

Heart Failure Society of America

An Official Publication of the Heart Failure Society of America • Volume 3, Number 1 • February 2001

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HFSA's Fourth Annual Scientific Meeting Draws Record Attendance

An exciting array – from late-breaking clinical trial results, basic science lectures, clinical practice sessions, practical how-to workshops, informative poster presentations, the Hyde Park Hypotheses, and debates – greeted the record-breaking number of attendees who gathered at the HFSA's Fourth Annual Scientific Meeting in Boca Raton, Florida, September 10-13, 2000.



Opening Session

At the opening session, Scientific Program Co-Chair Michael Bristow observed, "Two thousand participants from 25 countries have come together to attend this program that is a careful blend of basic science and clinical practice issues and developments." Co-Chair Leslie Leinwand agreed, noting, "The program achieves a fusion of all types of investigation in heart failure issues." Outgoing President Arthur Feldman provided a state-of-the-Society

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Milton Packer Named HFSA President



Milton Packer,
President, HFSA

The HFSA's new President, Milton Packer, brings a wealth of research and clinical experience to his new leadership position. He is Dickinson W. Richards Jr. Professor of Medicine, Professor of Pharmacology, Chief of the Division of Circulatory Physiology at Columbia University College of Physicians and Surgeons, and Director of the Heart Failure Center at the Columbia-Presbyterian Medical Center in New York City. He is a leading investigator in pathophysiology and the treatment of heart failure and has served as the Society's Vice President for two years.

Dr. Packer serves on the editorial boards of eight major medical journals and has been elected to numerous societies, including the American Society for Clinical Investigation and the Association of University Cardiologists. He is a primary consultant on heart failure, cardiovascular research, and drug development to the National Institutes of Health and the Food and Drug Administration, and he is chair of the FDA's Cardiac and Renal Drugs Advisory Committee.

Dr. Packer, a graduate of Jefferson Medical College, completed his residency at Albert Einstein College of Medicine and his fellowship in cardiology at Mt. Sinai School of Medicine. He became a Professor of Medicine and Director of Cardiovascular Training at Mt. Sinai, and later went to the Columbia-Presbyterian Medical Center. He is the author of more than 250 papers and has lectured extensively in the United States and abroad. □

Heart Failure Society News

Editors

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Marvin A. Konstam, MD
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Message from the President

Now is an exciting time for the Heart Failure Society of America. We have grown enormously during the past four years, and we have achieved a great deal. We can certainly be proud of what we have done. The future is bright. More than ever, we need to steer the right course.

What are the challenges facing us? We know that we want to be more than just a successful annual meeting, but how much more? We want to do more than just increase heart failure awareness, but how much can we do? Do we want to lobby Congress for increased research support or raise funds ourselves? Do we want to become involved in determining the quality as well as financing of care for patients with heart failure? Do we want to set standards of care for patients or standards for training of health care professionals?

Before we can answer these questions, we must first decide who we are and what we stand for. Are we simply a professional club that is interested in heart failure? Are we an advocacy group for both patients and health care professionals?

Are we an educational and scientific organization with academic goals? Are we all of these things at different times?

Up to now, we have not had to deal with these difficult questions. We had the luxury of running as fast as we wanted to without having to think too much. But now the world has noticed us and is paying attention to what we are doing and saying. Now we find that what we say matters. So we cannot simply run; we need to decide what we are running toward. In the past the goal was to grow; now the goal is to grow up.

The transition from unbridled growth to reasoned maturation is always difficult, but there is no better time to tackle this transition than the present. This is my mission for the next two years. I cannot tell you with certainty where we will be and what we will look like at the end of 2002, but I can tell you that I will need everyone's help to get there. □

Milton Packer, MD
President, HFSA

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Meeting draws record attendance

report on the successes that the Society has achieved in a few short years:

- An impressive growth in membership, from 642 in 1997 to 1514 in 2000. Approximately 55% of the members are MDs, 27% are RNs, 10% are PhDs, and 8% are allied health professionals.
- Publication of its first clinical practice guidelines for the management of left ventricular systolic dysfunction in 1999, under the chairmanship of Kirkwood Adams, and the continuing development of additional guidelines.
- The first annual national Heart Failure Awareness Week in February 2000, with symposia, grand rounds, television and radio interviews, health fairs, medical and community education programs, and other activities to promote understanding of heart failure among primary care physicians, nurses, and the general public. The



Founding President Jay N. Cohn (left) presents an award to outgoing President Arthur Feldman.

U.S. Senate, in passing Resolution 256 unanimously, declared the week of February 9-14, 2000, as Heart Failure Awareness Week. President Clinton issued a Presidential Proclamation in support of Heart Failure Awareness Week as well.

- The move of the HFSA corporate headquarters to new facilities to enable the expansion of services.

- Publication of the quarterly newsletter, *Heart Failure Society News*.
- Formation of a partnership with the Health Care Financing Administration (HCFA) to develop ways to reduce the cost of care for patients with heart failure.
- Creation of a committee to provide a forum for activities and issues of special interest to nurses, a task force to focus on the development of a Pediatric Heart Failure Committee, and a new Education Committee to develop and coordinate the Society's educational activities.

Jay N. Cohn, founder and first President of the Society, praised Dr. Feldman for his contributions to the Society. Dr. Cohn commented, "It is never easy to be the second President, but Art Feldman exhibited the excellent leadership skills and good judgment that carried this organization remarkably forward. We are most appreciative." □

Planning Under Way for Second National Heart Failure Awareness Week

Building on the success of last year's first national campaign, the Heart Failure Awareness Ad Hoc Committee is preparing for the launch of Heart Failure Awareness Week 2001. Last year, the United States Senate passed Resolution 256, which declared the week of Valentine's Day to be National Heart Failure Awareness Week. This year, the Senate again passed the resolution, this time as a rolling resolution. This significant milestone assures the ongoing continuation of National Heart Failure Awareness Week for years to come.

To mark the official start of National Heart Failure Awareness Week, a press conference will be held on Monday, February 12, in New York City. In support of the national campaign, HFSA members and colleagues in over 70 localities will host activities designed to educate health professionals as well as

members of the general public about the symptoms, risk factors, and treatment options for heart failure. The many events being planned include



HFSA Executive Director Cheryl Yano, Heart Failure Awareness Week spokeswoman Linda Evans, and Past President Arthur Feldman discuss plans for the annual national education campaign.

grand rounds, symposia, continuing medical education programs, health fairs, media interviews, and luncheons. To help with some of the local events, the Health Care Financing Administration's peer review organizations (PROs) have teamed up

enthusiastically to lend support. In addition to publicizing the events in their statewide newsletters for beneficiaries and physicians, the PROs will be instrumental with the outreach and educational components of the events.

"There has never been more need for heart failure awareness. National Heart Failure Awareness Week highlights that heart failure is a public health concern of epidemic proportions," stated Arthur Feldman, MD, Heart Failure Awareness Committee Chairman. "With this initiative, we have the ability to enhance the public's recognition of heart failure and make certain that more can be done to

put an end to this disease."

Awareness Campaign Messages

Key messages of the campaign are:

- Heart failure is not a heart attack.
- Heart failure is not a death sentence.
- Heart failure is a disease of epidemic proportions.
- People should talk with their doctors if they think they are at risk.

As the scope of Heart Failure Awareness continues to grow, so does the number of lives reached. To better educate the public, HFSA will continue to provide educational materials free of charge. Materials include brochures and an educational video that covers signs and symptoms of the disease and highlights personal experiences of those living with heart failure. Individuals can receive the brochures and video by visiting the website (www.abouthf.org) or calling a toll-free number (1-877-510-HFSA). Clinics can order multiple copies via the website as well. □

Heart Failure Awareness Roundtable Supports Awareness Campaign

The HFSA's National Heart Failure Awareness campaign is successful because of the support from a wide array of HFSA members, health professionals, industry sponsors, and patients across the country. This year's Heart Failure Awareness Roundtable is made up of the following corporate sponsors: AstraZeneca Pharmaceuticals; Guidant Corporation; Medtronic, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Sanofi-Synthelabo, Inc.; Roche Pharmaceuticals; and SmithKline Beecham Pharmaceuticals.

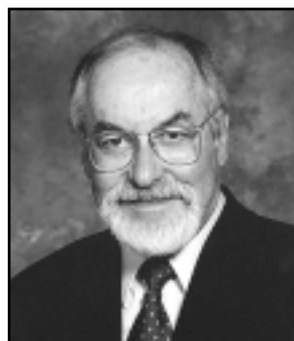
Jay N. Cohn Announces Retirement as Editor of *Journal of Cardiac Failure*

Jay N. Cohn, Minneapolis, Minnesota, the founding editor of the *Journal of Cardiac Failure (JCF)*, has announced he will retire as editor-in-chief at the end of 2001. He has served in that capacity since the first issue was published in October 1994.

Dr. Cohn explained that he founded the journal because of the need to provide a vehicle for the publication of research in the growing field of heart failure. The similar need for a focused vehicle led Dr. Cohn to form the HFSA a few years later. The Society adopted *JCF* as its official journal; it is also the official journal of the Japanese Heart Failure Society. Some members of the HFSA and the Japanese Society serve as editorial board members. The Publications Committee of HFSA oversees journal content and policies.

Dr. Cohn said, "As the research publication arm of HFSA, the journal serves as a repository of critical science re-

lated to heart failure. The membership of HFSA consists of basic scientists, clinicians, and health care workers, and the *JCF*'s goal has been to cover basic and clinical science in a balanced way that reflects the membership of the Society. We have tried to be as broad based as we can. It has achieved that goal very well, and the quality of the science is excellent."



Jay N. Cohn

Asked about the future of the journal, Dr. Cohn said, "We hope it will continue to grow. I would like to see more frequent publication, from four times a year to six times and ultimately to monthly publication. The journal is dependent on the submission of manuscripts, and I hope the level of submissions will continue to increase."

Marc Pfeffer, chairman of the HFSA Publications Committee, is overseeing the search for the new editor. □

Journal of Cardiac Failure

Committed to scientific excellence

The Heart Failure Society of America has initiated a search for the next

Editor-in-Chief

Term of office: beginning January 2002

Application deadline: June 1, 2001

Application procedure: Interested individuals should contact:

Marc Pfeffer, MD, PhD

Chair, Publications Committee

Professor of Medicine

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David Engel Receives Young Investigator Award

David Engel was the recipient of the Jay N. Cohn Young Investigator Award for his research into the role that apoptosis may play in development of left ventricular (LV) remodeling in heart failure. His work focused on the transgenic mouse model of heart failure that overexpresses the tumor necrosis factor (TNF) specifically in the heart.

"We looked at the molecular mechanisms of cardiac myocyte apoptosis in these mice and the relationship of apoptosis to the development of LV remodeling in heart failure," he reported. Since caspases are key mediators of apoptosis, he explained, he used broad-based caspase inhibitors "to determine how well we could modify the LV remodeling process and reverse some of the heart failure phenotype." His rationale was that cardiac myocyte apoptosis has been identified in humans with end-stage heart failure, yet the significance of apoptosis to the development of LV remodeling in heart failure is not known. "These studies may help us to understand the role that apoptosis may play in development of LV remodeling in human heart failure," he concluded.

Dr. Engel received his BA in biology from Yale University

Heart Failure Society News is an official quarterly publication of the Heart Failure Society of America, Court International, Suite 238N, 2550 University Avenue West, St. Paul, MN 55114; (651) 642-1633; www.hfsa.org. It is published by BioScience Communications, 1875 Eye Street, N.W., Washington, D.C. 20006.

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Young investigator

and graduated from Cornell University Medical College, New York. He completed his internal medicine residency at Baylor College of Medicine, Houston, Texas, where he pursued the medical residence investigator track of the internal medicine residency program. Dr. Engel said, "I had been interested in heart failure for a long time and wanted to be involved in research, and Baylor offered a very good track where I could pursue clinical activities and be involved in high level research at an early phase of my career." He spent two years in the laboratory of Douglas Mann, where he conducted the research for which he received the Young Investigator award. Now in the clinical year of his cardiology fellowship at

Columbia University College of Physicians and Surgeons, New York, he plans to continue his research into the mechanisms of LV remodeling



(left to right) Michael Bristow, Malcolm McNabb, Leslie Leinwand, David Engel, and Jay N. Cohn celebrate Dr. Engel's award.

and the mediators involved in the development and progression of heart failure in humans.

Dr. Engel was one of five finalists

selected from numerous entries to present abstracts in a special session at the annual scientific meeting. The presentations were judged by a panel of the bases on scientific merit, presentation, use of appropriate graphics, and effectiveness of discussion. The winner was announced at the opening of Wednesday's plenary session chaired by Michael Bristow. The award was presented by Malcolm McNabb, Vice President, Cardiovascular Medicine, Novartis Pharmaceuticals, which provided funding for this high-profile competition. Dr. Bristow explained that the award is an important part of the

HFSA's commitment to provide forums for young researchers and is named in honor of the Society's key founder and first President, Jay N. Cohn. □

Hyde Park Hypotheses Offer Interactive Opportunity

Attendees once again enjoyed the rollicking good time that characterizes the annual Hyde Park Hypotheses, as speakers and participants joined in the fun of the free exchange of opinions that ranged from plausible to preposterous. Back by popular demand were moderators Arnold Katz, Norwich, Connecticut, and Carl Leier, Columbus, Ohio, who presided over the enthusiastic session that included six presentations followed by a highly interactive discussion:

- **Heart Failure Does Not Exist in the Majority of Patients with Heart Failure: Time for a New Name** – Michael Fowler, Stanford, California
- **The Fatter, the Better: The Golden Rule for Longevity in Chronic Heart Failure** – Stefan Anker, London, UK
- **Quality of Life Should Not be Measured in Heart Failure Trials** – Paul Hauptman, St. Louis, Missouri
- **Crossover Between Functional and Proliferative Signaling: The Real Problem in Heart Failure** – Arnold Katz, Norwich, Vermont



Carl Leier (left) and Arnold Katz co-moderated the popular Hyde Park Hypotheses Session.

- **Surgical Left-Ventricular Reconstruction and Medical Therapy Optimizes Clinical Outcomes After Anterior Myocardial Infarction** – Randall Starling, Cleveland, Ohio
- **Guidelines for the Eligible and Ideal Heart Failure Patient: A Solution for the Spherical Cow** – Paul Sobotka, Detroit, Michigan

Debates Invite Audience Participation in Controversies

The four debate sessions of the annual scientific meeting, held at two sessions, provided excellent opportunities for stimulating exchanges of ideas on controversial areas. Audience participation via voting at the conclusion of each debate provided an immediate gauge of the effectiveness of the presentations. The first session was co-moderated by Michael Fowler, Stanford, California, and Kanu Chatterjee, San Francisco, California; the second session's co-moderators were Lynne Warner Stevenson, Boston, Massachusetts, and Inderjit Anand, Minneapolis, Minnesota. Topics included the use of inotropes in patients with advanced heart failure, the expanded use of LVADs, the use of beta blockers in patients with advanced heart failure, and the role of apoptosis.

Inotropes are Beneficial in Chronic Heart Failure



Evan Loh

Recognizing the absence of a definitive guideline or good data on the use of inotropes in class IV patients, Evan Loh argued that the use of inotropic agents is an effective bridge therapy for severely decompensated patients. He distinguished between progressively decompensated patients versus patients with ultra-decompensated symptoms, including end-organ damage, the need for balloon pumps, and perhaps ventricular assist. It is the latter group that can benefit from inotropic therapy to prolong life until transplantation can be performed.

In addition to inadequate data are difficulties interpreting data, demographic uncertainties, and heterogeneity of clinical presentation on admission. Given the heterogeneity of symptoms at presentation, he stated that the development of selection criteria is essential. Placing clinical trial data in perspective is a key

element of selection criteria. He pointed out that the decade of the clinical trial is important, because our understanding has evolved. Additionally, we have concomitant therapy with ACE inhibitors as well as beta blockers, other endpoints such as quality of life, and better monitoring devices. He urged caution in interpreting clinical trial data, asking "Does intention to treat represent real world care?" "You can't take clinical trial data in and of itself and apply it to every patient. Every patient is different," he said. He cited more recent 1998 and 1999 data from small trials that suggest that intermittent intravenous dobutamine therapy, carefully monitored, may be beneficial in severely decompensated individuals.

"Quality of life is important," he said, "and our patients want to feel better." He raised the issue of optimum dosing and recommended lower doses. He said, "We have gone from the use of inotropes to beta blockers. The pendulum is swinging back, and I wonder if our ability to use beta blockade in patients with heart failure may allow us to move ahead in the future and use inotropic therapy as a component of managing patients with advanced decompensated heart failure."

Stephen Gottlieb disagreed. "The use of inotropes in class IV patients," he said, "has been shown to be consistently deleterious, contributing to the progression of heart failure, arrhythmias, and sudden death." He charged that the positive trials cited by Dr. Loh were "small, uncontrolled, unblinded, and did not reflect acute effects and short term." He argued that inotropes should only be used under investigational protocols and even then their use is questionable.

"There is no doubt that the use of positive inotropes increases mortality," he said, noting that the patients who did the worst were class IV patients. He disputed the relevance of beta-blocker tolerability, reviewing the results of the COPERNICUS trial showing a 35% rate of increased survival in patients receiv-

ing these agents. He recommended the use of beta blockers to address the quality-of-life issues and was strong in his opposition to the combined use of inotropes and beta blockers.

The audience sided with Dr. Gottlieb. Before the start of the debate, 20% of the audience approved of the affirmative position. At the conclusion of the debate, 30% approved of the affirmative position.

The Time Has Come for Long-Term LVAD Treatment of Heart Failure (Beyond Bridge to Transplant)

Leslie Miller reminded the audience that there are 4.8 million patients with heart failure, over 1 million of whom are class III or class IV, and that there are more than 250,000 deaths annually. Clinical trials have shown that class IV patients have a 35% mortality rate; population studies suggest higher rates of 40% to 50%. Given these statistics, he asserted, the increased use of left-ventricular assist devices (LVAD) is warranted.

The complications that can accompany the devices include bleeding, infection, stroke, and emboli. The benefits, however, are impressive: increased exercise capacity; improved quality of life; improved LVED; improved histology, including less apoptosis and hypertrophy; decreased neurohormonal levels, including TNF and cytokines; cellular functional recovery increases; and increased gene expression. He concluded, "The data are overwhelming, as are the benefits of effectiveness, safety, durability, portability, total implantability, and simplicity of design." "The future is bright," he said, with three new devices in clinical trials and five more expected in 2001.

Gary Francis opposed more widespread use of LVADs, pointing to the paucity of data and the absence of a protocol for weaning patients from the devices, as well as increased risk of myocardial fi-

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Practice Guidelines Committee Explores Comprehensive Guideline Development

Following upon the 1999 publication of the Clinical Practice Guidelines for the Management of Patients with Heart Failure Due to Left Ventricular Systolic Dysfunction, the HFSA's Practice Guidelines Committee members have been actively identifying new areas for guideline development, including a comprehensive guideline. Committee members discussed the results of their work in four treatment areas at a session moderated by committee chair Kirkwood Adams, Chapel Hill, North Carolina, on Wednesday, September 13.

Marvin Konstam, Boston, Massachusetts, explored treatment approaches to heart failure in patients with preserved left ventricular ejection fraction.

Mikai Gheorghide, Chicago, Illinois, addressed the management of patients hospitalized with acute decompensated heart failure.

Denise Hermann, San Diego, California, spoke on an algorithm for diagnostic evaluations of heart failure and LV dysfunction in adults.

Kirkwood Adams discussed algorithms for combining drugs for optimal treatment outcomes, including beta blockers, ACE inhibitors, digoxin, diuretics, and aldosterone antagonists.

Following the annual scientific session, the committee members expanded their focus to explore the development of a comprehensive guideline for heart failure manage-

ment and to identify the major issues it would encompass. According to Dr. Adams, a comprehensive guideline would include the four areas discussed at the annual scientific session, as well as surgical options, the role of electrophysiology, approaches to patients with CAD and heart failure disease management, and other topics.



(left to right) Kirkwood Adams, Denise Herman, Marvin Konstam, and Mihai Gheorghide discuss results of committee work on guideline development.

The tentative date for publication of a comprehensive guideline is 2002. One of the difficulties the committee members face in developing guidelines is the paucity of clinical trial data, particularly on several new agents, including

endothelin-1 antagonists and recombinant natriuretic peptide, but these data are likely to be available as a comprehensive guideline is developed. However, Dr. Adams noted, "In some areas, we will still be dealing with expert opinion as the basis for the guideline recommendations." "It is important for HFSA to present a comprehensive guideline," he stated, "even if partly on the basis of expert opinion. The rapid evolution of our understanding of the complex nature of heart failure requires that the Society provide a synthesis to assist practicing physicians as they develop treatment strategies. Guideline development constitutes the fulfillment of a key element of the HFSA's mission statement," he concluded.

Dr. Adams anticipates a period of public comment once the draft of new guideline is available. "We will solicit input via a variety of sources now under discussion, including the Society's website, and we are exploring ways to make the site as user-friendly as possible," he said. □

Heart Failure Society
of America

5th Annual
Scientific Meeting

September 9-12,
2001
Washington, DC

Abstract Deadlines

Heart Failure Society of America
Fifth Annual Scientific Meeting
September 9-12, 2001, Washington, DC

Deadline for receipt of paper abstracts: Monday, April 9, 2001.
Deadline for receipt of electronic abstracts: Monday, April 16, 2001.

For information on submission, please visit the HFSA website or call the HFSA office at (651) 642-1633.

The same abstract may be submitted to and presented at the 2001 meetings of the HFSA and the American Heart Association.

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Debates invite audience participation



Gary Francis

bro sis and sys-temic infection and the possible need for additional medication to improve function. "The future is promising," he said, "but we are not there yet."

Members of the audience changed their opinions significantly, with few expressing initial agreement with the affirmative position but 50% agreeing at the conclusion of the debate.

Should We Be Treating Advanced Heart Failure with Beta Blockers?

Henry Krum discussed three criteria by which to gauge the value of beta-blocker therapy in patients with advanced heart failure: mechanistic rationale, clinical trial evidence base, and clinical need. When looking at mechanistic rationale, he argued that it makes sense to use beta blockers because of the high level of activity in the adrenergic system of these patients. "If we believe that these processes are important in the progression of heart failure, of mortality, and symptoms, then blocking the sympathetic nervous system becomes even more important in patients with severe heart failure. Clinical trial data, he said, strongly suggest the beneficial effects of beta blockers. "However," he said, "since only 10% of the patients enrolled in most trials are class IV patients, we are reliant on small studies or meta-analyses to make determinations in this population." These data show that the sickest patients, in terms of NYHA class and ejection fraction, benefit. Benefits extend beyond mortality to symptom improvement, enhancing quality of life.

Dr. Krum's report card for beta blockers in severe heart failure assigns the fol-

lowing grades: mechanistic rationale: A; clinical trial evidence: mortality: A, symptom relief: A, tolerability: A; clinical need: A.

Michael Domanski agreed that "We know that class III patients benefit from beta blockers." However, he maintained, the benefits for class IV patients are not as clear. He cited data showing reduced effect on ejection fraction and increased mortality with beta-blocker therapy in class IV patients, suggesting that patients with a sufficiently diminished contractile reserve may have a worsened prognosis with anti-adrenergic therapy. Data from the BEST trial, for example, indicate that improvement in patients with heart failure on beta blockade may be related to the degree of viability before treatment, with sufficiently compromised patients having a worse outcome on beta-blocker therapy. Dr. Domanski pointed out that in the MERIT-HF trial, regardless of the endpoint, class IV patients were the only class to consistently show no improvement. In his opinion, there is no randomized trial that speaks directly to the effect of beta-blockade therapy on class IV patients, underscoring the need for further research to define the role of beta blockers in this patient population.

Is Apoptosis Important?

The role of apoptosis, according to Dr. Narula, is the most important question for physicians who care for patients with heart failure. "What causes the progressive loss of cardiomyocytes in the segments of the heart that are not affected during the initial injury?" he asked. He argued that it is becoming increasingly evident that various compensatory mechanisms in the heart may lead to apoptotic cell loss, which results in turn in a gradual loss of ventricular function.

Going beyond DNA fragmentation to an upstream cascade evaluation of apoptosis, he reported that the final step in apoptosis

is the activation of caspase 3 and other substances, which leads to various proteolytic enzymes that cleave cytoplasmic and cytochromic proteins. He concluded, "Apoptosis is a reality in a failing heart. It should not be a numbers game, since we can't afford to miss anything."



Jutta Schaper

Jutta Schaper responded that, during the last two decades, the role of diverse structural abnormalities in the failing heart has been explored. These

abnormalities include decreases in contractile proteins, increases in cytoskeletal proteins and membrane-associated proteins, and a greatly increased degree of fibrosis. For Dr. Schaper, "All of these determine the progressive loss of cardiac function."

She agrees that apoptosis is a basic biological phenomenon with wide-ranging implications in tissue kinetics. However, she disputes the extent of its significance. "DNA fragmentation does occur, but we found it only in 2% of hearts we investigated," she said. "We have evaluated 20 failing hearts and more than 1 million myocytes, and we only came up with 45 cells positive for apoptosis."

Her research indicated that approximately 14 hours elapse until DNA fragmentation occurs, and she calculated that 2% of cardiomyocytes would be lost to apoptosis at 1 year. "These numbers are too small to be the cause of heart failure," she argued. In the human failing myocardium, she stated, it is the degeneration of myocytes and the occurrence of fibrosis that are the structural correlates of declines in left ventricular function. "Apoptosis is observed at a very low rate, and its importance is questionable," she said. □

New Session Explores Respiratory Dysfunction Role in Heart Failure

An exciting new session at the annual scientific meeting, moderated by Gary Francis, Cleveland, Ohio, focused on the role of respiratory dysfunctions and their relationship to the progression of heart failure.

Apnea

Shahrokh Javaheri, Cincinnati, Ohio, discussed the prevalence of apnea in patients with heart failure, the types of apnea, and its relationship to the fatigue these patients commonly experience. "Of the 5 million Americans who have heart failure, 2.5 million have apnea," he reported.

The types of apnea include apnea cessation, in which there are ≥ 10 seconds of disrupted breathing during sleep; hypopnea, in which there is a decrease in ventilation during sleep without breathing being completely stopped and terminated only by arousal; and obstructive apnea, in which there is no airflow. In one study of heart failure patients with systolic dysfunction, he said, some patients had 44 episodes per hour at night.

Dr. Javaheri explored whether fatigue in patients with heart failure is attributable to the heart failure or to apnea and sleep habits. Heart failure patients with apnea, he reported, have twice as many arousals during the course of a night as heart failure patients who do not have apnea. Analyses of nocturnal ventricular arrhythmias in patients with apnea have shown an increase in the number of arrhythmias, a decrease in LVEF, and an increase in mortality.

Jack Floras, Toronto, Ontario, Canada, discussed the role of apnea in the progression of heart failure. "We know that sympathetic activation, hypertension, and intrathoracic load are all important when looking at apnea in heart failure," he said, noting that sleep-related disorders are associated with higher rates of mortality and transplantation, as well as increases in the sympathetic nervous drive, blood pressure, cardiac load, stroke volume, and catecholamines. Heart failure patients with apnea have been found to have changes in their breathing patterns while awake as well, he said.

The types of apnea vary in patients with heart failure. One survey of 450 patients found that one third had obstructive apnea, one third had central apnea, and one third had no apnea. The prevalence was higher in women. Treatment can improve outcomes, he suggested. "Since heart failure and apnea are intimately linked, we have seen marked improvement in survival through a pharmacologic approach. For example, it has been shown that treating patients with Continuous Positive Airway Pressure (CPAP) can stabilize breathing patterns, decrease norepinephrine, and increase ejection fraction." He concluded by noting that the relationship between apnea and pulmonary hypertension is under investigation.

Primary Pulmonary Hypertension



Peter Liu

Peter Liu, Toronto, Ontario, Canada, explained that primary pulmonary hypertension (PPH) occurs in 2 million people and results in an increase in pulmonary vascular resistance and a decrease in right ventricular function. "Lately we have seen a higher rate in mortality in patients with PPH,

probably due to an increase in prevalence. This disease affects more blacks than whites, with black females having the highest mortality," he said.

The additional problems with obesity in this population are compounded by the fact that patients who use drugs for obesity are at a risk for high mortality. He urged particular attention to preserving right ventricle function and determining when a heart/lung transplant may be important. "Future pharmacologic therapies will target the pathophysiology of this disease," he concluded.

Stephen Archer, Edmonton, Alberta, Canada, told attendees that "As we begin to look at treatment strategies for PPH, we must first understand the new World Health Organization nomenclature, the latest comprehension on plexiform lesions, and new etiological theories. According to the guidelines, a patient with PPH will have a history of dyspnea, chest pain, and syncope defined by an increase in PVR."

He reported that 6% to 12% of PPH cases are familial and that the female to male ratio is 3/1. The 5-year survival rate is only 40%. "This disease becomes more malignant over time," he added, so that future generations who contract the disease do so at increasingly earlier ages. He suggested the possibility of a genetic etiology and commented that research on families to map the disease locus led to a 27-cM region on chromosome 2Q31032 in familial PPH. Plexiform lesions composed of proliferating endothelial cells occur in between 20% and 80% in this irreversible pulmonary vascular disease.

The etiologic theories include endothelial dysfunction, increased serotonin, and defects in Kv channels. Based on these etiologies, early treatment strategies included calcium channel blockers and still are widely used. Pharmacologic management now focuses on prostacyclin in various formulations. Future strategies he anticipated include ET therapy, gene therapy, chronic inhaled nitric oxide, MMP inhibitors, PDV inhibitors, and metabolic modulators. □

New Approaches for the Treatment of Heart Failure in the Future: A Story of Mice and Men



Arthur Feldman

Effectively transitioning advances in science into improved patient care is the challenge facing the professionals who treat patients with heart failure in the coming years, outgoing President Arthur Feldman told attendees at his President's Lecture.

“Our understanding of this disease and the development of better pharmacological

treatments are the result of two centuries of investigation, from the extract of foxglove in 1792, to diuretic agents in the 1950s, to dobutamine, milrinone, beta blockers, and ACE inhibitors in more recent decades. He identified three categories of discovery: the serendipitous, which includes digoxin; those focused on the activation of constitutive endogenous targets, such as dobutamine and milrinone; and those involving agents developed for other purposes but applicable to heart failure therapy, such as beta blockers and ACE inhibitors.

Dr. Feldman reviewed the last two decades, which he described as particularly fruitful in terms of scientific advances in the understanding of heart disease. In 1980, the primary focus was still at the macro level of the physiology of heart failure; in 1982, the focus shifted to the micro level of cell biology and protein chemistry; in 1987 it was refined even further to molecular biology, aided by progress in transgenic technology by such researchers as L. Field in 1988, J. Robbins in 1990, M. Charron in 1992, R.J. Lefkowitz in 1994, and S. Vatner in 1996.

Two developments clarified the need for a pharmacological model for gene therapy: identification of the role of mutations of cardiac genes beginning in developmental abnormalities or myopathy and the enhanced understanding of the effects of abnormalities in protein and/or gene expression in the failing human heart. Dr. Feldman cited the contributions of Michael Bristow, C.F. McTiernan, and Guillermo Torre-Amione in these areas. Increased understanding of the mechanisms of mutations in cardiac genes, he explained, began with animals with the heart failure phenotype, led to the option of gene replacement or competition via gene transfer or development of an anti-protein-monoclonal AB. Better descriptions of the structures and mechanisms of adrenergic receptors opened up new areas for research. S.B. Liggett's work identified the effectiveness of controlled overexpression of B_2 -AR in improving cardiac contractility and function, as well

as the adverse consequences of excessive overexpression. J. F. Englehardt's work demonstrated the harmful effects of B_1 overexpression.

Transgenic research, Dr. Feldman said, has shown the strengths and weaknesses of beta-blocker therapy in humans. “Transgenic technology,” he said, “has taken from the defect in the failing human heart the possibility of getting more exact information.” He identified the limitation of transgenic models, which include the validity of extrapolation to humans, the critical factors of dose titration and timing on outcomes, the role of secondary effects, the recognition that overproduction of foreign proteins may produce an illicit phenotype, and potential differences between constitution expression and transient expression. However, he said, the benefits these models provide are numerous.

Dr. Feldman listed several important recent advances. Douglas Mann's study of the effects of increased overexpression of proinflammatory cytokines in dilated cardiomyopathy identified increased mortality at 6 months, increased interstitial infiltrates, decreased SERCA expression, activation of downstream cytokine expression, and diminished adrenergic sensitivity. Differences in gender in TNF mice showed higher survival rates in females, leading to the use of exclusively male or female mice. Other research analyzed the role of the activation of metalloproteinases (MMP) in the myocardium of TNF-6 transgenic mice, linking higher MMP levels with dilated cardiomyopathy, providing an exciting new target for therapy. Other progress was achieved in the development of TNF $_{\alpha}$ soluble receptor therapy, the ability to reverse myocarditis by the use of AdTNFRI, and in the role of the TNF receptor fusion protein enbrel in advanced heart failure now being studied in the RENAISSANCE trial.

Technological innovations made these advances in knowledge possible. Among those Dr. Feldman cited were mouse conductance catheters, implantable ECG telemetry, mouse treadmills, magnetic resonance imaging, and echo-cardiography.

The current work with transgenic models has already produced exciting knowledge about the mechanisms underlying the development of protein abnormalities in mice and the role of those abnormalities on the progression of heart failure. Dr. Feldman concluded, “We are identifying the physiological significance of altered gene expression using animal models to replicate human disease. Although these models have limitations, the future lies in effectively transitioning these results to the development of improved treatments for heart disease in humans.” □

Partnership in Care Aims to Measure and Improve Quality

As part of the Society's initiative to enhance the quality and duration of life for patients with heart failure, the HFSA devoted a session at the annual scientific meeting to fostering partnerships among the groups involved in providing care: the heart failure community; primary care providers; and representatives of the provider systems, health care plans, and the government.

Moderators Marvin Konstam, Boston, Massachusetts, and Ileana Pina, Cleveland, Ohio, introduced the program by reporting that the HFSA's Care Standards Committee is developing guidelines for patient care. The committee has formed a collaborative relationship with the Health Care Financing Administration (HCFA) and hosted the first roundtable discussion with managed care groups.

Academic Community

Edward Havranek, Denver, Colorado, defined the role of and the challenges faced by the academic community: "The academic community needs to lead quality improvement efforts through quantitative demonstration, intellectual support, and proof of which interventions are most effective." "However," he noted, "barriers to academics in this area exist, and there is no traditional niche in cardiology divisions to cover these issues. Limited funding for these projects is always a problem, no academic credit is given to such activities, and there are cultural differences with collaborators."

Primary Care Providers

David Baker, Cleveland, Ohio, explained that the problems that primary care providers face include an inadequate understanding of the disease, a reluctance to initiate medications, a tendency to provide suboptimal dosing of ACE inhibitors, and the lack of support they receive for patient education and follow-up.

"Continuing medical education does not change practice through passive learning," he explained, "and alternatives need to be explored. We should shift to sequential case-based learning that can deal with such issues as proper diagnosis and use of diuretics through a variety of different venues such as internet programs or hands-on learning in HF clinics," he said. Guidelines should be written for the primary care physician level and a program developed to disseminate information targeted to this community that includes review articles, a website with fax-on-demand options, peer-peer education, and programs on heart failure at national meetings of primary care providers. Primary care providers should be involved in quality improvement projects, and a peer is the best opinion leader for a primary care physician. Primary care physicians would benefit from support systems, and nurses who specialize in heart failure can work with doctors as well as provide patient education.

Provider System

Douglas Gregory, New York, New York, examined the roles of revenue and disease management. According to Dr. Gregory, disease management can result in decreased admissions and reduced overall cost of care. However, he elucidated the misalignment between payers and providers, which will impair implementation of disease management. It will be difficult to achieve real progress until incentives are more properly aligned.

Health Care Plans

Randall Krakauer, New York, New York, representing Cigna in the states of New York, New Jersey, and Connecticut, provided information on Medicare patients with heart failure. He said, "65% of Medicare patients are diagnosed at the first admission, and 80% do not see a doctor between the first and second admissions....

50% of these patients are not on ACE inhibitors." He reported that 80% suffer from some form of chronic illness; 15% consume 85% of their health services; and 78% do not comply with diet and medication regimens. "Heart failure management programs can improve compliance, outcomes, and costs," he indicated.

A collaborative relationship between the physician and the case manager can produce important benefits, including increased patient compliance. Since case managers are responsible for approximately 30 patients, it is important that they know their patients well and work with them in overcoming barriers. An effective working relationship between case managers and physicians can produce important results, including better quality care for the patient, shared rewards and responsibilities, cost savings, and a focus on the management of individual cases and needs.

Government

Diana Ordin, Boston, Massachusetts, reported on the initiatives implemented by HCFA to improve quality of care. One such initiative is the National Quality Improvements Projects (NQIP) (1999-2001). Modeled on the Collaborative Cardiovascular Project, NQIP has targeted six conditions: heart failure, acute myocardial infarction, stroke, diabetes, breast cancer, and pneumonia.

"They will be looking at mortality and morbidity, opportunities to improve care, and the peer review organization (PRO) experience with quality assessment and improvement," she explained. "To improve care, we need to recruit hospitals, to facilitate hospital improvement, and to create state level partnership for improvement among providers and professionals," she said.

The PRO facilitation activities include

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Needs of Special Patient Populations Explored

The HFSA explored the needs of special populations of patients with heart failure – those with diabetes, children, older patients, and African Americans – at a session chaired by Katherine Hoercher, Cleveland, Ohio.

Patients with Diabetes

Laura Quinn, Chicago, Illinois, described the growing number of patients with diabetes, from 124 million worldwide in 1997 to a projected 220 million in 2010. In addition to the increasing prevalence, she noted, “The face of diabetes has changed.” Type 1 diabetes has increased in adults; type 2 diabetes has increased in minority group members, children, and adolescents; atypical forms are being identified. The effect will be an increase in the rate of heart failure accompanied by a change in demographics as heart failure occurs more often and at younger ages.

She identified the special considerations that should be given to patients with heart failure and diabetes: the cost of respective treatments, diabetes-related complications, comorbidities, polypharmacy issues, and the balance between good metabolic control versus optimal control.

Pediatric Patients

The treatment of children with heart failure, according to Mark Boucek, Denver, Colorado, presents additional challenges to those imposed by the disease. Physicians need to develop strategies that address the physical, emotional, and mental needs of these patients even more than they do when treating adults. He identified the importance of avoiding growth failure and developmental arrest, but he added that a skilled awareness of the psychosocial development is important to understand the patients’ need to avoid isolation, dependence, conformity to a peer group, and compliance with treatment regimens. “These difficulties can be overcome,” he said, “through family support, peer influence, and a good health care system, since you can’t always count on the first two.”

An additional challenge is presented by the absence of an effective classification system: The NYHA system is not particularly helpful for children, he said. “The Ross system is better, but others need to be developed, and they are in process.” Quality of life is an important consideration. The combination therapy of beta blockers and ACE inhibitors, while helpful in reducing symptoms, may not result in an acceptable quality of life.

Dr. Boucek noted that pediatric patients seldom experience sudden death and do not respond well to mechanical support. Males have a poorer prognosis than do females, as do patients whose LVEF is less than 30% and whose LVEDP is greater than 25 mmHg. He concluded by stating that trans-

plantation is often more effective if performed earlier in this group of patients because of the limitation of other options.

Older Patients

Maureen Friedman, Rochester, New York, described her experience in the Framingham study that evaluated the roles of age and gender. Men and women, she reported, had similar patterns of progression up to their forties; however, by the time women reach their seventies, they experienced a significantly higher rate of heart failure. The most prominent across-the-board symptoms include dyspnea, fatigue, and weakness.

Dr. Friedman stressed the need for physicians to be aware of the special needs of older patients, who are more likely to have multiple ongoing symptoms, impaired physical function, especially in women, a higher rate of depression, and higher rates of rehospitalization and mortality.

African-American Patients

Stephanie Dunlap, Chicago, Illinois, focused on the apparent differences in the etiology of heart failure in African-American patients. “African Americans,” she said, “have lower ejection fractions, a higher incidence of hypertensive cardiomyopathy, and onset of the disease at an earlier age. A higher proportion of women have heart failure.” The SOLVD trial, she said, showed that the mortality rates of African Americans and whites were similar, with African Americans having higher hospitalization rates. VHeFT showed no difference in survival rates for white patients; African-American patients treated with isosorbide dinitrate did have an improved survival rate. VHeFT-II showed that whites with hypertension responded to treatment with enalapril with increased survival rates, while African-Americans did not, irrespective of whether they had hypertension. In the SOLVD trial, differences between the two groups included higher rates of non-ischemic heart disease in African Americans, higher rates of hypertension, and higher rates of diabetes, and increased all-cause mortality and heart failure progression.

Analyzing the UNC heart failure database, she said that hypertension was the sole etiology for 25% of patients, 13% of whom were African American. African Americans had a higher body mass index and an increased risk of developing hypertensive cardiomyopathy. “However,” she pointed out, “they had a lower incidence of ischemic heart disease, less need for CABG procedures, and lower incidence of atrial fibrillation.”

“What we have learned from this database,” she concluded, “is that to better care for these patients, a larger enrollment of this population is needed in trials. Investigations are needed on genotype and phenotype of hypertension in African Americans to determine the best therapy, and we need better blood pressure control and optimal body mass index for women.” □

How-To Sessions Offer Practical Information

How-to sessions held on two days of the annual scientific meeting provided practical information to attendees and balance to the scientific and clinical program.

How to Use and Perform Expression Profiling in Heart Failure

M. Benjamin Perryman, Denver, Colorado
Mark Geraci, Denver, Colorado
Meredith Bond, Cleveland, Ohio

How to Treat Complicated Heart Failure Cases

Ileana Pina, Cleveland, Ohio
Marc Silver, Oak Lawn, Illinois

How to Transition LVAD Patients into a Home Setting

Julie Shinn, Stanford, California
Tiffany Buda, Cleveland, Ohio
Ashley Sims, Cleveland, Ohio

How to Utilize a Nurse Managed Heart Failure Program to Improve Outcomes and Quality of Life

Carol Main-Benner, Cary, Illinois
Terry Strzelcyk, Chicago, Illinois
Karen Janoski, Pittsburgh, Pennsylvania

Genetic Counseling in Inherited Cardiomyopathies in Heart Failure

Jeffrey Towbin, Houston Texas
Luisa Mestroni, Aurora, Colorado
Timothy Olson, Rochester, Maryland

How to Measure Quality of Life

Thomas Rector, Minnetonka, Minnesota
Edward Havranek, Denver, Colorado
John Spertus, Kansas City, Missouri

How to Select and Evaluate Heart Failure Patients for AICDs

Leslie Saxon, San Francisco, California
William Stevenson, Boston, Massachusetts
Mark Carlson, Cleveland, Ohio

Mining the Data Bases

David Port, Denver, Colorado
Michael Eisen, Berkeley, California

How to Obtain Research Funding

William Little, Winston-Salem, North Carolina
William Abraham, Lexington, Kentucky

Landmarks of Heart Failure

The two Landmarks of Heart Failure lectures featured leading researchers speaking on milestones in the treatment of heart failure.

- Daniel Levy, Framingham, Massachusetts, identified the major risk factors for the development of heart failure: age, hypertension, prior myocardial infarction, angina, diabetes, left ventricular hypertrophy, left ventricular systolic and diastolic dysfunction, and valve disease. He reviewed clinical trial data on each and listed effective preventive measures, including early and aggressive control of hypertension, reduction or elimination of smoking, management of diabetes, control of obesity, and treatment of systolic and diastolic dysfunction. "Hypertension control is the single greatest means by which heart failure can be prevented," he stressed, citing four trials that cumulatively demonstrated a 50% reduction in the development of heart failure with reduction in blood pressure.

Trial	n	HF↓
SHEP	4736	-54%
STOP-1	1627	-51%
Syst-Europe	4695	-27%
Syst-China	2394	-58%

- Finn Waagstein, Goteborg, Sweden, related the history of the use of beta blockers, from the initial skepticism of many in 1975 when the first use in cardiomyopathy was reported to the present. "In 1979," he said, "we actually began to see improvement in survival using beta blockers in heart failure, but it was not until 1985 that the first positive, placebo-controlled trial showed an effect on heart function and exercise tolerance." Subsequent studies in the 1980s and early 1990s evaluated improved contractility and long-term morbidity. "Now," he said, "after several consistent prospective mortality reduction trials have been completed, beta blockers are part of the heart failure treatment strategy."

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Partnership in care

education programs, sample quality improvement tools, opportunities for communication sharing among hospitals, and ongoing assistance to identify and overcome barriers to improvement. She stressed, "It is important to note that quality improvement in heart failure will be mandatory in 2001."

She cited two partnership roles that are especially promising:

- HCFA and PROs have an infrastructure and a goal of quality care improvement. They need partners with expertise in heart failure to overcome barriers and to raise the national sense of urgency to improve care for patients. Research is needed on quality improvement, and primary care providers need education programs.

- She stressed the importance of the growing partnership between HCFA and the HFSA that will concentrate on disseminating information through conference presentations, a column in *Congestive Heart Failure*, the *Heart Failure Society News*, Heart Failure Awareness Week, and the potential creation of HFSA education and patient management tools. She concluded, "HCFA and HFSA share many of the same goals and have numerous opportunities to achieve them." □

Late-Breaking Clinical Trials Analyze New Data

Multisite STimulation In Cardiomyopathy (MUSTIC)

Serge Cazeau, St. Cloud, France, reported on MUSTIC, the first controlled trial to assess the efficacy and safety of biventricular pacing in patients with severe chronic heart failure and major electrical ventricular discoordination.

The study's rationale was based on the prevalence of intraventricular conduction disorders in the heart failure population. The randomized, crossover, single-blinded design enrolled patients in two groups. The 58 patients randomized in group 1 had stable sinus rhythm and had no traditional indication for pacing. The 46 patients in group 2 exhibited chronic atrial fibrillation and slow ventricular rate, either spontaneous or induced, and were randomized to biventricular or right ventricular pacing. Enrollment criteria included severe heart failure, stabilization in NYHA class for at least 1 month under optimized drug treatment, LFEV <35, inability to walk more than 450 meters in the 6-minute walk test, and evidence of ventricular conduction delay. The primary endpoint was the distance achieved in the 6-minute distance. Secondary endpoints were the quality of life as measured by the Minnesota score, peak VO₂, hospital admissions for decompensated heart failure, and the patients' preference at the end of the crossover period.

Patients who received the biventricular pacing increased the 6-minute walk test distance to 430 meters, compared with 360 meters for the non-paced patients ($P=0.05$). The peak VO₂ increased by 12%. The mean Minnesota score decreased from 46 at randomization to 33 at crossover completion, indicating improvement; the rate increased to 43 during the non-pacing phase. Patients indicated their preference for the biventricular pacing.

Dr. Cazeau said, "The MUSTIC trial validated the new concept of ventricular resynchronization to treat patients with severe heart failure and major ventricular discoordination." He said that atrial biventricular pacing probably significantly improves exercise tolerability and quality of life and reduces hospitalization in sinus rhythm patients. He said that the benefit of biventricular pacing is less pronounced in patients with atrial fibrillation, but the higher than expected dropout rate in this group limited the statistical power for analysis. Larger trials are needed to better evaluate the long-term effects, he concluded, especially in terms of mortality and cost efficacy.

Beta Blocker Evaluation of Survival Trial (BEST)

Eric Eichhorn, who presented the results of the BEST trial at the annual meetings of the American College of Cardiology and at the American Heart Association, reviewed the results and provided new mechanistic insights to explain them.

Bucindolol was selected because it was well tolerated and non-selective, does not upregulate beta receptors, lowers plasma norepinephrine, has no intrinsic sympathomimetic activity in human systems, and is a mild vasodilator. The trial stratified 2708 patients in four areas: etiology, LVEF (20 vs >20), gender, and race. The primary endpoint was all-cause mortality; the secondary endpoints were cardiovascular mortality, hospitalizations, death or transplant, ejection fraction, incidences of myocardial infarction, quality of life, and the need for cotherapy.

The results indicate that compared to placebo, bucindolol reduces plasma norepinephrine levels, improves LVEF at 3 and 12 months, reduces cardiovascular death by 14%, reduces hospitalization by 12% reduction, and reduces myocardial infarctions by 50%. The drug showed a non-significant trend to reductions in hospitalization; reductions in all-cause mortality, sudden death and pump death, and non-cardiovascular death were not significant.

Dr. Eichhorn suggested that the absence of a statistically significant reduction in the primary endpoint of all-cause mortality could be attributed to a heterogeneous response to the drug and to the inclusion of patients with class IV heart failure. Specifically, African Americans had a 17% increase in mortality and higher rates of hypertension. If this subgroup is removed from the analysis, the remaining 2100 patients experienced statistically significant reductions in all-cause mortality. "If patients with ejection fractions <20% and patients who are African Americans are excluded, the BEST trial demonstrates improvements in outcomes similar to CIBIS II," he said. African-American patients receiving bucindolol did have improved ejection fractions compared to placebo, almost equivalent to the rate experienced by whites. However, they also had significant decreases in plasma norepinephrine levels at 3 months compared to placebo.

Dr. Eichhorn concluded that the heterogeneous response to therapy based on race and heart failure class calls for further research on subgroups. "The BEST results highlight the need to further examine gender and racial differ-

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ences in cardiovascular disease," he said. He suggested that the norepinephrine-lowering effect may have mitigated the benefits of the drug and maintained that there is a beneficial role for beta blockers.

COPERNICUS



Milton Packer

Milton Packer provided the first American presentation of the results of the COPERNICUS trial, a prospective, placebo-controlled, randomized investigation of carvedilol in patients with advanced ischemic or non-ischemic heart failure. The trial randomized 2289 patients with ejection fractions <25% to placebo (n=1133)

or carvedilol (n=1156). Patients also received conventional therapy, including ACE inhibitors. Two-thirds of the patients had been hospitalized within the preceding year for heart failure.

The results show even greater benefits of beta-blocker therapy than have been demonstrated in other trials. The primary endpoint of all-cause mortality was 18.5% for placebo vs. 11.4% for carvedilol ($P=0.00014$). The respective rates of decrease in the U.S. carvedilol trial was 65%, compared with 34% in MERIT, 34% in CIBIS and 10% in BEST. The COPERNICUS trial was terminated in March 2000 by the Data Safety and Monitoring Board because of the positive results.

Dr. Packer stated, "The results with carvedilol were consistent both in direction and magnitude across all subgroups. The benefits were apparent regardless of age, gender, ejection fraction, etiology of heart failure, or history of hospitalization within the previous year. No patients were so severe that they did not respond. Carvedilol decreased the risk of death, all subgroups benefited, and the drug was well tolerated. If the survival benefit seen during the first year is extrapolated, the results indicate that for every 1000 patients treated for 3 years, 200 lives could be saved."

OPTIME

Mihai Gheorghide, Chicago, Illinois, presented the results of OPTIME, a prospective, multicenter, double-blind, placebo-controlled trial to evaluate milrinone as adjunctive to the best medical therapy to improve intermediary outcomes.

The purpose of the study was to evaluate the ability of milrinone, which can improve hemodynamics, to improve outcomes in heart failure symptoms and hospitalizations.

Patients were at least 18 years of age, had ejection fractions less than 40%, and had been hospitalized for increased heart failure. The primary endpoint was decreased length of hospitalization for cardiovascular events within 60 days of therapy. Secondary endpoints were treatment failures within 48 hours, subjective clinical outcomes, length of initial hospitalization, or adverse events. The trial was conducted from 1997-1999 and enrolled 951 patients at 78 centers in the United States.

Patient Demographics

	Placebo (n=472)	Milrinone (n=477)
male	68	64
race	67	63
EF	23	23
Class II	7	7
Class III	45	46
Class IV	48	47
SBP	119	120
HR	85	85

Results showed no statistically significant differences between milrinone and placebo in number of hospitalizations or length of stay. There was a trend to higher doses of ACE inhibitors in the milrinone group. There were no significant differences in subjective health. However, patients receiving milrinone experienced higher rates of adverse events and increased failures ($P<0.001$); in-hospital mortality differences were not significant. Rates of mortality or rehospitalization in less than 60 days were similar: 35% vs 35%, respectively ($P=0.917$). Sustained hypotension was significantly higher in the patients receiving milrinone, 11% vs 3% in the placebo group.

The following predictors of 60-day mortality were decreased blood pressure, decreased serum sodium, age, heart failure class, and increased BUN. For the primary endpoint of increased days in the hospital, the predictors included blood pressure, serum sodium, function class, and BUN. There was a slight difference between the ischemic and non-ischemic groups in primary endpoints: the ischemic group receiving milrinone had poorer outcomes, with an event rate of 41% vs 35% for placebo.



Mihai Gheorghide

Dr. Gheorghide concluded that the use of milrinone was not supported. "The potential benefits of the drug in non-ischemic heart failure, as well as the possible deleterious effects in patients with ischemic heart failure, merit further investigation," he concluded. □



5th Annual Scientific Meeting

September 9-12,
2001
Washington, DC

For information, visit the HFSA website at
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Mission Statement

The Heart Failure Society of America, Inc. (HFSA) represents the first organized effort by heart failure experts from the Americas to provide a forum for all those interested in heart function, heart failure, and congestive heart failure (CHF) research and patient care.

The mission of HFSA is to:

- **Promote research** related to all aspects of heart failure and to provide a forum for presentation of basic, clinical, and population-based research.
- **Educate** physicians and other members of the profession through programs, publications, and other media to enable them to diagnose and treat heart failure and concomitant medical conditions more effectively.
- **Encourage** primary and secondary preventive measures to reduce the incidence of heart failure; to serve as a resource for government, private industry, and health care providers to facilitate the establishment of programs and policies that will better serve the patient.
- **Enhance** quality and duration of life in those with heart failure.
- **Promote and facilitate** the formal training of physicians, scientists, and allied health care providers in the field of heart failure.

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