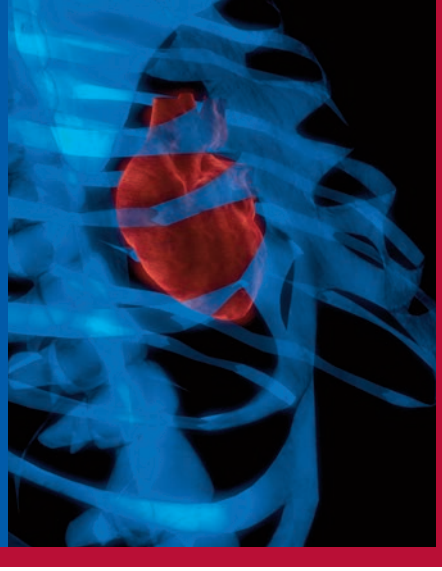

SUMMER 2015

BRIGHAM AND WOMEN'S HOSPITAL

Heart & Vascular Center Update

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Results of Two Late-breaking Clinical Trials Presented by Brigham and Women's Hospital TIMI Study Group at the American College of Cardiology Annual Scientific Session

At the 64th Annual Scientific Session of the American College of Cardiology, Marc S. Sabatine, MD, MPH, Chairman of the Thrombolysis in Myocardial Infarction (TIMI) Study Group at Brigham and Women's Hospital, presented late-breaking clinical trials of experimental approaches that demonstrated significant reduction in cardiovascular events.

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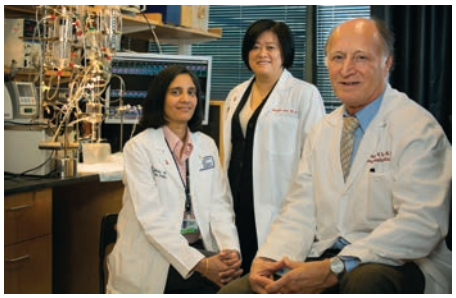
Cardiovascular Genetics Center Specialists Aim to Alter Course of Hypertrophic Cardiomyopathy, Offer Targeted Approach to Sarcomere Mutation Carriers

Cardiomyopathy experts in the Cardiovascular Genetics Center at Brigham and Women's Hospital are leading an international trial investigating the benefits of therapy given in early hypertrophic cardiomyopathy.



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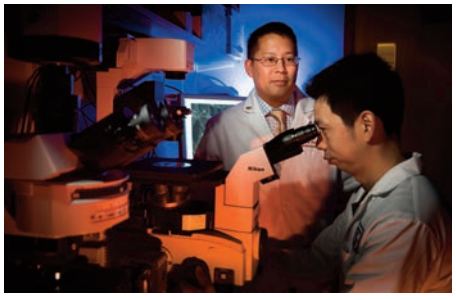
Novel Approaches to Treating AL Amyloidosis using Innovative Models

Based on groundbreaking research using zebrafish models, Brigham and Women's Hospital investigators are introducing novel approaches to address the underlying pathogenesis of AL amyloidosis.



Page 6

Origins of Pulmonary Hypertension Uncovered by Team at Brigham and Women's Hospital

A team of researchers and clincians at Brigham and Women's Hospital has identified molecules responsible for the metabolic underpinnings of pulmonary hypertension and confirmed the hypothesis in a patient with previously undiagnosed exercise-induced pulmonary hypertension.

brighamandwomens.org/heart

BEST REGIONAL HOSPITALS U.S.News & WORLD REPORT BOSTON, MA CARDIOLOGY & HEART SURGERY 2015–16

BWH Ranked 4th in U.S. for CARDIOLOGY & HEART SURGERY

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Results of Two Late-breaking Clinical Trials Presented by Brigham and Women's Hospital TIMI Study Group at the American College of Cardiology Annual Scientific Session

At the 64th Annual Scientific Session of the American College of Cardiology (ACC), Marc S. Sabatine, MD, MPH, Chairman of the Thrombolysis in Myocardial Infarction (TIMI) Study Group and Lewis Dexter, MD, Distinguished Chair in Cardiovascular Medicine at Brigham and Women's Hospital (BWH), presented two late-breaking clinical trials. In both studies the experimental therapy significantly reduced cardiovascular events in the studied patient populations.

"Our team is focused on conducting large-scale, practice-changing clinical trials in patients with cardiovascular disease or risk factors for cardiovascular disease," said Dr. Sabatine.

Extension of PCSK9 Inhibition

In previous short-term studies, evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), has been shown to reduce low-density lipoprotein (LDL) cholesterol levels. Extension studies (the OSLER program) were conducted from these parent trials in which 4,465 patients from 12 parent studies were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every two weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Patients were followed for a median of 11.1 months.

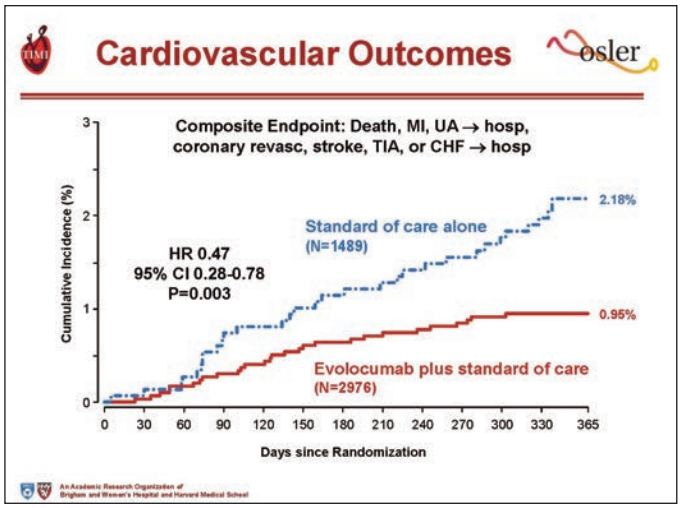
Cardiovascular Disease Prevention Program

The preventive cardiology team in the Heart & Vascular Center at Brigham and Women's Hospital delivers specialized approaches for complex cardiometabolic disorders and integrated care and management for patients with conditions that often exist alongside and contribute to cardiovascular disease.

Led by Jorge Plutzky, MD, the team delivers specialized cardiovascular care within dedicated clinics for patients with obesity; diabetes and pre-diabetes; rheumatologic disease; sleep disorders; lipid disorders; premature cardiovascular diseases; and women's cardiovascular disease issues. They have introduced novel therapeutic approaches to severe hypertriglyceridemia and recurrent pancreatitis and have successfully reduced issues with statin intolerance in order to maintain statin therapy. The team's research has also helped to inform national and international guidelines for cardiovascular risk reduction and cardiac rehabilitation and has highlighted improvements in patient safety in myocardial infarction and heart failure care.

For more information, or to refer a patient to our Cardiovascular Disease Prevention program, please call our HVC Navigation Center access line at **(857) 307-4000**.

Figure 1



As compared with standard therapy alone, evolocumab reduced the level of LDL cholesterol by 61 percent, from a median of 120 mg per deciliter to 48 mg per deciliter. The rate of cardiovascular events at one year was reduced by 53 percent, from 2.18 percent in the standard-therapy group to 0.95 percent in the evolocumab group *(Figure 1)*. The treatment appeared to be safe and well tolerated. In mid-June 2015, Dr. Sabatine spoke about evolocumab at the FDA Advisory Committee meeting, at the end of which the committee voted to recommend approval.

The first PCSK9 inhibitor was approved by the FDA at the end of July, with the second such agent being reviewed later this year. "The PCSK9 inhibitor data is remarkable and represent important findings that are helping open up a new era in lipid-lowering therapies," said Jorge Plutzky, MD, Director of Preventive Cardiology.

Prolongation of P2Y12 Antagonist Therapy

Current guidelines recommend adding a P2Y12 receptor antagonist to aspirin only for the first year after an acute coronary syndrome. In the PEGASUS-TIMI 54 study, researchers theorized that the addition of ticagrelor, a potent, reversibly-binding, direct acting P2Y12 antagonist, to standard therapy would reduce the incidence of major adverse cardiovascular events during long-term follow-up in patients with a history of myocardial infarction.

The study randomized 21,162 patients who had had a myocardial infarction one to three years earlier to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo. All patients received low-dose aspirin and were followed for a median of 33 months. The primary efficacy

continued on back cover

Cardiovascular Genetics Center Specialists Aim to Alter Course of Hypertrophic Cardiomyopathy, Offer Targeted Approach to Sarcomere Mutation Carriers

Cardiomyopathy experts in the Cardiovascular Genetics Center at Brigham and Women's Hospital are leading an international trial investigating benefits of therapy given in early hypertrophic cardiomyopathy (HCM).

"Current therapy for HCM only palliates symptoms," said Carolyn Y. Ho, MD, Medical Director of the Cardiovascular Genetics Center. "We are continuing our efforts to find ways to change the course of HCM by providing therapy early in the disease process with the ultimate goal of preventing HCM from developing at all."

VANISH Trial

The **V**alsartan for **A**ttenuating Disease Evolutio**n** **i**n Early **S**arcomeric **HCM** (VANISH) trial is a multicenter, Phase II, randomized clinical trial to assess the safety and efficacy of valsartan, an angiotensin receptor blocker, in attenuating disease evolution in early HCM. Sarcomere mutation carriers with asymptomatic or mildly symptomatic overt disease (NYHA class I-II) and mutation carriers without left ventricular hypertrophy (LVH) are being studied over a two-year period. Trial participants are between 8 and 45 years of age and are currently being enrolled at over 14 sites in the United States and Canada. Expansion to South America and Europe is planned in the near future.

A composite z-score statistical analysis approach will be used to detect treatment response reflecting different domains of myocardial injury, hemodynamic stress, collagen metabolism, functional capacity, myocardial fibrosis, cardiac morphology, and cardiac function. The study also will measure the impact of valsartan treatment on disease pathology, clinical outcomes and assessment of symptom burden, and incidence of adverse drug reactions, frequency of subject drop-out, and responses to validated quality-of-life metrics.

For more information or to refer a patient for consideration for the VANISH trial, please contact Principal Investigator Carolyn Y. Ho, MD, at (617) 732-7317 or cho@partners.org.

Pilot Study Success

The VANISH trial builds on the results of the team's recent pilot trial that randomly assigned 38 sarcomere mutation carriers without LVH to therapy with diltiazem or placebo (*JACC Heart Fail.* 2015 Feb;3(2):180-8.). Treatment duration of the pilot study ranged from 12 to 42 months. Study procedures included electrocardiography, echocardiography, cardiac magnetic resonance imaging, and serum biomarker measurement.

Diltiazem was well tolerated and was not associated with serious adverse events. Some promising results of this pilot study included:

- Left ventricular end diastolic diameter improved towards normal in the diltiazem group but decreased further in controls;
- Mean LV thickness-to-dimension ratio was stable in the diltiazem group, but increased in controls;
- Among MYBPC3 mutation carriers, LV wall thickness and mass, diastolic filling, and cardiac troponin I levels improved in those taking diltiazem compared with controls.

"Genetic testing to identify sarcomere mutation carriers offers us the opportunity to modify the progression and emergence of disease at a time when disease-modifying therapy may be most effective. Such strategies have the potential to transform clinical practice in HCM," said Dr. Ho. "The goal of our Center is to use our research discoveries to improve clinical care for our patients and families with HCM and other inherited heart disease using targeted approaches."

Cardiovascular Genetics Center

The Cardiovascular Genetics Program at Brigham and Women's Hospital is composed of a multidisciplinary team of internationally recognized physicians and investigators who collaborate to apply the latest discoveries in research on inherited cardiac disease to deliver personalized care for patients.

Christine Seidman, MD
Director, Cardiovascular Genetics Center

Carolyn Y. Ho, MD
Medical Director, Cardiovascular Genetics Center

Neal K. Lakdawala, MD
Cardiovascular Genetics Center

Calum A. MacRae, MD, PhD
Chief, Division of Cardiovascular Medicine;
Cardiovascular Genetics Center

Access and Information

For more information or to refer a patient to the Cardiovascular Genetics Center, please contact administrator Irene Ediger at (617) 732-7317 or iediger@partners.org.

Novel Approaches to Treating AL Amyloidosis using Innovative Models

Based on groundbreaking research using zebrafish models, Brigham and Women's Hospital (BWH) investigators, led by Ronglih Liao, PhD, in collaboration with Calum A. MacRae, MD, PhD, Chief of Cardiovascular Medicine, and Rodney H. Falk, MD, Director of the BWH Cardiac Amyloidosis Program, are introducing novel approaches to address the underlying pathogenesis of AL amyloidosis.

"As there are no targeted therapies for amyloid cardiomyopathy, and prognosis for these patients remains poor, our goal is to bring new treatments to patients as quickly as possible through a strong translational research collaboration between basic science researchers and clinical experts," said Dr. Liao.

Building a Foundation

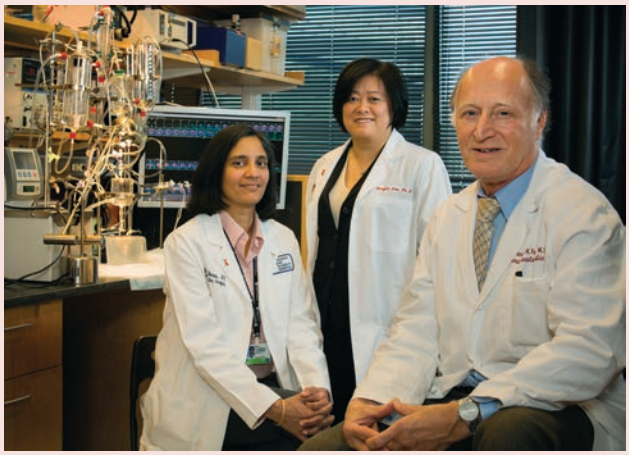
Previously, the team discovered that human amyloidogenic light chain proteins resulted in cardiac dysfunction, cell death, and early mortality in zebrafish – establishing zebrafish as ideal models for research in AL amyloidosis. This work was published in the *American Journal of Physiology - Heart and Circulatory Physiology* (*Am J Physiol Heart Circ Physiol*. 2013 Jul 1;305(1):H95-103.) and has led to ongoing study of the mechanisms of disease and potential therapeutic targets using zebrafish. Previous findings by BWH researchers also have found that human AL light chain proteins bring about excessive reactive oxygen species (ROS) production and subsequent cellular dysfunction and cell death *(Figure 1)*, but the cellular pathogenesis was unknown.

Uncovering Targeted Therapeutics

The team used human amyloidogenic light chains isolated from patients with amyloid cardiomyopathy to reveal that lysosomal dysregulation of autophagic flux is critical for mediating amyloidogenic light chain proteotoxicity (*EMBO Mol Med*. 2014 Nov; 6(11): 1493–1507.). Restoration of autophagic flux in cardiomyocytes exposed to AL-LC was achieved through the use of rapamycin, an mTOR inhibitor and potent enhancer of both autophagosome formation and clearance *(Figures 2 and 3)*.

Along with decreased p62 levels, rapamycin-treated cardiomyocytes showed significant attenuation of both mitochondrial dysfunction and intracellular ROS levels and protection against AL-LC-induced cellular contractile dysfunction. These findings were present in both cellular and zebrafish models *(Figure 4)*.

"Our work suggests that rapamycin may be a potential therapeutic approach for the treatment of AL amyloidosis," said Dr. Falk. "This is exciting, as rapamycin is already FDA approved for other uses."



Cardiac Amyloidosis Program

The Brigham and Women's Hospital (BWH) Cardiac Amyloidosis Program is one of few clinical programs in the United States that is focusing exclusively on cardiac amyloidosis. Led by Rodney H. Falk, MD, this program was established to address an unmet need in the diagnosis and treatment of systemic amyloidosis, with the goal of acquiring a better understanding of the disease and improving care for patients.

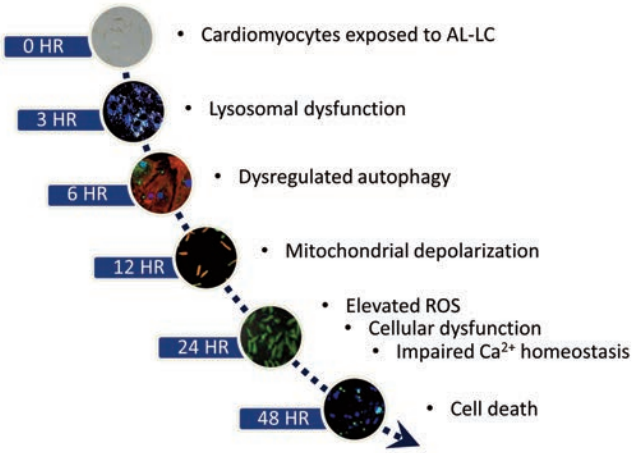
Advances in evaluation and treatment in the Cardiac Amyloidosis Program rely on a critical collaboration between clinicians and researchers at BWH. Recent highlights include:

- Largest clinical study of patients with transthyretin-related amyloidosis, evaluating a new drug specifically designed to halt disease progression;
- Establishment of the safety of endomyocardial biopsy for the diagnosis of cardiac amyloidosis and the effectiveness and outcome of treating atrial rhythm disturbances in amyloidosis;
- Evaluation of new radiotracers to facilitate the earlier detection of systemic amyloidosis.

"Our team serves as a comprehensive resource for referring physicians and their patients with suspected or documented cardiac amyloidosis, providing them with access to the latest diagnostic techniques, clinical trials, and therapies," said Dr. Falk.

Figure 1

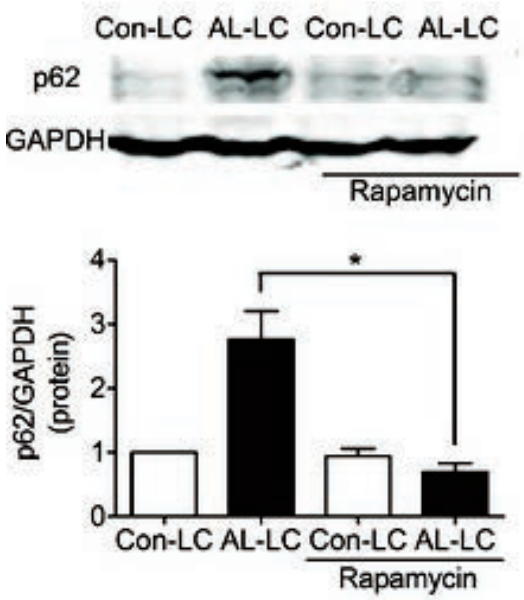
Human AL amyloid cardiomyopathy is associated with impaired autophagy and defective lysosomal function



Schematic illustration of temporal events involved in AL-LC-induced pathology. (*EMBO Mol Med.* 2014 Nov; 6(11): 1493–1507.)

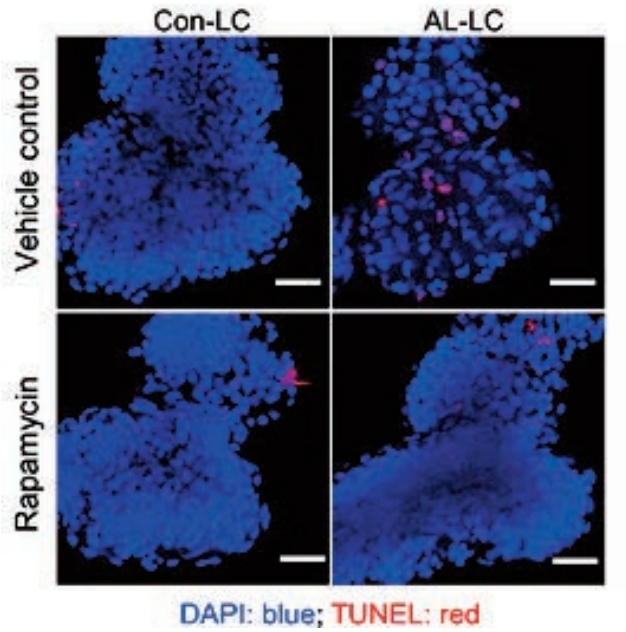
Figure 2

Rapamycin protects against AL-LC proteotoxicity *in vivo*



Zebrafish were treated with 10 nM rapamycin after receiving Con-LC or AL-LC injection. Immunoblot analysis was performed to measure p62 expression and normalized to GAPDH as a loading control. Fifteen fish were homogenized per experiment. Quantitative analysis is shown for comparison below representative blots. (*EMBO Mol Med.* 2014 Nov; 6(11): 1493–1507.)

Figure 3



Representative confocal images of hearts isolated from zebrafish 3 days post-injection with or without rapamycin treatment. Hearts are stained for TUNEL-positive nuclei (red) and DAPI counterstain. TUNEL-positive nuclei are quantified and graphed in the right panel. Scale bar = 25 μm. N = 4 per group. (*EMBO Mol Med.* 2014 Nov; 6(11): 1493–1507.)

Ronglih Liao, PhD
Division of Genetics,
Division of Cardiovascular Medicine

Calum A. MacRae, MD, PhD
Chief, Cardiovascular Medicine

Rodney H. Falk, MD
Director, Cardiac Amyloidosis Program

Information and Referrals

For more information on our Cardiac Amyloidosis Program, or to refer a patient, please contact our Referral Coordinator at (617) 732-9894 or email bwhreferrals@partners.org.

Origins of Pulmonary Hypertension Uncovered by Team at Brigham and Women's Hospital

In a significant discovery, a team of clinicians and basic science researchers at Brigham and Women's Hospital (BWH) identified molecules responsible for the metabolic underpinnings of pulmonary hypertension (PH) and confirmed their hypothesis in a patient with previously undiagnosed exercise-induced PH.

"Currently, therapy for pulmonary hypertension is used to extend survival and palliate symptoms, with most of the focus at the end stages of disease," said Stephen Y. Chan, MD, PhD, lead author of the study. "But, very little is known about the initiating molecular triggers for this disease. We believe that discoveries in this regard would constitute a major advance in our goals to design more effective methods to alter or prevent PH."

Non-traditional Molecules: microRNA -210 and ISCU

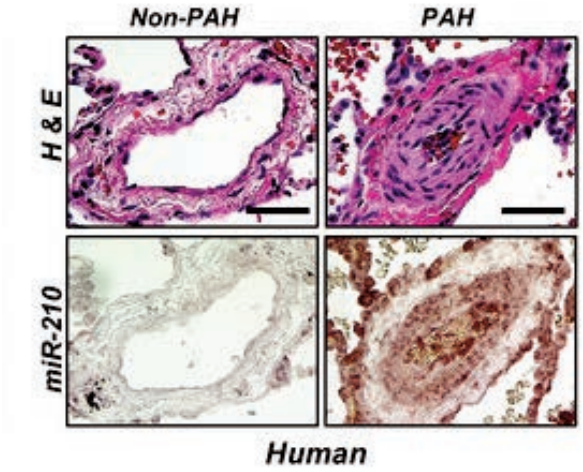
For nearly a decade, BWH researchers have been investigating the complex molecular mechanisms related to hypoxic or ischemic injury of pulmonary and peripheral blood vessels. As a post-doctoral fellow working with Joseph Loscalzo, MD, PhD, Chairman of the Department of Medicine at BWH, Dr. Chan initially identified the hypoxia-induced microRNA-210 (miR-210) as a critical regulator of iron-sulfur cluster formation, mitochondrial metabolism, and acute cellular survival in the hypoxic pulmonary vasculature (*Cell Metabolism.* 10 (4); 273-84, 2009).

Using a variety of methods ranging from computational biology, biophysics, molecular biology, and in vivo physiology, the team established that miR-210 decreases expression of its target gene ISCU, which is critical to the production of iron-sulfur clusters. These clusters are essential for normal mitochondrial function and metabolism. In preclinical models, this metabolic shift results in vascular proliferation, remodeling, and the catastrophic consequences of PH (*EMBO Molecular Medicine* (2015) emmm.201404511).

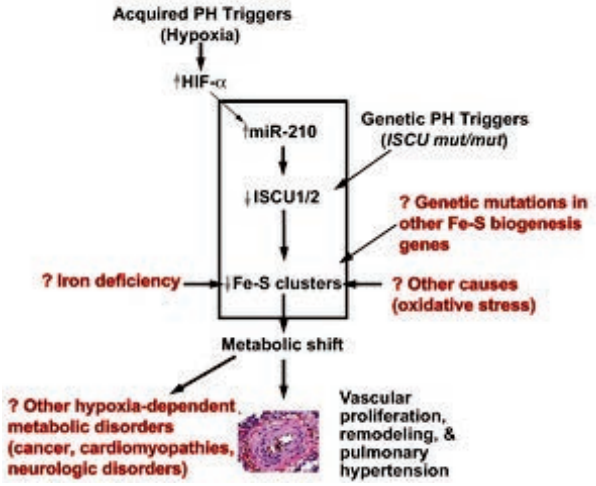
Pulmonary Vascular Disease Program

The Pulmonary Vascular Disease Program at BWH, led by Aaron B. Waxman, MD, PhD, provides highly-specialized, multidisciplinary evaluation and care for patients with complex pulmonary vascular conditions, including unexplained dyspnea, pulmonary arterial hypertension, and pulmonary hypertension associated with heart disease, COPD, chronic thromboembolic disease, liver disease, and other conditions.

For more information, or to refer a patient to our Pulmonary Vascular Disease Program, please call our HVC Navigation Center access line at **(857) 307-4000**.



Increased miR-210 in < 200-µm remodeled pulmonary vessels of patients suffering from PAH (N = 19) as compared with non-PAH donor control lung (N = 10). Serial staining with hematoxylin and eosin is displayed in the top row of micrographs; quantification of miRNA ISH, right graph, *P = 0.0167.



Model of acquired and genetic Fe-S deficiency as a central cause of metabolic dysfunction and PH in mice and humans. Among others, potential translational implications are highlighted in red text.

Basic Science and Clinical Research Collaboration

To apply the theory in a study subject, Dr. Chan, Aaron B. Waxman, MD, PhD, Director of the Pulmonary Vascular Disease Program, David M. Systrom, MD, and others in the Heart & Vascular Center at BWH collaborated to study a 29-year-old Norwegian woman with known homozygous intronic ISCU mutations.

At rest, echocardiography showed normal right ventricular function and size. Pulmonary arterial catheterization revealed normal right and left heart filling pressure but with a mean pulmonary arterial pressure at the upper limits of normal (mPAP of 21 mmHg). Advanced cardiopulmonary exercise testing performed in the catheterization laboratory at BWH, however, revealed exertional dyspnea and abnormally increased pulmonary vascular resistance (PVR) during exercise (maximum PVR at exercise = 135 dynes s/cm5), accompanied by elevated mean pulmonary arterial pressure (maximal mPAP = 31 mmHg). Importantly, the patient's symptoms improved significantly when she was placed on the PDE5 inhibitor tadalafil.

Six-Minute Walk Test

Improvement of 6-min walk test (6 MWT) in an ISCU *mut/mut* individual after initiation of pulmonary vasodilator therapy (PDE5 inhibitor)

Pulmonary vasodilator	6MW distance (meters)
None	240
Tadalafil (20 mg daily for 7 days followed by 40 mg daily for 40 days)	360
Tadalafil (20 mg daily for 7 days followed by 40 mg daily for 166 days)	364

"This is the first known observation of pulmonary vascular dysfunction in a person with ISCU deficiency," said Dr. Chan. "This case helps to establish a definitive connection between ISCU and PH."

The findings also highlight the potential of designing new therapeutic approaches to treat PH that focus on ISCU proteins, miR-210, and other genes known to be directly linked to iron-sulfur production. Dr. Chan and his colleagues are currently collaborating with companies that manufacture pharmacologic agents that inhibit microRNAs.

"There is still a lot of work to be done, but we feel that these findings represent a major advance in our ongoing efforts to fight this disease," said Dr. Waxman.

Stephen Y. Chan, MD, PhD
Division of Cardiovascular Medicine

Aaron B. Waxman, MD, PhD
Director, Pulmonary Vascular Disease Program

Leadership Announcement

New Chief of Cardiac Surgery

Prem S. Shekar, MD, has been appointed Chief of the Division of Cardiac Surgery and Surgical Director of the Heart & Vascular Center at BWH. Dr. Shekar joined BWH in 2001 as a cardiothoracic surgical fellow and became a faculty member in 2004. A highly-skilled, respected, collaborative, and caring surgeon, Dr. Shekar's clinical and research interests include surgery for hypertrophic cardiomyopathy, surgical correction of aortic root and mitral valve pathologies in patients with Marfan's syndrome and other connective tissue disorders, and minimally invasive valve surgery for radiation induced heart disease aside from conventional surgery. He is well known among his colleagues for his thoughtful approach to complex cases. Dr. Shekar received his medical degree from Bangalore University, India, completed his postgraduate training at the Command Hospital – Indian Air Force and Jawaharlal Institute of Postgraduate Medical Education and Research, India and advanced cardiothoracic fellowships at the Fremantle Hospital and Royal Adelaide Hospital in Australia and the Brigham and Women's Hospital. He is also the Fellow of the Royal College of Surgeons of Edinburgh.

Heart & Vascular Center Access Information

For more information on the Heart & Vascular Center and our programs and services, please contact us at BWHHeartandVascularCenter@partners.org.

To reach us immediately for patient-related issues:

- For an ambulatory consultation or to reach a specific physician or research: (857) 307-4000
- For direct inpatient transfers and cardiovascular interventional procedures: (617) 543-4170
- For direct assistance with patient referrals and consultations with one of our specialists, please contact physician liaison Ellen Steward at (617) 582-4733 or esteward@partners.org

Results of Two Late-breaking Clinical Trials Presented by Brigham and Women's Hospital TIMI Study Group at the American College of Cardiology Annual Scientific Session . . . continued from page 2

end point was the composite of cardiovascular death, myocardial infarction, or stroke.

Compared with placebo, the two ticagrelor doses each reduced the rate of the primary efficacy end point at three years, with a 15 percent reduction with the 90 mg dose and a 16 percent reduction with the 60 mg dose (3-year event rate of 7.85 percent and 7.77 versus 9.04 percent) *(Figure 2)*. Although rates of TIMI major bleeding were higher with ticagrelor than with placebo, the rates of intracranial hemorrhage or fatal bleeding did not differ between the treatment and placebo groups. (*N Engl J Med*. 2015 May 7;372(19):1791-800.).

About the TIMI Study Group

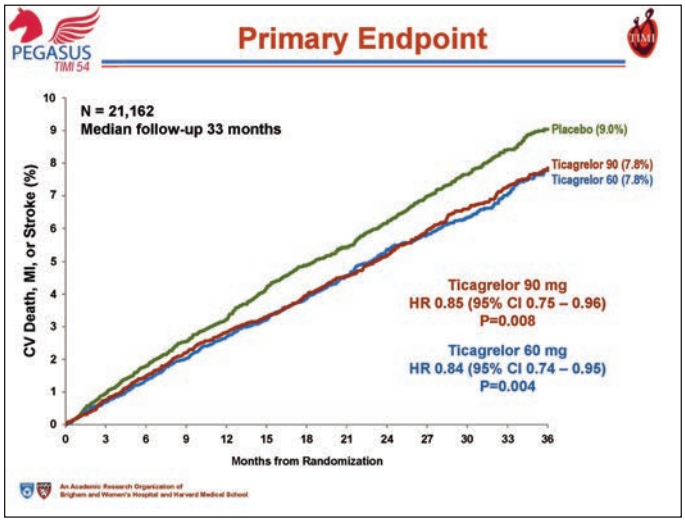
Established in 1984, the TIMI Study Group at BWH is the oldest cardiovascular Academic Research Organization (ARO) in North America and was led by Founding Chairman Eugene Braunwald, MD, until 2011. The first TIMI trial compared the effects of the then-new intravenously administered tissue plasminogen activator (tPA) with streptokinase on coronary and clinical outcomes in patients presenting with an ST-elevation myocardial infarction (STEMI). The trial was a success and demonstrated the superiority of tPA, which became the preferred fibrinolytic therapy. Since that time, the TIMI Study Group has conducted more than 60 clinical trials spanning from phase I to phase IV studies. Trials have ranged from less than 30 subjects to more than 26,000 subjects and have been conducted at more than 5,000 separate sites in 50 countries.

TIMI Investigators have studied a wide range of interventions including fibrinolytic, antiplatelet, anticoagulant, anti-ischemic, lipid-modifying, anti-inflammatory, anti-diabetes, and anti-obesity agents, as well as percutaneous coronary intervention. In addition, the TIMI Study Group has used its large database of clinical findings, biomarkers, and genotypes to enhance the understanding of cardiovascular disease and its risk factors.

For More Information on TIMI

To learn more about TIMI Study Group trials, latest publications, and recent news, visit **TIMI.org**.

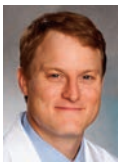
Figure 2



By leading large-scale, international, randomized controlled trials of novel therapeutics and performing sophisticated analyses, the TIMI Study Group has helped shape the very practice of cardiovascular medicine for over a quarter of a century.

Marc S. Sabatine, MD, MPH
Chairman, TIMI Study Group;
Lewis Dexter, MD Distinguished Chair in Cardiovascular Medicine

Eugene Braunwald, MD
Founding Chairman, TIMI Study Group



Marc P. Bonaca, MD, MPH
Cardiologist, TIMI Study Group

Jorge Plutzky, MD
Director, Preventive Cardiology

BRIGHAM AND WOMEN'S HOSPITAL

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A FOUNDING MEMBER OF PARTNERS HEALTHCARE