JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 9, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.12.036

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Evaluation and Treatment of Patients With Lower Extremity Peripheral Artery Disease

Consensus Definitions From Peripheral Academic Research Consortium (PARC)

Manesh R. Patel, MD,* Michael S. Conte, MD,† Donald E. Cutlip, MD,‡§ Nabil Dib, MD,‖ Patrick Geraghty, MD,¶ William Gray, MD,#** William R. Hiatt, MD,†† Mami Ho, MD, PHD,‡‡ Koji Ikeda, PHD,§§ Fumiaki Ikeno, MD,‖‖ Michael R. Jaff, DO,¶¶ W. Schuyler Jones, MD,* Masayuki Kawahara, MD,‡‡ Robert A. Lookstein, MD,## Roxana Mehran, MD,# ## Sanjay Misra, MD,*** Lars Norgren, MD,††† Jeffrey W. Olin, MD,## Thomas J. Povsic, MD, PHD,* Kenneth Rosenfield, MD,‡‡‡ John Rundback, MD,§§§ Fadi Shamoun, MD,‖‖‖ James Tcheng, MD,* Thomas T. Tsai, MD,¶¶¶ Yuka Suzuki, PHD,### Pascal Vranckx, MD,**** Bret N. Wiechmann, MD,†††† Christopher J. White, MD,‡‡‡‡ Hiroyoshi Yokoi, MD,§§§§ Mitchell W. Krucoff, MD*

ABSTRACT

The lack of consistent definitions and nomenclature across clinical trials of novel devices, drugs, or biologics poses a significant barrier to accrual of knowledge in and across peripheral artery disease therapies and technologies. Recognizing this problem, the Peripheral Academic Research Consortium, together with the U.S. Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency, has developed a series of pragmatic consensus definitions for patients being treated for peripheral artery disease affecting the lower extremities. These consensus definitions include the clinical presentation, anatomic depiction, interventional outcomes, surrogate imaging and physiological follow-up, and clinical outcomes of patients with lower-extremity peripheral artery disease. Consistent application of these definitions in clinical trials evaluating novel revascularization technologies should result in more efficient regulatory evaluation and best practice guidelines to inform clinical decisions in patients with lower extremity peripheral artery disease. (J Am Coll Cardiol 2015;65:931–41) © 2015 by the American College of Cardiology Foundation.

From the *Duke Clinical Research Institute, Duke University, Durham, North Carolina; †University of California-San Francisco, San Francisco, California; ‡Harvard Clinical Research Institute, Boston, Massachusetts; §Beth Israel Deaconess Medical Center, Boston, Massachusetts; ‖University of California-San Diego, San Diego, California; ¶Washington University Medical School, St. Louis, Missouri; #Cardiovascular Research Foundation, New York, New York; **Columbia University Medical Center, New York, New York; ††University of Colorado School of Medicine, and CPC Clinical Research, Aurora, Colorado; ‡‡Office of Medical Devices I, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; §§Tohoku University Hospital, Sendai City, Miyagi, Japan; ‖‖Stanford University, Palo Alto, California; ¶¶VasCore, Massachusetts General Hospital, Boston, Massachusetts; ##Mount Sinai Medical Center, New York, New York; ***Mayo Clinic, Rochester, Minnesota; †††University Hospital, Orebro, Sweden; ‡‡‡Massachusetts General Hospital, Boston, Massachusetts; §§§Holy Name Medical Center, Teaneck, New Jersey; ‖‖‖Mayo Clinic Arizona, Phoenix, Arizona; ¶¶¶Kaiser Permanente Colorado Institute for Health Research, University of Colorado, Denver, Colorado; ###Office of Medical Devices II, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; ****Cardialysis, Rotterdam, the Netherlands; ††††Vascular and Interventional Physicians, Gainesville, Florida; ‡‡‡‡Ochsner Medical Center, New Orleans, Louisiana; and the §§§§Kokura Memorial Hospital, Kitakyuku, Japan. Grants were provided from the industry sponsors and representative listed to the International Society for Cardiovascular Translational Research and the Duke Clinical Research Institute to cover the costs of travel, lodging, and the meeting expenses for academic attendees to the meetings in Silver Spring, Maryland. Dr. Patel has received research grants from Johnson & Johnson Pharmaceutical Research and Development, AstraZeneca, the National Heart, Lung, and Blood Institute, Agency for Healthcare Research and Quality, and Maquet; and has served on the advisory board and/or as a consultant to Bayer Healthcare, Janssen, and Genzyme. Dr. Conte has served as a member of the steering committee for AstraZeneca; and has served as a consultant/advisory board member for Cook Medical and Medtronic. Dr. Dib is the Medical Director of CSI. Dr. Cutlip has received research grants or contracts from Medtronic, Boston Scientific, Abbott Vascular, STENTYS, and Celonova. Dr. Geraghty has served as a consultant and trial principal investigator for Bard/Lutonix; has served

ABBREVIATIONS AND ACRONYMS

CLI = critical limb ischemia

LE-PAD = lower extremity peripheral artery disease

MI = myocardial infarction

PAD = peripheral artery disease

Lower extremity peripheral artery disease (LE-PAD) is a manifestation of systemic atherosclerotic disease, which affects over 8 million Americans (1) and conveys a significant health burden globally (1–3). Although LE-PAD can be asymptomatic and subclinical, it is associated with a reduction in functional capacity and quality of life when symptomatic, and, in its most severe form, is a major cause of limb amputation (1–3). Patients with LE-PAD are at an increased risk for myocardial infarction (MI), stroke, and death (1–5). Given this substantial health burden, LE-PAD is the focus of a number of evolving medical, endovascular, and surgical therapies aimed at improving the limb manifestations of the disease. This proliferation of revascularization devices and therapies has highlighted the need for studies that elucidate the direct mechanistic effect, the impact on systemic outcomes (including death, MI, and stroke), and the overall safety of both individual and combined therapeutic strategies.

Systematic safety and effectiveness evaluations of the clinical utility of LE-PAD revascularization therapies and devices (4,6) require high-quality clinical trials data, both for regulatory approval and for the development of best practice guidelines to inform clinical decisions in patients with LE-PAD. Currently, 1 of the biggest barriers to accrual of knowledge in and across peripheral artery disease (PAD) therapies and technologies is the lack of consistent definitions and nomenclature between clinical trials. Although validated, standardized definitions exist for coronary artery disease endpoints for clinical trials, significant variation exists in data elements used to describe both patients undergoing treatment for LE-PAD and the outcomes for evaluation of treatments. Professional societies, academic research organizations, regulatory agencies, and representatives of the pharmaceutical and device industry have recognized both

as an advisory board member for Bard/Lutonix and Boston Scientific; was on the trial steering committee for Covidien; and has served as a speaker and trial principal investigator for Cook Medical. Dr. Gray has received consultant fees from Cordis, Medtronic, Abbott, Boston Scientific, and WL Gore; and research support from Cordis, Medtronic, Abbott, WL Gore, Mercator, The Medicines Company, and Cardiovascular Systems Incorporated. Dr. Hiatt has received grant support from CPC Clinical Research (a nonprofit affiliate of the University of Colorado), AstraZeneca, Bayer Healthcare, the National Institutes of Health, CSI, DNAVEC, GlaxoSmithKline, Kyushu University, Pluristem, ReNeuron, and Rigel. Dr. Jaff was a noncompensated advisor to Abbott Vascular, Boston Scientific, Cordis Corporation, Covidien Vascular, and Medtronic Vascular; has served as a board member for VIVA Physicians, a 501(c) 3 not-for-profit education and research organization; and has equity investment in Embolitech, Hotspur, Icon Interventional, PQ Bypass, and Vascular Therapies. Dr. Jones has received research grants from the American Heart Association, AstraZeneca, Boston Scientific, and Bristol-Myers Squibb; and has served as an advisory board member for AstraZeneca. Dr. Lookstein has served as a consultant to Boston Scientific, Bayer Healthcare, and Cordis Corporation. Dr. Mehran has received institutional research grant support from The Medicines Company, Bristol-Myers Squibb/Sanofi, Lilly/Daiichi Sankyo, Regado Biosciences, and STENTYS; has served as a consultant to Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen (Johnson & Johnson), Maya Medical, and Merck; has served on the advisory board of Covidien, Janssen Pharmaceuticals, Merck, Sanofi, and Endothelix, Inc.; and has equity/is a shareholder in Endothelix, Inc. Dr. Misra was the Chair for the Data Safety and Monitoring Board for the FLEXSTENT study sponsored by CORDIS (modest grant); and received research grants from the National Institute of Health. Dr. Norgren was a steering committee member/consultant for Otsuka Pharma, AnGes, AstraZeneca, and Novartis. Dr. Olin was on the member steering committee clinical trial on placental stem cells for claudication and medical advisory board for PAD related studies for Pluristem; was on the international steering committee for EUCLID trial and was the site investigator for EUCLID trial for AztraZeneca; was on the steering committee TRA2P trial for Vorapaxar and the medical advisory board for Vorapaxor clinical trials for PAD for Merck; and was on the medical advisory and safety board for Tyrosine Kinase Inhibitors and Cardiovascular Risk for Novartis. Dr. Rundback has served on the clinical events committee for Biotronik and St. Jude; has served as a principal investigator for Covidien and Symbionix; has served as a course director for CSI; and has served as a consultant for Covidien, CSI, Sil Vascular, and Intact Vascular. Dr. Povsic was supported by research grants and received advisory fees from Baxter Healthcare; and has served on the data safety monitoring board of Pluristem, Inc. Dr. Tcheng has served on the advisory board of Philips Medical Systems and Cardiovascular Systems, Inc.; and has received research grants from the Food and Drug Administration. Dr. White has served on the research/advisory board of St. Jude and Neovasc; and has served as the steering committee chair for NCDR CathPVI, as the executive committee co-chair for the BEST trial, and as a member of the steering committee for EUCLID (AstraZeneca). Dr. Wiechmann has served on the advisory boards of Boston Scientific and Bard Peripheral Vascular; has received research funding from The Medicines Company; has served as a consultant to Cordis Corporation, Terumo Medical, and Bard Peripheral Vascular; has received clinical trial support from Cordis Corporation, and Bard Peripheral Vascular; and has an equity interest in PQ Bypass. Dr. Krucoff has received modest consulting fees from Medtronic, CSI, Covidien, Abbott Vascular, and Boston Scientific; and has received significant grant funding from Medtronic, CSI, and Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Michael H. Criqui, MD, MPH, has served as Guest Editor for this paper.

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

You can also listen to this issue's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received April 21, 2014; revised manuscript received December 15, 2014, accepted December 15, 2014.