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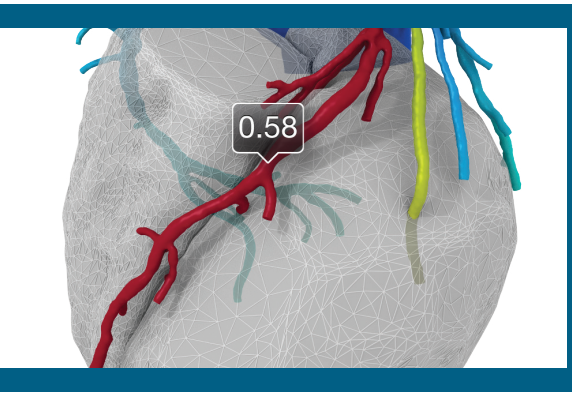
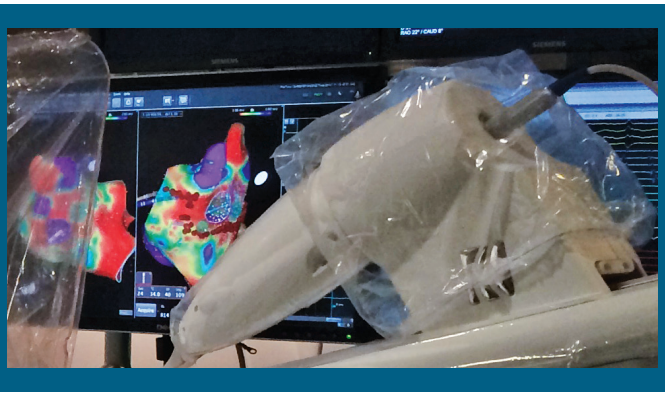
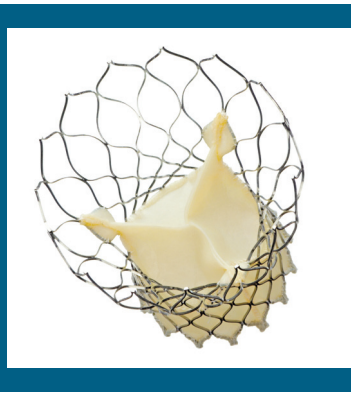
INNOVATIONS







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WINTER 2015

CONTROVERSIES IN CARDIOLOGY:
PARADIGM-HF TRIAL - A NEW "WONDER DRUG"?

Dr. Daniel Simon: Guilherme, you must be pretty excited about LCZ696, the first new heart failure drug in almost 20 years to show clinical benefits in a mega-trial?

Dr. Guilherme Oliveira: Dan, I would say that I am excited enough to raise half an eyebrow.

Dr. Simon: You have been prescribing the same heart failure drugs your whole career and now that you have a new drug with positive results published in the New England Journal of Medicine, all you do is raise a half an eyebrow?

Dr. Oliveira: We need to be careful here. There are real issues of trial design, control drug and minimal U.S. enrollment.

Dr. Simon: I thought it showed definitively that LCZ696 is better than Enalapril – fewer deaths, fewer hospitalizations. You're not convinced?

Dr. Oliveira: Let's forget about the media frenzy and start with the trial design and, in particular, the run-in phase. The purpose of the run-in phase is to weed out patients intolerant to the new medication and increase the odds of a positive effect. When the drug is approved, physicians are generally not so careful, raising potential safety concerns.

Dr. Simon: But LCZ696 was compared to Enalapril. Was that not good enough?

Dr. Oliveira: Not only is Enalapril hardly used anymore, but it was given in half of the maximal dose and mandated not to be adjusted upwards. In other words, you had a maximum dosed ARB against a modestly dosed ACE-I. In fact, there was significantly more hypotension in the LCZ group, suggesting greater drug effect.

Dr. Simon: Are you suggesting that possibly most of the effect we saw could be attributed to just a dose discrepancy between two similar drugs?

Dr. Oliveira: All I'm saying is that it cannot be ruled out by this trial's design.

Dr. Simon: The trial was well conducted, by recognized leaders in the heart failure field with diverse patient representation, right?

Dr. Oliveira: This trial examined patients with HF and reduced ejection fraction or HFrEF, mostly all Caucasian males outside the United States. Entry criteria pre-specified NYHA class II-IV patients. I am not sure why 5 percent of patients had NYHA class I symptoms (or no clinical HF), suggesting protocol deviation.

Dr. Simon: Do you think this drug should be approved in the U.S.?

Dr. Oliveira: I am honestly uncertain at this point. I am concerned that fewer than 10 percent of patients in the trial were enrolled in the U.S.

Dr. Simon: That is a legitimate concern. I have to ask you a question that all non-heart failure cardiologists want to know: If LCZ696 were approved, would you take your patients off an ACE-I and put them on LCZ696?

Dr. Oliveira: I would probably not use LCZ696 for patients in stable class II heart failure. However, for a patient going downhill with class III-IV heart failure despite optimal doses of ACE-I, I would strongly consider it. We need more trials. Stay tuned!

View the full discussion online at **UHhospitals.org/LCZ696**.

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ONCO-CARDIOLOGY

Overcoming Severe Coronary Vasospasm with 5-Fluorouracil

C.R. is a 48-year-old man with a history of metastatic cancer of the ileum diagnosed in 2011, for which he underwent surgery followed by chemotherapy with FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin).

In January 2013, C.R.'s oncologist detected a new metastatic lesion of the liver on MRI and elected to resume chemotherapy. However, during his first cycle, C.R. developed severe chest pain, nausea and difficulty breathing accompanied by atrial flutter and echocardiographic evidence for new left ventricular dysfunction (LVEF= 25%). His chemotherapy was discontinued.

However, a repeat PET scan in July 2013 indicated cancer progression with a new metastatic lesion in the liver and new lymph nodes in the abdominal cavity.

"From an oncology point of view, the best treatment at this time would have been FOLFOX or FOLFIRI (folinic acid, 5-fluorouracil, irinotecan)," says **Guilherme H. Oliveira, MD**, Director of the Advanced Heart Failure Center and Onco-Cardiology Program at University Hospitals Harrington Heart & Vascular Institute. "However, because of his dramatic cardiac side effects, his oncologist felt the risks of 5-fluorouracil were unacceptable. This meant that C.R.'s chances of survival were close to zero."

C.R. was referred to the UH Onco-Cardiology Program in November 2013. Dr. Oliveira recommended a coronary angiogram, which definitively ruled out significant coronary artery disease, confirming the diagnosis of 5-fluorouracil-induced coronary vasospam.

"Once we ruled out significant coronary artery disease, we decided to treat him prophylactically with medications that prevent vasospasm and re-challenge him with 5-fluorouracil," Dr. Oliveira says. "In close collaboration with his oncology team, we admitted him to the intensive care unit where he could be closely monitored at all times. We gave him potent, intravenous vasodilators concomitant to 5-fluorouracil infusion and were pleased to see no recurrent symptoms, ECG changes, arrhythmias or left ventricular dysfunction."

While C.R. began his treatment in the cardiac intensive care unit and transitioned to the telemetry unit of the hospital, he has now transitioned home, where he takes a prophylactic combination of oral vasodilators before and after his chemotherapy infusions. At an appointment in October 2014, C.R. reported that his cancer has stabilized and that he has completed his 23rd chemotherapy treatment successfully.

"C.R's case is a great example of how onco-cardiology can collaborate with oncology to help in the successful treatment of cancer patients," Dr. Oliveira says. "If it were not for the medications to prevent vasospasm, this patient would have not received life-prolonging chemotherapy and would have probably succumbed to his cancer. Optimizing his cancer treatment gives us all great satisfaction."

LEARN MORE. For more information about the Onco-Cardiology Program at UH or to refer a patient, call 216-844-3800.

ONCO-CARDIOLOGY SERVICES

The UH Onco-Cardiology Program assesses and monitors cancer patients who are receiving cardiotoxic drugs or chest radiation, allowing for prompt treatment adjustments when cardiac problems arise. Tools include strain echocardiography, cardiac MRI, functional exercise testing and endomyocardial biopsy. Abnormal strain can occur prior to changes in ejection fraction, thereby enabling physicians to initiate cardioprotective therapies, such as beta-blockers, ACE inhibitors and statins that prevent both cardiac dysfunction and premature discontinuation of cancer treatments.

CASE STUDY

SRI KRISHNA MADAN MOHAN, MD
Chief Quality Officer, UH Harrington Heart & Vascular Institute; and Assistant Professor of Medicine, Case Western Reserve University School of Medicine

HIRAM BEZERRA, MD, PhD
Director, Cardiovascular Imaging Core Laboratory, UH Harrington Heart & Vascular Institute; and Assistant Professor of Medicine, Case Western Reserve University School of Medicine

FFR-CT: A Revolution in CAD Diagnosis

The clinical tests currently used to diagnose coronary artery disease have well-known limitations.

"The diagnosis of coronary artery disease using stress echo or nuclear stress testing remains sub-optimal even today," says **Sri Krishna Madan Mohan, MD**, Chief Quality Officer with University Hospitals Harrington Heart & Vascular Institute. "Sensitivity, specificity, positive and negative predictive values are simply not adequate to definitively rule in or rule out CAD. While CT-based angiography has improved dramatically as a highly sensitive, non-invasive test for the diagnosis of CAD, it only provides an anatomic assessment, not a physiological one. Therefore, CT angiography has limited specificity. We can also measure fractional flow reserve (FFR) in the catheterization lab to assess functional significance of the stenosis, but that's an invasive test."

"We know that 40-50 percent of heart catheterizations performed in the U.S. show no significant coronary artery disease," says **Hiram Bezerra, MD, PhD**, Director of the Cardiovascular Imaging Core Laboratory of UH Harrington Heart & Vascular Institute at UH Case Medical Center. "If we had a better diagnostic tool, these invasive procedures could be avoided, thereby reducing costs, radiation exposure and potential complications."

LEARN MORE

For more information about FFR-CT and UH's role in testing and applying the technology, call **216-844-3800**.

Daniel Simon, MD, President of UH Harrington Heart & Vascular Institute, shares Dr. Madan Mohan's and Dr. Bezerra's frustration. "To date, we have operated with diagnostic screening tests with insufficient diagnostic accuracy," he says.

According to UH cardiologists, FFR-CT technology has the potential to change all that.

"For the first time, we have access to a non-invasive diagnostic test that provides both anatomic assessment and functional significance of coronary artery disease," Dr. Simon says. "I believe FFR-CT has the potential to completely transform the diagnosis of coronary artery disease."

"This is the first time we have a non-invasive way of looking at both anatomy and physiology," Dr. Madan Mohan says. "It's a one-stop shop."

"The beauty of it is that there's no special scanner or special protocol," Dr. Bezerra says. "It's based on a standard CTA that you do every day. By combining the CTA with a physiological assessment, unnecessary catheterizations based previously on false-positive stress tests can be avoided."

HOW IT WORKS

FFR-CT technology, developed by HeartFlow, Inc., takes coronary CTA scans, uploaded to the cloud, and combines them with proprietary computer algorithms based on computational fluid dynamics to create a color-coded, 3-D model of the patient's coronary arteries, showing both derived FFR information and anatomy. FFR-CT is calculated as a distal-to-proximal pressure ratio, just as it is derived from invasive measurements in the catheterization lab.

It is anticipated that HeartFlow will receive approval from the U.S. Food and Drug Administration for FFR-CT in November 2014. UH Case Medical Center is one of the early adopters of this technology.

WHAT THE RESEARCH SHOWS

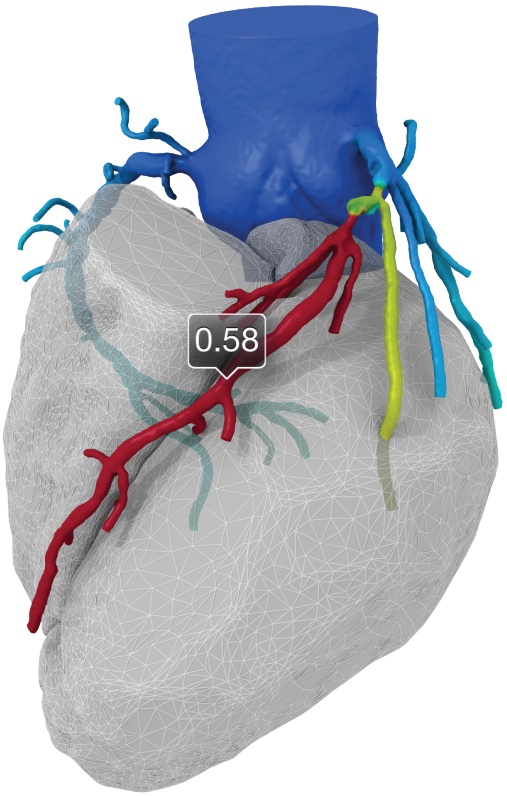
Investigators have evaluated the diagnostic accuracy (i.e., sensitivity, specificity, positive- and negative-predictive values) of FFR-CT technology compared to traditional CTA alone in three multicenter clinical studies.

A report of the HeartFlow NXT study, involving 254 patients, was published in the Journal of the American College of Cardiology in April 2014. It indicated that FFR-CT is more accurate than coronary CT alone, largely due to a more than two-fold increase in diagnostic specificity. Specificity of FFR-CT was 79 percent versus only 34 percent for coronary CT alone. Importantly, the study also found good direct correlation between FFR-CT and FFR measured invasively on a per-vessel basis.

"The data for this study were all independently analyzed by our Cardiovascular Imaging Core Laboratory at UH," says Dr. Bezerra, who was a co-author of the study.

A similar study of 252 patients, dubbed the DeFACTO study, was published in the Journal of the American Medical Association in September 2012. It found a diagnostic accuracy rate of 73 percent for FFR-CT, compared with 64 percent for coronary CT alone. Other findings from this study, published in Circulation: Cardiovascular Imaging in November 2013, indicated that FFR-CT technology was especially precise in clarifying the significance of intermediate-grade stenoses, which can be the most challenging to correctly diagnose.

Dr. Bezerra has also conducted other research on whether the FFR-CT test has an acceptable level of reproducibility for a diagnostic test. Writing in the Journal of Cardiovascular Computed Tomography in the summer of 2014, Dr. Bezerra and colleagues from Denmark, Scotland, Canada and Germany reported that FFR-CT has a high overall level of reproducibility, with a coefficient of variation of 3.4 percent.



ECONOMIC AND PATIENT-CARE IMPLICATIONS

Beyond its clinical utility, FFR-CT also has the potential to reduce health care costs, UH cardiologists say. A team of researchers writing in Clinical Cardiology in December 2013, for example, concluded that using FFR-CT as the diagnostic test to select the appropriate patients for invasive coronary angiography and percutaneous coronary intervention would result in a cost reduction of 30 percent.

"In the new value-based health care environment, FFR-CT offers significant advantages over our current screening tests," Dr. Madan Mohan says. "We not only reduce the number of tests, radiation exposure and total costs, but we improve patient outcomes by revascularizing patients with functionally important coronary artery disease."

"This is only the first generation of this transformative technology," Dr. Bezerra adds. "FFR-CT also offers great promise as a procedural planning tool for the interventional cardiologist."

MAURICIO S. ARRUDA, MD
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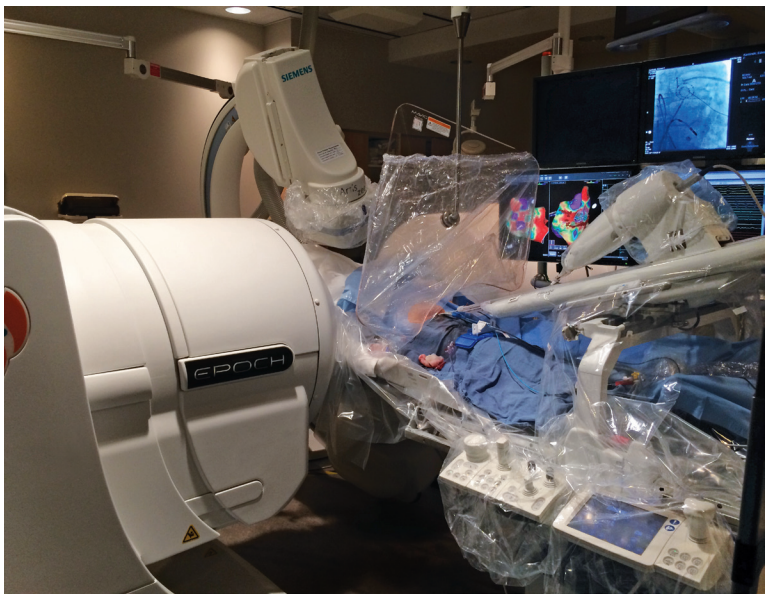
FULLY ROBOTIC AF ABLATION

Pilot experience at UH combining two robotic technologies shows promise

Remote catheter navigation technology, also known as "robotic" navigation, has revolutionized the treatment of atrial fibrillation (AF) over the past decade. The Stereotaxis EPOCH Solution and Amigo remote catheter system have been shown to be safe and effective tools for ablation of AF, leading to good outcomes with less radiation exposure for both patients and health care providers.

Still, challenges remain. "Despite advances in technology, concomitant mapping and ablation of spontaneous or induced tachyarrhythmia often makes for a prolonged AF ablation procedure," says **Mauricio S. Arruda, MD**, Director of the Atrial Fibrillation Center and Electrophysiology Center at University Hospitals Harrington Heart & Vascular Institute. "Electrogram (EGM)-guided AF ablation remains limited because the physician is required to leave the control room and wear a heavy lead apron to manipulate the circular catheter manually, often with radiation exposure."

To address these issues, Dr. Arruda and colleagues at UH evaluated whether the Stereotaxis and Amigo technologies could be safely combined to create a completely robotic AF ablation procedure. "There is no previous experience combining both robotic technologies for mapping and ablation of AF," says Dr. Arruda.



Robotic ablation laboratory

The UH team evaluated the combined approach in 11 patients. First, they used the circular catheter of the Amigo system to perform the necessary electrophysiological mapping for each patient. Then they used the magnet-guided Stereotaxis system to perform electrical isolation of the pulmonary veins (PVI) and additional ablation lines.

Results showed that the combined approach is both safe and feasible. All 11 patients successfully completed the ablation procedure, and there were no acute or late complications. Importantly, in the last eight patients, left atrial and right atrial mapping and ablation were performed without radiation exposure.

"The concomitant use of the Stereotaxis and Amigo remote catheter systems allowed a fully robotic EGM-guided ablation with only minimal X-ray exposure," Dr. Arruda says.

Although the preliminary findings are encouraging, Dr. Arruda says they must be validated by further research. "A large, multicenter, randomized controlled study is warranted to investigate the impact of fully robotic AF ablation in comparison to the conventional manual approach," he says.

However, he says, there is reason to be hopeful about the new approach. "This pilot experience suggests that a fully robotic EGM-guided AF ablation can be performed safely and with minimal radiation exposure," he says. "This novel strategy may improve AF ablation efficiency, as well as the safety of patients and operators."

LEARN MORE. For more information about AF ablation or to refer a patient, call the Atrial Fibrillation Center at **216-844-3800**.

THE EVOLUTION OF TAVR

ADVANCES AND REFINEMENTS HAVE IMPROVED OUTCOMES AND COST EFFECTIVENESS

When it first emerged 10 years ago, transcatheter aortic valve replacement (TAVR) offered new hope for patients with severe aortic stenosis who, because of age, co-morbidities and prior heart surgery, were high or extreme risk for open-heart surgery. Randomized, controlled trials comparing TAVR and surgical AVR in high-risk patients with aortic stenosis demonstrated that TAVR was comparable to surgical AVR, but vascular complications and stroke remained significant challenges.

LESS IS MORE

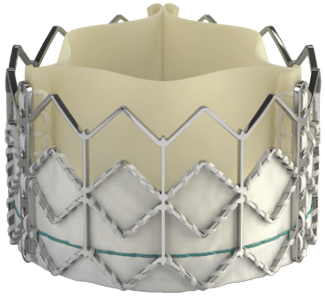
Technical and procedural advances have improved outcomes and cost effectiveness of TAVR. Among the most notable procedural enhancements is the use of moderate sedation rather than general anesthesia. Patients remain awake and talking with local anesthesia and conscious sedation. Intubation and general anesthesia are avoided, thereby improving hemodynamic stability and reducing pulmonary complications. Technical advancements also include lower profile and more flexible devices that permit a totally percutaneous approach with lower risk of vascular complications and stroke. "The minimalist approach reduces overall length of stay, intensive care unit time and total costs with equivalent valve-related outcomes to the general anesthesia approach," notes **Guilherme Attizzani, MD**, Co-Director of the Cardiovascular Imaging Core Laboratory at University Hospitals Harrington Heart & Vascular Institute.

In addition, third generation TAVR devices are undergoing active clinical investigation. Design refinements include fabric skirts to reduce paravalvular leak and the ability to deploy and re-position for optimal hemodynamic performance. Trials are also actively enrolling patients to expand TAVR indications for intermediate-risk patients.

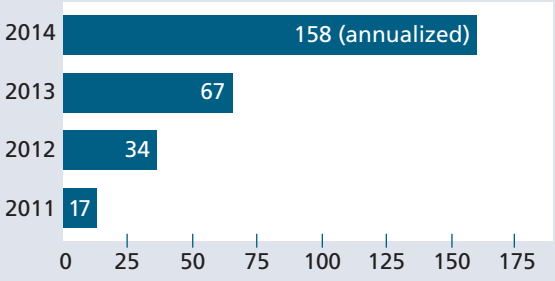
LEADING THE FIELD

These enhancements represent a unique aspect of care within the UH Harrington Heart & Vascular Institute – particularly that of moderate sedation. Most institutions in the United States perform TAVR using general anesthesia, whereas in Europe, moderate sedation is the norm. "This year alone, 92 percent of TAVR cases at UH Case Medical Center were performed without general anesthesia," says **Alan Markowitz, MD**, Chief Surgical Officer, UH Harrington Heart & Vascular Institute. "As a result of this experience, we are now a Center of Excellence for interventional cardiologist and surgeon training in this minimalist approach.

"We benefit from our network of collaborators in Europe," adds **Marco Costa, MD, PhD**, Director, Interventional Cardiovascular Center at UH Harrington Heart & Vascular Institute. "Our partners are responsible for national TAVR registries in Italy and Portugal. Additional partners in Belgium, Latvia, England, the Czech Republic and Spain are leaders in other advanced technologies. These relationships accelerate our access to new devices and techniques that truly advance care for our patients."



UH CASE MEDICAL CENTER TAVR VOLUMES



For more information or to schedule a clinical evaluation, call **216-844-3800**. For information about expanded TAVR research protocols, call Angela Davis, RN, BSN, at **216-844-6138**.

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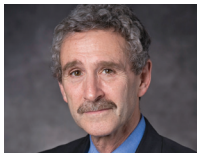

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CONTROVERSIES IN CARDIOLOGY: DURATION OF DUAL ANTIPLATELET THERAPY (DAPT)

The optimal duration of DAPT after stent placement is unknown. The DAPT study – an international, multicenter, randomized placebo-controlled trial to determine the benefits and risks of continuing dual antiplatelet therapy beyond one year after treatment with coronary stents – was presented recently as a late-breaking clinical trial at the national Scientific Sessions of the American Heart Association and published simultaneously in the New England Journal of Medicine. **Daniel Simon, MD**, President, UH Harrington Heart & Vascular Institute, served as the co-principal investigator of the Cordis/Johnson & Johnson contributing study, member of the DAPT advisory committee, and co-author of the manuscript.

Subjects were enrolled after a drug-eluting stent (DES) procedure. After 12 months of thienopyridine (clopidogrel or prasugrel) with aspirin, subjects were randomized to continued thienopyridine or placebo for another 18 months. The co-primary effectiveness end points were stent thrombosis and MACCE (a composite of death, myocardial infarction or stroke) at 12 to 30 months. The primary safety end point was moderate or severe bleeding. DAPT beyond one year after DES significantly reduced the risks of stent thrombosis by 71 percent, MI by 53 percent and MACCE by 29 percent compared with aspirin alone, but was associated with increased bleeding. Non-cardiovascular mortality was increased with prolonged DAPT.

The results of this seminal trial were a surprise to many cardiologists at the AHA meeting and the topic of considerable conversation and debate. We urge our readers to review the results of the DAPT trial carefully. Stay tuned for a future webinar on the duration of DAPT.

View a video discussion at **UHhospitals.org/DAPTduration**.

University Hospitals Case Medical Center and Case Western Reserve University School of Medicine are consistently recognized as two of the premier institutions in the nation, according to U.S. News & World Report's annual rankings.

Heart & Vascular Innovations Winter 2015, Volume 6
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To receive future cardiovascular-related communications from UH Case Medical Center, please email HVInnovations@UHhospitals.org.