

Top Advances in Cardiovascular and Stroke Research in 2011



Top Ten Advances in Cardiovascular Research in 2011

1. Lifestyle factors make a difference

Multiple new studies this past year supported the importance of lifestyle factors such as diet and physical activity in improving and controlling cardiovascular risks. These findings are especially important given that 39 percent of Americans believe they are in ideal cardiovascular health when in reality less than 1 percent are. Increasing levels of physical activity were confirmed to have increasing benefit and both home-based exercise programs and community interventions were shown to have significant value, while increased TV viewing was associated with an increased risk of type II diabetes, cardiovascular disease and mortality. The DASH pattern of diet was affirmed to be associated with less weight gain over time. Disappointingly, fewer than 40 percent of the public can identify the important Simple 7 – seven components of ideal cardiovascular health, including health behaviors (not smoking, regular exercise, and healthy diet) and health factors (ideal body mass index, cholesterol, blood pressure, and blood glucose), and those with less education and lower socioeconomic status are less able to identify these components than those who are wealthier and have more education. Clearly, more education for all Americans will be critical.

- **Sattlemair J** et al. *Circulation* 2011;124:789-95; <http://circ.ahajournals.org>; Funding: National Institutes of Health and the Donald and Sue Pritzker Scholarship Fund
- **Berz JPB** et al. *Arch Pediatrics and Adolescent Med.* 2011;165(6):540-46; www.archpediatrics.com; Funding: National Institute of Diabetes and Digestive and Kidney Diseases
- **Gardner AW** et al. *Circulation* 2011;123:491-498. <http://circ.ahajournals.org>; Funding: National Institute on Aging, Oklahoma Center for the Advancement of Science and Technology grant and Oklahoma University Health Sciences Center General Clinical Research Center grant sponsored by the National Center for Research Resources
- **Mozaffarian D** et al. *N Engl J Med.* 2011;364(25):2392-404; www.nejm.org; Funding: National Institutes of Health and the Searle Scholars Program
- **Grøntved A** et al. *JAMA.* 2011 15;305(23):2448-55; <http://jama.ama-assn.org>; Funding: Danish Heart Foundation, Sygekassernes Helsefond (the Danish Health Fund), the Oticon Foundation, the Augustinus Foundation and a National Institutes of Health grant
- **Siddharth W** et al. *American Journal of Cardiology*; 107(10): 1480-8; www.ajconline.org; Funding: No funding sources listed
- **Brown IJ** et al. *Hypertension* 2011; 57(4): 695-701; <http://hyper.ahajournals.org>; Funding: United Kingdom Medical Research Council studentship, the National Heart, Lung, and Blood Institute, National Institutes of Health; the Chicago Health Research Foundation, national agencies in China, the Japanese Ministry of Education, Science, Sports, and Culture, West Midlands National Health Service Research and Development and the Chest, Heart and Stroke Association, Northern Ireland
- **Jenkins DJ** et al. *JAMA* 2011; 306(8):831-9; <http://jama.ama-assn.org>; Funding: CRCE of the Federal Government of Canada; CIHR, AFM Net, Loblaw Brands Ltd, Solae (St Louis, Missouri), and Unilever (Vlaardingen, the Netherlands, Toronto, Ontario)
- **Kaczorowski J** et al. *BMJ* 2011;342:d442; www.bmj.com; Funding: Canadian Stroke Network and the Ontario Ministry of Health Promotion—Ontario Stroke System

2. New treatments for valve replacement and repair

A number of new options are available for replacing or repairing faulty or blocked aortic valves. Transcatheter aortic valve implantation (TAVI) was previously proven useful for patients who aren't candidates for conventional surgery, and new studies comparing TAVI to surgical valve replacement suggested that it can also be safe and effective in patients who could undergo but were at high-risk for surgery. While the rate of major stroke was higher in patients receiving TAVI, the difference was not significant. Overall, there were similar rates of survival and of symptoms at one year after the two procedures, although there were differences in the types of associated complications. Patients and physicians need to consider these outcomes carefully in deciding on a procedure. Additionally, a new percutaneous procedure showed promising results in improving symptoms in patients with mitral regurgitation.

- **Smith C** et al. *N Engl J Med.* 2011 Jun9;364(23):2187-98; www.nejm.org; Funding: Edwards Lifesciences
- **Feldman T** et al. *N Engl J Med.* 2011 Apr 14;364(15):1395-406; www.nejm.org; Funding: Abbott Vascular

3. Regeneration of heart muscle

Myogenesis is an emerging frontier, with promise that robust approaches can be found to replace heart muscle lost or injured in heart attacks or other disorders, or not appropriately formed in the setting of congenital heart disease. While regeneration of heart muscle is seen in lower life forms, it had not been demonstrated in mammals. One study found that for a transient period shortly after birth, neonatal mouse hearts can regenerate, providing the possibility for that understanding the mechanisms underlying this phenomenon will lead to future treatments for some types of congenital or even acquired heart disease, such as myocardial infarction.

• **Heallen T** et al. *Science*. 2011 April; 332 (6028):458-461; www.sciencemag.org; Funding: National Institute of Health

4. Genetic and molecular pathways in those susceptible to heart disease

Important findings in genetic research are identifying new links to cardiovascular disease risk. This study establishes a link between genetic susceptibility to coronary artery disease and the response to inflammatory signaling in a human cell type that lines our arteries. This is an important finding on its own for its implications for atherosclerosis, but also demonstrates the utility of genome-wide association studies in uncovering novel areas in the genome related to biological processes relevant to important diseases.

• **Harismendy O** et al. *Nature*. 2011;470:264-8; www.nature.com; Funding: National Center for Research Resources, National Institutes of Health, Department of Defense, Prostate Cancer Foundation

5. The genetics of high blood pressure

It's long been known that high blood pressure runs in families; two studies this year provided new specificity about the genetic underpinning of this observation. A genome-wide association study of blood pressure was done in 200,000 individuals of European descent and was able to identify ten new areas within the genome as well as confirming six areas containing genes that had previously been suggested to have a role in regulating blood pressure. Using this information, the investigators developed a genetic risk score for high blood pressure as well as stroke and coronary artery disease. This score was also helpful in individuals of East Asian, South Asian and African ancestry. A second study, using the large (>13,000) dataset from the Family Blood Pressure Program identified five new genetic areas (QTLs) that were sufficiently robust to suggest the need for subsequent candidate gene studies. Together these studies provide evidence of the growing utility of information from the Human Genome study, and demonstrate that we are developing new insights into the genetics of blood pressure, which may help in early determination of the risk for hypertension and lead to new approaches to the prevention of stroke and cardiovascular disease.

• **Ehret, GB** et al. *Nature*. 2011;478:103–109; www.nature.com; Funding: NIH/NHLBI, European and private funding agencies
• **Simino, J** et al. *American Journal of Hypertension* 24, 347-354; www.nature.com/ajh; Funding: National Heart, Lung, and Blood Institute

6. Role of CT angiography in management of chest pain

Coronary Computed Tomographic Angiography (CTTA) can allow us to visualize the coronary arteries non-invasively, and while the resolution has not equaled that of regular coronary angiography, the technology has continued to improve. These studies assessed the utility of CCTA in the emergency department in the evaluation of patients presenting with chest pain. This is a very common reason for emergency department visits, and the causes can range from very serious disorders such as heart attacks to very benign problems that can safely be treated without a hospital stay. In situations where the usual evaluation of patients does not provide a clear answer, and where high-risk conditions have been excluded, CCTA was compared to rest-stress imaging, and allowed more rapid diagnosis of coronary artery disease, allowing for quicker decisions to be made. It also appears to add incremental prognostic value to conventional risk scoring in some patients with coronary disease by adding specific information about the coronaries themselves as well as about the functioning of the heart.

• **Goldstein, JA** et al; *J Am Coll Cardiol*. 2011 Sep 27;58(14):1414-22; <http://content.onlinejacc.org>; Funding: Bayer Pharmaceuticals
• **Chow, BJW** et al; *Circulation: Cardiovascular Imaging*. 2011; 4: 463-472; <http://circimaging.ahajournals.org>; Funding: Canadian Institute of Health Research and the Swiss National Science Foundation

7. Human metabolic individuality

Several studies offer new approaches to improving understanding of the mechanisms underlying common diseases. Individuals can be categorized by their metabolic function, and this information (called a metabolic phenotype) can be added to current information when we search for genes associated with diseases such as diabetes. Including consideration of metabolic phenotypes (referred to as utilizing metabolomics) has allowed the identification of areas in the genome associated with important blood chemicals and providing new insights for cardiovascular and kidney disorders, type 2 diabetes, and venous thromboembolism (a tendency for clots to form in the veins). New regulators of genetic function related to these areas in our genetic makeup are also likely to be important in advancing our knowledge of the genetic basis of metabolic individuality in humans and could generate many new possibilities for effective treatments.

- **Wang TJ** et al. *Nat Med*. 2011;17(4):448-53. www.nature.com/nm; Funding: National Institutes of Health, Donald W. Reynolds Foundation, Leducq Foundation, American Heart Association
- **Small KS** et al. *Nat Genet*. 2011;43:561-4; www.nature.com/ng. Funding: Wellcome Trust Program
- **Suhre K** et al. *Nature*. 2011;477:54-60; www.nature.com/nature; Funding: German Federal Ministry of Education and Research

8. Rapid treatment of ST-elevation heart attacks

Patients with complete blockage of a coronary artery causing a heart attack (called a STEMI or ST-elevation myocardial infarction) do best if the artery can be opened to restore blood flow to the heart muscle as soon as possible. There have been substantial improvements in the United States in door-to-balloon time (the time from when a patient arrives in the emergency department until the artery is opened with angioplasty in the catheterization laboratory). However, not all patients are near or are taken to hospitals that can do these procedures, and getting patients quickly to the right hospital requires the development of systems of care, with emergency medical services and several kinds of hospitals working together. These studies report on important efforts nationwide to improve systems of care for these patients, including new measures that will help assess the performance of hospitals.

- **Krumholz HM** et al. *Circulation*. 2011;124(9):1038-45; <http://circ.ahajournals.org>; Funding: U.S. Centers for Medicare and Medicaid Services.
- **Wang, TA** et al. *JAMA*. 2011 Jun 22;305(24):2540-7; <http://jama.ama-assn.org>; Funding: ACTION Registry-GWTG, American College of Cardiology Foundation and the American Heart Association, Bristol-Myers Squibb/Sanofi Partnership

9. Variability in the use of complex and high-cost technology

Several studies have assessed the use of high-cost cardiovascular technologies such as percutaneous coronary interventions and implantation of cardioverter-defibrillators in the United States in comparison with previously-defined evidence-based guidelines and appropriate use criteria. While some of the current discrepancies may reflect the reasonable and appropriate use of clinical judgement regarding patients not matching the data available in clinical trials, they also offer us the initial steps needed to arrive at a better understanding of the degree to which these technologies may be deployed excessively.

- **Chan, PS** et al. *JAMA*. 2011 Jul 6;306(1):53-61; <http://jama.ama-assn.org>; Funding: National Cardiovascular Data Registry
- **Al-Khatib SM** et al. *JAMA*. 2011 Jan 5;305(1):43-9; <http://jama.ama-assn.org>; Funding: National Heart, Lung, and Blood Institute

10. Advances in research on surgery for congenital heart disease

Children with some forms of congenital heart disease may require one or more heart operations when they are in infancy or early childhood. Frequently this requires that the heart not work to pump blood to the body and brain while the surgery is done, and various techniques have been developed to protect vital organs during the operation. A pioneering randomized trial studied the long-term neurologic outcomes of complex surgical procedures done in infancy using different forms of vital organ support, deep hypothermia with either total circulatory arrest or continuous low-flow cardiopulmonary bypass. This study of the results in adolescents, using sophisticated imaging of the brain as well as testing of how well cognitive function has been preserved, is a true landmark and will continue to have an impact on considerations in the management of patients with congenital heart disease.

- **Bellinger, DC** et al. *Circulation*; 2011;124:1361-9. <http://circ.ahajournals.org>; Funding: National Heart, Lung, and Blood Institute

1. Genetic variants influence risk of stroke

It's well known that blood pressure is affected by inherited genetics, although not in a simple "one gene = high blood pressure" manner. A number of different biologic systems are potentially involved, and modifiable influences such as diet and exercise also have a major impact. This year, advances in genetics have led to major progress. A study in a large population (200,000) of European descent identified 16 areas in the genome related to blood pressure. While six of the areas included genes previously related to blood pressure, the remaining 10 were new and should provide new insights into the biology of blood pressure. Additionally, information from this study was used to develop a genetic risk score associated with stroke as well as hypertension, left ventricular wall thickness and coronary artery disease, but not kidney disease or kidney function. The associations with blood pressure were also seen in people of Asian and African ancestry. This kind of advance is likely to lead to new therapeutic targets for the prevention of stroke and heart disease.

- **Ehret, GB** et al. *Nature*. 2011;478:103–109; www.nature.com; Funding: NIH/NHLBI, European and private funding agencies

2. Risk of atrial fibrillation, a major risk factor for stroke

While we know that atrial fibrillation (AF) is an important risk factor for stroke, we have lacked information about how much of this could be prevented. A study of a large population followed for an average of 17 years suggested that half of atrial fibrillation in both blacks and whites might be avoided if people maintained normal body mass index and blood pressure, didn't smoke and didn't develop diabetes or any signs of cardiovascular disease. High blood pressure was the most important factor.

- **Huxley RR** et al. *Circulation*. 2011; 123: 1501-8; <http://circ.ahajournals.org>; Funding: National Heart, Lung, and Blood Institute and the American Heart Association

3. Assessment of one medication to prevent stroke in atrial fibrillation

Because atrial fibrillation is such an important risk factor for stroke, there's been great interest in evaluating which medications may help prevent stroke in patients with this rhythm abnormality. Negative studies can be just as important as positive ones, as they help avoid the use of ineffective medications. A carefully done study found that irbesartan, an angiotensin receptor blocker that controls blood pressure, did not reduce cardiovascular events, including stroke, in patients with atrial fibrillation.

- **ACTIVE I Investigators**, *N Engl J Med*. 2011 Mar 10;364(10):928-38; www.nejm.org; Funding: Bristol-Myers Squibb and Sanofi-Aventis

4. Aggressive medical therapy trumps stenting for patients with narrowing of arteries within the brain

The SAMMPRIS trial compared aggressive medical treatment, with careful attention to multiple risk factors, to the placement of stents in these small, intracranial arteries (blood vessels within the skull). The risk of intracranial stenting was higher than expected, while aggressive medical therapy directed at all known risk factors was associated with a lower than expected risk of future stroke.

- **Chimowitz MI** et al. *N Engl J Med*. 2011;365-993-1003; www.nejm.org. Funding: Natl Institute of Neurological Disorders and Stroke

5. New medical options are tested and approved for preventing stroke in atrial fibrillation

For nearly 60 years, patients with atrial fibrillation have been treated with the "blood thinner" or anti-thrombotic agent warfarin to reduce the chance that blood clots will form in the heart and travel to the brain, causing a stroke. While this preventive treatment is highly effective, reducing the incidence of stroke by more than 50 percent, patients must have frequent and ongoing blood tests to assure that the dosage is adjusted properly, and foods, other drugs, and even intercurrent illnesses can alter the amount needed. Several alternative anti-thrombotic agents that reduce clotting by acting on alternative parts of the clotting cascade have now been studied and subsequently approved by the FDA to be used in the prevention of stroke in patients with AF, including dabigatran and riveroxaban.

- **Connelly SJ** et al. AVERROES, *N Engl J Med*, 2011 Mar 3;364(9):806-17; www.nejm.org; Funding: Bristol-Myers Squibb; Pfizer
- **Granger CB** et al. ARTISTOLE, *N Engl J Med*. 2011 Sep 15;365(11):981-92; www.nejm.org; Funding: Bristol-Myers Squibb; Pfizer
- **Shah SV and Gage, BF**. *Circulation*. 2011;123:2562-2570; <http://circ.ahajournals.org>; Funding: American Heart Association, Knowlton Foundation
- **Eikelboom, JW** et al. *Circulation*. 2011, 123:2363-2372; <http://circ.ahajournals.org>; Funding: Boehringer Ingelheim

- **Patel MR**, *N Engl J Med*. 2011 Sep 8;365(10):883-91; www.nejm.org; Funding: Johnson & Johnson Pharmaceutical Research and Development and Bayer HealthCare
- **Nagrakanti R** et al; *Circulation*. 2011 Jan 18;123(2):131-6; <http://circ.ahajournals.org>; Funding: Boehringer Ingelheim

6. Recovery and rehabilitation

Recovery of the ability to walk is a critical function after stroke. While rehabilitation of various types has been studied after stroke and demonstrated to provide benefit, locomotor (walking) training using body weight support in stepping on a treadmill, and especially the timing of this training after stroke, had not been well studied. A critical study demonstrated that this locomotor training was equivalent to progressive exercise at home under the care of a physical therapist in improving the ability to walk even if the intervention is started long as six months after a stroke is completed. This demonstration that motor deficits are not fixed even at this late stage has the potential to lead to improved mobility and quality of life for stroke patients.

- **Duncan PW** et al. *N Engl J Med* 2011; May 26;364(21):2026-36; www.nejm.org; Funding: National Institute of Neurological Disorders and Stroke and the National Center for Medical Rehabilitation Research

7. Benefits of improving door to needle time in Stroke Centers

In one of the first studies to look at actual patient outcomes, this American Heart Association/American Stroke Association research found that more timely administration of tPA in acute ischemic stroke could be achieved by the Get With The Guidelines-Stroke quality improvement program. This increase in timely treatment resulted in improved outcomes for patients, including increased survival.

- **Fonarow GC** et al; *Circulation*. 2011 Feb 22;123(7):750-8. <http://circ.ahajournals.org>; Funding: The GWTG-Stroke program is currently supported in part by a charitable contribution from Bristol-Myers Squibb/Sanofi Pharmaceutical Partnership

8. Treatment of brain aneurysms to prevent hemorrhagic strokes

Although cerebral aneurysms have long been treated with catheter-based techniques, a new approach, using a novel type of stent was tested this year. This device, which can be used alone or with intra-aneurysmal coils, is designed to divert flow away from the aneurysm and preserve flow in the parent vessel. The first prospective, multicenter (Europe and South America), but not comparative trial of the device was published and demonstrated safety and efficacy.

- **Nelson PK** et al. *Am J Neuroradiol*. 2011 Jan;32(1):34-40. www.ajnr.org. Funding: Chestnut Medical Technologies

9. The role of traditional risk factors in causing disparities

There are important racial disparities in the risk of stroke, with a significantly increased risk in African-Americans. Some of the increased incidence is attributable to higher levels of traditional stroke risk factors such as hypertension and socioeconomic factors play a role in access to care and treatment; however, this new work found only about half of the racial disparity is attributable to these. This is important because it demonstrates how much is still unknown regarding the well-known black-white disparities in stroke mortality and stroke incidence. It suggests other important contributing factors may include differential susceptibilities to the traditional risk factors, differences in the development of the risk factors, or nontraditional risk factors.

- **Howard G** et al. *Stroke* 2011 Sept 29 [Epub ahead of print]; <http://stroke.ahajournals.org>; Funding: National Institute of Neurological Disorders and Stroke

10. Defining treatment options for patients with carotid narrowings but no symptoms

Most patients with asymptomatic carotid stenosis fare better with medical therapy, but it's not been clear how to select those who may not. New studies have suggested that those who could benefit from surgery (carotid endarterectomy) or from carotid stenting can be identified with appropriate use of transcranial Doppler ultrasound (a different kind of ultrasound evaluating blood vessels in the brain). Additionally, it has been demonstrated that patients with asymptomatic carotid stenosis undergoing coronary bypass surgery do not need to have these stenosis treated prior to or during surgery.

- **Topakian R** et al. *Neurology*. 2011 Aug 23;77(8): 751-58; www.neurology.org; Funding: British Heart Foundation
- **Madani A**. *Neurology*. 2011 Aug 23;77(8):744-50; www.neurology.org; Funding: Heart & Stroke Foundation of Ontario and the Stroke Prevention & Atherosclerosis Research Centre

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