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Heart Failure Society News

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HFSA Annual Scientific Meeting Opened with a Look into the Future

The opening plenary session kicked off with a tribute to the HFSA outgoing President, Marvin Konstam, MD (President 2002-2004). The Society extended their gratitude and appreciation for his dedication, endless energy and outstanding leadership to the HFSA.

What does the future hold for heart failure?

This was the question addressed in the opening plenary session of the 2004 Annual Scientific Meeting of the HFSA, September 12-15th, Metro Toronto Convention Centre, Toronto, ON, Canada. Topics covered in the session included therapeutic innovations, strategies for preventing heart failure, and knowledge creation and transfer.



Marvin Konstam honored for his outstanding service to the HFSA

Heart Failure Therapy: Innovations for Tomorrow

Gerald W. Dorn, Cincinnati, OH, opened by reviewing the evolution in paradigms for treating heart failure, starting with remedies for dropsy, moving to the theory of catecholamine support in the 1960s, and ending with the paradigm shift that led to the current use

of ACE inhibitors and beta blockers. Despite the benefits of these drugs, Dorn said they are not a panacea, since their effectiveness may vary from patient to patient.

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2004 HFSA Research Fellowships, New Investigator and Nursing Research Winners Named

Winners of the 2004 HFSA Research Fellowships; the Jay N. Cohn New Investigator Awards in basic science and in clinical/integrative physiology; and the Nursing Research Award were announced at a ceremony on September 14 at the HFSA Annual Scientific Meeting.

HFSA Research Fellowships

The HFSA established the one-year research fellowship program in 2003 to develop clinician-investigators in the field of heart failure. The fellowship program is open to applicants with a doctoral degree in medicine, osteopathy, or nursing.

The recipients of the 2004 HFSA Research Fellowship awards are:

- **Brett E. Fenster, MD** (Stanford University, Palo Alto, CA) "Functional Role of CBFA1 in Myocardial Fibrosis"

- **Srinivas Iyengar, MD** (Ohio State University, Columbus, OH) "Effects of Cardiac Resynchronization Therapy on Myocardial Gene Expression in Patients with Congestive Heart Failure"

- **Ajoy Kapoor, MD** (University of Pittsburgh, Pittsburgh, PA) "Genetic Modulation of Clinical Outcomes in Pulmonary Arterial Hypertension"

- **David E. Lanfear, MD** (Washington University, St. Louis, MO) "Pharmacogenetic Analysis of Angiotensin Converting Enzyme Inhibitor and Beta Adrenergic Antagonist Efficacy"

The 2004 HFSA Research Fellowship program has been made possible through generous contributions from: AstraZeneca, GlaxoSmithKline, Guidant Foundation, Merck, Scios Inc., and Vasomedical.

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HFSA Annual Scientific Meeting Opened with a Look into the Future

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The challenge for the future is to look at tailoring treatment to individual patients. A new approach to treating and managing heart failure would encompass the identification of genetic risk factors and their interaction with traditional physiological stressors. This would allow for tailored therapies.

Prevention: Why Let the Heart Fail at All

"We're all on the trajectory to heart disease. It's called age," said Jay N. Cohn, Minneapolis, MN, in a presentation challenging the audience to focus on prevention of heart failure.

Heart failure can be prevented or at least delayed, said Dr. Cohn. The keys to

prevention include identifying and treating individuals most at risk of developing left ventricular remodeling. Ideally, research would identify a biological marker with high sensitivity and specificity for disease. It would then be possible to intervene early and slow the downward slope. This approach is better than a generalized

approach of prescribing a "poly-pill" designed to prevent heart failure. "We don't have to go to the entire population," he said.

Dr. Cohn went on to describe his work on early detection, focusing on a test that measures patients' endothelial dysfunction and small vessel disease. Questions remain concerning who should pay for the screening, who should do the screening, and at what age screening should be done.

Dr. Cohn again challenged the audience when he asked if society was ready to cope with a large population of healthy elderly people. He cited the likely negative impacts to the "health care industrial complex" of the reduced need for advanced care and medical specialists.

Knowledge Creation and Transfer to Address the Challenges of Heart Failure

Bruce McManus, Vancouver, BC, Canada, Scientific Director of the Institute of Circulatory and Respiratory Health of the Canadian Institutes of Health Research (CIHR), concluded the

session by addressing use of a systematic, interdisciplinary outcomes approach to the challenge of heart failure.

For a successful national heart failure research agenda, synergy is needed between the various stakeholders at the national and community levels, improved cooperation between basic and clinical investigators, and more emphasis on true translational research. Informatics and the computational sciences will play a greater role in maximizing the data and knowledge in this effort.

Future Annual Scientific Meeting Dates

2005: September 18-21, Boca Raton, FL

2006: September 10-13, Seattle, WA

2007: September 16-19, Washington, DC

2008: September 21-24, Boca Raton, FL

2004 HFSA Research Fellowships, New Investigator and Nursing Research Winners Named

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Jay N. Cohn New Investigator Awards

Ten finalists, selected from an outstanding group of abstract submissions, presented their work during a session at the Annual Scientific Meeting. The winners (Tomohisa Nagoshi and Patrick McConnell) were chosen based on the scientific merit of the work, manner of presentation, use of appropriate graphics, and effectiveness of the discussion.



Min Xie, Sam Wang, Carmen Sucharov, Fernando Martin, Tomohisa Nagoshi, Jay N. Cohn

■ **Tomohisa Nagoshi, MD**, Massachusetts General Hospital, Boston, MA won in the basic science category for his work on "Adenoviral Expression of Activated P13-Kinase Rescues Cardiac Dysfunction and Injury Induced by Ischemia-Reperfusion in Akt Transgenic Mice."



Horng Chen, Patrick O'Connell, Abdul Al-Hesayen, Saumya Sharma, Sukesh Burjonroppa, Jay N. Cohn

■ **Patrick I. McConnell, MD**, Ohio State University Medical Center, Columbus, OH won in the clinical/integrative physiology category for his work on "Autologous Skeletal Myoblasts Restore the Myocardial Electrical Impedance, But Not the Refractory Period of Infarcted Myocardium: Engraftment Versus Integration."

Thomas Force, Boston, MA, and Peter P. Liu, Toronto, ON, Canada, who presented the awards, both commented on the difficulty of judging, given the high quality of the work and the presentations.

The Jay N. Cohn New Investigator Award competition is supported by an educational grant from Novartis Pharmaceuticals.



Cheryl Westlake, Misook Chung, Maria De Jong, Brooke Bentley

Nursing Research Award

■ **Cheryl A. Westlake**, University of California, San Francisco, CA was named winner of the 2004 Nursing Research Award for her work on "Are Norepinephrine Levels at Baseline Related to Depression Levels at 12 Months?"

Ms. Westlake's submission was chosen from a field of four finalists who presented their work at the Annual Scientific Meeting. The papers were judged on the basis of scientific excellence, overall scholarship and merit, originality, relevance to patients with heart failure, and potential for further nursing research. The HFSA Nursing Investigator Award was established in 2001 as a way to foster research by nurses on topics that improve the management and care of patients with heart failure.

Challenges of Drug Development and Selection for Acute Decompensated HF

Representatives of industry, government, and clinical practice discussed the challenges of drug development and selection for acute decompensated heart failure (ADHF) in a symposium moderated by Drs. Uri Elkayam, Los Angeles, CA, and Cesare Orlandi, Rockville, MD.

Industry Point of View

"Clinical trials of drugs for ADHF are now at a crossroad", said Dr. Orlandi, Vice President of Clinical Development, Otsuka Maryland Research Institute. "The FDA is moving away from hemodynamics as an endpoint," he said. Instead mortality, functional capacity, patient assessed symptoms, and composite endpoints are being used. The reality of the change in endpoints is that mortality in the hospital is low; not all patients have all of the symptoms; and functional capacity and quality of life is difficult to measure in this patient population.

The definition of "adequate safety margin" is also changing. With heart failure, an acute treatment may affect long-term outcomes.

Conducting a double-blind, randomized, placebo controlled trial to test a drug on top of optimal base therapy is difficult in this environment. The base drug regimen, devices, and other coronary interventions increase the noise level. This means a larger sample size, longer follow-up, and higher costs.

Investigator's Point of View

"These are difficult studies," said Dr. Elkayam, speaking for the heart failure clinician.

Hemodynamic monitoring is not a standard of care for ADHF. The main goal of therapy is to remove fluids safely while preserving renal function.

Making matters more difficult, the majority of patients admitted with ADHF do not meet the inclusion criteria for the studies, while the patients that meet the selection criteria may not represent the ADHF population. Are the results of these trials applicable to patients with acute decompensated heart failure? asked Dr. Elkayam.

Regulatory Point of View

Jeffrey S. Borer, New York, NY, chairman of the FDA Cardiovascular and Renal Drugs Advisory Committee, said the patient population studied must be limited or the data will be hard to analyze. Wide-ranging inclusion criteria lead to a high level of background noise. "What you study is what you will likely get on the labeling," he said.

Studies of acute decompensated heart failure should encompass as much of the expected recovery period as possible. Mortality is probably too infrequent an event to serve as a primary endpoint, he said.

Shari Targum, Rockville, MD, representing the FDA, said that a drug may be approved if it makes people feel better, even if life expectancy is shorter. "We need a risk-benefit analysis," she said citing the example of nesiritide. The FDA rejected the drug in 1999. It was resubmitted and received FDA approval in 2001 with labeling for a lower dose. The mortality data was trending in the wrong direction, but the drug improved symptoms.

Discussion of inclusion criteria and study size--mega trials versus smaller targeted studies--continued during the question and answer session.

Drug Selection

William T. Abraham, Columbus, OH, and Lynne Warner Stevenson, Boston, MA, discussed drug selection for ADHF.

Registries include more people and can provide a more real-world outlook on what is going on, said Dr. Abraham, who presented lessons learned from the ADHERE registry of patients hospitalized with heart failure.

Dr. Stevenson said guidelines on managing ADHF are very limited and that patient goals must be taken into account.



Mark Dunlap (Case Western Reserve) challenging a speaker at the 2004 annual scientific meeting.



Opening plenary session at the 2004 annual scientific meeting.



A lighter moment during a session at the 2004 annual scientific meeting.

New Data and Application to Patient Care Discussed: Late Breaking / Recent Clinical Trials Session

On the final morning of the 2004 Annual Scientific Meeting the Late Breaking and Recent Clinical Trials session was held. Moderated by Daniel Levy, Framingham, MA, and Dirk L. Brutsaert, Antwerp, Belgium, the session included presentations and discussions of trials investigating varied techniques of managing heart failure including drugs, an herbal remedy, bone marrow transfer, and genetic testing.

EMOTE – Oral Enoximone in Intravenous Inotrope-Dependent Subjects

Results of the EMOTE trial, as presented by Arthur M. Feldman, Philadelphia, PA, showed that low dose oral enoximone can replace i.v. inotropes in a substantial number of patients with ultra advanced heart failure.

The use of i.v. inotropes in heart failure patients is associated with high morbidity, possible increases in mortality and the cost of protracted hospitalizations. The EMOTE trial was designed to evaluate the effectiveness of a low dose oral inotrope for patients taken off i.v. inotrope therapy. It was a Phase III, randomized, double-blind, placebo-controlled parallel study of 201 NYHA Class III and IV heart failure patients who were dependent on either continuous or intermittent i.v. inotrope therapy.

Dr. Feldman reported that low dose oral enoximone improved wean success in advance heart failure patients previously dependent on i.v. inotropes. Low dose oral enoximone significantly reduced the number of days patients required i.v. inotropic administration and caused no significant increase in mortality over 26 weeks. The adverse events were acceptable with a reduction in catheter related morbidities.

HERB CHF – Hawthorn Extract Randomized Blinded Chronic HF Study

Keith Aaronson, Ann Arbor, MI, reported there was no evidence that hawthorn extract results in functional or structural improvement in heart failure patients. There was no effect on the 6-minute walk, no effect on a quality of life assessment, and modest relative benefit in measures of the left ventricular ejection fraction (LVEF).

Hawthorn is a small tree producing berries that have been used for cardiac complaints in a variety of traditional medicines since ancient times. The HERB

CHF trial was designed to study cardiac benefits of the herb. The trial included 120 heart failure patients in NYHA Classes II-IV with an ejection fraction \leq 40% who were randomized to receive either hawthorn extract or placebo and followed for six months.

Discussion pointed out that the study was too small and the patients included were probably not sick enough to allow definitive conclusions about the herbal remedy. A much larger study (2600 patients) using the same herb, the SPICE study, is underway in Eastern and Central Europe.

The WATCH Trial: Updates

Although enrollment in the WATCH trial (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) was discontinued prior to reaching its target of 4,500 patients, it is still the largest trial of antithrombotics in heart failure, said Barry M. Massie, San Francisco, CA.

The study of 1,587 patients found no differences between warfarin, aspirin, and clopidogrel in terms of the primary endpoint of a nonfatal myocardial infarction (MI), stroke, or death. Similarly, there were no statistical differences between the treatments when the composite endpoint of death, nonfatal MI, stroke, HF hospitalization, and embolism was considered.

However, there were some differences between the three treatments:

- Patients taking aspirin had a significantly greater number of hospitalizations than the warfarin group. There was no difference in hospitalizations between the aspirin and clopidogrel groups.
- There were impressive trends toward lower stroke rates with warfarin compared to aspirin.
- As far as adverse events, major bleeding was more common with the warfarin group than with aspirin or clopidogrel.

In conclusion, Dr. Massie said the lower hospitalization rate with warfarin is intriguing and supports the need for additional trials.

BOOST – Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration

Intravenous infusion of autologous bone marrow into the coronary arteries that

supply the infarcted tissue resulted in a highly significant 6% increase in the LVEF at six-month follow-up, reported Kai C. Wollert, Hanover, Germany. However, there was no significant difference in left ventricular diastolic index volume, indicating that bone marrow transfer has no effect on remodeling after MI. No significant differences in terms of deaths, hospitalization for heart failure, reinfarction, the induction of ventricular tachycardia or ventricular fibrillation, or intraluminal stenosis were seen in the treated group.

The BOOST study involved 60 patients and was designed to study the impact of autologous bone marrow infusion on LV remodeling and functional regeneration in patients with an ST segment elevation MI after a successful percutaneous cardiac intervention. The patients were randomized 1:1 to receive either a bone marrow infusion or no infusion. Treated patients were infused an average of 5 days after the primary intervention.

Discussion of this novel cell therapy for heart failure centered on the need for further trials with a double-blind design and a larger sample size.

BEST – β_1 Adrenergic Receptor Polymorphisms Predict the Clinical Response to Bucindolol in HF

Stephen Liggett, Cincinnati, OH presented data from an analysis of 1040 patients in the BEST study. This analysis showed that patients who were carriers of the ARG 389 variant of the β_1 adrenergic receptor (β_1 AR) experienced positive pharmacological benefits from bucindolol when compared to carriers of the GLY 389 variant.

Patients who were homozygous for the ARG 389 variant experienced about a 36% improvement in terms of the endpoints of death or deaths plus hospitalizations when compared to ARG 389 carriers receiving placebo. In contrast, carriers of the GLY 389 variant of the β_1 AR showed no response to bucindolol and had outcomes curves identical to the placebo group.

The BEST study was a double blind placebo controlled study of bucindolol patients with NYHA Class III and IV heart failure with follow-up of up to five years. Dr. Liggett concluded from the study that genetic testing may be useful in predicting response to beta-blockers.

Hyde Park Session Engages Annual Meeting Attendees

Hyde Park Hypotheses, a beloved feature of the HFSA Annual Scientific Meetings, once again generated an enthusiastic response from the audience with a series of presentations that covered topics ranging from science to pseudo science to current affairs.

In this session, speakers are allowed to expound on any topic of their choosing as long as it is related to heart failure. The goal is to provide an opportunity to present concepts or stimulate thoughts in a democratically structured session, unfettered by the usual standards of peer review. Speakers may wish to present a novel hypothesis, which may or may not be supported by real data. Speakers may elect to present a contrarian point of view, just for the fun of taking an unpopular position. Some decide to use the time allocated to posit, complain, cajole or provoke, all in an effort to bring out reactions from the audience which might include anger, disbelief, fear, depression, guilt, laughter or tears.

Arnold M. Katz, Norwich, VT, and Carl V. Leier, Columbus, OH, reprised their perennial role as session moderators, succeeded at crowd control, while offering speakers a combination of encouragement and skeptical remarks about the topics at hand. "We expect our speakers to think and speak outside of the box, while they are standing on the box," said Dr. Leier.

This year's Hyde Park Session featured the following topics and speakers:

■ **Thiazolidinediones (TZDs) Should Be Indicated (Not Contraindicated) in Heart Failure**, Lazaros A. Nikolaidis, Pittsburgh, PA

Although there are many unanswered questions, the use of TZDs for the treatment of CHF remains a promising metabolic approach to the energy-starved failing myocardium.

■ **United States Presidents and Cardiovascular Disease: What Bush, Nader, and Kerry Should Know**, Paul J. Hauptman, St. Louis, MO

Dr. Hauptman posited that all U.S. presidents have been older white males, and cardiovascular disease is common in older white males.

Based on a review of more than 40 sources, Dr. Hauptman concluded that 18 of the 37 dead presidents died of cardiovascular disease; 10 died of heart failure; and cardiovascular disease was a contributing factor in 3 other deaths.

"The burden of office takes its toll." Presidents live an average of 2.5 years less than their aged matched counterparts. Cardiovascular disease is a common problem among presidents, especially in the 20th century cohort. Dr. Hauptman did acknowledge that



Drs. Arnie Katz and Carl Leier slip into their role as moderators for the Hyde Park Session.

the longevity of Presidents Reagan and Ford was wreaking havoc with this analysis.

■ **The Triumph of the Cold Humors: Or Why I Should Have Become a Nephrologist**, John R. Teerlink, San Francisco, CA

Dr. Teerlink set out to demonstrate that in the not-so-distant future no heart failure patient will die due to progressive pump failure or sudden death. Instead the main cause of death for heart failure patients will be renal failure; therefore heart failure specialists should become nephrologists.

■ **Back to The Future: The Case for Patient Testimonials in Re-Evaluating 19th Century Remedies and Cures for Heart Failure**, Douglas D. Schocken, Tampa, FL

Dr. Schocken presented vivid reproductions of selected real testimonials for agents to manage all manners of cardiovascular affliction. These maladies included dropsy and various types of catarrh, both synonyms for heart failure. For example, Killmore's Ocean Weed Heart Remedy was touted as "the perfect blood purifier, especially useful if you feel as though water was gathering around the heart, dropsy, vertigo, dizzy spells, ringing in the ears, or if you are disposed to nervous prostration, apoplexy, shock, or sudden death."

He concluded that many of these agents which were abandoned long ago deserve to be reconsidered and that personal testimonials should take their rightful place in the evaluation of therapeutic modalities for heart failure.

■ **It's Time to Start Screening for Systolic Dysfunction**, Paul A. Heidenreich, Palo Alto, CA

In this presentation Dr. Heidenreich attempted to demonstrate that if further research were conducted, there might be ways to identify better markers for LV systolic dysfunction which is known to be preceded by a period of asymptomatic LV dysfunction, treatment for which delays the onset of heart failure.

■ **CHF Guidelines Reality 2004: To Treat a Patient with Severe CHF with Effective Immune Suppression You Need to Transplant the Heart First**, Stefan D. Anker, London, UK

Dr. Anker set out to convince the audience that the value of immune modulation in the management of heart transplant patients is much undervalued and may be more important than the surgical procedure. He believes that immune suppression without transplantation would have a chance: it simply has not been tried yet. He argued that immune suppression would suppress inflammation and trigger weight gain for this identified group of patients waiting for transplant.



Jay N. Cohn (University of Minnesota) comments on an issue raised by a speaker at a scientific session during the 2004 annual scientific meeting

Genetic Determinants of Heart Failure

Genetic issues related to heart failure were the focus of several sessions. One session moderated by Calum A. MacRae, Boston, MA, and Elizabeth McNally, Chicago, IL, outlined clinical lessons learned from familial studies of heart failure.

Familial Dilated Cardiomyopathy and Left Ventricular (LV) Noncompaction

Dilated cardiomyopathy is an etiologically heterogeneous disorder in which approximately 35 to 40 percent of cases are inherited, said Jeffrey A. Towbin, keynote speaker in this session.

Work over the past few years suggests that the sarcomere/sarcolemma link is the common pathway causing a variety of left ventricular dysfunction including dilated cardiomyopathy. Focus has been on the genes responsible for encoding the proteins in this linkage.

Dr. Towbin explored LV noncompaction, a condition previously considered rare, but now considered more common. LV noncompaction is caused by an arrest in the last phase of cardiac development and is characterized by deep

trabeculations in the LV endocardium and apical hypertrophy.

Dr. Towbin, who recently reported on a study of 36 children with LV noncompaction, said a number of genes have been identified with the disorder. Targeted therapy within the next five years is a possibility, he said.

Familial Atrial Fibrillation

Atrial fibrillation (AF) is a genetically heterogeneous disorder that exhibits the same complexity that has been identified for most human disorders, said Calum A. MacRae. The predisposition to AF is often inherited, and AF may share a common biology with heart failure. A recent study suggests that individuals who have AF may be at increased risk of developing heart failure.

Genotype-Phenotype Correlation and Their Clinical Implications to Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is not a rare disease: its natural history is variable,

familial transmission is frequent, and a genetic defect is invariably present, said Luisa Mestroni, Aurora, CO. The disease is characterized by genetic, allelic, and phenotypic heterogeneity. More than 13 genes and 300 mutations have been associated with the disease. Despite the complexity, a large number of cases can be identified by screening the three main genes. This has clinical implications in terms of diagnosis as well as in prevention and follow-up.

Mitochondrial Myopathies

John M. Shoffner, Atlanta, GA, a neurologist and geneticist, addressed the complexities involved in diagnosing cardiac myopathy due to mitochondrial disorder. The goal of identification is not so much to treat the disease, since most mitochondrial disorders are not amenable to treatment, but to manage the disease, identify those at risk and counsel family members.

Mark Your Calendars

January, 2005:

Registration opens for the 9th Annual Scientific Meeting

Monday, February 7, 2005:

2005 Research Fellowship Application Receipt Deadline

Saturday, February 12, 2005:

Primary Care Symposium, Sacramento, California

February 13 – 19, 2005:

Heart Failure Awareness Week

Monday, April 11, 2005:

Abstract Submission Deadline for the 9th Annual Scientific Meeting

Monday, May 9, 2005:

Hyde Park Submission Deadline for the 9th Annual Scientific Meeting

Friday, May 27, 2005:

Late Breaking Clinical Trials Submission Deadline for the 9th Annual Scientific Meeting

September 18 – 21, 2005:

9th Annual Scientific Meeting

