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Cardiovascular Working Group

John F. Keaney, Jr., MD

In January, the Cardiovascular Working Group featured a presentation from both Scot Wolfe, Ph.D. and Nathan Lawson, Ph.D., both of Molecular Medicine and the Program in Gene Function and Expression. Scot's presentation focused on his exciting work "engineering" zinc-finger

nucleases that can be inserted into cells to cleave DNA at specified sites. He presented data that his group now has a library of nucleases that are specific for certain sequences and afford the modification of organismal DNA in vivo. One of the obvious implications of this work was the generation of genetically modified animals, particularly knockouts, using the zinc

finger nucleases. To this end, Nathan presented his data on zebrafish where they have been able to use the nucleases to produce targeted mutations in the zebrafish germ line. One example they recently published was modulation of the VEGF receptor known as kdr. These exciting new findings have the potential to break new ground in the production of genetically modified animals, particularly species other than the mouse, where this capacity is lacking.



Faculty Spotlight

Ira Ockene, MD

This month's feature attending is *Ira Ockene MD*. Dr. Ira S. Ockene is the David and Barbara Milliken Professor of Preventive Cardiology and the Director of the Preventive Cardiology Program.

He is an active clinician and teacher, working with students, house staff,

fellows and his peers in the catheterization laboratory, coronary care unit, hospital wards and in the clinics. He has been continuously NIH funded for over 20 years, with his research interests specifically directed at increasing our knowledge of methodologies to improve preventive interventions directed at

the patient, the provider, and the system. He is presently in the analysis phase of the Lawrence Latino Diabetes Prevention Program, an NIDDK-sponsored project designed to prevent the development of diabetes in Latino pre-diabetic participants living in Lawrence, Massachusetts. The analysis is disclosing a



Joseph Bouchard, MD

Research Summary:

During the past months, we have continued our work on stress cardiomyopathy (SC). We recently presented an abstract at the 12th Annual Scientific meeting of the Heart Failure Society of America, in Toronto. Below is a brief synopsis:

Stress cardiomyopathy, was first reported by Japanese authors in the early 1990s¹. Since that time, it has become an increasingly recognized entity and is currently thought to represent 0.7%-2.0% of patients presenting with what was thought to be acute coronary syndrome^{2-3, 5}.

The treatment and outcome of SC differs from that of acute coronary syndrome, but the initial presentation and diagnostic approach is usually similar. As SC overwhelmingly afflicts women, we compared initial clinical characteristics, biomarkers, EKGs and cardiac diagnostics of women with SC with those presenting with acute anteroapical myocardial infarction (AAMI).

The aim of this study was to develop prospective criteria to distinguish between SC and AAMI and compare their hospital course and treatment. 27 women with SC were identified and compared to 25 consecutive women with AAMI. We found that in general the demographics and initial clinical data of women with SC is virtually indistinguishable from those with AAMI. The only statistically different parameter that we found was a longer QTc in SC group. We concluded that the initial approach to SC patients should be identical to that of AAMI.

We have now collected over 100 patients in our stress cardiomyopathy database and are in the process of writing a descriptive study of our findings. Our future focus will turn to the mechanisms responsible for stress cardiomyopathy.

1. Dote K, Sato H, Tateishi H *et al*. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. *J Cardiol*. 1991;21(2):203-214.
2. Pilliere R, Mansencal N, Digne F *et al*. Prevalence of Tako-Tsubo Syndrome in a large urban agglomeration. *Am J Cardiol*. 2006;98:662-665.
3. Kurowski V, Kaiser A, von Hof K *et al*. Apical and midventricular transient left ventricular dysfunction syndrome. Frequency, Mechanisms, and Prognosis. *Chest*. 2007;132:809-816.
4. Prashad A. Apical Ballooning Syndrome. An important differential diagnosis of acute myocardial infarction. *Circ*. 2007;115e56-59.
5. Gianni m, Dentali F Grandi A *et al*. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *European Heart Journal*. 2006;27:1523-1529.

Publications

Peer Reviewed:

- Bouchard JL, Aurigemma GP, Hill JC *et al*. Usefulness of the pulmonary arterial systolic pressure to predict pulmonary arterial wedge pressure in patients with normal left ventricular systolic function. *Am J Cardiol*. 2008 Jun 1;101(11):1673-6.
- Bouchard JL, Aurigemma GP, Goldberg RJ *et al*. Heart failure in the "oldest old": clinical and chocardigraphic insights. *Am J Geriatr Cardiol*. 2007 Jul-Aug; 16(4):236-42.
- Nguyen GH, Bouchard JL, Boselli MG *et al*. DNA stability and Schizophrenia in Twins. *Am J Med Genet B Neuropsychiatr Genet*. 2003 Jul 1;120B(1):1-10.
- DiFranza JR, Savageau JA, Bouchard JL. Is the standard compliance check protocol a valid measure of the accessibility of tobacco to underage smokers? *Tob Control*. 2001 Sep;10(3):227-32.

Book Chapters:

- *Handbook of Molecular-Genetic Techniques for Brain and Behavior Research*. Analyzing genomic DNA discordance between monozygotic twins. Bouchard J, Goulon C, Storm N, Nguyen GH, Smith CL. Elsevier Science 1999. Volume 13, 237-256.

Presentations:

- Clinical Characteristics of Stress Cardiomyopathy ("Takotsubo Syndrome") vs. Acute Anterior Myocardial Infarction: A Case Control Study in Women. Bouchard JL, Fitzgibbons T, Seth A, Tighe TA, Aurigemma GP. Presented at the 12th Annual Scientific meeting of the Heart Failure Society of America, Toronto, ON Canada; September 21-24th, 2008.
- Right Ventricular Dysfunction in Transient Stress Cardiomyopathy: Prevalence and Clinical Characteristics. Fitzgibbons TP, Madias C, Seth a, Bouchard JL, Pandian NG, Kuvin JT, Patel AR, Meyer TE, Aurigemma GP, Tighe GP. Presented at the American College of Cardiology 57th Annual Scientific Session, Chicago, IL; March 29th-April 1st 2008.
- Circumferential strain is independent of left ventricular geometry. Narayanan A, Aurigemma GP, Hill JC, Hurlburt HM, Bouchard JL, McNamee A, Zichittella Z, Ennis CA, Tighe DA. Presented at the 18th Annual Scientific Session, Seattle, WA; June 16-20th 2007.
- Pulmonary Artery Systolic Pressure: The "Poor Man's" Left Atrial Pressure? Bouchard JL, Aurigemma GP, Hill JC, Ennis CA, Tighe DT. Presented at the 17th Annual Scientific Session of the American Society of Echocardiography, Baltimore, MD; June 3-7th 2006.
- Heart failure in the "oldest old": clinical and echocardiographic insights. Bouchard J, Aurigemma GP, Goldberg RJ *et al*. Presented at the 16th Annual Scientific Session of the American Society of Echo-cardiography, Boston, MA; June 15-18th 2005.

Spotlight on Research

Allison McNamee, RN

Title: A Comparison of Prasugrel And Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed - The Trilogy ACS Study



Acronym:
Trilogy (ACS)

Purpose of Study:

To find out if Prasugrel can help patients with a heart attack or symptoms associated with a threatened heart attack by reducing death, future heart attacks or stroke.

Study Design:

Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled

Inclusion Criteria:

1. UA/NSTEMI index event within 7 days of randomization
2. A decision for medical management only
 - Subjects who are randomized no later than 24 hours following onset of the index event, prior Clopidogrel treatment is not a consideration for eligibility.
 - Subjects who are randomized beyond 24 hours of onset of the index, commercial Clopidogrel must have been received no later than 24 hours following the onset of the index.
3. Have had at least one of the following 3 high-risk features at the time of the event
 - Age greater than or equal to 60 years
 - Prior MI as evidenced by pre-existing
 - Q wave, or demonstration of infarction on imaging studies, or prior documentation of elevated cardiac markers
 - Diabetes Mellitus
4. Have at least one coronary artery stenosis greater than 50%.

Study Plan:

- Subjects will be randomly assigned in a 1:1 ratio to study treatment with either Prasugrel or Clopidogrel and a low dose of aspirin.
- Subjects receiving commercial Clopidogrel treatment at the time of randomization will have this discontinued.
- Subjects who are randomized less than 24 hours following the onset of the index event and who are not receiving commercial Clopidogrel will receive a loading dose of randomized Prasugrel or Clopidogrel.
- The randomized maintenance dose of prasugrel will differ based upon age and body weight.

800 sites globally

Total duration of study -30 months

News from the Clinic



Karen Berni-Giarusso, RN, BSN and Theo Meyer, MD, DPhil

DOSE-AHF TRIAL: Diuretic Optimal Strategy Evaluation in Acute Heart Failure

Study sponsor: National Institute of Health and National Heart, Lung and Blood Institute.

Rationale: Although most patients admitted with AHF receive IV furosemide treatment, little data exist to guide dosing or route of administration. Observational data suggest little relationship between dose and efficacy, and the possibility of dose related adverse effects on renal function and mortality.

Objectives: To evaluate the safety and efficacy of:

- High intensification diuretic strategy vs. low intensification diuretic strategy in AHF
- IV continuous infusion vs. intermittent IV bolus Q12 hours

Study Design: 300 patient randomized, controlled, multicenter double-blind-double dummy clinical trial using a 2 x 2 factorial design

Treatment Regimens:

- High intensification (2.5 x oral dose) IV furosemide by Q12 hours bolus
- High intensification (2.5 x oral dose) IV furosemide by continuous infusion
- Low intensification (1 x oral dose) IV furosemide by Q12 hours bolus
- Low intensification (1 x oral dose) IV furosemide by continuous infusion

Primary Endpoints

Safety: Change in serum creatinine from randomization to 72 hours

Efficacy: Patient global well being assessment by Visual analog scale (VAS) area under the curve for 72 hours

Key Inclusion Criteria : Prior clinical diagnosis of heart failure with daily home use of oral loop diuretic for ≥ 1 month

- Daily oral dose of furosemide ≥ 80 mg and ≤ 240 mg.
- Identified within 24 hours of hospital admission.
- Anticipated need for IV loop diuretics for ≥ 48 hours

Key Exclusion Criteria:

- BNP < 250 ng/mL
- SBP < 90 serum creatinine > 3.0 mg/dL
- ACS within the past 4 weeks

Faculty Spotlight, continued from page 1

Ira Ockene, MD

number of very interesting findings and will be discussed at medical grand rounds on February 12th.

Dr. Ockene is also applying for NIH funding to carry out a study of vitamin D. Once thought to be only of importance for bone health, vitamin D receptors have been found in almost every organ system, and of particular interest, vitamin D deficiency has been correlated with both cardiac and overall mortality. Dr. Ockene is planning to take advantage of data and serum samples from his previous study of Seasonal Variation of Cholesterol, in which blood samples and data on diet, physical activity, light exposure, C-reactive protein, and a number of other variables were collected five times over the course of a year in 600 individuals. Analyzing available sera for vitamin D will permit the definitive analysis of seasonal variation of vitamin D levels and those factors that relate to such variation. This analysis will be followed by the development of a short survey instrument that will allow the prediction of vitamin D deficiency without the need for a blood test, which turns out to be very important on a public health level, as there is substantial evidence that as much as half of the US population is vitamin D deficient. This will be followed by a validation study and ultimately the development of web-based instruments for vitamin D prediction.

Recent publications

McManus DD, Ockene IS. Brief Supported Lifestyle Counseling: Modest Interventions Yield Modest Effects (Editorial). Arch Intern Med 2008;168:129-30.

Ma Y, Pagoto SL, Ockene IS, Merriam PA, and Olendzki BC A Randomized Clinical Trial Comparing Low-Glycemic Index versus ADA Dietary Education among Individuals with Type 2 Diabetes. Nutrition 2008;24:45-56

Griffith JA, Ma Y, Chasan-Taber L, Olendzki B, Chiriboga D, Stanek EJ, Merriam P, Ockene IS. Association between dietary glycemic index, glycemic load and high-sensitivity C-reactive protein. Nutrition 2008; 24(5): 401-6

Olendzki BC, Ma Y, Hebert JR, Pagoto SL, Merriam PA, Rosal MC, and Ockene IS. Underreporting of energy intake and associated factors in a Latino population at risk of developing type 2 diabetes. J Amer Dietetic Assoc 2008;108:1003-1008.

Ma Y, Li W, Olendzki B, Pagoto S, Merriam P, Chiriboga D, Griffith J, Bodenlos J, Wang Y, Ockene I. Dietary Quality One-Year after Diagnosis of Coronary Heart Disease. J Am Diet Assoc 2008;108:240-246

Ma Y, Hébert JR, Li W, Bertone-Johnson ER, Olendzki B, Pagoto SL, Tinker L, Rosal MC, Ockene IS, Ockene JK, Griffith JA, Liu S. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. Nutrition (in press).

Chiriboga DE, Ma Y, Li W, Stanek III EJ, Merriam PA, Rawson E, Hébert JR, Ockene IS. Gender Differences in Seasonal Variation of High-Sensitivity C-Reactive Protein in Healthy Adults: A Longitudinal Study. Clinical Chemistry (in press)

Pagoto S, Olendzki B, Ma Y, Bodenlos J, Rosal M, Ockene I, Merriam P. Association of Depressive Symptoms and Lifestyle Behaviors among Latinos at Risk of Type 2 Diabetes. J Am Dietetic Assoc (in press).

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Faculty News

New Faculty Member:

Please welcome Peter B. Gibson, M.D., FACC who started with the Division of Cardiovascular Medicine here at UMass Medical School last month.



New Title:

Also, please congratulate Naomi Botkin, M.D., for accepting the position of Fellowship Co-Director. Dr. Botkin will work with the Program Director and assist with our recruiting efforts and provide professional and academic mentorship to our trainees.

New Title:

We are delighted to announce that Dr. Theo Meyer has agreed to become the Clinical Chief for Cardiovascular Medicine. In this position, he will be responsible for the day-to-day clinical operations of Cardiovascular Medicine. Please join me in welcoming Theo to this very important role.

By Dr. John F. Keaney, Jr., Chief, Cardiovascular Medicine

Cardiovascular Working Group Meeting Schedule

Tuesdays at 5:00 PM, Faculty Conference Room S1-342 University Campus

Date	Speaker	Topic
February 17, 2009	Eicke Latz, MD, PhD	"Role of the NALP3 inflammasome in inflammation in atherosclerosis".
March 17, 2009	Marcus P. Cooper, MD	To be determined.

