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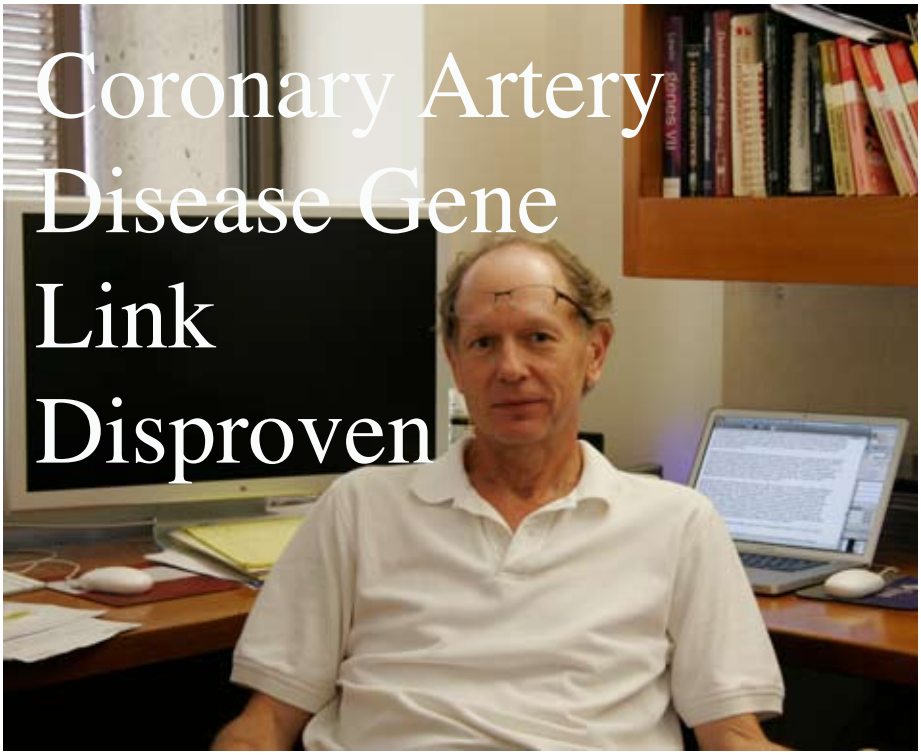


Stanford-led study shows no link between CAD and KIF6 variant

A genetic marker touted as a predictor of coronary artery disease is no such thing, according to a study led by researchers at the Stanford University School of Medicine.

The massive international study, published online Oct. 7 in the Journal of the American College of Cardiology, assessed the predictive value of a leading genetic assay for risk of atherosclerosis.

The study analyzed the data from more than 17,000 patients with cardiovascular disease and 40,000 others to assess whether carrying a particular variant of the KIF6 gene indicated a greater risk for coronary artery disease — a disease characterized by a buildup of cholesterol plaque in the walls of the arteries of the heart. The disease can lead to chest pain as well as heart attacks, which are often fatal. >>

No link between CAD and KIF6

(Cont. from Page 1)

The study found essentially no association between the gene variant and the risk of coronary disease. “This study puts the nail in the coffin,” said Tom Quertermous, MD, the William G. Irwin Professor in Cardiovascular Medicine at Stanford and the study’s senior author. “This is such a big study — if there was a significant association between this variant and coronary disease, we would have found it.”

Celera Corp., which pioneered the mapping of the human genome, owns the assay and currently performs the majority of the testing services. In June, as part of its effort to make the assay more widely available, Celera announced it had received approval from the European Union to market a test kit for the variant that would make it easier for physicians to collect patients’ samples. The company said it would also submit an application to the U.S. Food and Drug Administration this year for approval of the test kit.

Previous studies of the variant were less conclusive because they were based on fewer patients with coronary artery disease, said the new study’s leader, assistant professor of medicine Themistocles Assimes, MD, PhD. These earlier studies had suggested a 22-55 percent greater risk for those who had the variant. “We are showing that the additional risk is almost certainly nil in subjects of European ancestry,” Assimes said.

The study pulled together data from research groups around the world that have genetically fingerprinted individuals with known coronary disease as well as subjects with no known disease. Most of the data were from people of European descent, but a lack of association was also noted in smaller number of subjects of non-European ancestry. The Stanford researchers’ co-authors include more than 130 scientists, clinicians and administrators at over 70 research organizations in Europe and North America.

The study offers good news to patients whose KIF6 test result had indicated they were

Tim Assimes (left) and Tom Quertermous

at risk for heart attacks. “They don’t need to worry so much,” Quertermous said. “If they are on medications strictly because of their KIF6 test result, they should ask their doctor to reconsider the need for these medications.”

Because of the study’s design, it could not directly confirm or refute the marker’s ability to identify the subjects’ response to statins, which are drugs that lower cholesterol levels. However, Assimes cautioned that the original observation, which found the KIF6 variant indicated a good response to the medication, assumed that carriers of the variant not on statins were at significantly increased risk of coronary disease compared to non-carriers.

“In light of our findings, the marker’s ability to identify statin responders is also in doubt,” said Assimes. “Until very large-scale studies are performed to directly test the marker’s ability to identify statin responders, I would not withhold statins from patients just because their KIF6 test was negative.”

The finding’s larger message is that more caution is warranted when using genetic markers to guide health care. There’s understandably great desire to use the information about human genetics that’s been amassing since the sequencing of the human genome 10 years ago, said Quertermous, who has worked in the field for more than 20 years. “It’s something I’ve been waiting for, for a long time.”

$1.5 million grant for study of how mechanical forces affect cell communication, behavior

Alexander Dunn, an assistant professor of chemical engineering, was one of three Stanford researchers who were chosen by the National Institutes of Health to receive a prestigious grant of $1.5 million over five years. The grant is intended to support researchers who are doing creative or risky projects that have the potential to produce game-changing research results.

Dunn studies molecular protein motors that generate mechanical force inside living cells. When functioning properly, mechanical forces help guide the changes in size and shape that occur during normal development of the embryo. When acting out-of-line, the forces generated by these tiny motors contribute to a cancer cell's ability to travel throughout the body.

"What really interests me is how mechanical force functions in biology," Dunn said. "Cells communicate in part by pushing and tugging on their neighbors."

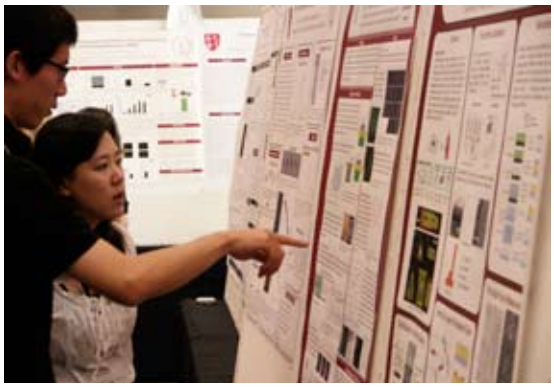
Dunn's research is especially applicable to cardiovascular research. "Every form of heart disease is a form of mechanical failure, from aneurysm to cardiomopathy, valvular disease, and of course heart failure itself," Dunn says.

Dunn is also interested in how cells decide which path to take due to information imparted by mechanical forces. After myocardial infarction, whether tissue regenerates as healthy myocardium or scar tissue depends in part, he believes, on mechanical information transmitted between cells.

One of the molecules he is looking at is fibronectin, a stretchy molecule that may be regulated in part by how much tension is put on it. "The idea is that stretching the molecule opens up new domains to proteolysis, which can then lead to differences in cell behavior.

Part of Dunn's research is developing new tools to measure mechanical strain at the cellular level. "Mechanical forces are turning out to be important, but the tools to study mechanical force at that scale are historically lacking," he says. Dunn and his group are using new light microscopy techniques to measure the forces generated by individual motor proteins in living cells to see how, when and where cells exert force on each other. Understanding these processes requires a research team with skills spanning genetics, cell biology, engineering and physics. "This grant makes it possible to put all of that talent together in one place," Dunn said.

2010 Cardiovascular Institute Retreat



Highlights of the CVI retreat, held Friday September 10, 2010:

- State of the Institute: Robert Robbins, MD, CVI Director, outlined the strategic plan, and showed significant progress in each of the themes: Discovery, Education, Clinical Care, and Organizational Development. As plan implementation continues, new goals and strategies will be defined.

- Keynote Address: Michael Gimbrone, MD, Harvard Medical School: "Vascular Endothelium in the Postgenomic Era: New Insights into its Pathobiology"

- Panel Discussion: A panel of five CVI faculty members, representing the CVI strategic areas, presented new, interesting, exciting, and unexpected findings from their own work. Dr. Gimbrone and the audience were invited to share their comments and opinions. Panel included Phil Tsao, PhD, Euan Ashley, MRCP, PhD, Tim Assimes, MD, PhD, Michael McConnell, MD, MSEE, Charles Taylor, PhD.

- Speed Science: With only five minutes each to speak, new CVI faculty Alex Dunn, PhD, Josh Elias, PhD, Ngan Huang, MD, Josh Knowles, MD, PhD, and Pilar Ruiz-Lozano, MD, provided a quick taste of their research interests.

- 2009 Seed Grant Updates: Seed grant recipients Euan Ashley, MRCP, MD, Lisa Chen, MSc (Ada Poon, PI) Stacy Sims, PhD (Marcia Srtefanick, PI), CP Chang, MD, PhD, and Sang Oh, MS (Bala Rajaratnam, PI) presented their work and discussed their progress, obstacles, and next steps.

- Poster Session: The entire audience voted for the top three of thirty posters presented in a lively poster session.

Congratulations to the winners of the CVI Retreat Poster Competition

1st place - **Rufaihah Jalil** (Cooke lab) *Directed Differentiation Of Human Induced Pluripotent Stem Cells Into Arterial, Venous And Lymphatic Endothelial Lineages*

2nd place - **Calvin Hang** (Chang lab) *Chromatin Regulation By Brg1 Underlies Heart Muscle Development And Disease*

3rd place - **Ngan Huang** (Huang lab) *Vascular Cell Morphology And Function On Aligned Collagen Matrices*

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CVI NEWS

CIRCULATION
Goings on about the Institute

Fridays at Falk 4-5:30 PM - A postdoc-centric afternoon series
CVI postdocs kicked off the Fridays at Falk happy hour in September. A mix of informal talks, discussion, and happy hour the gathering is intended to provide a venue for postdocs, graduate students, and interested faculty to learn more about who's doing what, where, and when in the CVI. The planning committee includes Arwen Hunter, PhD, from the Cooke lab, Ildi Toma, PhD, and Elaine Wang, PhD from the Yang lab.

Speaker nominations
The new weekly CVI seminar series will commence January 11, 1011. The series features speakers from the national and international community, bringing the latest science to the CVI. The speakers reflect the broad range of CVI interests (2011 schedule is available at cvi.stanford. edu.), and we are eager for nominations for this series. Please send your suggestions including (1) Name, (2) Affiliation, and (3) A brief description of the speaker's work, to Mitra Haddad (mhaddad@stanford.edu).

New mailing list for postdoctoral fellows and graduate students to sign up
Along with Fridays at Falk, a new mailing list has been generated to keep fellows and students informed about new funding, seminars, workshops, and other events of interest to this constituency. This is also a means for list members to easily communicate with each other. To subscribe, please visit:
https://mailman.stanford.edu/,ailman/listinfo/cvifellows

Congratulations to the 2010 Younger Fellows!

• **Jack Chai** (Dunn lab)	*Effect of Mechanical Load on Fibronectin Proteolysis*
• **Nick Conley** (Scott lab)	*High Throughput Mutagenesis of Neuropilins to Elucidate Domains Required for Hedgehog Signalling*
• **Toshiro Kitagawa** (McConnell lab)	*Angiogenesis Imaging in Abdominal Aortic Aneurysms Using a New Positron Emission Topography Agent*

About this newsletter: please direct comments, suggestions and news to: mhaddad@stanford.edu

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CVI NEWS

CIRCULATION
Goings on about the Institute

Highlighted Resource

WHI study-wide analyses of cardiovascular disease in 162,000 women

Dr. Marcia Stefanick, PI of the Western Regional Center for the five-year extension of the Women's Health Initiative (WHI) study, is funded to play the lead role in study-wide cardiovascular disease analyses of the WHI dataset. Areas of particular interest include atrial fibrillation and congestive heart failure.

CVI members are encouraged to contact Dr. Stefanick to discuss possible collaborations and projects for fellows. Current collaborators include Drs. Paul Wang, Marco Perez, Mark Hlatky and Tim Assimes. Interested members are also invited to attend an SPRC brainstorming session on the use of WHI data, Wednesday November 10, from 9:30-11 AM at LKC LKS101

The Women's Health Initiative provides a rich phenotypic, biomarker, and genotypic dataset accumulated over 15 years to date in 162,000 multi-ethnic postmenopausal women, aged 50-79 at baseline. This dataset includes the NHLBI SHARe project, to which WHI provided GWAS data in 12,000 black and Hispanic women. The WHI tested three different interventions in randomized, controlled trials, menopausal hormone therapy (N~27,000), low-fat diet (N~49,000), and Calcium/Vitamin D supplementation (N~36,000) and followed an additional ~94,000 women in a longitudinal, prospective study, all of which have centrally adjudicated cardiovascular outcomes.

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Stent procedures via the wrist require no overnight stay

You can have a percutaneous coronary intervention through your femoral artery or radial artery. Put another way, you can have a catheter stuck into your groin or your wrist. Not sure which you'd prefer?

A coronary stent is a tiny mesh tube that helps open up blood vessels clogged with cholesterol, fat and other stuff that leads to heart disease. Stenting is usually preceded by angioplasty, which involves expanding a balloon inside the artery to crush the plaque. Sometimes angioplasty is used exclusively. In any case, the procedures practically guarantee a night in a hospital bed if done the traditional way — through the femoral artery. But patients getting the intervention through the wrist usually leave the hospital just a few hours after the procedure.

Patients at Stanford usually owe their fast exit to cardiologist Jennifer Tremmel, MD — or, more specifically, to the minimally invasive technique she has mastered for diagnosing clogged blood vessels, performing angioplasties and placing stents. Instead of going through the femoral artery, Tremmel inserts a slim catheter into a small puncture in the left wrist and slides it up through the arm, via the radial artery, until it reaches the heart. Then she places stents into the left anterior descending artery and the left circumflex artery.

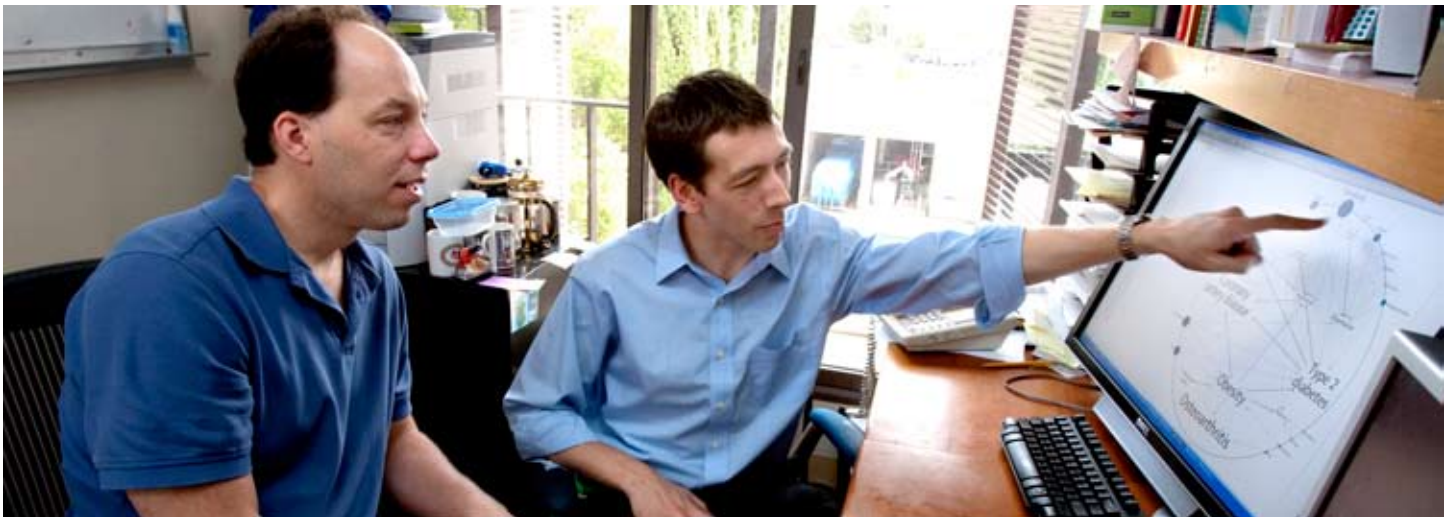
More than 1 million angioplasties and stent placements, known collectively as percutaneous coronary interventions, or PCIs, are performed each year in the United States. But it's tough to find a hospital that will do them transradially — that is, through the wrist.

A 2008 report in the *Journal of the American College of Cardiology Interventions* found that of nearly 600,000 PCIs between 2004 and 2007, only 1.32 percent were transradial.

However, the technique is rapidly gaining ground in the United States. Tremmel, who is director of the Transradial Interventions Program at Stanford Hospital, said that the transradial approach now accounts for almost 5 percent of all PCIs nationwide. Tremmel regularly travels around the country speaking about transradial PCI, and has turned Stanford into a West Coast training center where she trains two to three interventional cardiologists per month in the technique. In the spring, she will oversee a big course on it at Stanford.

Several studies have shown that transradial PCIs reduce bleeding complications, shorten hospital stays and cost less compared with the femoral approach. A meta-analysis published last year in the *American Heart Journal* found that transradial PCI reduced the risk of major bleeding by 73 percent and the length of hospital stays by about half a day as compared with femoral PCIs. For women, the risk of bleeding complications from transfemoral PCI are two to three times greater than for men, Tremmel said, which makes women ideal candidates for transradial PCI.

A longer version of this article is at http://cvi.stanford.edu



Searching a complete genome sequence for health risks

For the first time, researchers have used a healthy person's complete genome sequence to predict his risk for dozens of diseases and how he will respond to several common medications. The risk analysis, from the Stanford University School of Medicine, also incorporates more-traditional information such as a patient's age and gender and other clinical measurements. The resulting, easy-to-use, cumulative risk report will likely catapult the use of such data out of the lab and into the waiting room of average physicians within the next decade, say the scientists.

"The $1,000 genome is coming fast," said cardiologist Euan Ashley, MD, assistant professor of medicine, referring to the cost of sequencing all of an individual's DNA. "The challenge lies in knowing what to do with all that information. We've focused on establishing priorities that will be most helpful when a patient and a physician are sitting together looking at the computer screen."

Priorities that include whether a certain medication is likely to work for that particular patient, or if it's likely to have adverse side effects. Priorities that include ascertaining how a patient's obesity or smoking combine with his or her inherent genetic risk for — or protection against — heart attack or diabetes. In short, priorities that result in concrete clinical recommendations for patients based on a degree of data that has never existed before.

"We're at the dawn of a new age in genomics," said Stephen Quake, PhD, who is the Lee Otterson Professor of Bioengineering. "Information like this will enable doctors to deliver personalized health care like never before. Patients at risk for certain diseases will be able to receive closer monitoring and more frequent testing, while those who are at lower risk will be spared unnecessary tests. This will have important economic benefits as well, because it improves the efficiency of medicine."

Quake made national headlines last August when he used a technology he helped invent to sequence and publish his own genome for less than $50,000, and it is his genome that the researchers analyzed in this newest study. Ashley is the lead author of the research, published in the May 1 issue of the Lancet.

An accompanying article about the ethical and practical challenges of such research, authored by a subset of the researchers involved in the first study, will appear in the online-only version of the Lancet on the same day. Hank Greely, JD, professor and director of Stanford's Center for Law and the Biosciences, is the senior author of the online piece.

"Patients, doctors and geneticists are about to hit by a tsunami of genome sequence data. The experience with Steve Quake's genome shows we need to start thinking — hard and soon — about how we can deal with that information," said Greely.

Physicians failing to follow recommended heart-failure treatment guidelines, study finds

Physicians are losing ground in prescribing the types of medications that have proven most effective in treating a condition known as congestive heart failure, according to a new study from the Stanford University School of Medicine.

The study shows that the use of two types of drug therapy for treating heart failure has steadily declined since the early and mid-2000s, and that the medications are being prescribed to only about one-third of the patients who would benefit from them.

"Tried-and-true therapies are not getting the attention they really deserve," said senior author Randall Stafford, MD, PhD, associate professor of medicine at the Stanford Prevention Research Center. "These therapies are of great value to the vast majority of heart-failure patients, and to see them being used in less than 40 percent of patients is a concern."

The research is published in the Aug. 9/23 issue of the Archives of Internal Medicine.

The paper is a follow-up to an earlier study indicating that through the early 2000s physicians were slowly increasing their adoption of heart-failure treatment recommendations developed by the American Heart Association and the American College of Cardiology.

Heart failure — a condition in which the heart doesn't pump enough blood to the body's other organs — often leaves sufferers tired, short of breath and carrying extra fluid in their bodies. About 20 percent of those who are diagnosed with the condition die within a year, and 80 percent die within eight years.

Clinical trials have shown that two types of medication therapy are highly effective in treating the condition. One, which includes drugs known as ACE-inhibitors and angiotensin receptor blockers, expands blood vessels to improve blood flow. The other, known as beta blockers, improves the pumping efficiency of the heart.

Stafford and lead author Dipanjan Banerjee, MD, a clinical instructor in cardiovascular medicine, used a national database of physician survey responses to determine which medications were being prescribed to treat heart-failure patients from 1994 through 2009. They found that use of the ACE-inhibitors and ARBs increased from 34 percent in 1994 to 45 percent in 2002, but then decreased to 32 percent by 2009. With beta blockers, use went from 11 percent in 1998 to 44 percent in 2006, but had dropped to 37 percent by 2009.

"Our expectation was that there would be continued improvement in the use of these drugs, but that hasn't happened," Stafford said. "We're not sure what's gone wrong."

He and Banerjee hypothesize that the lack of new clinical trial findings about the medications in recent years may have lowered the treatments' profile among physicians and patients. "The longer it's been since an important trial is published, the more difficult it becomes to reinforce the value of those findings," Stafford said.

He said he hopes the study highlights the "quality gap" between actual and recommended heart-failure treatment, as well as spurring deeper investigations into why the recommended treatments aren't being adopted.

The study was funded by the National Heart, Lung and Blood Institute.

New treatment for severe aortic stenosis shown to save lives, researchers say

Implantation of a new bioprosthetic-tissue valve into the hearts of patients who have severe aortic stenosis and are too sick or too old for open-heart surgery has been found to both save lives and improve the quality of those lives, according to a new multicenter study, to be published online today in the New England Journal of Medicine.

The study was presented Sept. 23 at the Transcatheter Cardiovascular Therapeutics Conference in Washington, D.C.

"This is exciting because it does save lives and is a major medical paradigm shift," said D. Craig Miller, MD, the Thelma and Henry Doelger Professor of Cardiovascular Surgery at the Stanford University School of Medicine and one of the manuscript's principal authors. "These patients were really sick with a fatal problem, and now they're feeling better and staying out of the hospital. Before, there was nothing we could really offer them. "

Stanford University Medical Center was one of 21 institutions to participate in the study, known as the PARTNER Trial. It is the first randomized clinical trial comparing the efficacy of using a transcatheter heart valve called "TAVI" — which is implanted percutaneously through an artery in the groin directly into the beating heart — with routine medical therapy, which includes aortic balloon valvuloplasty to relieve symptoms. The trial was sponsored by Edwards Lifesciences Corp., based in Irvine, Calif., which designs, manufactures and markets tissue heart valves.

A total of 358 patients with severe aortic stenosis, a heart disease characterized by obstruction of the aortic valve due to calcification, participated in the trial. The patients who qualified were debilitated by the disease, which causes shortness of breath, fatigue and congestive heart failure. While the standard of care for most patients with this condition would be open-heart surgery to replace the diseased valve, that was not a realistic option for the specific patients selected for this study, who were too sick or too old to undergo such an operation. For them, the standard of care is medical therapy.

At one year after randomization, 30.7 percent of patients who had received the percutaneous valve replacement had died compared with 50.7 percent of those who received standard medical therapy.

"The most impressive finding in the study is the 20 percent reduction in mortality," said William Fearon, MD, associate professor of cardiovascular medicine at Stanford, who also participated in the study. "This is very dramatic. The effect was so powerful that by just treating five people you can save one life. But beyond just the survival benefit, the improvement in the patients' quality of life based on their symptoms and their ability to exercise is dramatic."

Stanford enrolled more than 80 patients in the PARTNER study, of which 14 were these very sick patients. Future studies are planned to determine the durability of the TAVI valves and also to determine whether this procedure may be beneficial in other lower-risk and younger patients for whom open-heart surgery is a low-risk and durable option.

Additional Stanford faculty and staff on the PARTNER team included Alan Yeung, MD, the Li Ka Shing Professor of Medicine and chief of Stanford's division of cardiovascular medicine, cardiovascular surgeon Michael Fischbein, MD; cardiologist David Liang, MD, PhD; cardiovascular anesthesiologists Pieter van der Starre, MD, PhD, and Charles Hill, MD; and nurse coordinators Martina Speight and Cheryl McWard.

A longer version of this article is at http://cvi.stanford.edu