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

VOL. 65, NO. 15, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.03.016

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Cardiovascular Drug Development

Is it Dead or Just Hibernating?

Christopher B. Fordyce, MD, MSc,* Matthew T. Roe, MD, MHS,* Tariq Ahmad, MD, MPH,* Peter Libby, MD,† Jeffrey S. Borer, MD,‡ William R. Hiatt, MD,§ Michael R. Bristow, MD, PhD,§ Milton Packer, MD,‖ Scott M. Wasserman, MD,¶ Ned Braunstein, MD,# Bertram Pitt, MD,** David L. DeMets, PhD,†† Katharine Cooper-Arnold, MPH,‡‡ Paul W. Armstrong, MD,§§ Scott D. Berkowitz, MD,‖‖ Rob Scott, MD,‖ Jayne Prats, PhD,¶¶ Zorina S. Galis, PhD,‡‡ Norman Stockbridge, MD, PhD,## Eric D. Peterson, MD, MPH,* Robert M. Califf, MD*

ABSTRACT

Despite the global burden of cardiovascular disease, investment in cardiovascular drug development has stagnated over the past 2 decades, with relative underinvestment compared with other therapeutic areas. The reasons for this trend are multifactorial, but of primary concern is the high cost of conducting cardiovascular outcome trials in the current regulatory environment that demands a direct assessment of risks and benefits, using clinically-evident cardiovascular endpoints. To work toward consensus on improving the environment for cardiovascular drug development, stakeholders from academia, industry, regulatory bodies, and government agencies convened for a think tank meeting in July 2014 in Washington, DC. This paper summarizes the proceedings of the meeting and aims to delineate the current adverse trends in cardiovascular drug development, understand the key issues that underlie these trends within the context of a recognized need for a rigorous regulatory review process, and provide potential solutions to the problems identified. (J Am Coll Cardiol 2015;65:1567–82) © 2015 by the American College of Cardiology Foundation.

From the *Duke Clinical Research Institute, Durham, North Carolina; †Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ‡State University of New York Downstate Medical Center, Brooklyn, New York; §University of Colorado School of Medicine, Aurora, Colorado; ‖Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas; ¶Amgen, Inc., Thousand Oaks, California; #Regeneron Pharmaceuticals, Tarrytown, New York; **University of Michigan School of Medicine, Ann Arbor, Michigan; ††University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; ‡‡National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; §§Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada; ‖‖Bayer HealthCare Pharmaceuticals, Whippany, New Jersey; ¶¶The Medicines Company, Parsippany, New Jersey; and the ##Division of Cardiovascular and Renal Products, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland. The Cardiovascular Drug Development Think Tank was supported by Amgen, Inc., Bayer HealthCare Pharmaceuticals, Bayer Pharma AG, Bristol-Myers Squibb, Janssen Pharmaceuticals, Regeneron, and The Medicines Company. Dr. Fordyce has received support from the Clinician Investigator Program of the University of British Columbia. Dr. Roe has received research grants from Eli Lilly & Co., Sanofi-Aventis, Daiichi-Sankyo, Amgen, and Familial Hypercholesterolemia Foundation; has received lecture fees from AstraZeneca and Bristol-Myers Squibb; and has received consulting fees from AstraZeneca, Eli Lilly & Co., Merck & Co., Janssen Pharmaceuticals, Elsevier Publishers, and Amgen. Dr. Ahmad has served as a consultant to Roche; has received an educational grant from Thoratec Corporation; and has received a grant from the Daland Foundation. Dr. Libby is an unpaid consultant or involved in clinical trials for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Esperion Therapeutics, Genzyme, GlaxoSmithKline, Kowa Pharmaceuticals, Merck, Novartis, Pfizer, Sanofi-Regeneron, Takeda Pharmaceuticals; is a member of the scientific advisory board for Athera Biotechnologies and Interleukin Genetics; and his laboratory receives research funding from General Electric, GlaxoSmithKline, and Novartis. Dr. Borer has been a paid consultant, clinical trial executive committee member, data and safety monitoring committee chair or member, and clinical events adjudication committee member during the past year for Amgen, Boehringer-Ingelheim, JenaValve, Takeda USA, Celgene, Cleveland Biolabs, Somahlution, Cardiorentis, Celladon, Biotronik, BioMarin, Salix, Novartis, ARMGO, Pfizer, and Laboratoires Servier; and has stock in BioMarin. Dr. Hiatt has received research grants from AstraZeneca and Bayer; and his research organization affiliate of the University of Colorado receives funds from companies including AET Biotech, AstraZeneca, Bayer, Cardioxyl, National Institutes of Health, CSI, GlaxoSmithKline, Janssen, Kyushu University, Merck, Pluristem, Reneuron, and Takeda. Dr. Bristow is an employee, shareholder, and board member of ARCA biopharma. Dr. Packer is a consultant for Actelion, Amgen, CardioKinetix,

ABBREVIATIONS AND ACRONYMS

AD = adaptive design

NME = new molecular entity

PFS = progression-free survival

ROI = return on investment

Despite significant improvements in cardiovascular mortality over the last several decades, cardiovascular disease remains the leading cause of death both in the United States and the rest of the world (1–3). Heart disease and stroke will result in an estimated 24 million deaths/year worldwide by 2030, and will continue to represent the dominant cause of death among the most prevalent chronic diseases (4–6) (**Figure 1**). Furthermore, mortality and morbidity due to cardiovascular events continue to climb globally as a result of rising cardiovascular disease rates in low-income countries, resulting in increasing disparities in outcomes as a function of wealth and education (7). The burden of cardiovascular disease clearly remains both a major public health concern and growing global challenge.

Notwithstanding this increase in cardiovascular disease prevalence worldwide, investment in cardiovascular drug development has stagnated over the past 2 decades, with relative underinvestment compared with other therapeutic areas (8–13). This alarming trend appears to reflect the business strategy in the pharmaceutical industry of maximizing return on investment (ROI) by focusing on areas currently felt to be most lucrative (8,9). As discussed in the following text, the reasons for these trends are multifactorial. However, a particularly important factor is the high cost of conducting cardiovascular outcome trials in the current regulatory environment that demands a direct assessment of risks and benefits using clinically-evident cardiovascular endpoints for approval rather than biomarkers or putative surrogates. These realities suggest that although the cardiovascular disease burden continues to grow and innovative scientific discoveries continue to occur, investors have concerns regarding what they describe as regulatory uncertainty and high development costs, leading to negative effects on ROI for novel cardiovascular therapies.

To work toward consensus on improving the environment for cardiovascular drug development, stakeholders from academia, industry, and government convened in July 2014 in Washington, DC. This paper summarizes the proceedings of this "think tank" meeting, the specific aims of which were to:

1. Delineate the current adverse trends in cardiovascular drug development;
2. Understand the key issues that underlie these trends within the context of a rigorous regulatory review process that is a key aspect of drug development; and
3. Provide potential solutions to the problems identified.

CURRENT TRENDS IN CARDIOVASCULAR DRUG DEVELOPMENT

Between 2000 and 2009, U.S. Food and Drug Administration (FDA) approvals for new cardiovascular drug therapies declined by approximately 33% compared with the prior decade (11). During the discussions, FDA representatives reported parallel adverse trends in investigational new drug applications to the

Cardiorentis, Janssen, Novartis, Pfizer, and St. Jude Medical. Dr. Wasserman is an employee of Amgen, Inc. Dr. Braunstein is an employee of Regeneron Pharmaceuticals and a retired employee of Merck; and owns stock in both Regeneron Pharmaceuticals and Merck. Dr. Pitt is a consultant for Pfizer, Bayer, AstraZeneca, scPharmaceuticals, Relypsa, Aurasense, Da Vinci Therapeutics, Stealth Peptides, and Tricida; has stock options in Relypsa, scPharmaceuticals, Aurasense, Tricida; has a patent pending for site-specific delivery of eplerenone to the myocardium; has served on data monitoring boards of Novartis, Johnson & Johnson, Oxygen Biotherapeutics, and Cytopherx; and has served on the events committee of Juventis. Dr. DeMets is a consultant to the National Institutes of Health, the Food and Drug Administration, and the pharmaceutical and medical device industry on the design, monitoring, and analysis of clinical trials; and receives compensation for serving on several industry-sponsored data and safety monitoring committees, including AstraZeneca, Amgen, Actelion, GlaxoSmithKline, Merck, Sanofi, Boehringer Ingelheim, Teva, and AbbVie. Dr. Armstrong received research grants from Boehringer Ingelheim, Merck Sharp & Dohme in conjunction with Duke Clinical Research Institute (DCRI), GlaxoSmithKiline, Amylin Pharmaceutical, Inc. in conjunction with DCRI, Merck & Co., Inc., Sanofi-aventis Research and Development, and Regado Bioscience; and received consulting fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck & Co., Inc., F. Hoffmann-La Roche Ltd., Axio/Orexigen, Merck, Eli Lilly, and Bayer. Dr. Berkowitz is an employee of Bayer HealthCare. Dr. Scott is an employee of and shareholder of Amgen, Inc. Dr. Prats is an employee of The Medicines Company. Dr. Stockbridge is an employee of the Food and Drug Administration. Dr. Peterson has received research grants from the American College of Cardiology, American Heart Association, Eli Lilly & Co., Janssen Pharmaceutical Products, and the Society of Thoracic Surgeons; and has received consulting fees from AstraZeneca, Bayer AG, Boehringer Ingelheim, Genentech, Janssen Pharmaceutical Products, Merck & Co., and Sanofi-Aventis. Dr. Califf has received research grants from Amylin, Bristol-Myers Squibb, Eli Lilly & Co., Janssen Research and Development LLC, Merck, and Novartis; and received consulting fees from Amgen, Bayer Healthcare, BMEB Services LLC, Medscape LLC/heart.org, Merck, Novartis, Regado NJ, and Roche; and has equity in N30 Pharma and Portola. The views expressed are those of the authors and do not necessarily reflect official National Heart, Lung, and Blood Institute positions. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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 January 28, 2015; accepted March 3, 2015.