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Cardiovascular Working Group

John F. Keaney, Jr. MD

Last month's Cardiovascular Working Group featured Yong-Xu Wang, Ph.D., from the Program in Molecular Medicine. Dr. Wang presented his recent findings on brown fat metabolism. Brown fat is more common in rodents than in humans, although a recent series of New

England Journal of Medicine articles provided evidence for brown fat metabolism in humans. Dr. Wang and his team identified twist-1, a transcriptional regulator, as an important component of brown fat metabolism. In particular, they found that twist-1 expression is largely restricted to adipose tissue and that it interacts with peroxisome proliferator gamma coactivator-1alpha (PGC1alpha) to negatively regulate genes involved in mitochondrial metabolism. They also found that twist-1

expression is regulated by PPARdelta. Mice lacking full expression of twist-1 are resistant to diet-induced obesity. Collectively, Dr. Wang's team has identified a new pathway of fat metabolism that may have important implications for both human obesity and its interaction with cardiovascular disease.



Faculty Spotlight

Gerard P. Aurigemma, MD

Dr. Gerard P. Aurigemma was born and raised in Brooklyn, NY and is a graduate of Harvard College (1975) and Harvard Medical School (1979). He completed his medical residency at the University of California at San Francisco and was Chief Medical Resident there following residency. He completed his fellowship in cardiovascular diseases at

the Hospital of the University of Pennsylvania in 1987 and joined the faculty at the University of Massachusetts Medical School that year.

Dr. Aurigemma has a longstanding interest in LV systolic and diastolic function in hypertension, valvular heart disease, and diastolic heart failure. He has devoted much of his career to applying noninvasive imaging techniques, both MRI and echocardiography, to the study of LV function in these disease states.

Dr. Aurigemma is the author of over 120 peer-reviewed original articles and reviews on LV function and other topics in cardiology. He is a member of the American Board of Internal Medicine, Cardiology group and is serving as an associate editor of the textbook *Cardiology* and has edited a monograph on stress echocardiography. He has also served on the editorial board of several cardiology journals, and on the board of directors of the *American Society of Echocardiography* (ASE). He has served as course director for the ASE Board Review



Christopher Ruisi, MD

Dr. Ruisi is currently involved in the revision of 2 manuscripts to be re-submitted to peer-reviewed journals. The first project is under the supervision of Dr.'s Botkin, Gore, and Goldberg and seeks to compare the safety and efficacy of multi-vessel percutaneous coronary revascularization (PCI) to culprit vessel only PCI in the setting of an acute coronary syndrome (ACS). As background, multi-vessel coronary artery disease (MVD) is discovered in a substantial percentage of patients who undergo cardiac catheterization during hospitalization for ACS and is associated with increased morbidity and mortality. While an early invasive strategy is recommended and associated with improved clinical outcomes for patients with high-risk characteristics, it remains uncertain whether the performance of multi-vessel PCI during an ACS is associated with a reduced risk of adverse cardiovascular events. Current guidelines do not specify whether multi-vessel PCI should be considered in the setting of a non-ST-segment elevation ACS while revascularization of the culprit artery only is recommended for most patients with an acute ST-segment elevation myocardial infarction (STEMI). However, no large-scale randomized controlled trials have been performed to address this issue. Accordingly, using data from the multinational Global Registry of Acute Coronary Events (GRACE), they examined the frequency of MVI in patients with MVD who were hospitalized for the spectrum of ACS, examined the clinical features associated with MVI, and compared the efficacy of multi-vessel PCI (MVI) to revascularization of the culprit vessel only (CVI) with respect to various in-hospital and post-discharge outcomes.

To their knowledge, this study would represent the largest multinational study to compare in-hospital and intermediate term

outcomes between MVI and culprit vessel only PCI among patients hospitalized with ACS. In their original version of the manuscript, they observed no differences in the multivariable adjusted hospital risk of recurrent ischemia, coronary artery bypass grafting, major bleeding, and mortality between their two primary comparison groups. At six months after hospital discharge, MVI was associated with a lower incidence of scheduled PCI although the adjusted six month risks of repeat hospitalization, myocardial infarction, and mortality were similar between patients who underwent MVI or CVI. Their study supports findings from other observational reports which have suggested that MVI performed during hospitalization for ACS is relatively safe. However, it also fails to provide substantial evidence to suggest that multi-vessel PCI is associated with improved clinical outcomes. Given the heterogenic nature of their initial population (comprised of patients admitted with unstable angina, NSTEMI, and STEMI) and based upon suggestions from reviewers, they have decided to revise their study to compare MVI with culprit vessel only PCI only among patients admitted with a non-ST segment elevation ACS. In addition, they hope to compare the efficacy of MVI performed in one sitting with MVI performed in a staged approach.

The second manuscript that Dr. Ruisi is revising for resubmission is under the supervision of Dr. Pape and aims to understand the effect of assessing the ascending aorta (AA) at different anatomic and time coordinates using trans-thoracic echocardiography (TTE). As background, two-dimensional TTE provides a non-invasive method of measuring the AA

without the need for contrast or radiation in order to detect pathological dilation. Unfortunately, TTE imaging beyond the sino-tubular junction (STJ) is often limited in routine studies. Furthermore, there is no clearly established method for obtaining measurements and a paucity of published data defining the normal AA dimensions by TTE. Specifically, there are no recommendations about the precise time in the cardiac cycle and at which location in the ascending aorta that measurements should be obtained. The establishment of a standard TTE method for assessment of the AA is crucial in order to define pathologic dilation and allow reliable serial comparisons.

In their original paper, they found that AA diameter significantly increased when measured at progressively further distances from the sino-tubular junction (STJ). Obtaining measurements at end-systole (ES) allowed for better visualization of the more distal aspects of the AA. In addition, measurements obtained during end-systole and mid-systole were slightly but significantly greater than those measurements obtained during end-diastole. Based upon their observations, they recommend standardizing TTE assessment of the AA to a location of 2 cm distal to the STJ during ES and constructed a nomogram defining the normal limits of AA diameter according to age and body-surface area at this location and time. Based upon reviewer suggestions, they are in the process of constructing an additional nomogram to define the normal limits of AA diameter at 2 cm distal to the STJ during end-diastole.

Course for the past few years and has edited a board exam review DVD on behalf of the ASE as well. Dr. Aurigemma is currently Professor of Medicine and Radiology at the University of Massachusetts Medical School and has directed its cardiology fellowship program since 1990. He has been Director of Noninvasive Cardiology at UMass Memorial Health Care, Worcester, MA since 1992.

His current research interests include:

- 1) Systolic and diastolic function in hypertensive heart disease. In collaboration with Jeffrey Hill, RDCCS, Drs. Tighe, Heather Hurlburt, Aru Narayanan, Marcello Chinali (a visiting scholar from the University of Naples) our group is trying to identify subclinical abnormalities in hypertensive heart disease. Our goal is to better understand the cascade of events which characterizes the transition from stable hypertensive disease to heart failure. Under Dr. Chinali's leadership, we have been able to investigate the phenomenon of the transition to LV dysfunction and heart failure among hypertensives enrolled in the LIFE study. We believe that the ultrasound technique of speckle tracking imaging, a cutting-edge ultrasound technique, will enable us to discern subtle abnormalities in systolic function which precede the development of heart failure. Thus far we have completed 2 studies; the first established normal values for this technique and the second was a more comprehensive study of cardiac mechanics in hypertensive disease, which is currently under review at *Circulation*. We are hoping to extend this technique to the study of systolic and diastolic function in knockout mice.
- 2) Reversible LV dysfunction, including the intriguing syndrome of stress cardiomyopathy. This is an entity which Dr. Aurigemma first encountered and was fascinated by almost 25 years ago, during fellowship training. The UMass group, comprised of doctors Dennis Tighe, Theo Meyer, Timothy Fitzgibbons, Joseph Bouchard, and Paula Seth, as well as Dr. Aurigemma, has published or has had accepted for publication 4 papers on descriptive aspects of the syndrome of stress cardiomyopathy, including RV involvement. Current areas of investigation include a review of the first 100 patients seen at UMass Memorial with this syndrome; an investigation of personality traits of stress cardiomyopathy patients (in collaboration with investigators from the Division of Behavioral Medicine); a description of the phenomenon of torsades-des-pointes complicating stress cardiomyopathy; and a description of regional systolic function by speckle tracking imaging in these patients.

Selected publications since 2005:

- Baicu CF, Zile MR, Aurigemma GP, Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. *Circulation* 2005;111:2306-2312.
- Franklin KM, Aurigemma GP. Prognosis in diastolic heart failure. *Prog Cardiovasc Dis* 2005;47:333-9.
- Tighe DA, Aurigemma GP, Vinch CS, Hill JC, Meyer TE. Assessment of left ventricular diastolic function by Doppler echocardiography. *Cardiac Ultrasound Today* 2005;11(5):89-116.
- Aurigemma GP. President's Message Cardiovascular Ultrasound: No age limits. *J Am Soc Echocardiogr* 2005;18(8):A21-2.
- Vinch CS, Aurigemma GP, Simon HU, Hill JC, Tighe DA, Meyer TE. Analysis of left ventricular systolic function using midway mechanics in patients >60 years of age with heart disease and heart failure. *Am J Cardiol* 2005;96(9):1299-303.
- Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons ≥65 years of age (the cardiovascular health study). *Am J Cardiol* 2006;97(1):83-9.
- Aurigemma GP, Tighe DA: Echocardiography and reversible left ventricular dysfunction. *American Journal of Medicine* 2006;119:18-21.
- Aurigemma GP, Zile MR, Gaasch WH: Contractile Behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation* 2006;113:296-304.
- Liao L, Jollis JG, Anstrom KJ, Whellan DJ, Kitzman DW, Aurigemma GP, Mark DB, Schulman KA, Gottdiener JS. Costs for heart failure with normal vs reduced ejection fraction. *Arch Intern Med* 2006;166:112-118.
- Aurigemma GP. Diastolic heart failure—a common and lethal condition by any name. *N Engl J Med* 2006;355(3):308-10.
- McManus D, Aurigemma GP. Clinical advances in diastolic heart failure. *Minerva Cardioangiol* 2006;54(6):695-713.
- Janardhanan R, Daley WL, Naqvi TZ, Mulvagh SL, Aurigemma G, Zile M, Arndt MO, Artis E, Purkayastha D, Thomas JD, Solomon SD, for the VALIDD Investigators. Rationale and design: The VALSartan In Diastolic Dysfunction (VALIDD) Trial: Evolving the management of diastolic dysfunction in hypertension. *American Heart Journal* 2006;152:246-52.
- Hurlburt HM, Aurigemma GP, Hill JC, Narayanan A, Gaasch WH, Vinch CS, Meyer TE, Tighe DA. Direct ultrasound measurement of longitudinal, circumferential and radial strain using 2-dimensional strain imaging in normal adults. *Echocardiography* 2007;24(7):723-731.
- Aurigemma GP. Acute stress cardiomyopathy and reversible left ventricular dysfunction. *Cardiology Rounds* 2006;10(10):1-6.
- Liao L, Anstrom KJ, Gottdiener JS, Pappas PA, Whellan DJ, Kitzman DW, Aurigemma GP, Mark DB, Schulman KA, Jollis JG. Long-term costs and resource use in elderly participants with congestive heart failure in the Cardiovascular Health Study. *Am Heart J* 2007;153(2):245-52.
- Tighe DA, Rosetti M, Vinch CS, Chandok D, Muldoon D, Dahlberg ST, Aurigemma GP. Real-time 3-dimensional echocardiography to measure left ventricular volumes in unselected patients. A comparison with gated-SPECT imaging. *Echocardiography* ;24(10):1073-1080.
- Bouchard JL, Aurigemma GP, Goldberg RJ, Fournier JB, Vinch CS, Hill JC, Ennis CA, Meyer TE, Tighe DA. Heart failure in the "oldest old": clinical and echocardiographic insights. *Am J Geriatr Cardiol* 2007;16(4):236-42.
- Narayanan A, Hill JC, Aurigemma GP. Tissue mitral annular displacement (TMAD): A novel descriptor of global left ventricular function. *US Cardiovascular Disease* (in press).
- Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP; for the Valsartan In Diastolic Dysfunction (VALIDD) Investigators. 2007;369(9579):2079-87.

Research Study

The Medtronic RESOLUTE US Clinical Trial Synopsis

Title:

A Clinical Evaluation of the Medtronic Endeavor Resolute Zotarolimus-Eluting Coronary Stent System in the Treatment of *De Novo* Native Lesions in Native Coronary Arteries with a Reference Vessel Diameter of 2.25 mm to 4.2 mm

Sponsor:

Medtronic Vascular

Design:

Prospective, multi-center, controlled trial. The trial is comprised of three studies: the 2.25 mm - 3.5 mm Main Study, the 2.25 mm - 3.5 mm Angio/IVUS Sub-study and the 4.0 mm Sub-study. A patient's inclusion in a given study is dependent on the size (diameter) of the stent(s) the patient receives.

All patients may have one or two lesions, if the two lesions are located in separate coronary arteries. A patient with one or two lesions treated with stents of diameter 2.25 mm - 3.5mm will be designated as a participant in the 2.25 mm - 3.5 mm Main study, if the site is not participating in the Angio/IVUS Sub-study.

Patients with at least one lesion treated with a 4.0 mm stent will be designated as a participant in the 4.0 mm Sub-study

Investigational Device:

Medtronic Endeavor Resolute Zotarolimus-Eluting Coronary Stent System.

Objective:

To assess the safety and efficacy of the Endeavor Resolute Zotarolimus-Eluting Coronary Stent System for the treatment of *de novo* lesions in native coronary arteries with a

reference vessel diameter (RVD) of 2.25 mm to 4.2 mm.

Primary Endpoint:

The 2.25 mm - 3.5 mm Main Study: Target lesion failure (TLF) at 12 months post-procedure, defined as cardiac death, target vessel myocardial infarction (Q wave and non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. The 2.25 mm subset and 2.5 mm - 3.5 mm subset will be analyzed separately.

The 2.25 mm - 3.5 mm Angio/IVUS Sub-study: In-stent late lumen loss (LLL) at 8 months post-procedure as measured by quantitative coronary angiography (QCA).

The 4.0 mm Sub-study: In-segment late lumen loss (LLL) at 8 months post-procedure as measured by quantitative coronary angiography (QCA).

Enrollment:

A total of 1399 patients will be enrolled in the trial.

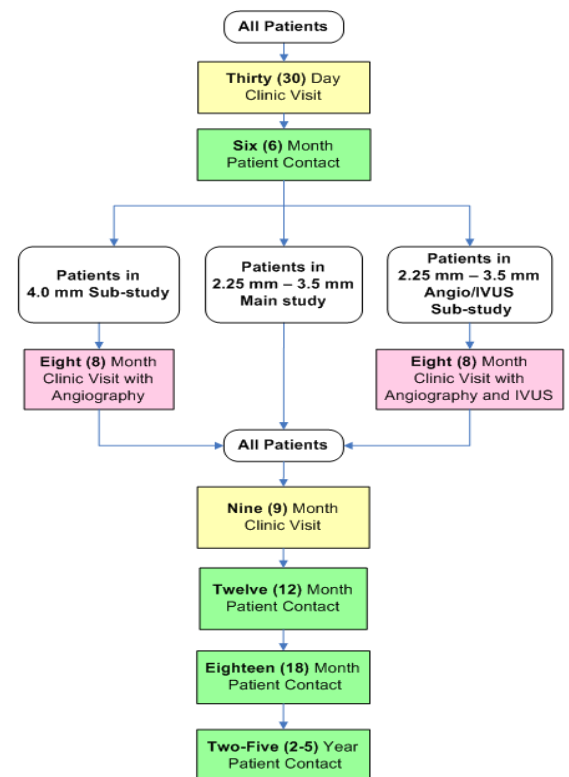
Patient Population:

Patients with ischemic heart disease due to stenotic lesions contained within *de novo* native coronary arteries with reference vessel diameters between 2.25 mm and 4.2 mm and lesion lengths \leq 27 mm that are amenable to percutaneous treatment with a stent. Patients may receive of treatment of up to two lesions, if the lesions are located in separate coronary arteries.



Steven Ball, RN

RESOLUTE US Clinical Trial Patient Follow-up Flowchart



PI: Daniel Fisher, MD

Study Coordinator: Steven Ball, RN

Call the Cardiovascular Research Hot Line:
4-ENRL (4-3675) or 508-334-3675

Cardiovascular Working Group Meeting Schedule

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

Date	Speaker	Topic
June 16, 2009	John F. Keane, Jr.	"Mitochondrial Modulation of Endothelial Phenotype"
Sept. 8, 2009	TBA	TBA

Please note:

During the months of July and August, the Cardiology Working Group (CWG) lectures will not be held and the monthly Cardiology Newsletter (CARE) will not be published.



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Selected publications since 2005 (Cont'd):

Liao L, Anstrom KJ, Gottdiener JS, Pappas PA, Whellan DJ, Kitzman DW, Aurigemma GP, Mark DB, Schulman KA, Jollis JG. Long-term costs and resource use in elderly participants with congestive heart failure in the Cardiovascular Health Study. *Am Heart J* 2007;153(2):245-52.

Hill JC, Tighe DA, Narayanan A, Aurigemma GP. Cardiac resynchronization therapy: Utility of echocardiography in the evaluation of dyssynchrony. *Cardiac Ultrasound Today* 2007;13(8):185-212.

Floyd K, Tighe DA, Aurigemma GP, Chandok D, Meyer TE. Echocardiographic evaluation of the right ventricle. *Cardiac US Today* (in press).

Bouchard JL, Aurigemma GP, Hill JC, Ennis CA, Tighe DA. *Am J Cardiol*. 2008 Jun 1;101(11):1673-6. Epub 2008 Apr 15. Usefulness of the pulmonary arterial systolic pressure to predict pulmonary arterial wedge pressure in patients with normal left ventricular systolic function.

Fitzgibbons TP, Meyer TE, Aurigemma GP. Mortality in diastolic heart failure: an update. [Cardiol Rev](#). 2009 Mar-Apr;17(2):51-5.

Aurigemma GP, Gottdiener JS, Kitzman D, Arnold A, Hill JC. Left Atrial Volume and -Geometry in Healthy Aging: The Cardiovascular Health Study: *Circulation: Cardiovascular Imaging* 2009 (in press).

Chinali M, Aurigemma G, de Simone G et al. Mitral E Wave Deceleration Time to Peak E Velocity Ratio and Cardiovascular Outcome in Hypertensive Patients During Anti-Hypertensive Treatment (from the LIFE Echo-Substudy). *American Journal of Cardiology* (in press)

Joffe S, Chalian A, Tighe D, Aurigemma G, et al, Trends in the use of echocardiography and left ventriculography to assess left ventricular ejection fraction in patients hospitalized with acute myocardial infarction. *American Heart Journal* (in press)

