svelte Medical Systems, Volcano, St. Jude Medical, and Xeltis. Dr. Leon serves on the PARTNER executive committee for Edwards (unpaid) and on the scientific advisory boards of Medtronic, Abbott, and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. P.K. Shah, MD, served as Guest Editor-in-Chief for this paper. Thomas Luescer, MD, served as Guest Editor for this paper.

Manuscript received November 15, 2016; revised manuscript received January 9, 2017, accepted February 15, 2017.