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PROGRAM

AND

ABSTRACTS

Association of University Cardiologists  
Fiftieth Annual Meeting  
Arizona Biltmore Resort & Spa  
Phoenix, AZ

January 5 – 7, 2011

2011

2011 AUC ANNUAL MEETING  
PROGRAM

**Wednesday, January 5, 2011**

- 2:00 PM – 5:00 PM Council Meeting – Kaibab  
 3:00 PM – 5:00 PM Emeritus Forum – Casa Grande  
*Implications of ACA & Health Care Reform*  
**W. Douglas Weaver**, M.D., Henry Ford Hospital  
*Endothelial Dysfunction: A 25-Year Perspective*  
**R. Wayne Alexander**, M.D., Emory University  
 6:00 PM-8:00 PM **Reception** – Grand Ballroom

**Thursday, January 6, 2011**

- 7:30 AM – 8:30 AM Continental Breakfast – Main Foyer
- 8:30 AM – 12:00 PM The President's Program** - Flagstaff
- 8:30 – 8:45 50 Years of AUC  
 J. Michael Criley, M.D., David Giffen School of  
 Medicine at UCLA
- 8:45 – 9:45 **THE 25th GEORGE BURCH MEMORIAL  
 LECTURE**  
*Network Medicine & Human Disease: A System  
 Pathobiology Approach to Personalized  
 Cardiovascular Medicine*  
**Joseph Loscalzo**, M.D., Ph.D., Harvard Medical  
 School
- 9:45 – 10:30 **FEATURED LECTURE**  
*Use of Stem Cells for the Treatment of Ischemic  
 Cardiomyopathy: Basic Concepts, Clinical  
 Applications, & Future Perspectives*  
**Roberto Bolli**, M.D., University of Kentucky
- 10:30 – 11:00 Break –
- 11:00 – 11:45 **PRESIDENT'S LECTURE**  
*Reperfusion Therapy to Salvage Myocardium: The  
 Journey From Concept to Cath Lab to Every  
 Community*  
**Alice Jacobs**, M.D., Boston University School of  
 Medicine
- 11:45 – 12:00 Discussion
- 12:00 – 1:00 Lunch – Majestic Ballroom
- 1:00 – 5:10 First Scientific Session – Flagstaff**
- 1:00 – 1:05 Introduction of New Members in Attendance  
 Brian Annex Jeffrey Olgin  
 Deepak Bhatt Douglas Sawyer  
 Samuel Dudley Peter Stone  
 Christopher Kramer



2011 AUC ANNUAL MEETING  
PROGRAM

**Thursday, January 6, 2011, cont.**

- 1:05 – 1:35 *Growing Old: Insights into Vascular Aging*  
**Marschall S. Runge**, M.D., Chair, Department of  
 Medicine and McAllister Heart Institute, University of  
 North Carolina, Chapel Hill
- 1:35 – 2:05 *Genetic Modifiers of Peripheral Arterial Disease*  
**Brian H. Annex**, M.D., Professor of Medicine, Chief,  
 Division of Cardiovascular Medicine, University of  
 Virginia Health System
- 2:05 – 2:35 *Comprehensive Magnetic Resonance in Peripheral  
 Arterial Disease*  
**Christopher M. Kramer**, M.D., Professor of Medicine  
 and Radiology, University of Virginia Health System
- 2:35 – 3:05 *In-Vivo Risk Stratification of Individual Coronary Artery  
 Plaques: A New Preemptive Paradigm for Management  
 of Patients with Coronary Artery Disease*  
**Peter H. Stone**, M.D., Associate Professor of Medicine,  
 Co-Director, Cardiac Unit, Brigham & Women's Hospital
- 3:05 – 3:20 Break
- 3:20 – 3:50 *25 Years of Endothelial Research in Humans: Where We  
 Have Been and Where We are Heading*  
**Peter Ganz**, M.D., Maurice Eliaser Jr., Distinguished  
 Professor of Medicine, Chief, Division of Cardiology,  
 San Francisco General Hospital and University of  
 California, San Francisco
- 3:50 – 4:20 *Reproductive Health and Cardiovascular Disease*  
**Pamela Ouyang**, M.B.B.S., Professor of Medicine,  
 Johns Hopkins University



2011 AUC ANNUAL MEETING  
PROGRAM

**Thursday, January 6, 2011, cont.**

4:20-4:50 *Role of Epoxyeicosatrienoic Acids in Syndrome X in Woman*  
**Sanjiv Kaul**, M.D., Distinguished Professor of Cardiology, Professor of Medicine and Radiology, Head Cardiovascular Division, Oregon Health & Science University

4:50-5:20 *Antiplatelet Therapy and Proton Pump Inhibition- Good Idea or Unnecessary Risk?*  
**Deepak L. Bhatt**, M.D., Associate Professor of Medicine and Chief of Cardiology, VA Boston Healthcare System

**5:20 PM Adjoin for the day**

**7:00 PM – 11:00 PM RECEPTION AND DINNER (BLACK TIE)**

7:00 – 8: 00 Reception **Gold Room & Gold Room Patio**

8:00 – 11:00 Dinner **Gold Room & Gold Room Patio**

**Friday, January 7, 2011**

7:30 AM – 8:00 AM Continental breakfast – **Main Foyer**

**8:00 AM – 9:00 AM Business Meeting – Flagstaff**

Memorial Minutes  
Election of New Members  
Election of Officers  
Other New Business

**9:00 AM – 12:00 PM Second Scientific Session - Flagstaff**

9:00 – 9:30 *Abnormal Cardiac Sodium Channel mRNA Splicing in Human Heart Failure and the Possibility of a Blood Test to Help Predict Arrhythmic Risk*  
**Samuel D. Dudley, Jr.**, M.D., Ph.D., Professor of Medicine, Chief of Cardiology, University of Illinois at Chicago



2011 AUC ANNUAL MEETING  
PROGRAM

9:30 – 10:00 *Neuregulin/erbB Signaling in the Heart – Update on Biology and Clinical Implications/Applications*  
**Douglas B. Sawyer**, M.D. Ph.D., Lisa M. Jacobson Professor of Medicine, Chief, Division of Cardiovascular Medicine, Vanderbilt University Medical Center

10:00 – 10:30 Break

10:30 – 11:00 *AMP-Activated Protein Kinase Conducts the Stress Response Orchestra in the Heart*  
**Lawrence H. Young**, M.D., Professor of Medicine, Section of Cardiovascular Medicine, Yale University School of Medicine

11:00 – 11:30 *Role of Transforming Growth Factor in Atrial Fibrillation*  
**Jeffrey Olgin**, M.D., Chief, Division of Cardiology, Chief, Cardiac Electrophysiology, University of California San Francisco

11:30 – 12:00 *The 3600 ECG Challenge for Fellows & Faculty: Problem and Solution*  
**John Michael Criley**, M.D., Emeritus Professor of Medicine & Radiological Sciences, Harbor-UCLA Medical Center

**Adjourn**



### Growing Old: Insights into Vascular Aging

Nageswara R. Madamanchi, PhD, Marschall S. Runge, MD, PHD . University of North Carolina, Chapel Hill, NC

With age, our arteries stiffen, atherosclerosis progresses and the incidence of clinically significant cardiovascular diseases (CVD) increases in concomitant manner. Though this certainly is a multifactorial process, activation of inflammatory signaling pathways in the vasculature has been proposed as a common mechanism through which many cardiovascular risk factors, including age, exert their effects. However, the effect of chronologic age variably affects vascular phenotypes throughout the age spectrum and some individuals appear impervious to age-related vascular disease. Reactive oxygen species (ROS) are centrally involved in inflammatory signaling. Our laboratory has focused on the modulation of ROS as an approach to determine whether oxidative stress is indeed important in vascular aging and whether ROS regulation may partially account for the biologic variability seen in clinical settings.

To examine the interplay of aging, ROS and CVD, we determined vascular phenotype of young (4 months) and aged (16 months) mice (and VSMC from these mice) in which ROS generation was altered. C57BL/6 mice genotypes studied included: wild-type, pro-atherosclerotic (apoE<sup>-/-</sup>), with decreased cytoplasmic superoxide generation (lacking p47phox NADPH oxidase subunit, p47phox<sup>-/-</sup>) and with increased mitochondrial superoxide generation (superoxide dismutase heterozygous, SOD2<sup>+/-</sup>). Because ROS-induced inflammatory signaling activates receptor and cytosolic tyrosine kinases implicated in CVD, we examined whether oxidative inactivation of protein tyrosine phosphatases (PTPs) with aging enhances inflammatory mechanisms and atherosclerosis susceptibility.

These studies yielded several consistent themes: 1) Modulation of either NADPH oxidase activity or SOD2 expression or both alters superoxide levels in both cytoplasm and in mitochondria. Surprisingly, Nox 4 (a NADPH oxidase isozyme) is important in mitochondrial superoxide generation. 2) Loss of aortic compliance occurs with aging (in association with increased superoxide levels) in mice on apoE<sup>-/-</sup> background. Upregulation of superoxide (in aged SOD2<sup>+/-</sup> mice) in the absence of atherosclerosis also increases aortic stiffness. 3) Increased aortic stiffness contributes to left ventricular hypertrophy, increased LV diastolic volumes and decreased LVEF. 4) Mice with reduced cellular superoxide levels have decreased atherosclerosis at young ages, but by 16 months the impact of age outweighs modulation of superoxide levels. 4) Total PTP activity as well as the activity of specific PTPs (PTPs (PTB1B and dual-specificity lipid and protein phosphatase, PTEN) are decreased in aged VSMC compared with young VSMC, correlating with both enhanced oxidation of these proteins and increased cytokine-induced inflammatory signaling, adhesion molecule expression and monocytes adhesion.

Taken together, these data provide a global indication that ROS, aging and CVD are tightly related and that multiple pathways are involved in ROS regulation and resulting physiologic abnormalities.



### Genetic Modifiers of Peripheral Arterial

Brian H. Annex, MD, University of Virginia, Charlottesville, VA

Although long under-recognized and therefore under-diagnosed in the medical community, peripheral arterial disease (PAD) caused by atherosclerosis that impairs blood flow to the lower extremity is now recognized as a significant public health problem. The incidence of PAD is now recognized to be nearly equal to that of coronary artery disease. The prevalence of PAD increases with advancing age, and diabetes, and cigarette smoking account for 80% of the age-adjusted increase risk for PAD. The two major clinical manifestations of PAD are intermittent claudication (IC) and critical limb ischemia (CLI). IC is characterized by inadequate blood flow to the lower limb during walking which causes pain that is relieved with rest. CLI is characterized by rest pain with or without associated ulcers or gangrene. While it is logical to assume that CLI simply represents a late stage manifestation of PAD, the risk factors for IC and CLI are the same, patients with IC and CLI can have identical hemodynamic measures and even the same anatomy of occlusive atherosclerosis.

Genetic screens in mouse models of disease have been successfully employed to elucidate the genetic contribution to and potential targets for a number of disease states. These discoveries have opened up new avenues into physiological pathways involved in their respective disease phenotypes. Thus, utilizing mouse models we identified strain-specific differences in outcomes following surgical induced hind-limb ischemia, an accepted pre-clinical model of PAD. Specifically, we found distinct outcomes in wild-type C57BL/6 and BALB/c mice. Utilizing additional genetic approaches we identified a quantitative trait locus (QTL) on the short arm of mouse chromosome 7 that contains a gene or gene(s) that are responsible for the genetic differences in mice. Ongoing efforts have been underway to allow us to begin to identify the gene or gene of interest and an update on this approach will be presented. In addition, work is underway to identify potential human homologues to the mouse genes.

This approach offers the opportunity to identify potential new diagnostic and therapeutic approaches for patients with PAD (either IC or CLI) and has the advantage of not "a priori" requiring that a gene or gene(s) meet a preset profile to be a candidate. Peripheral arterial disease is a major health care problem for which new therapeutic approaches are desperately needed.



### Comprehensive Magnetic Resonance in Peripheral Arterial Disease

Christopher M. Kramer, M.D., University of Virginia, Charlottesville, VA

Peripheral arterial disease is common, affecting almost 15% of individuals over 70 and there are few effective medical therapies. The goal of our recent work has been to develop novel imaging methods for clinical trials in PAD to enhance development of new therapies. Techniques our group has developed and validate include black-blood MRI of atherosclerotic plaque volume and characteristics in the superficial femoral artery for plaque progression/regression studies. We have shown that measuring phosphocreatine recovery kinetics at peak exercise using 31) MR spectroscopy is a reproducible technique for differentiating patients with PAD from normal subjects. First-pass contrast-enhanced imaging of calf muscle at peak exercise can be used to assess calf muscle blood flow and differentiates PAD from normal subjects at equivalent workloads. Measuring stress and rest perfusion to enable assessment of perfusion reserve reduces overall reproducibility of the technique because of the extremely low perfusion in resting skeletal muscle. In patients who cannot receive gadolinium due to underlying severe chronic renal disease, we have applied arterial spin labeling techniques to measure peak exercise calf muscle flow on a ml/min/g basis without contrast.

All of these techniques have been put together along with MRA and exercise performance measures in a clinical trial of LDL lowering in 87 patients with PAD. At baseline, we demonstrated that both phosphocreatine recovery kinetics and calf muscle perfusion correlate with exercise performance but not with each other, suggesting an intrinsic mitochondrial defect in PAD. Statin-naïve patients were randomized to either simvastatin 40 mg (S) or simvastatin 40 mg/ezetimibe 10mg (S+E). Patients already on statins with an LDL still >80 were treated with open-label ezetimibe (E). Patients were studied at baseline and annually at 2 years. LDL fell lowest in the S+E group but all groups had significant LDL lowering. In the statin-naïve patients, SFA plaque regressed without a difference between S and S+E. In E, plaque progressed significantly at a rate of 4% per year. These results suggest that the baseline status of statin therapy is an important determinant of benefits of LDL lowering and that adding ezetimibe to a patient already on a statin allowed plaque regression despite effective LDL lowering. Analysis of plaque components has shown that LDL lowering is associated with a reduction in lipid component in the plaque without a significant change in calcification, loose matrix, or fibrous tissue. Results of the studies of physiology did not demonstrate any benefit of LDL lowering in the patient group as a whole on phosphocreatine recovery kinetics, calf muscle perfusion, macrovascular disease by MRA, exercise treadmill performance, VO<sub>2</sub>, or 6-minute walk test. The resting ABI did improve somewhat at the 2 year time point. Thus, LDL lowering does not improve exercise capacity or calf muscle physiology in PAD although there was no decline in these parameters as might be expected.

Ongoing and future studies include optimization of non-contrast methods of calf muscle perfusion, development of cuff occlusion/hyperemia measures of calf blood flow for use in critical limb ischemia, testing of these techniques before and after percutaneous revascularization, and demonstrating the mechanisms of benefit of exercise therapy in PAD.



### In-Vivo Risk Stratifications of Individual Coronary Artery Plaques: A New Preemptive Paradigm for Management of Patient with Coronary Artery Disease

Peter H. Stone, M.D., C.L. Feldman, Y. Chatzisis, K. Koskinas, G.K. Sukhova, E. Edelman, Peter Libby, Brigham & Women's Hospital, Boston, MA

Atherosclerosis is a systemic disease with multifocal manifestations. Multiple coronary plaques at different stages of progression coexist within the same patient and even within the same artery, and each plaque develops and progresses in a highly individual manner. If it were possible to identify the early stages of a coronary plaque destined to become high-risk either to rupture and cause an ACS or to progress rapidly and cause severe stable angina then preemptive, highly selective, local interventions could be applied to avert adverse cardiac events.

Local intravascular hemodynamics, especially endothelial shear stress (ESS), and local plaque/arterial wall morphology characteristics determine the natural history of each coronary plaque. ESS is the tangential stress derived from the friction of blood flowing across the endothelial surface of the arterial wall. ESS is low in the inner aspects of curves, downstream from an obstruction, and at the outer waist of a bifurcation; ESS is high on the outer portion of curves and at the throat of an obstruction. In-vitro and ex-vivo studies have demonstrated that low ESS is intensely pro-atherogenic and pro-inflammatory, which physiologic ESS fosters quiescence, and high ESS may lead to platelet activation/adhesion. New methodologies ("vascular profiling" utilizing coronary angiography and IVUS) now allow for in-vivo detailed characterization of ESS and plaque/wall morphology in coronary arteries.

Using serial, in-vivo vascular profiling assessment in diabetic, hypercholesterolemic pigs we demonstrated that: (1) low ESS is an independent predictor of the development of high-risk coronary plaque; (2) there is a close correlation between the magnitude of local low ESS and the severity of the local atherosclerotic phenotype; (3) low ESS augments the expression/activity of elastases and collagenases in the intima; (4) the local arterial remodeling patterns and local ESS change substantially over time and determine future plaque evolution; and (5) the combined assessment of ESS, arterial remodeling, and plaque severity enable the early identification of plaques that evolve to high-risk lesions.

On the basis of supportive pilot studies in humans we designed, and just completed, a large clinical trial (The PREDICTION Study) to investigate the hypothesis that in-vivo vascular profiling results can predict local plaque progression and anatomic sites response for new cardiac events. We studied 506 pts in Japan treated with a stent for an ACS, who underwent 3-vessel vascular profiling following stent placement, and were then followed for 1 yr. In 374 consecutive pts routine follow-up vascular profiling was repeated 6-10 months later to determine local plaque natural history. All pts with a clinical event during follow-up underwent follow-up cath and vascular profiling to attribute the baseline plaque which was responsible for the new clinical event. The study will determine the effect of local ESS, plaque morphology, and arterial remodeling on the natural history of individual coronary plaques and whether culprit lesions can be predicted prior to the onset of a clinical event. Available results will be presented.



## 25 Years of Endothelial Research in Humans: Where We Have Been and Where We Are Heading?

Peter Ganz, M.D., San Francisco General Hospital and University of California, San Francisco, CA

Much progress has occurred in the understanding of the biology of the endothelium since the discovery of endothelium-dependent vasorelaxation by Furchgott in the rabbit aorta in 1980 and our first published description of endothelial function in humans in 1986. Nitric oxide (NO) mediates many of the protective functions of the endothelium. In humans, endothelial dysfunction has been linked to all known risk factors for atherosclerosis. It has been detected in conduit arteries and in resistance arterioles and in coronary as well as peripheral arteries. This recognition of endothelial dysfunction as a systemic disorder has facilitated non-invasive testing of endothelial function in accessible peripheral arteries. Clinical investigations strongly support an anti-atherogenic role for NO. Coronary endothelial dysfunction in cardiac transplant recipients is associated with rapidly progressive vasculopathy. Endothelial dysfunction in the brachial artery is associated with rapid progression of carotid intima-medial thickness. Numerous studies demonstrate a strong association between endothelial dysfunction and cardiovascular events. Commonly used therapies in the treatment of atherosclerosis reverse endothelial dysfunction. Improvement in endothelial function also partly accounts for the lipid-independent benefits of statins. The observation in clinical studies that therapeutic interventions restores normal endothelial function in some subjects but fails to do so in others has been used to differentiate clinical responders from non-responders. As endothelial function is a central component of cardiovascular disorders, it is used by the scientific community as well as by pharmaceutical industry to gain pathophysiologic insights and develop novel therapies.

Current research in Dr. Ganz's laboratory examines the molecular basis of endothelial dysfunction in human subjects. The approach is made possible by using guidewires to retrieve viable endothelial cells from human arteries or veins. Such cells can then be studied to reveal quantities of key proteins and also the cell's functional modifications of such proteins, particularly their phosphorylation state. These endothelial cells can also be examined for the abundance of nitrotyrosine, a footprint of nitric oxide inactivation by excess superoxide free radicals common in cardiovascular diseases. Also an assessment of the level of messenger RNA expression will provide further mechanistic insights into the biology of endothelial dysfunction in human diseases; important factors in the identification of therapeutic targets. Human endothelial studies are an extraordinary example of successful research over the past 25 years.



## Reproductive health and Cardiovascular Disease

Pamela Ouyang, MBBS with thanks to collaborators and participants of the Multi-Ethnic Study of Atherosclerosis (MESA). Johns Hopkins University, Baltimore, MD

Women have less cardiovascular (CV) disease than men. Ovarian dysfunction and pregnancy may impact CV health. Pregnancy is associated with marked hemodynamic changes. It is not clear whether the changes occurring during pregnancy are cumulative such that an increasing number of pregnancies are associated with differences in later left ventricular (LV) function/structure. Ovarian failure manifest as early menopause has been associated with increased CV mortality in some populations. We explored these questions within the MESA study, which includes White, African-American, Hispanic and American Chinese women free of CV disease at study entry.

Parity: We used linear regression models to relate singleton live births (SLB) and LV measures on cardiac MRI. LV structural measures were indexed to height. Models were adjusted for sociodemographic factors. Among 2234 women (mean age 62 y), the number of SLB was positively associated with LVED volume, LVES volume, end-diastolic mass, and stroke volume and inversely associated with LVEF. SLB was not associated with LV mass-to-volume ratio. Additional adjustment for potential biologic mediators attenuated the results only slightly. There was no effect modification by ethnicity. This analysis shows that the number of singleton live births is associated with key LV structural and functional measures in middle to older ages, even after adjustment for sociodemographic factors and CV disease risk factors, suggesting that hemodynamic changes during pregnancy may have long-term effects on cardiac structure/function beyond childbearing years.

Menopausal age: This analysis included 2509 postmenopausal women. Early menopause (either natural or surgical) was defined as occurring at age <46 y. CV events were MI, resuscitated cardiac arrest, angina, stroke, stroke death, CHD death, or other CVD death. Kaplan-Meier statistics estimated the proportion of women experiencing CV events with age as the underlying timescale, allowed for delayed entry at enrollment. Adjusted survival age analyses included race, risk factors, and whether menopause was natural or surgical. Early menopause was reported in 693 of the 2509 women (28%: 10% early surgical and 18% early natural). Kaplan-Meier curves showed women with early menopause had an increased risk for CVD events (logrank  $p=0.0003$ ). After adjustment for risk factors, this association remained statistically (HR 2.11, 95% CI 1.34, 3.32) which was largely unaffected by adjustment for HRT and BMI. Thus early age at menopause (natural or surgical) is positively associated with CVD events, independent of cardiovascular risk factors and HRT use.

Reproductive factors should be considered in evaluating later life CVD in women.



### Role of Epoxyeicosatrienoic Acids in Syndrome X in Women

Sanjiv Kaul, Nandita Gupta, Nabil Alkayed, Diana Rinkevich, Oregon Health and Science University, Portland, OR

**Background:** Women with chest pain and a positive imaging stress test in the absence of obstructive coronary artery disease are thought to have microvascular disease (syndrome X). More the arachidonic acid metabolite, epoxyeicosatrienoic acids (EETs), has been shown to be a potent endothelium-derived vasodilators of the coronary microcirculation. We therefore hypothesized that patients with syndrome X have reduced levels of EETs that can explain their coronary microvascular abnormalities.

**Methods and Results:** We studied 9 such women (group I) and 14 controls (group II). Coronary flow reserve (CBFR) was measured with myocardial contrast echocardiography (MCE). Plasma levels EETs' stable metabolite, 14,15-Dihydroxy-eicosatrienoic acid (DHETs), were quantified in both groups of women using liquid chromatography. MCE revealed significantly reduced CBFR in group I compared to group II patients ( $1.5 \pm 0.7$  versus  $2.9 \pm 1.0$ ,  $p=0.003$ ). Similarly, DHETs levels were significantly reduced in group I compared to controls (247 ng/mL versus 336.76 ng/mL,  $p<0.05$ ).

**Conclusions:** Women with syndrome X have lower CBFR which is associated with lower levels EETs, which are potent endothelium-derived vasodilators of coronary micro-circulation. These preliminary results indicate that EETs should be investigated as the causal link between ischemia and reduced CBFR in women with syndrome X.

### Antiplatelet Therapy and Proton Pump Inhibition – Good or Unnecessary Risk?

D L Bhatt, B L Cryer, C F Contant, et al. Brigham & Women's Hospital & VA Healthcare System

**Background:** Gastrointestinal complications are an important problem with antithrombotic therapy. Proton pump inhibitors are believed to decrease this risk, though no randomized trial has proved this with dual antiplatelet therapy. Recently, concerns were raised about the potential for proton pump inhibitors to blunt clopidogrel's efficacy.

**Methods:** Patients with an indication for dual antiplatelet therapy were randomized to receive combination clopidogrel plus omeprazole versus clopidogrel plus placebo, in addition to aspirin. The primary GI endpoint was a composite of overt or occult bleeding, symptomatic gastroduodenal ulcers or erosions, obstruction, or perforation. The primary cardiovascular endpoint was a composite of cardiovascular death, myocardial infarction, revascularization, or stroke. The trial was terminated prematurely when the sponsor lost financing.

**Results:** Out of a planned ~5,000 patients, 3,873 were randomized; 3,761 patients were available for analysis. GI event rates (N = 51 first events) were 1.09% with omeprazole and 2.92% with placebo at 180 days, HR = 0.34, 95% CI: 0.18-0.63,  $p<0.001$ . GI bleeding was also reduced, HR 0.13, 95% CI: 0.03-0.56,  $p = 0.001$ . Cardiovascular events (N = 109) were 4.88% with omeprazole and 5.67% with placebo, HR = 0.99, 95% CI (0.68, 1.44),  $p = 0.96$ ; high-risk subgroups showed no heterogeneity. There was no difference in serious adverse events, though diarrhea was increase with omeprazole.

**Conclusions:** In patients receiving aspirin and clopidogrel, prophylactic proton pump inhibitors reduced upper gastrointestinal bleeding. There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but the results do not rule out a clinically meaningful difference.

**Abnormal Cardiac Sodium Channel mRNA Splicing in Human Heart Failure and the Possibility of a Blood Test to Help Predict Arrhythmic Risk**

Ge Gao, An Xie, Shu-Ching Huang, Anyu Zhou, Amanda M. Herman, Sssan Ghassemzade, Euy-Myoung Jeong, Michael A. Sobieski, II, Geetha Bhat, Antone Tatoes, Edward J. Benz, Jr., Timothy J. Kamp, Samuel C. Dudley, Jr., University of Illinois at Chicago, Chicago, IL

**Introduction:** Heart failure (HF) remains a substantial clinical problem affecting millions of Americans, and HF-associated arrhythmia remains a cause of the high morbidity and mortality. A number of human diseases are associated with alternative mRNA splicing.

**Methods and Results:** Gene array comparisons between normal human and HF tissue demonstrated with 47 splicing factors, associated with all major spliceosome components, were upregulated. This suggested that alternative mRNA splicing may be a major pathological feature of and contribute to the arrhythmic risk in HF. We have shown that abnormal mRNA splicing in human HF affects the cardiac Na<sup>+</sup> channel (encoded by SCN5A), the main ion channel generating current for conduction in the heart. In HF, SCN5A has two truncated mRNA alternative splicing variants that are upregulated with a concomitant decrease in the full-length transcript. The SCN5A variants encode prematurely truncated, nonfunctional Na<sup>+</sup> channel proteins missing the segments from domain IV, S3 or S4 to the C-terminus. These splice variations help explain a loss of Na<sup>+</sup> channel protein seen in HF. Angiotensin II and hypoxia were shown to lead to upregulation of two splicing factors, LUC7L3 and RBM 25, responsible for abnormal mRNA splicing of SCN5A in human HF. LUC7L3 and RBM 25 were elevated in human HF tissue and mediated truncation of SCN5A, mRNA in both Jurkat cells and human embryonic stem cell-derived cardiomyocytes. White blood cell (WBC) SCN5A splicing was shown to correlate with that in heart, consistent with WBC mRNA abundances of RBM25 and LUC7L3 being increased in HF. The WBC ratios of SCN5A variants E28C normalized to the full-length SCN5A transcript were increased in HF patients as compared to a control group. Elevations in SCN5A variant ratios predicted implanted cardiac defibrillator (ICD) shock risk.

**Conclusions:** Downregulation of the cardiac sodium channel in human HF occurs in part because of an upregulation of mRNA splicing factors, LUC7L3 and RBM25. Similar events occur in circulating WBC's of HF patients, suggesting that assessment of WBC mRNA splicing may serve as a surrogate for the arrhythmic risk related to Na<sup>+</sup> channel downregulation in the heart. Finally, therapies directed at reducing the activation of RBM25 and LUC7L3 or their upstream inducing stimuli may prevent the reduction in cardiac Na<sup>+</sup> channels seen in HF and reduce arrhythmic risk in this condition.

**Neuregulin/erbB Signaling in the Heart – Update on Biology and Clinical Implications/Applications**

Douglas B. Sawyer, M.D., Vanderbilt University Medical Center, Nashville, TN

The neuregulin-1 (NRG-1) gene encodes a family of growth factors that play a critical role in cardiac development and the maintenance of the adult heart. The biological effects of NRG-1 are mediated through a set of tyrosine kinase receptors including ErbB2 (a.k.a. HER2/neu), ErbB3 and ErbB4. Experimental work in animals shows that NRG-1/erbB signaling is involved in proliferation, differentiation and survival of cells in many tissues including both cardiac and skeletal muscles. One interesting facet of NRG-erbB biology is its ability to regulate focal adhesion formation at the intercalated disk of cardiac myocytes, where ErbB2 and ErbB4 receptors are most heavily localized. NRG-1 $\beta$  is expressed in cardiac microvascular endothelial cells, and is activated by oxidative stress via a metalloproteinase. Exercise leads to activation of skeletal muscle NRG/erbB signaling, and in healthy subjects a form of NRG-1 $\beta$  circulates in proportion to fitness. Thus in this context circulating NRG-1 $\beta$  may be an indicator of cardiovascular health. We have also found that in rodent heart NRG-1 $\beta$  is activated by ischemia-reperfusion injury, and that in a cohort of heart failure subjects serum NRG-1 $\beta$  levels are proportional to severity of illness and correlates with likelihood of adverse events. Thus in this context NRG-1 $\beta$  appears to be an indicator of ongoing myocardial stress or injury. Inhibition of NRG/erbB signaling during ischemia-reperfusion injury results in disruption of cell-cell contact and impaired recovery of mechanical function. Parenteral administration of recombinant NRG-1 $\beta$  to animal models of systolic heart failure leads to improved cardiac function and animal survival, laying the groundwork for ongoing clinical trials with recombinant NRG-1 $\beta$  in systolic heart failure.

**AMP-Activated Protein Kinase Conducts the Stress Response Orchestra in the Heart**

Edward Miller, Ji Li, Ramyond Russell, Dake Qi, Vlad Zaha, Jenna Ross, Richard Bucala, Lawrence H. Young. Yale University School of Medicine, New Haven, CT

AMP-activated protein kinase (AMPK) has emerged as an important stress signaling pathway and a potential target for pharmacologic intervention in ischemic heart disease, diabetes and cancer. AMPK is a ubiquitously expressed protein that acts as a sensor of cellular energetics and is activated by several types of cell stress including myocardial ischemia. Activated AMPK orchestrates an array of downstream pathways that work in a coordinated fashion to increase energy production and inhibit energy utilization by non-essential anabolic pathways. We originally identified AMPK as the trigger for increased GLUT4 translocation to the sarcolemma which augments glucose transport in the ischemic heart, and then went on to establish a broader role for AMPK in protecting against apoptosis and necrosis during ischemia-reperfusion. Intrinsic AMPK activation conserves energy during ischemia and also prevents reperfusion injury by inhibiting JNK pathway activation and mitochondrial permeability transition pore opening. Treatment with novel compounds that directly activate AMPK, through interaction with its regulatory beta-subunit, prevent cardiac injury during ischemia to a degree similar to ischemic preconditioning. Although AMPK is critically regulated by energetics, other factors modulate its activation. We demonstrated a novel action for the inflammatory cytokine macrophage migration inhibitory factor (MIF) as an autocrine-paracrine activator of heart AMPK. Human cells with a low expression polymorphism in the MIF promoter have diminished MIF secretion and AMPK activation during hypoxia and increased JNK activation during reoxygenation. Thus, MIF appears to have a functionally adaptive role to amplify AMPK activation and individuals with the low expression MIF promoter might be at increased risk for ischemic injury and stand to benefit most from AMPK-directed therapy. Finally, AMPK is activated by an upstream kinase, LKB1, which phosphorylates an activating site in the catalytic domain of the AMPK alpha subunit. While critical to AMPK activation during ischemia, LKB1 also activates 12 other AMPK-related kinases, whose function is poorly understood in mammalian cells. Recently we found that cardiac-specific LKB1 deletion results in early onset atrial fibrillation, cardiomyopathy and early death in a mouse model. This phenotype is quite distinct from that specific AMPK inactivation in the heart pointing to a critical role for one or more AMPK-related kinases in heart growth and development. Thus, the LKB1-AMPK pathway is a critical cardiac signaling mechanism and has potential as a target for translational therapies to protect the heart and other solid organs against ischemia.



**Role of Transforming Growth Factor in Atrial Fibrillation**

Jeffrey Olgin, M.D., University of California, San Francisco, San Francisco, CA

Previous studies have shown that atrial fibrosis is an important substrate for atrial fibrillation (AF). A cardiac-restricted ( $\alpha$ -MHC promoter) transgenic mouse model (Tx) overexpressing TGF- $\beta$ 1 has previously been shown to result in selective atrial fibrosis and a greater propensity to AF. Our lab focuses understanding the mechanism of this selectivity and its relevance to human AF. Several studies in mice and in humans were undertaken. Transgenic mice overexpressing TGF- $\beta$ 1 revealed significantly greater atrial fibrosis, increased atrial conduction times, and substantially greater vulnerability to AF. Despite similar TGF- $\beta$ 1 transgene levels and TGF- $\beta$ 1 activity in each chamber, there was enhanced fibrosis in the atrium and none in the ventricle. Pharmacologic blockade of the TGF- $\beta$ 1 receptor-1 kinase with Ki26894 demonstrated a marked decrease in expression of fibrosis-related genes in the atria of the Tx mice, confirming that the observed atrial fibrosis was due to TGF- $\beta$ 1 signaling. Microarray analysis of the atria revealed that 80 genes were differentially expressed in response to TGF- $\beta$ 1 overexpression, whereas analysis of the ventricles revealed only 2 differentially expressed genes. TGF- $\beta$ 1 increased expression of fibrosis related genes and phosphorylation of Smad2 in the atrium but not the ventricle.

Human studies from our lab confirm the importance of this pathway in atrial fibrillation. Right atrial appendage samples from patients undergoing open heart surgery revealed significantly higher levels of TGF- $\beta$ 1 and significantly greater TGF- $\beta$ 1 activity (determined by a mink lung epithelial cell assay using a PAI-1 luciferase reporter) in those that subsequently developed post-operative AF. In a cohort of community dwelling men, variants in single nucleotide polymorphisms in the promoter region of TGF- $\beta$ 1 were more common in those with AF. Lastly, in patients with failing hearts, there is elevated levels of TGF- $\beta$ 1 in the atria but not the ventricles.

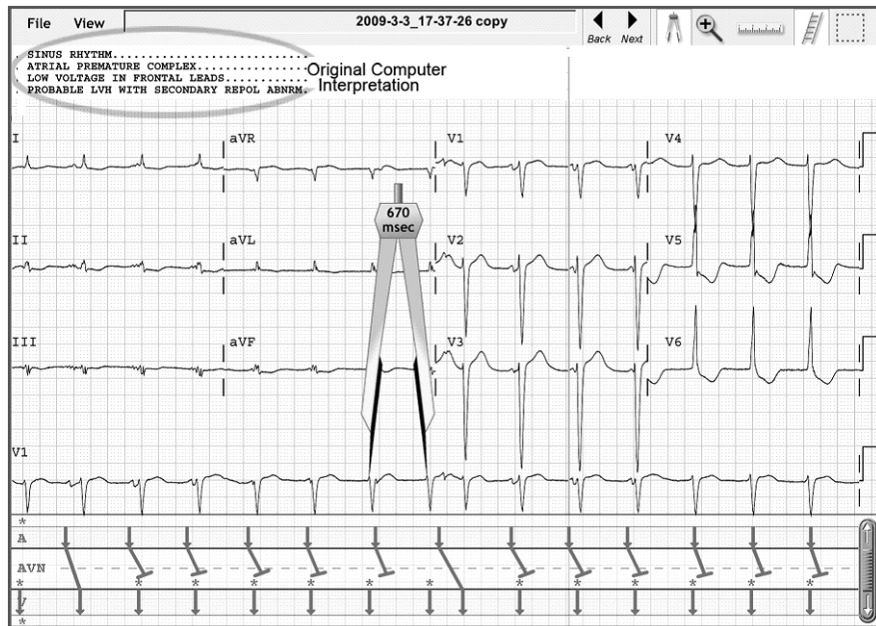
We conclude that TGF- $\beta$ 1 is important in AF, likely as a result of selective atrial fibrosis that occurs via the classical Smad pathway. The differential fibrotic response between the atrium and the ventricle appears to occur at the level of TGF- $\beta$ 1 receptor binding or phosphorylation.



### The 3600 ECG Challenge for Fellows & Faculty: Problem and Solution

John Michael Criley, David G. Criley, Melvin M. Schienman, Harbor-UCLA Medical Center, Torrance, CA and UCSF, San Francisco, CA

**Problem:** Cardiology Fellows (CFs) must interpret 3600 ECGs as a board requirement. If the mandate is to have educational value a 3-year program with 5 CFs requires over-reading by faculty of up to 6,000 ECGs/yr. **Our Solution:** CF's interpret ECGs on a commercial reading station, after which faculty approves correct interpretations while storing misread and "good teaching ECGs" on a flash drive. Selected ECGs are digitally projects at a weekly conference in **ECGviewer** format (shown below). The CF used mouse-driven tools: calipers, rate ruler, magnifier, and can construct onscreen ladder while being critiqued by peers and faculty. Automated conversion of pdf to **ECGviewer** format can be performed in less than one minute/ECG and stored as 100kB images.



## UPCOMING MEETINGS

January 12-14, 2012  
Carmel Valley Ranch, Carmel, California

January 9-11, 2013  
Renaissance Vinoy, St. Petersburg, Florida

