NEW HEART DEVICES OFFER HOPE

Temporary total artificial heart and HeartMate II provide new options for advanced heart failure

For years, the U-M Center for Circulatory Support has offered a wide range of advanced heart-assisting technologies for patients with advanced heart failure due to ischemic disease, all forms of cardiomyopathy and other conditions.

Now, with the addition of the CardioWest temporary total artificial heart and the publication of results from a pivotal multi-center trial of the HeartMate II investigational left ventricular assist device, the Center is prepared to offer even more options to its patients.

HeartMate II: a new generation of left-ventricle support

Left-ventricular support has been a focus for the Center for more than a decade, and the newly published HeartMate II trial continues that focus.

The study was published in the *New England Journal of Medicine* by a team co-led by Center director and U-M cardiac surgeon Francis Pagani, M.D., Ph.D., (right) with Keith Aaronson, M.D., M.S., medical director of U-M's heart failure program, as a co-author.

The results show that this device—one of a new generation of LVADs that provide continuous blood flow—does very well at helping severely ill heart-failure patients survive, and thrive, until they receive a heart transplant.

In all, 75 percent of 133 patients were still alive on LVAD support, or had received a transplant or recovered full cardiac function, six months after implant. Patients’ renal and hepatic function, and quality of life, also improved significantly.

HeartMate II is much smaller than older LVADs, including the HeartMate XVE, which is also made by Thoratec Corporation and has Medicare approval for destination and bridge-to-transplant use. Thus, HeartMate II has the potential to help more women and adolescents whose bodies are not large enough for other devices. It’s also quieter, and has a smaller cannula leading from the controller and battery pack.

Although the *NEJM* study did not directly compare the HeartMate II device with any other device, the results give further evidence that the new device is more reliable than previous heart-assisting implants.

U-M continues to recruit patients with advanced heart failure for the pivotal trial of HeartMate II, both for the bridge-to-transplant arm that was reported in the *NEJM* article, and for an arm that is enrolling patients ineligible to receive a heart transplant, who will receive the device as destination therapy.

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Each fiber in the brain’s network of white matter is crucial to a particular aspect of how our brain communicates with our body.

But until now, these fibers have not been visible even with the most sophisticated neuroimaging, and they’ve fallen victim to even the most careful surgeon’s hand during operations to remove malignancies or treat medically refractory epilepsy. The resulting damage can diminish a patient’s senses, movement, or cognitive function.

U-M neuroradiologists and neurosurgeons, however, have been developing techniques to image white-matter tracts, and to superimpose those images in the surgeon’s field of vision.

The imaging technique is called MRI tractography, and U-M is one of the first hospitals in the world to use it in image-guided surgery. The team feels that the technique holds great promise for other uses as it is developed further.

“In the past, we’ve never been able to see the direct connections from one part of the brain to another, or from one part of the brain to the spinal cord,” says one of the team’s leaders, Suresh Mukherji, M.D. “We can see those connections now, by looking at the sub-cellular level to see how the water molecules in the tissue move.”

Mukherji directs the U-M Division of Neuroradiology, whose brain-imaging specialists work closely with U-M neurosurgeons who perform thousands of brain and spine operations a year, and with U-M neurologists who treat seizure and movement disorders.

U-M neurosurgeon Oren Sagher, M.D., says this teamwork makes it possible for him to operate with the best possible information about each patient’s brain.

“Thoroughly imaging the brain is one of the keys to successful brain surgery. We have to be able to see all the
Merkel cell carcinoma, sometimes referred to as neuroendocrine carcinoma of the skin, is a rare form of skin cancer, caused when Merkel cells grow out of control. Merkel cells are found in the epidermis and are thought to function as touch receptors. Merkel cell carcinoma is most frequently found on sun-exposed areas of the skin, such as the head, neck, arms, and legs, but may occur on any part of the body. It does not have a distinctive appearance and is often confused with a cyst, lipoma, or other form of skin cancer such as basal cell carcinoma.

Merkel cell carcinoma is a potentially aggressive form of skin cancer. However, when diagnosed and treated at an early stage, Merkel cell carcinoma can be effectively treated with a high cure rate. Eventually, it may metastasize to the lymph nodes and later to internal organs such as the liver, lungs, brain, bone, and other parts of the body.

Merkel cell carcinoma is treated in the Merkel Cell Carcinoma Clinic, part of the U-M Health System’s Dermatology Department. The Multidisciplinary Merkel Cell Carcinoma Program offers coordinated and comprehensive evaluation, treatment and follow-up care for patients with all biopsy-proven stages of Merkel cell carcinoma. The Program helps patients ranging from those with the earliest stages of Merkel cell carcinoma to those with the most advanced disease. The multidisciplinary physician team develops a coordinated treatment plan with input from all necessary specialists.

**Find More on the Web**
www.med.umich.edu/derm/patient/skinmerkel.shtml

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The technique relies on U-M’s three-Tesla MRI (magnetic resonance imaging) capabilities, and a technique called diffusion-weighted imaging. The latter is made possible by digital post-processing of three-dimensional MRI images.

Diffusion images make it possible to trace the movement of water molecules within white matter and surrounding brain tissue. Inside the white-matter tracts, water can only move in a lengthwise direction, back and forth along the length of the thin strand. But in the rest of the brain tissue, the water can move around more freely.

This is the same principle that underlies the diffusion MRI technique that has been developed by the U-M team and others to determine if malignant cells are dying in response to chemotherapy or radiation. In that application, the images are based on the principle that water can move faster in dead or dying areas of cancerous tissue than it can in healthy brain cells.

In white-matter tractography, the 3-D images become a road map for surgeons, especially when cross-registered with other images that show the specific focal points for the patient’s epileptic seizures or the precise location of a malignant or benign growth.

“The computers can decipher the direction of the fibers, and then assign a color to them so we know that this group of fibers belongs to this tract, which has this function by virtue of where it is,” explains Sagher, who directs the U-M Image-Guided Surgery Program.

“It essentially makes the invisible visible.”

And that allows the surgeon to plan the route he or she will take to get to the area of the problem. Mukherji, Sagher and their colleagues predict that tractography will change brain surgery as dramatically as the first CT and MRI scans of the brain changed the diagnosis and treatment of many disorders. The team is pursuing research to improve the technique and show how it can best be used—and how it helps spare patients from unintended consequences.

“Instead of imaging the brain, we’re essentially able to image the mind,” says Mukherji. “We’re able to image how a person’s thoughts and brain impulses travel, and this is just the beginning.”

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One of U-M’s three-Tesla MRI machines.
Slicing certain pills in half could slice a hefty amount off of America’s prescription drug costs. And while only some types of pills can be split safely, the practice could be used by millions of Americans—including many of those who take statin drugs to control cholesterol.

Now, a new U-M study adds more evidence that patients can take half of a high-dose statin tablet that has been split, rather than taking a whole low-dose pill each time, with no impact on serum cholesterol levels.

The study was published in the June issue of the American Journal of Managed Care by a team from the U-M Health System and the U-M College of Pharmacy.

“The study was done in part to see what the impact would be of having some of the cost savings go back to the patient,” says first author Hae Mi Choe, PharmD, CDE, a clinical assistant professor in the College of Pharmacy and a UMHS clinical pharmacist.

While the study did not find that out-of-pocket costs had an impact on the participants’ tendency to split and take their pills during the six-month study, most participants said that reduced co-pays would be needed to entice them to continue splitting pills.

The findings have already had an impact on one large employer’s prescription drug plan: the University of Michigan used them to justify a pill-splitting program that launched in early 2006. In its first full year, the program saved the University $195,000, and saved more than 500 employees and retirees a total of more than $25,000 in drug co-pay costs.

Pill-splitting is made possible by the availability of tablet formulations in a variety of doses, some of which can be cut in half to produce two lower-dose tablets. Because drug manufacturers and wholesalers typically don’t charge twice the price for twice the dose, the cost of half of a high-dose pill is far lower than the cost of buying a whole lower-dose pill.

Pill-splitting can save money for insurers and pharmacy-benefit managers, and by extension for employers or government insurers.

Statins are among the most widely-used classes of medicines, and are good candidates for splitting.
But few prescription plans currently structure their benefits to encourage pill-splitting, by charging lower co-pays to patients who buy high-dose pills they intend to split.

Patients have been splitting pills on their own for years, some without their physicians’ knowledge, to try to save money. But others do it with help from physicians who write prescriptions for a higher dose and instruct patients on how to make one month’s supply last two months. However, this can result in confusion, and skew the patient’s and doctor’s records.

In recent years, pharmacists have worked to determine which tablets can be safely split, and which—such as drugs that exit the body quickly, or that have time-release coatings—cannot.

Statins are among the most widely-used classes of medicines, and are good candidates for splitting because they linger in the body for a relatively long time, and because small day-to-day dose fluctuations that can happen when pills are split don’t make a major difference in cholesterol levels.

The U-M study involved patients who were taking atorvastatin, pravastatin, or simvastatin, and were in the care of physicians at a single UMHS health center.

Two hundred eligible patients completed the initial survey regarding their perceptions of pill-splitting. Of them, 111 patients agreed to participate in a 6-month trial of pill-splitting in which half were randomized to receive a financial incentive of 50 percent reduction in their co-payment per refill and half did not.

All study participants were given two different pill-splitters to compare and to use for six months. They allowed the researchers to review their prescription information and cholesterol levels for a pre-study period as well as during the study. On average, the co-pay reduction was about $5 to $7 per month.

A total of 103 patients completed the entire six-month randomized study, and 109 completed the survey at the end. The follow-up survey showed that 89 percent of all participants would be willing to continue splitting pills if they would receive a co-pay reduction, and 80 percent said that splitting pills had been “no big deal” for them.

Although the study didn’t show that reducing out-of-pocket costs affected patients’ adherence to their statins over the six-month study period, the survey at the end of the study showed a clear desire among most participants to save money in return for long-term pill-splitting.

The U-M employee benefits office, which sponsored the study, offers a co-pay reduction in the pill-splitting program that it launched for all 80,000 U-M employees, retirees, dependents and survivors in January 2006. So far, more than 500 people who take statins have signed up; further medications are being considered for inclusion in the program.

For more information on the U-M pill-splitting program for employees and retirees, and their dependents, visit www.umich.edu/~benefits/plans/drugs/special.htm#pillsplit

Reference: American Journal of Managed Care, Vol. 13, No. 6, pp. 71-77
NEW WAY TO PREDICT MORTALITY FROM AORTIC DISSECTION?

Partial clotting in false lumen associated with much greater risk

Each year, 10,000 Americans suffer an aortic dissection, a sudden tear of the body’s largest blood vessel. Often misdiagnosed upon presentation, and often fatal if diagnosis is delayed, this condition has long carried a high mortality rate.

In recent years, advances in cardiothoracic imaging, medical management, and open and endovascular procedures have improved patients’ odds of surviving the initial hospitalization. But post-discharge, mortality risk is still extremely high, especially in the first few years. And reliable risk-stratification and clinical decision-making tools have yet to be developed.

Now, a study published in the July 26 New England Journal of Medicine by an international team of researchers may offer hope for aortic dissection survivors, and give guidance for their physicians.

The researchers, led by U-M Cardiovascular Center cardiologists, propose a new way to predict post-hospital mortality risk for aortic dissection patients, and a new model for the mechanism behind that risk.

The model focuses on a phenomenon that can easily be seen on modern CT and MRI images: the presence and extent of thrombosis in the false lumen—the channel created when the layers of the aortic wall separate.

As blood enters the false lumen after a dissection, it becomes trapped, and may begin to thrombose, depending on the rate of exit via small openings at the bottom of the newly formed channel. At the same time, pressure inside the false lumen increases.

The new study shows that post-hospital mortality was more than 2.5 times greater among patients who experienced partial thrombosis of the false lumen, compared with those whose false lumen was clear, or patent. Patients whose false lumen is totally thrombosed—which happens quite infrequently—were found to have an intermediate risk of death.

“It appears that this may be a new predictor of which patients are most at risk—knowledge that might help guide decisions about when it’s wise to proceed with more aggressive treatment and when we can hold off. But more research is needed,” says lead author Thomas Tsai, M.D., M.Sc., a U-M fellow in cardiovascular medicine.

The study involves data from 201 patients with dissections in their descending aortas, who were discharged from the hospital after treatment and followed for up to 36 months or until death.

The data are from IRAd, the International Registry of Acute Aortic Dissection, which is headquartered at the U-M Cardiovascular Center and includes treatment and patient outcomes data from 22 large medical centers in 11 countries.

Senior author and CVC director Kim Eagle, M.D., FACC, is a primary IRAd investigator. He says, “I believe that we are beginning a new era of scientific discovery in aortic diseases at U-M and in IRAd. By taking advantage of advances in imaging studies and genetic associations of aortic diseases, correlations with this entire care area will be transformed.”

The researchers propose that the excess mortality risk from partial thrombosis may be attributable to increased pressure within the false lumen, and to properties and responses of the torn aortic wall itself.

Data suggest that in a partially thrombosed false lumen, the systolic pressure is lower than the systolic pressure in the aorta, but that the diastolic pressure is higher—leading to a higher mean pressure in the false lumen, as compared to a patent or completely thrombosed false lumen.
Previously, U-M interventional radiologist David Williams, M.D., has studied the false lumen, and U-M vascular surgeon Ramon Berguer, M.D., has studied the dynamics of endoleaks in a similar model of abdominal aortic aneurysms treated with stent grafts. This research and work by others around the world lends further weight to the model proposed from the new data.

The NEJM paper is based on retrospective clinical data from 114 patients who had a patent false lumen when they were admitted to an IRAD hospital, 68 patients who had a partially thrombosed false lumen, and 19 who had a completely thrombosed false lumen.

By the end of the three-year follow-up period, nearly 25 percent of the patients had died. But the difference in death risk was striking: 13.7 percent of the patients with patent false lumens had died, compared with 31.6 percent of the partially thrombosed patients and 22.6 percent of the completely thrombosed patients. The difference held up after other demographic and clinical factors were corrected for.

In addition to the importance of the false lumen, the researchers found that patients with a history of atherosclerosis and of aortic aneurysm had higher mortality risk. The patients were all initially treated between 1996 and 2003, and were mostly male and in their 60s.

Tsai notes that the current trend toward increased use of endovascular stent-grafts in aortic disease is based on a belief that blocking the flow of blood into the false lumen will lead to clot completely, thereby decreasing pressures within the channel and possibly leading to gradual healing.

If further research validates the false-lumen thrombosis risk model, regular imaging to assess the extent of thrombosis might become part of the standard follow-up care for dissection patients. Currently, MR or CT imaging every six to 12 months after diagnosis is recommended.

The U-M team is now conducting prospective studies of aortic dissection patients, to determine how the false lumen changes. They are also pursuing the identification of blood markers that might permit an earlier diagnosis both early in the course of a dissection and later on, and working to further refine long-term risk prediction.

Meanwhile, the U-M Cardiovascular Center has expanded its multidisciplinary program in aortic disease. Among other activities, U-M surgeons G. Michael Deeb, M.D., Himanshu Patel, M.D., and Gilbert Upchurch, M.D. are pursuing refinements in open surgery and stent grafting, including clinical trials of new thoracic aortic endografts.

FOR MORE INFORMATION
The journal has prepared an animation of the proposed model of false lumen thrombosis and its impact on pressures within the false lumen. It is available online at www.nejm.org

Reference: NEJM, Volume 357, No. 4, pp. 349-359, July 26, 2007

KEY POINTS
• Despite advances in acute aortic dissection care, post-hospital mortality remains high, and reliable risk-prediction tools are not available.
• A recent review of hospital records and follow-up data from 201 AD patients treated at 22 centers showed that those whose false lumens were partially thrombosed had a post-discharge mortality risk 2.5 greater than that of other patients.
• Although further study is needed before false-lumen thrombosis can be validated as a risk-prediction tool, the authors note that the extent of thrombosis can be assessed using current CT and MRI technology.
• Current clinical guidelines call for CT or MRI imaging every 6 to 12 months, in any patient with an aortic dissection.

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Total artificial heart provides biventricular support

For patients with complex cardiac issues and severe biventricular dysfunction, the CardioWest temporary total artificial heart or TAH-t made by Syncardia offers a unique option.

U-M is the only center in Michigan, and one of only nine nationwide, certified to provide TAH-t treatment. The device has FDA approval as a bridge to transplant; it is the only artificial heart with this approval level. It is a much-updated version of the Jarvik Heart used in the 1980s.

The first patient treated in Michigan, Phillip Hall of Belleville (right), received a TAH-t in September 2006, after idiopathic cardiomyopathy had reduced his ejection fraction severely and he had been on the heart transplant waiting list for several months. Three weeks after his operation, Mr. Hall received a transplant and is doing well a year later. The second TAH-t patient at U-M was treated in August 2007 and is also doing well.

The TAH-t implantation requires excision of both ventricles, allowing the device to be connected to the atria, pulmonary artery and aorta. The device is connected to an external console that pulses pressurized air to drive the pumping chambers, and monitors pump function. The TAH-t pumps 9.5 liters of blood per minute, the highest rate of any heart-assisting device.

Although patients using the TAH-t cannot leave the hospital and must be near the console at all times, the device offers the chance to stay alive and regain function in vital organs until a transplant occurs, for select patients who have no other option.

In addition to the HeartMate II and the TAH-t, the U-M Center for Circulatory Support offers a wide range of devices for adult and pediatric heart failure patients.

The center offers extracorporeal membrane oxygenation (ECMO), the Thoratec and original HeartMate ventricular assist devices, the Novacor ventricular assist device, the Orqis and TandemHeart devices that are attached to the circulatory system percutaneously, and the Abiomed device. Soon, the team will begin recruiting patients for clinical trials of the Duraheart and Levacor rotary ventricular assist devices, and for a more portable console for the TAH-t.

Earlier this year, a U-M pediatric team implanted its first child with the Berlin Heart, after receiving special FDA permission.

For more information or if you would like to receive this newsletter via e-mail, please call M-LINE 800-962-3555.