Published in final edited form as:

Am Heart J. 2009 October ; 158(4 Suppl): S1–S5. doi:10.1016/j.ahj.2009.07.013.

Understanding Heart Failure Through the HF-ACTION Baseline Characteristics

Christopher M. O'Connor, MD, David J. Whellan, MD, MHS, FACC

As heart failure afflicts over 5.5 million people in the United States and is the only cardiovascular condition that continues to grow in prevalence,¹ we need a better understanding of the relationships between patient characteristics and the pathophysiology underlying their left ventricular dysfunction. These relationships enable us to recognize the characteristics of the disease in our patients and to identify incongruities that need further evaluation and that may warrant a different therapeutic strategy. As our standard practices grow to incorporate recent advances, past studies describing the relationships among patient characteristics become outdated. With the introduction of new diagnostic tests, the relationship between these new parameters and traditional tests allows clinicians to integrate all the patient descriptors into a coherent understanding of a patient's condition.

An understanding of the relationship between these physiologic parameters and clinical characteristics will help us to identify more potential targets for novel therapies. However, although treatment options for heart failure have increased tremendously over the past 20 years, recent pharmacologic trials have not led to new therapies, and the disease still carries an unacceptable level of morbidity and mortality. An enhanced understanding of the different phenotypes of disease within a patient population can help us to build on the lessons from early clinical studies and to do a better job in targeting therapies. Identification of these relationships also plays an important role in defining appropriate surrogate endpoints for earlier studies.

Prior to the HF-ACTION (Heart Failure and a Controlled Trial Investigation Outcomes of Exercise Training) study, 16 single-center randomized controlled trials had shown that exercise training improves physiologic measurements, such as peak oxygen consumption, autonomic function, plasma norepinephrine levels, endothelin levels, 6-minute walk distance, quality of life, and clinical outcomes. However, none of these studies was large enough to explore the important relationships among physiologic baseline characteristics, biomarker analysis at baseline, echocardiographic and functional status with baseline demographics, and clinical characteristics of heart failure patients with reduced left ventricular function.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Publisher's Disclaimer: Disclaimer: The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health.

The HF-ACTION trial was a multicenter randomized controlled trial that enrolled medically stable outpatients with heart failure and a reduced ejection fraction.² Patients were enrolled from 82 centers within the United States, Canada, and France. Patients received usual care and aerobic exercise training, consisting of 36 supervised sessions, followed by home-based training or usual care alone. Before randomization, all patients underwent a cardiopulmonary exercise test. In addition, patients were required to have an echocardiogram within one month of randomization. The study also supported ancillary biomarker, genomic, and nuclear imaging studies.

In the 2331 patients enrolled and followed for a median of 30 months, the HF-ACTION investigators found that exercise training resulted in a modest nonsignificant reduction in the primary endpoint of all-cause mortality or hospitalization and in key secondary clinical endpoints.³ After adjustment for predictors of the primary endpoint, the investigators found that exercise training was associated with modest and significant reductions for both all-cause mortality or all-cause hospitalization and cardiovascular mortality or heart failure hospitalization. In addition, the study revealed a modest improvement in quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).⁴

The HF-ACTION database remains the largest single database to characterize heart failure patients, as it includes not only baseline demographics and clinical characteristics but also exercise physiologic parameters, functional status, unique biomarker and genetic profiling, and comprehensive quality of life and psychometric analysis. Twenty-eight percent of enrollees were women; and 40% were from minority populations. The exceptionally high use of evidence-based medical therapies, with 95% of study patients taking a beta-blocker and ACE inhibitor or angiotensin receptor blocker, along with high use of implantable cardioverter-defibrillators or biventricular pacemakers, makes this a contemporary cohort that reflects the highest standard of care to date within a clinical trial. Due to the protocol-driven testing, focused attention on enrolling women and minorities, and the commendable use of guideline-recommended treatments, the data from HF-ACTION provide an excellent opportunity to characterize stable symptomatic heart failure patients with reduced left ventricular function.

The supplement you are about to read includes nine manuscripts derived from baseline testing data from the HF-ACTION study. These papers cover a broad range of topics and provide invaluable information describing the HF-ACTION cohort. The articles by Forman et al., Piña et al., Russell et al., and Horwich et al. reveal new data on the relationships among patient characteristics, including age, gender, race, functional class, body mass index, and exercise test results. An analysis from the biomarker ancillary study was designed to evaluate the capacity of NT-proBNP to identify patients with low peak VO₂ test results. HF-ACTION investigators led by Dr. Gardin found that, in patients with reduced left ventricular function, diastolic parameters were independent predictors of peak oxygen consumption (peak VO₂). Further results from the HF-ACTION nuclear ancillary study describe the relationship between resting single photon emission computed tomography imaging, including a novel dyssynchrony measurement, and exercise capacity. Flynn et al. provide further description of the relationship between changes in the KCCQ and the EuroQol Visual Analog Scale (VAS) scores and changes in peak VO₂ and 6-minute walk distances. These

investigators established that a 5-point change in KCCQ or a 3-point change in VAS is clinically significant. Another critical manuscript by Keteyian et al., which will be important for both clinicians and researchers, incorporated not only baseline data but also follow-up exercise testing data to evaluate the safety of having a cohort of symptomatic HF patients perform cardiopulmonary exercise tests.

We hope this information will offer readers a better understanding of chronic heart failure patients and stimulate other investigators to develop new baseline databases with HF-ACTION as a model.

Appendix

Acknowledgments

Funding/Support:

HF-ACTION was funded by grants 5U01HL063747 (Duke University, C. O'Connor, coordinating center), 5U01HL066461 (Duke University, K. Schulman, economics and quality of life), 5U01HL068973 (Boston Medical Center, W. Colucci), 5U01HL066501 (Case Western Reserve University, I. Piña), 5U01HL066482 (Emory University, A. Smith), 5U01HL064250 (Henry Ford Hospital, S. Keteyian), 5U01HL066494 (Ohio State University, W. Abraham), 5U01HL064257 (Oregon Health & Science University, R. Hershberger), 5U01HL066497 (University of Alabama at Birmingham, V. Bittner), 5U01HL068980 (University of California, Los Angeles, G. Fonarow), 5U01HL064265 (University of Colorado Health Sciences Center, E. Wolfel), 5U01HL066491 (Wake Forest University, D. Kitzman), and 5U01HL064264 (Washington University in St. Louis, G. Ewald) from the National Heart, Lung, and Blood Institute.

Role of the Sponsor:

The National Heart, Lung, and Blood Institute had a role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; and in the preparation, review, and approval of the manuscript.

HF-ACTION Investigators:

Executive Committee:

Christopher M. O'Connor, MD; Kerry L. Lee, PhD; Stephen J. Ellis, PhD; David S. Rendall, BA, PA-C; Duke University, Durham, North Carolina; David J. Whellan, MD, Thomas Jefferson University, Philadelphia, Pennsylvania; Ileana L. Piña, MD, Case Western Reserve University, Cleveland, Ohio; Steven J. Keteyian, PhD, Henry Ford Hospital, Detroit, Michigan; Lawton S. Cooper, MD, MPH; Robin Boineau, MD; Lawrence J. Fine, MD, DrPH; Jerome L. Fleg, MD; Eric S. Leifer, PhD; National Heart, Lung, and Blood Institute, Bethesda, Maryland; Virginia Erickson, RN, PhD, University of California, Los Angeles; Jonathan G. Howlett, MD, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; Nancy Houston Miller, RN, BSN, Stanford University, Stanford, California; Debra Isaac, MD, Foothills Hospital, Calgary, Alberta; Robert McKelvie, MD, Hamilton Health Sciences, Ontario; Faiez Zannad, MD, PhD, Université Henri Poincaré, Nancy, France.

Coordinating Center (Duke Clinical Research Institute):

Sharon Boozer, BA; Patty Connolly; Anthony Doll, BA; Stephen J. Ellis, PhD; Camille Frazier, MD, MHS; Deb Mark; Michelle McClanahan-Crowder, AA; Marcia Meyer, RN, BSN; Brenda S. Mickley, BS; David S. Rendall, BA, PA-C; Molly Rich; Hoss Rostami, BSMSE; Sharon Settles, MS; Kathy Spinella, BBA; Jessica Staib, PhD; Omar Thompson, BA; Duke University, Durham, North Carolina.

Steering Committee (U01 Grant Sites):

William Abraham, MD; Danuta Biniakiewicz, PhD; Joann Homan, RN; Ohio State University, Columbus; Vera Bittner, MD, MSPH; Meredith Fitz-Gerald, RN, BSN; University of Alabama at Birmingham; Gregory Ewald, MD; Heidi Craddock, RN; Jean Flanagan, RN, MSN; Washington University in St. Louis, Missouri; Gregg Fonarow, MD; Virginia Erickson, RN, PhD; University of California, Los Angeles; Wilson Colucci, MD; Nancy Z. Lim, RN; Elena Tokareva, PhD; Boston Medical Center, Massachusetts; Rami Alharethi, MD; Ray Hershberger, MD; Deirdre Nauman; Oregon Health & Science University, Portland; Steven J. Keteyian, PhD; Matthew Saval, MS; Henry Ford Hospital, Detroit, Michigan; Dalane W. Kitzman, MD; Brittney L. Fray, MS; Brian Moore, MS; Wake Forest University, Winston-Salem, North Carolina; Ileana L. Piña, MD; Marianne Vest, MA, BSN; Case Western Reserve University, Cleveland, Ohio; Andrew Smith, MD; Gail Snell, RN, BSN, CCRC; Emory University, Atlanta, Georgia; Eugene Wolfel, MD; Mona Cantu, RN, NP; University of Colorado Hospital, Aurora.

Steering Committee (Non-U01 Grant Sites):

Kirkwood Adams, MD; Jana Glotzer, RN, MSN, ACNP; Valerie Johnson, RN; Kate Schumacher; UNC Hospitals, Chapel Hill, North Carolina; Gordon Blackburn, PhD; Carrie Geither, RN; Susan Moore, RN, BSN; Cleveland Clinic Foundation, Cleveland, Ohio; A. Bleakley Chandler, Jr, MD; Shanda Browning Vaughn, RN; Paula J. Easler, RN, CCRC; Debbie Williams; University Hospital, Augusta, Georgia; Marc Colmer, MD; Jersey Shore University Medical Center, Neptune, NJ; Julius M. Gardin, MD; Kelly Dimick, RN; Sharon K. Sklar, LPN; Sherri Teller, RN, CCRP; St. John Hospital and Medical Center, Detroit, Michigan; Jalal K. Ghali, MD; Karen Hale-Stenson, RN; LSU Health Sciences Center, Shreveport, Louisiana; Mihai Gheorghiade, MD; Theresa Strzelczyk, APN, CNS; Northwestern University Medical Center, Chicago, Illinois; Maryl R. Johnson, MD; Cassondra Vander Ark, RN, MS, CCRC; University of Wisconsin-Madison; Lee R. Goldberg, MD, MPH; Andrew Kao, MD; Jennifer Dekerlegand, MPT, PhD; Hospital of the University of Pennsylvania, Philadelphia; William E. Kraus, MD; Johanna Johnson, MS; Brian D. Duscha, MS; Duke University Medical Center, Durham, North Carolina; Mandeep R. Mehra, MD; Hector Ventura, MD; Bobbett Harris, RN; Ochsner Clinic Foundation, New Orleans, Louisiana; Monica Colvin-Adams, MD; Kathy Duderstadt, BSN; Karen Meyer, RN, BSN; Melissa Steger, RN, CCRC; University of Minnesota Medical Center, Fairview; Barry Cabuay, MD; Ron M. Oren, MD; Page Scovel, RN, BSN, CCRC; University of Iowa Hospitals and Clinic, Iowa City; Andrew Kao, MD; Tracey Stevens, MD; Karen Haffey, RN, BSN, CCRC; Christy Mandacina; Ann Stewart, RN, BSN; Mid America Heart Institute, Kansas City, Missouri; Ann M. Swank, PhD, CSCS; John Manire, MS; University of

Louisville, Kentucky; Paul D. Thompson, MD; Ludmila Cosio-Lima, PhD; Marie Lagasse, MS; Hartford Hospital, Connecticut; Tehmina Naz, MD; Lynne Wagoner, MD; Susan K. Roll, RN, BSN; University of Cincinnati, Ohio; Frank G. Yanowitz, MD; Johnny Walker; Adam Mueller; LDS Hospital, Salt Lake City, Utah; Peter McCullough, MD; Cathy Coleman, RN, BSN, CCRC; Kimberly A. Dorrell; Tamika Washington; William Beaumont Hospital, Royal Oak, Michigan; Eileen Handberg, PhD; James A. Hill, MD; Jacqueline Bakos, RN; Alice Boyette; Pamela Smith; Cynthia Williams, RN, BSN, MS; University of Florida, Gainesville; Dalynn Badenhop, PhD; Susan Schroeder; Kelly Walter; Medical University of Ohio, Toledo; Peter Kokkinos, PhD; Elisse Collins; Lauren Korsak, MS; Washington DC VA Medical Center; Eric Eichhorn, MD; Allison Leonard, RN, BSN; Tina Worley, RN, BSN; Medical City Dallas Hospital, Texas; Gerald Fletcher, MD; Phil Peasley, RN; Pam Oldano, RN; Mayo Clinic Jacksonville, Florida; John Kostis, MD; Nora M. Cosgrove, RN, BS; University of Medicine and Dentistry of New Jersey, New Brunswick; Udho Thadani, MD; Lisa Rogan, RN, BSN; Michelle Thresher, RN, BSN; John Turner, RN; University of Oklahoma Health Sciences Center, Oklahoma City; Denise Barnard, MD; Denise Herman, MD; Annette Contasti, RN; Marcy Sagerian, RN; University of California, San Diego Medical Center; Elizabeth Ofili, MD; Anekwe Onwuanyi, MD; Sunday Nkemdiche, MD; Morehouse School of Medicine, Atlanta, Georgia; Howard Eisen, MD; James Fitzpatrick, MD; Joyce Wald, DO; Jennie Wong, RN, CCRP; Temple University Hospital, Philadelphia, Pennsylvania; Myrvin Ellestad, MD; Leslie Kern, RN, PhD; Long Beach Memorial Medical Center, California; Ezra A. Amsterdam, MD; Mary J. Burns, RN; UC Davis Medical Center, Sacramento, California; Savitri Fedson, MD; Ravi K. Garg, MD; Peggy Bennett, RN; Linda Bond, RN, MSN; University of Chicago Hospitals, Illinois; Leway Chen, MD, MPH; Janice Schrack, RN, BSN; Strong Memorial Hospital, Rochester, New York; Douglas Pearce, MD; Linda Bond, MSN, RN; Greg Palevo; Margaret Serfass, RN; Saint Thomas Hospital, Nashville, Tennessee; Daniel Forman, MD; Maria M. Lopez; Yemi Talabi-Oates; April Williams; Brigham and Women's Hospital and Boston VA Medical Center, Boston, Massachusetts; David Truite, MD; Cindy Baumann, RN, CCRN; Lynchburg General Hospital, Virginia; Jenny Adams, PhD; Anne Lawrence, RN; Baylor Hamilton Heart and Vascular Hospital, Dallas, Texas; Dennis McNamara, MD; Emily Gruendler, RN, BSN; Virginia Schneider; University of Pittsburgh Medical Center, Pennsylvania; Steven Hutchins, MD; Alyce Hartwick, RN; Heart Clinic Arkansas, Little Rock; Paul Campbell, MD; Michele Esposito; Northeast Medical Center, Concord, North Carolina; Carol Buchter, MD; Rebecca A. Letterer, RN, BSN; University of Washington Medical Center, Seattle; Robert Taylor, MD; Cheri Wells, RN, MSN; University of New Mexico Health Sciences Center, Albuquerque; Bruce Johnson, PhD; Beth Kaping, RN; Susan Leathes, RN; Mayo Clinic, Rochester, Minnesota; Joseph O'Bryan, MD; Lynn Langley, RN; Southwest Florida Heart Group, Fort Myers; Edward T. Hastings, MD; Cassandra Clancy, RN, CCRC; St. Luke's Medical Center, Milwaukee, Wisconsin; Neil Agruss, MD; Christine Lawless, MD; Robin Fortman, MS, APN/CNP, CCRC; Central DuPage Hospital, Winfield, Illinois; Timothy R. McConnell, PhD; Deb Wantz, MSN, RN, CCNS, CCRC; Geisinger Medical Center, Danville, Pennsylvania; Mary N. Walsh, MD; Regina Margiotti, CMS, CCRC; The Care Group, Indianapolis, Indiana; Stuart Russell, MD; Elizabeth Heck, RN, BSN; Johns Hopkins Hospital, Baltimore, Maryland; Justine Lachmann, MD; Diane Lippman, RN; Jeannette McLaughlin, RN; St. Francis Hospital,

Roslyn, New York; Joel Landzberg, MD; Susan Mathus, RN, BSN; Hackensack University Medical Center, New Jersey; David W. Cullinane, MD; Wyatt Voyles, MD; Dione Lenz, RN; Scott Kaczowski, BS, CCRC; Medical Center of the Rockies Foundation, Loveland, Colorado; Jack L. David, MD; Eve Gillespie, MD, PhD; Pat Keane-Richmond, RN, CCRC; Glacier View Cardiology, Kalispell, Montana; Steven K. Krueger, MD; Lori Heiss, RN, BS; BryanLGH Heart Institute, Lincoln, Nebraska; Stephen Gottlieb, MD; Nancy Greenberg, RN, BSN, MS; University of Maryland School of Medicine, Baltimore; Neil Gordon, MD; Emily Parks, BS; Melanie Willoughby, RN, BSN, CCRN; St. Joseph's/Candler Hospital, Savannah, Georgia; Marvin W. Kronenberg, MD; Jennie Glenn, RN; Carol Madison, RN; Vanderbilt University Medical Center, Nashville, Tennessee; Malcolm Arnold, MD; Julie K. Smith, RN; London Health Sciences Centre, Ontario; Eduardo Azevedo, MD; Glen Drobot, MD; Estrellita Estrella-Holder, RN, BN, MSA, CCN(C); St. Boniface General Hospital, Winnipeg, Manitoba; Jonathan Howlett, MD; Darlene Cooley-Warnell; Sheila Yarn, RN; Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; Debra Isaac, MD; Jane Grant, RN; Kim Lyzun; Foothills Hospital, Calgary, Alberta; Marie-Helene LeBlanc, MD; Rachel Vienneau, RN, BSc; Hôpital Laval, Sainte-Foy, Quebec; Robert S. McKelvie, MD; Linda Beare; Jill Hancock, LRN; Hamilton Health Sciences, Ontario; Gordon Moe, MD; Delores Golob, RN, BA; St. Michael's Hospital, Toronto, Ontario; Kenneth Melvin, MD; Anne Cymet, RN; Judith Renton, RN; Toronto General Hospital, Ontario; Anil Nigam, MD; Julie LaLonge; Montreal Heart Institute, Quebec; Karim Djaballah, MD; Hôpital Brabois, Vandoeuvre-lès-Nancy, France; Patrick Aebehard, MD; Centre Cardiologique du Nord, Saint-Denis, France; Marie Christine Iliou, MD; Hôpital Broussais, Paris, France; Remi Sabatier, MD; Annette Belin, MD; Centre Hospitalier Universitaire de Caen, France; Alain Cohen-Solal, MD; Hôpital Beaujon, Clichy, France; Luc Hittinger, MD, Hôpital Henri Mondor, Créteil, France.

Data and Safety Monitoring Board:

Bertram Pitt, MD (chair), University of Michigan, Ann Arbor; Philip A. Ades, MD, University of Vermont, South Burlington; Lotfy L. Basta, MD, San Francisco, California; Victor Froelicher MD, Stanford University and Palo Alto VA Medical Center, California; Mary Elizabeth Hamel, MD, Beth Israel Deaconess Medical Center, Boston, Massachusetts; Barry M. Massie, MD, San Francisco VA Hospital, California; Lemuel Moyé, MD, PhD, University of Texas Health Science Center at Houston; Lynda H. Powell, PhD, Rush University, Chicago, Illinois.

Cardiopulmonary Exercise Core Lab:

William E. Kraus, MD (director); Johanna Johnson, MS; Lucy Piner, MS; Duke University, Durham, North Carolina; Daniel Bensimhon, MD (codirector), LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina; Stuart Russell, MD, Johns Hopkins University, Baltimore, Maryland.

Echo Core Lab:

Julius M. Gardin, MD (director); Renee L. Bess, BS, RDCS, RVT; Gerald I. Cohen, MD; St. John Hospital and Medical Center, Detroit, Michigan.

Heart Rate Training Core Lab:

Steven J. Keteyian, PhD (director); Jonathan K. Ehrman, PhD (associate director); Clinton A. Bawner, MS (coordinator); Henry Ford Hospital, Detroit, Michigan.

Adherence Core Lab:

Nancy Houston Miller, RN, BSN (codirector), Stanford University, Stanford, California; James A. Blumenthal, PhD (codirector); Krista Barbour, PhD; Duke University, Durham, North Carolina; Tanya M. Spruill, PhD, Columbia University, New York City, New York; Bess Marcus, PhD, Brown Medical School and Miriam Hospital, Providence, Rhode Island; Jim Raczynski, MD, University of Arkansas for Medical Sciences, Little Rock.

Biomarker and DNA Core Lab:

Kirkwood Adams, MD, University of North Carolina at Chapel Hill; Mark Donahue, MD; Mike Felker, MD; Duke University, Durham, North Carolina.

Economics and Quality of Life Group:

Kevin A. Schulman, MD; Kevin P. Weinfurt, PhD; Kathryn E. Flynn, PhD; Shelby Reed, PhD; Ann Burnette, BS; Linda Davidson-Ray, MA; Joëlle Y. Friedman, MPA; Yanhong Li, MS; Li Lin, MS; Betsy O'Neal, BA; Duke University, Durham, North Carolina.

Clinical End Point Committee:

Michael Zile, MD (chair), Ralph H. Johnson; VA Medical Center and Medical University of South Carolina, Charleston; Daniel R. Bensimhon, MD, LeBauer Cardiovascular Research Foundation, Greensboro, North Carolina; Vera Bittner, MD, MSPH, University of Alabama at Birmingham; Robin Boineau, MD, National Heart, Lung, and Blood Institute, Bethesda, Maryland; Mark E. Dunlap, MD, Case Western Reserve University, Cleveland, Ohio; William E. Kraus, MD; Christopher M. O'Connor; Duke University, Durham, North Carolina; Gordon Moe, MSC, MD, FRCP(C), St. Michael's Hospital, Toronto, Ontario; John Wertheimer, MD, Thomas Jefferson University and Drexel University Medical Residents at Abington Memorial Hospital, Philadelphia, Pennsylvania; David J. Whellan, MD, Jefferson Medical College, Philadelphia, Pennsylvania.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics 2009 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;119:e1–e161. [PubMed: 19124668]
2. Whellan DJ, O'Connor CM, Lee KL, et al. Heart Failure and a Controlled Trial Investigating Outcomes of exercise training (HF-ACTION): design and rationale. *Am Heart J* 2007;153:201–11. [PubMed: 17239677]
3. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301:1439–1450. [PubMed: 19351941]
4. Flynn KE, Piña IL, Whellan DJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; 301:1451–9. [PubMed: 19351942]