

AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 03: Cardiovascular Disease

Potential High Impact Interventions Report

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
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Contract No. HHSA290201000006C

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January 2012

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHS29020100006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual Topic Profiles are developed for technologies and programs that appear to be closer to diffusion into practice in the United States. Drafts of those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify those interventions that experts deem, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually, and topics included may change depending on expert comments received on interventions issued for comment during the preceding six months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High Impact Interventions: Priority Area 03: Cardiovascular Disease. (Prepared by ECRI Institute under Contract No. HHS29020100006C.) Rockville, MD: Agency for Healthcare Research and Quality. January 2012. <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>.

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor target technologies and innovations in health care and to create an inventory of target technologies that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is the analysis of the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future utilization and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling a profile on topics and issuing topic profile drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses

the structured form to also disclose any potential intellectual or financial conflicts of interest (COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the 42 topics for which (1) preliminary phase III data for drugs or phase II data for devices and procedures, or some data for off-label uses were available; (2) information was compiled before November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February and November 1, 2011. (A total of 105 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present 16 summaries on 18 topics (indicated below by an asterisk) that emerged as potential high impact on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

| Priority Area 03: Cardiovascular | |
|----------------------------------|---|
| 1. | Anacetrapib for treatment of dyslipidemia |
| 2. | *Apo-B synthesis inhibitor (mipomersen) for treatment of familial hypercholesterolemia |
| 3. | *Baroreflex stimulation for treatment of drug-resistant hypertension |
| 4. | Bioabsorbable drug-eluting stent (ReZolve) for treatment of coronary artery disease |
| 5. | Bioabsorbable polymer-coated stent (Synergy) for treatment of coronary artery disease |
| 6. | Biodegradable scaffold (BL-1040) post-myocardial infarction in patients at high risk for heart failure |
| 7. | Bioengineered sirolimus-eluting stent for treatment of coronary artery disease |
| 8. | Bioresorbable stent (Absorb) for treatment of coronary artery disease |
| 9. | Cardiac contractility (Optimizer III) modulation for palliation of heart failure symptoms |
| 10. | *Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging |
| 11. | Cardio3KG software for differentiating old from new left bundle branch block abnormality |
| 12. | *CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation |

| Priority Area 03: Cardiovascular | |
|--|---------|
| 13. CINCOR contrast removal system during angiography | |
| 14. Double left-ventricular-assist device implantation for treatment of heart failure | |
| 15. Drug-coated balloon (Moxly) for treatment of coronary artery disease | |
| 16. Drug-coated balloon (Moxly) for treatment of peripheral artery disease | |
| 17. *Endovascular pipeline embolization device (PED) for treatment of brain aneurysms | |
| 18. *Factor Xa inhibitor (apixaban) for thromboembolism indications | |
| 19. *Factor Xa inhibitor (edoxaban) for thromboembolism indications | |
| 20. Xa inhibitor (rivaroxaban) for thromboembolism indications | *Factor |
| 21. Galectin-3 blood test for assessment of prognosis in heart failure patients | |
| 22. *Implantable cardiac monitor (AngelMed Guardian System) to detect impending myocardial infarction | |
| 23. Left ventricular end diastolic pressure-based hydration for renal protection during coronary angiography | |
| 24. Low-dose tPA for treatment of intraventricular hemorrhage | |
| 25. Magnetically levitated centrifugal pump ventricular-assist device (DuraHeart) as bridge to transplantation for end-stage heart failure | |
| 26. Magnetically levitated centrifugal pump ventricular-assist device (HeartWare) as bridge to transplantation for end-stage heart failure | Magne |
| 27. Magnetically levitated centrifugal pump ventricular-assist device (HeartWare) as destination therapy for end-stage heart failure | Magne |
| 28. Off-label use of minocycline with tPA for treatment of stroke | *Off- |
| 29. Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation | *Percut |
| 30. Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension* | |
| 31. Robotic system (CorPath 200) for remotely controlled percutaneous coronary intervention | |
| 32. School-wide electrocardiogram screening (Young Hearts for Life) for cardiac abnormalities in students | |
| 33. Self-expanding stent (Sesame) for saphenous vein graft lesions | Self- |
| 34. Self-expanding stent (Stentys) for treatment of bifurcated coronary lesions | |
| 35. Self-expanding stent (Stentys) for treatment of coronary artery disease during acute myocardial infarction | |
| 36. Side branch stent system (Tryton) for treatment of bifurcated lesions in coronary artery disease | Side |
| 37. Stem cell therapy (C-Cure) for treatment of heart failure | *Stem |
| 38. Subcutaneous implantable cardioverter defibrillator (S-ICD) for cardiomyopathy | *Subcu |

| Priority Area 03: Cardiovascular | |
|---|--------|
| 39. *Transcatheter aortic valve implantation (Sapien and CoreValve) for treatment of severe aortic stenosis | |
| 40. catheter mitral valve repair (MitraClip) for treatment of mitral regurgitation | *Trans |
| 41. catheter pulmonary valves (Melody and Sapien) for treatment of pulmonary valve congenital defects | *Trans |
| 42. *Vagus nerve stimulation for treatment of congestive heart failure | |

Discussion

The material on interventions in this Executive Summary and report is organized according alphabetically by disease state. This summary includes key facts and key expert comments, and the designation of impact potential that was assessed based on expert comments. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary. Research activity in all disease areas of the cardiovascular priority area is robust and addresses both novel and incremental innovations that could affect patient outcomes, shift care models, affect costs, and affect delivery of care.

Arrhythmia

According to the American Heart Association (AHA), arrhythmias (abnormal heartbeats) are a major source of cardiovascular-related morbidity and mortality. Ventricular tachycardia (rapid heartbeat) and ventricular fibrillation (unsynchronized heartbeat) reduce the heart's pumping ability and can cause collapse, cardiac arrest, and sudden death. These conditions are believed to contribute to the more than 400,000 deaths from sudden cardiac arrest (SCA) that occur in the U.S. each year. Numerous drugs and implantable devices exist to treat arrhythmia. Unfortunately, drugs for rhythm and rate control carry significant risks of adverse events, and currently available implantable devices often contraindicate certain procedures (e.g., magnetic resonance imaging [MRI]). Therefore, a significant unmet need exists for better and safer treatments for patients with various forms of cardiac arrhythmia. Experts highlighted two devices that could be of potentially high impact in the treatment of arrhythmia.

Cardiac Pacing System (Revo) for Patients Who May Require Future Magnetic Resonance Imaging

- Key facts:** To address concerns about pacemaker-compatible MRI imaging, a new pacemaker was developed and recently approved for marketing. The Revo MRI™ Sure Scan® pacing system (Medtronic, Inc., Minneapolis, MN) is a dual-lead electronic, implantable, cardiac pacemaker engineered to allow patients to safely undergo MRI scans under specific conditions. In February 2011, the pacemaker received U.S. Food and Drug Administration (FDA) approval as “MR-conditional,” meaning that it may be used in an MRI environment under certain conditions according to the type of MRI scanner and scanner settings. A phase III trial of 464 patients reported that no MRI-related complications—which include sustained ventricular arrhythmias, pacemaker inhibition or output failures, electrical resets, or other pacemaker malfunctions—occurred during or after MRI procedures. The list price for the Revo is \$13,000, according to Medtronic. Hospitals and group purchasing organizations typically negotiate significant discounts on such devices.

- **Key Expert Comments:** Experts providing comments on this topic agreed that with a growing population of older individuals and longer life expectancy overall, more individuals might benefit from the purported advantages of this MRI-compatible pacemaker. They also suggested that clinicians would continue to use a variety of pacemakers and choose the one that best addresses the needs of an individual patient, even with availability of the Revo system. A couple of the experts thought that the Revo does not address a significant unmet need because other imaging modalities are available, and imaging algorithms can be adapted to accommodate pacemakers.
- **Potential for High Impact:** Lower range of high impact

Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Prevention of Sudden Cardiac Arrest

- **Key facts:** Currently available implantable cardioverter-defibrillators (ICDs) that are intended to prevent sudden cardiac arrest (SCA) have been associated with lead failure that can generate unnecessary shocks or fail to provide necessary shocks. When faulty leads are removed and replaced, substantial morbidity and mortality has occurred. The S-ICD® System (Cameron Health, Inc., San Clemente, CA) in late-phase development is a subcutaneous ICD that is intended to be minimally invasive and does not require electrode leads to be placed in or on the heart. Furthermore, the device does not require imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks. The company announced plans to submit its premarket approval (PMA) application to FDA in January 2012.
- **Key Expert Comments:** Experts expressed strong opinions that this intervention has potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and post-implant adverse events from leads and associated secondary surgeries. Because the implantation procedure requires fewer resources and can be conducted in an outpatient setting, this intervention could shift some parameters of health care delivery. Experts thought that familiarity with and success of prior ICD devices would make the device easily adoptable into current care and infrastructure models.
- **Potential for High Impact:** High

Cerebrovascular Disease-Aneurysm

Endovascular Pipeline Embolization Device (PED) for Treatment of Brain Aneurysms

- **Key facts:** Despite advancements in the treatment of intracranial aneurysms (ICAs), clinical results for certain subtypes—large and wide-necked—have been unsatisfactory with recurrence rates of about 50% for each subtype. New technologies for these difficult-to-treat ICAs focus on a new class of endovascular devices called “flow diverters,” which are designed to reconstruct the main affected artery and divert blood flow along the normal course of the vessel and away from the aneurysm neck. This represents an exclusively endoluminal approach rather than the endosaccular approach that characterizes most currently used strategies for ICA treatment. The Pipeline™ Embolization Device (PED, ev3 Endovascular, Inc., Plymouth, MN) is the first flow-diversion device to become available in the U.S.. It was FDA approved in April 2011 for treatment of adults with large or giant,

wide-necked aneurysms of the internal carotid artery. Device cost information was not available. It offers a less invasive option than open surgery for these aneurysms and is an alternative to coil placement or use of liquid embolic material to block off the aneurysm. During the procedure, clips are used to block off the aneurysm from the parent artery. The cylindrical implant is a braided mesh woven from cobalt chromium nickel and platinum tungsten wires. The wires provide 30% to 35% metal coverage of the arterial wall surface area. The device is delivered via a microcatheter that is positioned across the neck of the aneurysm. The manufacturer claims that, once deployed, the device is flexible and conforms to the anatomy. The procedure, which is performed with the patient under general anesthesia, uses conventional angiography to determine working angles and parent vessel measurements. Researchers reported data from the trial on which the PMA was based (n = 111 enrolled patients); 100 patients had some data available 180 days postimplantation, and 92 patients had some data available 1 year after implantation. Researchers reported that overall, 37 “serious adverse events” occurred up to the point of the 180-day assessment, but the trial met its primary endpoint of effectiveness. At 1 year, 78 of 91 patients with angiographic data still had complete occlusion.

- **Key Expert Comments:** Most experts agreed that the intervention would offer an important new and minimally invasive endovascular treatment option for large or wide-necked ICAs, which are difficult to treat. Experts expressed the opinion that costs might not significantly increase with the adoption of this intervention, and potential savings could be realized because the procedure is minimally invasive and associated with a shorter average length of stay and less time in an intensive care unit.
- **Potential for High Impact:** High

Cerebrovascular Disease-Stroke

Off-label Intravenous Minocycline for Treatment of Stroke

- **Key facts:** Intravenous minocycline (Triax Pharmaceuticals, LLC, Cranford, NJ) is a semisynthetic derivative of tetracycline that is currently approved to treat or prevent infections caused by a broad spectrum of gram-positive and gram-negative bacteria. Researchers suggest that a drug combination of tPA and minocycline might reduce the risk of intracerebral hemorrhage and extend the window for treatment of stroke treatment beyond that currently afforded by tPA alone. Minocycline has been found to have neuroprotective properties in preclinical ischemic stroke models. Results of some research suggest that minocycline and tPA could potentially work synergistically to improve stroke outcomes. Use of the drug for this indication is under study by the National Institute of Neurological Disorders and Stroke, University of Kentucky, Oregon Health and Science University, and Georgia Health Sciences University. If found to improve efficacy over tPA alone, the drug combination could be delivered by intravenous injection in emergency departments treating patients with acute ischemic stroke within 6 to 24 hours after stroke onset. In clinical trials, various dosing regimens are under study. In a 2010 clinical trial of 60 patients experiencing acute ischemic stroke, minocycline was administered intravenously within 6 hours of stroke symptoms. Researchers concluded, “Minocycline is safe and well tolerated up to doses of 10 mg/kg intravenously alone and in combination with tissue plasminogen activator.”

- **Key Expert Comments:** Experts commenting on this intervention thought that it has the potential to dramatically improve patient health outcomes by increasing the treatment window for and safety profile of patients experiencing acute ischemic stroke. Experts also thought significant reductions in long-term costs and improvements in patient health outcomes and quality of life could be brought about by this intervention. Because of its low cost, wide availability, and simple administration, minocycline could be readily and easily adopted into current models of care, experts thought.
- **Potential for High Impact:** High

Coronary Artery Disease

Coronary artery disease (CAD) is a form of atherosclerosis in which fatty plaque accumulates inside the coronary arteries and obstructs the supply of oxygenated blood to the heart. CAD typically develops slowly over many years without symptoms. According to AHA, approximately 16 million people 20 years of age or older (8.7 million men, 7.3 million women) in the U.S. are living with CAD, and about 1.2 million cases of new (770,000) or recurrent (430,000) CAD are diagnosed annually. Approximately 450,000 Americans die of CAD each year, of whom more than 80% are 65 years of age or older. The lifetime risk of developing CAD after 40 years of age is about 49% for men and 32% for women. Experts identified one drug and one device related to diagnosis and treatment of CAD that they thought had potential for high impact.

Mipomersen for Treatment of Familial Hypercholesterolemia

- **Key facts:** Despite the availability of lipid-lowering pharmacotherapies, many patients with familial hypercholesterolemia (FH) do not achieve acceptable lipid levels and remain at increased risk for early coronary events and sudden death. Nonpharmacologic interventions, such as apheresis and liver transplantation, are costly, invasive, and not widely available. Mipomersen (ISIS Pharmaceuticals, Inc., Carlsbad, CA, and Genzyme Corp., now part of Sanofi-Aventis, Paris, France) might address this unmet need. It is an antisense oligonucleotide inhibitor of apolipoprotein-B (apo-B) mRNA under study for the treatment of homozygous and heterozygous FH. Apo-B provides the structural core for all atherogenic lipids (including low-density lipoprotein [LDL]) and is required for the release of cholesterol from the liver into the blood, rendering apo-B a viable target for treatment of FH. The drug is administered as a once-weekly, subcutaneous injection. Mipomersen has been evaluated in four phase III clinical trials, in which all primary, secondary, and tertiary outcomes were met, and the manufacturer stated that it planned to file for marketing approval in the fourth quarter of 2011 in the U.S. for patients with homozygous FH. The manufacturer also plans to seek FDA approval for use in patients with heterozygous FH, at a later date.
- **Key Expert Comments:** Experts agreed that this intervention is likely to meet the important unmet need for improved therapies for patients with FH, and they thought that this intervention, positioned as an add-on injectable therapy, would be easily adopted into the current health care infrastructure. Experts believe that questions remain about the agent's safety, and whether the LDL reductions seen in clinical trials will translate to improved clinical outcomes over time.
- **Potential for High Impact:** Lower range of high impact

Implantable Cardiac Monitor (Guardian system) for Detection of Impending Myocardial Infarction

- **Key facts:** Myocardial infarction (MI) requires rapidly removing arterial blockages to restore blood flow through the coronary arteries to limit permanent heart muscle damage or death. However, many people do not immediately recognize MI symptoms and often fail to seek prompt medical attention. The longer treatment is delayed, the more likely the patient will incur greater—and potentially fatal—injury to heart muscle tissue. The Guardian® system (Angel Medical Systems, Inc., Shrewsbury, NJ) is an implantable electronic device designed to warn patients of an impending MI by measuring electrical changes in the heart. According to the manufacturer, the system can detect rapid changes in the ST segment of an electrocardiogram and warn a patient by vibrating under the skin so that the patient seeks medical care immediately. The implantable component is intended to detect, analyze, and store the patient's electrocardiogram waveforms and other heart data, while an external telemetry device (about the size of a pager) collects data wirelessly from the implanted component and issues alarms and alerts to the patient, if necessary. Based on the severity of the alert, the telemetry device can advise the patient to seek emergency treatment or to contact his or her physician for a follow-up appointment. By connecting a laptop computer to an external telemetry device, the physician can program the implantable component and download stored patient data for analysis. The system is intended to be implanted in a fashion similar to pacemaker implantation, but the technology is not intended for use in patients who currently have implanted pacemakers or other cardiac devices. The Guardian system is in phase III clinical trials under FDA investigational device exemption (IDE) status. In 2010, investigators reported results from a trial of 37 patients at high risk for acute coronary syndrome who received the implant, stating, "During follow-up (median 1.52 years, range 126 to 974 days), four patients had ST-segment changes of <3 standard deviations (SDs) of their normal daily range, in the absence of an elevated heart rate. This in combination with immediate hospital monitoring led to angiogram and/or intravascular ultrasonography, which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 min. Alerting for demand-related ischemia at elevated heart rates, reflective of flow-limiting coronary obstructions, occurred in four patients. There were two false-positive ischemia alarms related to arrhythmias, and one alarm due to a programming error that did not prompt cardiac catheterization."
- **Key Expert Comments:** Experts commenting on this topic offered strongly divergent opinions on many issues, signaling much potential controversy for the technology. While some experts thought that the intervention has potential to reduce long-term costs and improve health outcomes by signaling MI patients to seek timely care, other experts were highly skeptical about the proposed intervention's mechanism of action, anticipated high cost for the device and procedure, invasive nature, and the unmet need it purports to address. Some experts thought that patients who have already had an MI are under aggressive care management and would not be the intended population for this device.
- **Potential for High Impact:** Moderately high

Heart Failure

Heart failure (HF), a debilitating condition that adversely affects quality of life as well as life expectancy, can develop from any condition that overloads, damages, or reduces the efficiency of the heart muscle, impairing the ability of the ventricles to fill with or eject blood. According to AHA,

approximately 5.7 million adults aged 20 years or older in the U.S. were living with HF in 2009. Those surviving a heart attack are the most at risk. AHA estimates that for the U.S. population 65 years of age or older, the incidence of HF is about 10 per 1,000 people. Nearly 550,000 new cases of HF occur each year. In 2005 (the most recent year for which mortality statistics are available), more than 292,000 patients died in the U.S. with a prior diagnosis of HF; it was listed as the underlying cause in nearly 59,000 of the deaths and a contributing (secondary) factor in the remaining cases. The prevalence of HF has increased during the past 20 years, and the number of patients who progress to end-stage HF is expected to grow because of increased survival in patients with CAD, an increased population of aging patients, and significant advances in the control of other potentially lethal diseases. Because of the clear unmet need for effective therapies for HF and its underlying cause, many new drugs, biologics, and devices are under study for treatment of patients with HF. Experts commenting on topics on HF identified one biologic and two devices they thought had potential for high impact.

Autologous Mesenchymal Stem Cell Therapy (C-Cure)

- **Key facts:** Available HF treatments are unable to reverse the disease process, and mortality from HF remains high, even when optimally treated. Also, determining which drugs will work in which patients is a challenge addressed by trial and error with medication regimens. A significant unmet need exists for disease-modifying therapies for this condition. C-Cure® (Cardio3 Biosciences, Mont-Saint-Guibert, Belgium) is a bone-marrow-derived, cardiopoietic (i.e., having cardiac cell-generating potential) mesenchymal stem cell therapy that the manufacturer claims can potentially regenerate damaged heart muscle tissue without risk of rejection. The therapy involves harvesting mesenchymal cells from the patient's bone marrow, treating the cells with growth factors (a "cardiopoietic cocktail") and then injecting the cells into the patient's heart. The cocktail includes transforming growth factor-beta1, bone morphogenetic protein-4, activin A, retinoic acid, insulin-like growth factor-1, fibroblast growth factor-2, alpha-thrombin, and interleukin-6. The company claims that treatment with these proteins can transform mesenchymal (undifferentiated) stem cells into cardiac progenitor cells to replicate natural cardiogenesis, without modifying the genome of the cell. The cardiac progenitor cells are designed to behave identically to cells lost during progression of HF, and they purportedly regenerate damaged heart muscle without risk of rejection. The therapy entered phase III study in the latter half of 2011 based on promising phase II results in which patients were reported to have shown an 18.1% improvement in left-ventricular ejection fraction.
- **Key Expert Comments:** Experts agreed that this therapy has potential to significantly shift treatment paradigms and care models for HF, care setting, staffing models, infrastructure needs, and costs. Some of the experts thought that stem-cell treatments are still unproven, citing the failure of first-generation stem cell therapies and the fact that "we don't really understand stem cell homing and it probably makes more sense to understand the science before just injecting the heart." On the other hand, two experts, one of whom has experience in tissue engineering, noted that this treatment contained sufficient growth factors to provide adequate cell homing. Experts generally stated that focus of care would shift to regeneration and the underlying cause of HF, rather than on treatment of symptoms.
- **Potential for High Impact:** High

Portable Freedom Driver for In-home Support of Total Artificial Heart

- **Key facts:** The Freedom® Driver System (SynCardia Systems, Inc., Tucson, AZ) is a wearable, pneumatic, portable driver under development to enable at-home support for the temporary Total Artificial Heart [TAH-t] (SynCardia) in patients awaiting a heart transplant. The TAH-t, approved as a bridge to transplantation by FDA in October 2004, is indicated for use in cardiac transplant-eligible patients at risk of imminent death from nonreversible biventricular failure. The TAH-t is currently powered by a conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart. A portable driver system that might allow patients to be discharged from the hospital while awaiting a suitable donor heart would address a significant unmet need for this small patient population. The Freedom Driver System weighs 13.5 lb and is carried in a backpack or shoulder bag. The driver is powered by two onboard batteries that can be recharged with an automobile adapter or a standard electrical outlet. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the skin in the left chest just below the ribs. The driver flashes a light or sounds an alarm when the system requires the user's attention. In November 2011, the company reported that 34 TAH patients had been enrolled in a clinical study, and 23 of these patients had been discharged from the hospital using the portable driver.
- **Key Expert Comments:** Although the patient population for which this device is intended is small and in-hospital driver systems already exist, experts commenting on this topic thought that it has potential to dramatically improve patient quality of life and shift the care setting by allowing patients to return home from the hospital while awaiting transplant. Experts also thought that this device has the potential to dramatically reduce patient costs associated with lengthy hospital stays and that using the device would require training on the part of the home caregiver, but it is not likely to affect many other health system parameters, such as treatment paradigms or current care models. Some experts expressed concern about whether at-home care of these patients would pose a greater risk of adverse events than in-hospital care.
- **Potential for High Impact:** High

Vagus Nerve Stimulation (CardioFit) for Treatment of Heart Failure

- **Key facts:** The CardioFit® System (BioControl Medical, Yehud, Israel) is an investigational device that is intended to stimulate the vagus nerve to increase activity of the parasympathetic nervous system thereby purportedly improving heart function. The system consists of an implantable stimulator; a sensing lead that passes through a vein into the right ventricle; and a stimulation lead that transmits electrical signals from the stimulator to the vagus nerve. According to the manufacturer, the system can be programmed on and off using external wireless communication. The system is in a phase III trial in the U.S. and was CE marked in December 2008 for distribution in Europe. Researchers reporting results of a pilot clinical trial of 32 patients receiving the implant stated, "Study data showed that patients experienced sustained significant improvement across key clinical measures including left ventricular function and structure, heart rate variability, and resting heart rate. Patients also showed improvement in self-reported quality of life surveys and six-minute hall walk tests." It appears that at least one other company is also investigating vagus nerve stimulation for the treatment of HF. Boston Scientific Corp.

(Natick, MA) has registered a clinical trial investigating “right vagal nerve stimulation in heart failure patients with a New York Heart Association [NYHA] Class III,” status with the National Clinical Trials database, but a search of the manufacturer’s Web site did not yield any additional information.

- **Key Expert Comments:** Despite the success of vagus nerve stimulation for treatment of other diseases and conditions, the intervention’s ability to effect meaningful change in patient outcomes in HF patients was met with some skepticism by experts commenting on this intervention. Experts suggested that, although this intervention would be easily incorporated into health care models, its high cost and invasiveness (compared to optimal medical management of HF) might be a barrier to diffusion, especially until longer-term outcomes data are available to confirm its potential benefits.
- **Potential for High Impact:** Moderately high

Hypertension

Baroreflex Stimulation (Rheos Baroreflex System) for Treatment-Resistant Hypertension

- **Key facts:** The Rheos™ Baroreflex Hypertension Therapy System (CVRx, Inc., Minneapolis, MN) is intended to lower uncontrolled blood pressure by electrically stimulating the carotid baroreceptors. The human baroreceptor reflex (baroreflex) system is a network of natural blood pressure sensors (baroreceptors) located throughout the arteries and veins that helps regulate blood pressure in concert with the central nervous system. In chronic hypertensive conditions, the carotid baroreflex signal is often insufficient, and many patients with diffuse atherosclerosis may have stiff vessels that are unable to respond to baroreflex signals. Drug therapy is standard care, but some forms of hypertension do not respond well to drug therapy. Furthermore, some patients find side effects of antihypertensive drugs intolerable, even at relatively low doses. The key role of carotid sinus baroreceptors in blood pressure regulation, therefore, makes them a potential target for treatment of drug-resistant hypertension. The system uses a pacemaker-like implantable pulse generator, inserted subcutaneously near the clavicle, to deliver electrical signals to baroreceptors in both the left and right carotid arteries in the neck by means of two carotid sinus leads. Because a pressure-sensing switch that could turn on and off as needed would quickly wear out within the carotid arteries, the electrical pulse generator is always on when in active mode. The system's external programming components allow physicians to noninvasively regulate the intensity of electrical stimulation and program the system according to individual patient needs. The device can deliver variable voltage to either or both carotid sinuses in a variety of modes. As with other implantable electronic devices, the Rheos system would require surgical replacement of the implantable pulse generator when the device's batteries have been depleted. Results from a phase III pivotal randomized controlled trial were published in August 2011 and researchers reported statistically and clinically significant endpoints of sustained blood pressure efficacy (≤ 140 mm Hg at 6 months) and device safety. Additional trials are ongoing, and the system was CE marked for distribution in Europe in 2007.
- **Key Expert Comments:** Experts providing comments on this topic generally agreed that an important unmet need exists for an intervention that can treat drug-resistant hypertension.

Should the baroreflex stimulation prove effective and safe, experts thought, its anticipated high cost (relative to drug therapy) and invasive nature could cause some disruption to the health system and processes of care, because it would introduce a surgical procedure into a clinical pathway that previously included only drug therapy.

- **Potential for High Impact:** High

Radiofrequency Ablation (Symplicity System) for Renal Denervation for Treatment-Resistant Hypertension

- **Key facts:** Lowering high blood pressure has been associated with significantly lower rates of stroke, heart attack, and HF, and inadequately controlled hypertension remains a problem for a growing number of people. The Symplicity™ Catheter System (Ardian, Inc., which Medtronic, Inc., Minneapolis, MN, acquired in January 2011) allows a physician to apply radiofrequency energy to ablate the renal nerves from within the renal artery without adversely affecting other nerves in the abdomen, pelvis, or lower extremities. The minimally invasive procedure takes about 40 minutes to perform; according to the company, physicians perform the renal denervation procedure in a catheterization laboratory using standard interventional techniques similar to those used for renal stent implantation. In July 2011, FDA approved a trial protocol for conduct of SYMPPLICITY HTN-3, a randomized, controlled trial in the U.S.
- **Key Expert Comments:** Experts agreed that this intervention has potential to fill an important gap in treatment of hypertension and would likely be widely accepted by clinicians and patients due to the fact that no other treatments are available if pharmacotherapy fails to achieve desired outcomes. Although several experts noted that the data available for the intervention are limited at this time, experts still thought that this intervention is likely to improve patient health, citing both the promising mechanism of action and efficacy data that have been reported to date. Most experts suggested that this intervention would not be especially disruptive to health care infrastructure because the procedure is similar to other procedures currently performed by interventional cardiologists.
- **Potential for High Impact:** Moderately high

Thromboembolism

Factor Xa Inhibitors for Prevention and Treatment of Thromboembolisms

- **Key facts:** Experts identified a new class of drugs, factor Xa inhibitors, including rivaroxaban, apixaban, and edoxaban, as having potential for high impact for various indications to prevent or treat blood clots. Anticoagulation therapy is regarded as an important and unavoidable component in the management of patients with, or at risk for, deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke. However, currently used anticoagulation agents, such as warfarin, heparin, low-molecular-weight heparin, and fondaparinux, are characterized by many limitations, including an unpredictable anticoagulation profile, undesirable routes of administration, need for frequent monitoring of clotting parameters, and frequent dose adjustments. One recently approved, novel agent, dabigatran etexilate (not a factor Xa inhibitor), may address some of these limitations in patients with atrial fibrillation (AF) who take the drug for prevention of stroke and blood clots. However, other orally administered factor Xa inhibitors in development exert their

effects via a different mechanism of action, and might have potential to address some of the limitations described above. One of these, rivaroxaban (Janssen Pharmaceuticals, Inc., a unit of Johnson & Johnson, Inc., New Brunswick, NJ, and Bayer AG, Leverkusen, Germany) was FDA approved in July 2011 for once-daily administration to prevent DVT that can lead to PE in patients undergoing knee or hip replacement surgery, and in November 2011, it was approved for the reduction of stroke risk in people who have nonvalvular AF. The makers of apixaban (Eliquis™; Bristol-Myers Squibb Co., and Pfizer, Inc., both of New York, NY) intended to file for FDA approval for stroke prevention in patients with AF by the end of 2011. Edoxaban (Daiichi Sankyo Co., Ltd., Tokyo, Japan) is in phase III trials for VTE and stroke related to AF.

- **Key Expert Comments:** Experts commenting on these drugs thought that these agents have potential to improve patient quality of life and reduce burdens on the health care system by obviating the need for ongoing lab monitoring, dose adjustments, and dietary restrictions. Because the drugs in this class are self-administered oral pills, the drugs are expected to be easily adopted into current care models, according to these experts.
- **Potential for High Impact:** Lower range of high impact

Valve Disorders

Percutaneous Annuloplasty (Carillon Mitral Contour System) to Treat Functional Mitral Regurgitation

- **Key facts:** Open surgical repair of the mitral valve—known as mitral annuloplasty—is considered the gold standard treatment for this disease. Percutaneous annuloplasty is a new minimally invasive surgical approach intended to achieve the same therapeutic result, using a catheter-based technique. The Carillon® Mitral Contour System™ (Cardiac Dimensions, Inc., Kirkland, WA) comprises a thin, flexible metal bridge or tether with a self-expanding anchor at each end. The device is delivered to the coronary sinus by a catheter inserted in the jugular vein at the neck. The physician places tension on the delivery catheter to reshape the mitral annulus sufficiently to reduce the degree of mitral regurgitation (MR) by squeezing the mitral leaflets together to close the gap that may have developed due to heart enlargement. Two mid-phase trials of the system were initiated in May 2011 on the basis of data from a completed trial that enrolled 48 patients. In that trial, 30 patients actually received the device, and the major adverse event rate at 30 days was 13%. In May 2011, Cardiac Dimensions announced the initiation of two new clinical trials. One trial will ascertain safety and efficacy of the device at 1, 3, 6, and 12 months by evaluating reduction in functional MR, heart size, and improvements in exercise capacity, and the other trial will be an extension of a recently completed trial. (Another company that had been developing a similar system [Viacor, Inc., Wilmington, MA] ended operations and suspended two phase II/III trials in spring 2011, leaving only one developer with an ongoing research program for this technology.) The Carillon system was CE marked in October 2011, and the company anticipated a product launch in Europe in early 2012.
- **Key Expert Comments:** Experts commenting on this intervention stated that, if shown effective, it could replace open chest surgery to repair the mitral valve with a minimally invasive option, which would be a significant change from the current treatment paradigm for the small percentage of patients with MR who need open surgery. If it does supplant open surgery for some patients, it could reduce hospital stays and days in intensive care, as well as

costs of care. Experts thought that patients could benefit through quicker recovery and faster return to normal activities. However, experts' expressed uncertainty about the technology because of a perceived high number of adverse events and complications, including migration of the ring and the need to recover it. Experts were interested in seeing more data to determine whether this approach can fulfill its potential benefits with an acceptable risk of harms.

- **Potential for High Impact:** High

Transcatheter Aortic Valve (CoreValve and Sapien) Implantation for Treatment of Severe Aortic Stenosis

- **Key facts:** New minimally invasive approaches may extend the therapeutic benefit of aortic valve replacement to patients with aortic stenosis who are not candidates for open heart valve surgery because of high surgical risk. One system is currently in development, while the other was recently approved by FDA. Edwards Lifesciences developed the Sapien Transcatheter Heart Valve (THV), which features a bovine pericardial tissue aortic valve affixed within a balloon-expandable, cobalt-chromium alloy frame. The bioprosthetic valve is available in 23 and 26 mm lengths. The company has developed delivery systems for implanting the valve using either a transfemoral or transapical approach, but only the transfemoral approach was evaluated by FDA for marketing approval at this time. The procedure is conducted in 1 to 3 hours, and the average hospital stay for a patient undergoing the implant procedure is 2 to 6 days. In November 2011, the manufacturer announced that it had received approval from FDA for the transfemoral delivery of the Sapien transcatheter aortic heart valve for the treatment of patients with inoperable, severe, symptomatic, aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from correction of the aortic stenosis. Medicare opened a National Coverage Analysis at the request of two cardiology professional societies in September 2011 to consider criteria for coverage, such as clinical expertise and appropriate patient population due to concerns about the technical difficulty of the procedure and learning curve to achieve and maintain proficiency. Medtronic is developing the aortic CoreValve® System, which features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame. The bioprosthetic valve is deployed using an 18-Fr delivery catheter with a set of disposable catheter-loading components in a procedure that lasts 1 to 3 hours and requires a 3- to 5-day hospital stay. Medtronic received an IDE designation for its CoreValve trial from FDA in October 2010 and trials are underway.
- **Key Expert Comments:** Experts agreed that this minimally invasive intervention would offer an important new treatment modality for patients with severe aortic stenosis who currently have no other medical or surgical treatment options. They thought this intervention has the ability to improve patient health outcomes and they expect an increase in patient volume and a shift in care setting (from outpatient to inpatient) if this intervention diffuses. Experts offered diverging opinions on whether this intervention would be particularly disruptive to health care infrastructure (it could drive the need for hybrid operating rooms or hybrid catheterization laboratories), but they agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs.

- **Potential for High Impact:** High

Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation

- **Key facts:** Transcatheter mitral valve repair with the MitraClip® device (Abbott Laboratories, Abbott Park, IL) is intended to simulate the functional effects achieved by the standard open surgery repair procedure used for treatment of MR. In the standard procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening. In a MitraClip procedure, the physician uses a transcatheter approach in which a two-armed, flexible metal clip covered in polyester fabric is used, rather than the sutures used during open surgery, to help the mitral valve close more completely. Researchers reported on outcomes of 279 patients from the EVEREST II randomized controlled trial stating a clinical success rate of 51.7 percent for patients treated with the MitraClip compared to a clinical success rate of 66.3 percent for surgery patients ($p = 0.04$) at two-year followup. The device is in phase III clinical trials in the U.S. It received the CE mark for marketing in Europe in 2008 for use as a nonsurgical option in patients with severe MR.
- **Key Expert Comments:** Overall, experts thought, this procedure has the potential to substantially affect many parameters of the health care system, changing care models, increasing infrastructure and staffing requirements, shifting care setting, and requiring substantial clinician training; they were split on whether it would increase or decrease costs. Though several experts noted the need for longer-term safety data, experts generally believe that this device has the potential to meet the need for minimally invasive interventions for treatment of MR.
- **Potential for High Impact:** High

Transcatheter Pulmonary Valves (Melody and Sapien) for Treatment of Congenital Pulmonary Valve Defects

- **Key facts:** Minimally invasive transcatheter pulmonary valves are new technologies intended as a temporary solution to treat congenital pulmonary valve defects and reduce the number of open heart surgeries these patients must undergo over a lifetime. The Melody® transcatheter valve (Medtronic, Inc., Minneapolis, MN) received humanitarian device exemption status by FDA in early 2010 as the first valve available in the U.S. for this purpose. Another system, the Sapien™ Transcatheter Heart Valve platform (Edwards Lifesciences, LLC, Irvine, CA) is commercially available only in Europe, but U.S. trials are ongoing. One difference between the two systems is that Sapien is intended to serve a patient population with larger failed conduits than are addressed with the Melody valve because the valve (23 and 26 mm) and delivery system (22 and 24 French [Fr] diameter) are available in larger sizes. Investigators reported results from a 2011 trial of 102 patients indicating that pulmonary regurgitation was significantly reduced in all patients receiving the valve. Some serious and 1 fatal adverse event occurred. Five stent fractures occurred, and during follow-up (median: 352 days; 99-390 days) one percutaneous valve had to be removed surgically 6 months after implantation due to bacterial endocarditis. In 8 of the

102 patients, a repeated dilatation of the valve was done due to a significant residual systolic pressure gradient, which resulted in a valve-in-valve procedure in four patients.

- **Key Expert Comments:** Overall, experts were enthusiastic about this technology's ability to meet the need for a less invasive solution for patients with congenital pulmonary valve defects who have to undergo open heart valve surgery many times over their lifetime. The number of patients with the condition is small, however. Because the intervention would reduce the number of open heart surgeries for a patient, or delay the need for open heart surgery, the device could have a significant impact by enabling patients to avoid open heart surgery, moving a procedure from the surgical suite to catheter laboratory setting, reducing costs related to open heart surgeries. Most experts anticipated a notable clinician learning curve in training and patient selection, and noted that adult heart catheterization labs are not set up for performing this procedure and would need some adaptation.
- **Potential for High Impact:** High

Arrhythmia Interventions

Intervention

Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging

As the use of cardiac pacemakers has grown, so has the use of magnetic resonance imaging (MRI) for various clinical indications. However, the strong magnetic fields produced by MRI are known to pose potential risks to patients with implanted cardiac pacemakers, which contain metal components. MRI scanner effects on implanted cardiac devices can include heating of the electrode tips, migration or movement of the device, malfunction or damage of the device, and changes in pacing thresholds.¹ MRI technologists have attempted to modify imaging sequences to avoid complications in patients with implanted pacemakers; however, many clinicians as well as these patients are unwilling to risk MRI. To address concerns about pacemaker-compatible MRI imaging, one company has developed a new pacemaker, which recently received marketing approval. The Revo MRI™ SureScan® pacing system (Medtronic, Inc., Minneapolis, MN) is a dual-lead, electronic, implantable cardiac pacemaker engineered to allow patients to safely undergo MRI scans under specific conditions. The complete system includes the Revo MRI SureScan IPG (implantable pulse generator) and two CapSureFix® MRI SureScan leads for use in an MRI environment. The U.S. Food and Drug Administration (FDA) approved Medtronic's premarket approval application on February 8, 2011. The pacemaker is approved as "MR-conditional," meaning that it may be used in an MRI environment under certain conditions according to the type of MRI scanner and scanner settings.²⁻⁴

Wilkoff and colleagues (2011) reported the results from a phase III, controlled trial of 464 bradycardia patients with a Revo pacemaker; 258 patients underwent MRI, and 206 control patients had no MRI. No MRI-related complications—which include sustained ventricular arrhythmias, pacemaker inhibition or output failures, electrical resets, or other pacemaker malfunctions—occurred during or after MRI procedures. Pacing capture threshold and sensed electrogram amplitude changes were minimal and similar between study groups.⁵

The list price for the Revo is \$13,000, according to Medtronic. Hospitals and group purchasing organizations typically negotiate significant discounts on such devices.

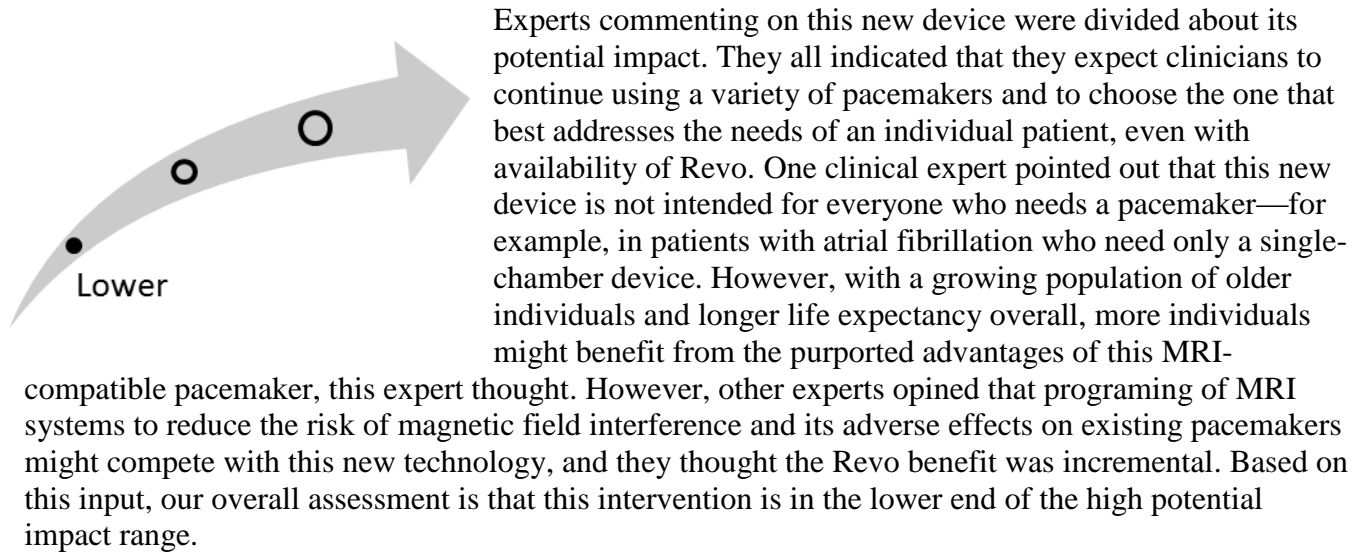
Clinical Pathway at Point of This Intervention

Cardiologists may recommend implantation of an electronic cardiac pacemaker for a number of conditions that create various heart rhythm abnormalities. Clinical guidelines recommend implantation of cardiac pacemakers for several indications (with various subcategories within each broad indication), including acquired atrioventricular block in adults, atrioventricular block associated with acute MI, chronic bifascicular block, hypersensitive carotid sinus syndrome, hypertrophic cardiomyopathy, neurocardiogenic syncope, and sinus node dysfunction. Permanent pacemaker implantation is recommended in children, adolescents, and adults with certain congenital heart defects. Certain patients who undergo heart transplantation may require permanent pacemaker implantation to treat bradycardia (slow heartbeat). Patients with certain neuromuscular disorders, such as myotonic dystrophy and Emery-Dreifuss muscular dystrophy, may require pacemaker implantation.⁶

The strong magnetic fields produced by MRI pose a risk to patients with implanted cardiac pacemakers, which contain metal components. These MRI-related device problems can cause arrhythmia or death. Thus, current clinical guidelines discourage the use of cardiovascular MRI in patients with implanted pacemakers. The exception would be when cardiovascular MRI is performed at highly experienced centers in cases with a strong clinical indication and when the potential benefits of cardiovascular MRI significantly outweigh the potential risks of the procedure.⁷ The dual-lead Revo

MRI SureScan pacing system would be used in place of conventional, non-MRI-safe, dual-chamber, cardiac pacemakers for the same types of clinical indications.

Figure 1. Overall High Impact Potential: Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging



Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.⁸⁻¹⁴ The main advantage a few of these experts noted is that this device could expand the eligibility for MRI in patients who need a pacemaker and an MRI. They also agreed generally that as the need for pacemakers increases because of an aging population, more individuals are likely to benefit from this intervention. However, clinical experts indicated that they did not think all patients would benefit from this intervention—for example, those in need of a single-chamber device (i.e., chronic atrial fibrillation). One expert with a research background mentioned that other imaging modalities (computed tomography and positron emission tomography) are often used safely in patients with pacemakers and are options when imaging is needed. Also, MRI systems are being programmed and adapted to reduce the risk of magnetic field interference with pacemakers, so more existing pacemakers could become compatible with MRI.

The cost of the new device and whether Medicare would cover its use were concerns expressed by one clinical expert. Another expert thought that the new device offered limited benefits and would not be widely adopted. Several experts commented that increases in technologic complexity and demands from physicians' time, as well as costs, could be barriers to acceptance of this new device. In particular, one clinical expert indicated that if this device requires remote programming of MRI equipment and if this increases the physician "hassle factor," its acceptability in the market might be limited. According to this expert, this would be particularly true if there were also an increase in price for the new technology.

The new device's impact on underinsured persons, as well as on health disparities, was a concern of some experts. Insurance coverage limitations and exclusions could affect the number of individuals receiving this new pacemaker if it is more expensive than other pacemakers. For those lacking coverage, access to this type of technology would be limited, thus increasing health disparities.

Intervention

Subcutaneous implantable cardioverter-defibrillator (S-ICD) for prevention of sudden cardiac arrest

While implantable cardioverter-defibrillators (ICDs) are established therapy for preventing sudden cardiac arrest (SCA), their transvenous electrode leads have been associated with lead failure that can generate unnecessary shocks or fail to provide necessary shocks. When faulty leads are removed and replaced, substantial morbidity and mortality can occur. Lead problems occur in an estimated 40% of cases and have prompted development of a leads-free ICD system.¹⁵

The S-ICD® System (Cameron Health, Inc., San Clemente, CA) is a subcutaneously implanted defibrillator that is being investigated for the prevention of SCA. According to its manufacturer, the S-ICD is intended to be minimally invasive and does not require electrode leads to be placed in or on the heart. Furthermore, the device does not require imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks.¹⁶

The manufacturer describes the system components as a pulse generator, an electrode, and a programmer.¹⁷ The battery-powered, computer-controlled pulse generator is intended to detect cardiac activity and provide defibrillation therapy. The subcutaneous electrode is partially coated and is designed to be implanted above and to the left of the sternum. The external programmer is designed to allow clinicians to set parameters for the pulse generator and to retrieve data.¹⁸

According to the manufacturer, the implant procedure for the S-ICD is as follows: (1) an incision is made on the left side of the chest, next to the rib cage; (2) a pouch is formed under the skin for the placement of the pulse generator; (3) two small incisions are made to the left of the sternum allowing placement of the subcutaneous electrode under the skin; (4) the subcutaneous electrode is connected to the pulse generator; (5) testing and adjustments are made using the external programmer; and (6) incisions are closed.¹⁹ Because the system is entirely subcutaneous and can be placed using only anatomic landmarks, imaging equipment is not required during the procedure. The manufacturer claims the procedure should not usually require an overnight stay.²⁰

The S-ICD system is being investigated in a trial in the United States under an investigational device exemption from FDA.²¹ The company expects to file for FDA approval in early 2012.²² The device was Conformité Européene (CE) marked in 2009 for marketing in Europe.²³

In a clinical trial published in July 2010, authors concluded, “Among patients who received a permanent subcutaneous ICD, [ventricular fibrillation] VF was successfully detected in 100% of 137 induced episodes. Induced VF was converted twice in 58 of 59 patients (98%) with the delivery of 65-J shocks in two consecutive tests. Clinically significant adverse events included two pocket infections and four lead revisions. After a mean of 10±1 months, the device had successfully detected and treated all 12 episodes of spontaneous, sustained ventricular tachyarrhythmia.”¹⁵

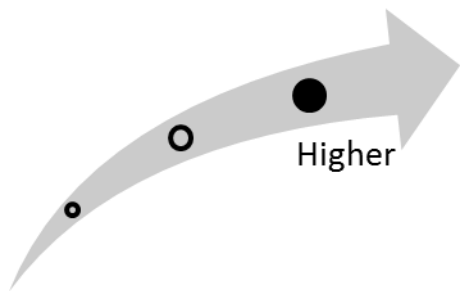
Clinical Pathway at Point of This Intervention

According to the American College of Cardiology (ACC) and AHA, prophylactic ICDs are the preferred treatment for patients with VF who are at risk for SCA. For patients who do not meet criteria for an ICD, beta blockers are considered first-line therapy, and radiofrequency ablation may be indicated. For patients with VF refractory to ICD, drug therapy and radiofrequency catheter ablation or antiarrhythmic surgery may be warranted.²⁴

If approved for marketing, the S-ICD system would compete directly with other nonsubcutaneous ICD systems. If the S-ICD system is shown to be safe and effective, clinicians might prefer it to other

ICD systems because it offers the potential to reduce lead-related adverse events and does not require imaging during placement.

Figure 2. Overall High Impact Potential: Subcutaneous implantable cardioverter-defibrillator (S-ICD) for prevention of sudden cardiac arrest



Overall, experts commenting on this topic expressed that this intervention has potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and associated secondary surgeries that carry a high risk of morbidity and some mortality. Because the implantation procedure requires fewer resources and can be performed in an outpatient setting, this intervention could shift care delivery to a less invasive setting and shorter hospital stays. Experts thought that familiarity with and success of prior ICD devices would make the device

easily adoptable into current care and infrastructure models. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.²⁵⁻³¹ These experts generally agreed that this intervention would meet the unmet need of solving lead failure issues. One expert suggested that these failures are a significant problem with ICDs, causing inappropriate shock therapy or requiring subsequent procedures to fix/replace the leads. Removal of leads in particular is complicated, expensive, and can cause patient injury, noted one expert. A clinical expert noted that this unmet need has been “highlighted by the recent recall of ‘Fidelis’ leads [Sprint Fidelis Cardiac Leads, Medtronic, Inc. (Minneapolis, MN)] resulting in substantial cost and comorbidity to explant such leads.”²⁶ However, one clinical and one research expert believe that “the unmet need is not a medical one [because current devices fill the medical need], but rather a process/infrastructure one in that a great deal of expertise, equipment, and time is required for IV lead placement that could be bypassed by this technology.”²⁶

These experts believe that the S-ICD would exert its greatest effect on patient outcomes, partly because of the sound theory underlying the technology, which is based on the efficacy of currently used ICDs. Experts were confident that the device would reduce the number of rare but serious lead-related complications and also reduce infection, which is often seen in the heart with leads, and which can lead to endocarditis, requiring explantation. However, several experts noted that these improvements are based on the assumption that the S-ICD is effective at cardioversion. One clinical expert expressed concern that, “the pacing capability is limited to ~30 seconds post-shock, since some patients require both pacing and ICD therapy. Some VT [ventricular tachycardia] can be at lower rates, and since this device does not have long term pacing, these episodes [may] not be detected and [provided with] pacing conversion.”³⁰

Because ICD placements are common, this intervention is unlikely to significantly disrupt current care models or operations processes, with a few exceptions, the experts noted. First, because the device is leadless and can be placed using only anatomic landmarks, it may allow for placement of devices by centers with less technologic expertise and equipment and by less experienced practitioners. For the same reasons, there might be less need for specialized procedure rooms and fluoroscopy/imaging, the experts commented. They also noted that surgeons implanting the device might require some initial S-ICD-specific training. Experts commenting also noted that the device can be implanted in an outpatient

setting, which would shift care from the inpatient setting to outpatient setting currently associated with available ICDs.

Although the S-ICD cost is similar to that of other ICD systems, the intervention has the potential to reduce the financial burden by avoiding the lead complications and shifting from inpatient to outpatient surgery, the experts generally indicated. Experts agreed that both patients and clinicians would likely adopt this device if it is effective relative to existing ICDs.

Cerebrovascular Interventions

Intervention

Endovascular pipeline embolization device (PED) for treatment of brain aneurysms

Despite advancements in the treatment of intracranial aneurysms (ICAs), clinical results for certain subtypes of treated aneurysms—large and wide-necked, in particular—remain unsatisfactory.³² Their recurrence rates are about 50% for each subtype. Manufacturers have begun exploring new methods for these difficult-to-treat ICAs. That exploration primarily centers on a new class of endovascular devices called “flow diverters,” which are designed to “reconstruct the parent artery and divert blood flow along the normal anatomical course of the vessel and away from the aneurysm neck.”³²

Theoretically, the flow diversion should hemodynamically uncouple the aneurysm from the parent artery, creating an environment conducive to thrombosis (of the aneurysm) and providing a scaffold over which a neointimal and endothelial seal can grow, thereby closing the neck of the aneurysm.³² The thrombosis occurs over days to weeks. This represents an exclusively endoluminal approach, rather than the endosaccular approach that characterizes most currently used strategies for ICA treatment.

The Pipeline™ Embolization Device (PED, ev3 Endovascular, Inc., Plymouth, MN) is a flow-diversion device for treatment of adults with large or giant, wide-necked brain aneurysms of the internal carotid artery. It offers a less invasive option for treating these aneurysms than open surgery in which clips are used to block off the aneurysm from the parent artery. It is also an alternative to coil placement or use of liquid embolic material to block off the aneurysm. The cylindrical implant is a braided cylindrical mesh. The mesh provides 30% to 35% metal coverage of the arterial wall surface area. It is designed to be delivered via a microcatheter that has been positioned across the neck of the aneurysm. The manufacturer claims that, once deployed, the device is flexible and conforms to the parent anatomy.³²

Placing of the PED is expected to disrupt the blood flow velocity of the aneurysm and not to have a deleterious effect on the flow of adjacent regional branch vessels, because of the differences in the structures' pressure gradients and the fact that branch vessels require more than 50% occlusion of their orifice before flow declines.³²

The procedure, which is performed with the patient under general anesthesia, uses conventional angiography to determine working angles and parent vessel measurements. The guiding catheter platform is placed, and the PED is inserted into the microcatheter. The PED is advanced through the catheter in a way that is similar to placing embolization coils until it can be visualized across the aneurysm neck. As the microcatheter is retracted, the PED expands, coming free of the “capture coil” mechanism that secured the PED to the delivery wire.³²

Data from the trial on which the premarket approval application was based reported on 111 enrolled patients; 100 had some data available 180 days postimplantation, and 92 patients had some data available 1 year after implantation. The study reported on 107 patients for the major safety endpoint of ipsilateral major stroke or neurologic death, and those events occurred in 6 patients, 3 of whom died. Overall, 37 “serious adverse events” occurred up to the point of the 180-day assessment. The trial met its primary endpoint of effectiveness. At 180 days, 81 of 99 patients who agreed to undergo angiography showed complete occlusion of the aneurysm; at 1 year, 78 of 91 patients with angiographic data still had complete occlusion.³³

The U.S. Food and Drug Administration (FDA) granted marketing approval for the PED under the premarket approval process on April 6, 2011. The device is Conformité Européene (CE) marked in Europe.³⁴ The FDA-approved labeled indication is “for the endovascular treatment of adults (22 years

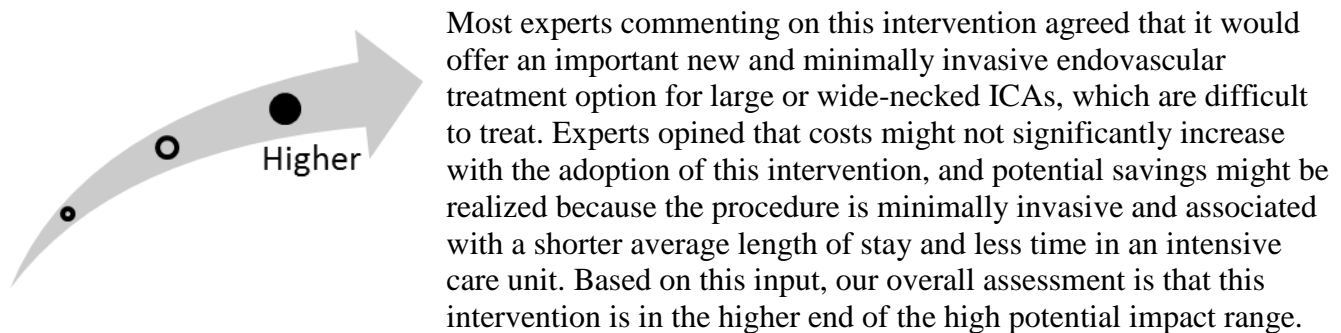
of age or older) with large or giant wide-necked [ICAs] in the internal carotid artery from the petrous to the superior hypophyseal segments. Labeling contraindications include:

- Patients with active bacterial infection
- Patients in whom antiplatelet therapy is contraindicated
- Patients who have not received dual antiplatelet agents prior to the procedure
- Patients in whom a preexisting stent is in place in the parent artery at the target aneurysm location”³³

Clinical Pathway at Point of This Intervention

The Brain Aneurysm Foundation recommends either endovascular coiling or open surgical clipping for the treatment of unruptured cerebral aneurysms.³⁵ The PED is a new type of flow diverter that targets a reconstruction of the normal hemodynamics of the parent artery rather than mechanically excluding the aneurysm sac from circulation.³⁶ The PED offers a new endovascular treatment option for large or giant wide-necked ICAs.

Figure 3. Overall High Impact Potential: Endovascular pipeline embolization device (PED) for treatment of brain aneurysms



Results and Discussion of Comments

Eight experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.³⁷⁻⁴⁴ Experts' comments concurred that this intervention offers a less invasive alternative (endovascular vs. open cranium) for brain aneurysms, especially those that are difficult to treat or in patients for whom traditional surgical techniques are not possible.

A potential safety issue most frequently cited by these experts was that as ICA pressure increases, aneurysms rupture. Some experts noted that trials comparing this intervention with current standard of care are needed. However, one expert with surgical experience suggested that this intervention offers a minimally invasive method with potentially reduced complications compared with standard therapy such as coiling or open clipping. This expert also mentioned the preservation of side branches as a key potential benefit of PED treatment and noted that the potential to change current models of care is great. The alternative of a less invasive procedure to correct these challenging-to-treat cerebral aneurysms could trigger a paradigm shift that moves away from open surgical clipping of aneurysms. Experts thought no significant infrastructure changes in facilities currently performing neurovascular interventions would be seen. They noted that decreases in overhead costs might be realized because of shorter hospital stays and less need for intensive care units post-ICA surgery. Experts also expected high acceptance by the clinical community and patients alike.

Experts agreed that any impact on health disparities depends on access and insurance coverage for treatment in tertiary facilities that would be performing this procedure. One expert reported that living near urban centers might provide access to this type of intervention for minorities and Medicaid populations living in those areas.

Intervention

Off-label minocycline with tissue plasminogen activator for treatment of stroke

The clot-dissolving drug tissue plasminogen activator (tPA) is the primary treatment for patients experiencing acute ischemic stroke. The drug is widely recognized as underused because of its narrow therapeutic window and associated risk of intracranial hemorrhage (ICH). Intravenous minocycline (Triax Pharmaceuticals, LLC, Cranford, NJ) is a semisynthetic derivative of tetracycline that is currently approved to treat or prevent infections caused by a broad spectrum of gram-positive and gram-negative bacteria. The drug is thought to exert its antimicrobial effect by the inhibition of protein synthesis.⁴⁵ According to researchers, the major target for tetracyclines in neurodegeneration could lie within the complex network that links mitochondria, oxidative stress, poly (ADP-ribose) polymerase (PARP)-1, and apoptosis (programmed cell death).⁴⁶ Minocycline has been shown to inhibit PARP-1 levels, which are correlated with a neuroprotective effect.⁴⁷

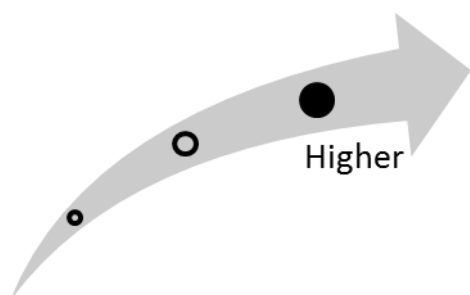
Investigators suggest that a drug combination of tPA and minocycline might reduce the risk of ICH and extend the window for treatment of stroke patients, making it a viable option for more stroke patients, because minocycline has been found in preclinical ischemic stroke models to have neuroprotective properties. Research suggests that minocycline and tPA could potentially work synergistically to improve stroke outcomes.⁴⁸ Use of the drug for this indication does not appear to be pursued by the manufacturer; rather, it is under study by the National Institute of Neurological Diseases and Stroke, University of Kentucky, Oregon Health and Science University, and Georgia Health Sciences University. If it diffuses off-label for this indication, the drug combination would be delivered by intravenous injection in emergency departments treating patients with acute ischemic stroke within 6 to 24 hours after stroke onset. In clinical trials, various dosing regimens are under study.⁴⁹

In a 2010 clinical trial of 60 patients experiencing acute ischemic stroke, minocycline was administered intravenously within 6 hours of stroke symptom onset in preset dose tiers of 3.0, 4.5, 6.0, or 10.0 mg/kg of body weight daily over 72 hours. Researchers concluded, “Minocycline is safe and well tolerated up to doses of 10 mg/kg intravenously alone and in combination with tissue plasminogen activator. The half-life of minocycline is approximately 24 hours, allowing every 24-hour dosing. Minocycline may be an ideal agent to use with tissue plasminogen activator.”⁵⁰ In results of a 2007 clinical trial of 152 patients who received minocycline 200 mg, administered orally 6 to 24 hours after onset of stroke, for up to 5 days, researchers concluded, “Patients with acute stroke had significantly better outcome with minocycline treatment compared with placebo. The findings suggest a potential benefit of minocycline in acute ischemic stroke.”⁵¹

Clinical Pathway at Point of This Intervention

Acute ischemic stroke is treated mainly with tPA. Experienced practitioners at stroke centers may also perform thrombectomy using a special catheter to extract blood clots. For hemorrhagic stroke, surgery or endovascular intervention might be needed to repair damaged vessels and treat bleeding complications.⁵² If diffused for this use, intravenous minocycline would be an adjuvant used in combination with tPA in emergency departments when patients with acute ischemic stroke arrive within 6 to 24 hours after stroke onset.

Figure 4. Overall High Impact Potential: Off-label minocycline with tissue plasminogen activator for treatment of stroke



Experts commenting on this intervention thought that it has the potential to dramatically impact patient health outcomes by increasing the treatment window and safety profile of patients experiencing acute ischemic stroke. Experts also thought significant reductions in long-term costs and improvements in patient health outcomes and quality of life could be seen. Because of its low cost, wide availability, and simple administration, minocycline could be readily and easily adopted into current models of care, experts thought. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Eight experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁵³⁻⁶⁰ Experts agreed that the unmet need for neuroprotection is extremely important, because of the poor outcomes associated with stroke (e.g., death and disability), the paucity of available treatment options, and the narrow therapeutic window within which patients can be treated. One expert went so far as to describe stroke neuroprotection as “the Holy Grail of biomedical research.”⁵⁴

Although experts generally supported the theory underlying minocycline’s mechanism of action in this population, two clinical experts pointed out that virtually all neuroprotective agents previously investigated have failed efficacy and/or safety trials, even when preclinical data showed positive outcomes. Therefore, some experts were skeptical about this drug’s ability to actually improve patient outcomes, and they were eager to see early results duplicated in larger trials. One research-based expert pointed out that while minocycline may increase both the therapeutic window and the number of people who can be treated with tPA, “tPA is not a magic bullet for acute ischemic stroke treatment,” and that even when administered within an appropriate time frame, it shows only moderate efficacy in improving stroke outcomes. Thus, this expert asserted that use of minocycline in this patient population should not be expected to actually improve the efficacy of tPA, only to increase the therapeutic window and safety profile associated with tPA use.

As several experts pointed out, only a small proportion of patients with ischemic stroke receive tPA, because of the narrow treatment window and fear of ICH. The extended treatment window that might be afforded by minocycline might also improve access to care for many patients, giving them more time to get to a hospital and receive tPA. Alternatively, some experts suggested that this intervention might improve access to care by allowing rural patients to be treated initially at a local hospital and then transferred to a specialty center for more highly specialized care during the increased treatment timeframe.

Experts commenting on this intervention indicated that it has the potential to dramatically reduce costs associated with stroke treatment and recovery, if it is shown to be effective, because minocycline is relatively inexpensive, and the long-term costs associated with stroke disability, inpatient care, rehabilitation, lost productivity, and long-term care are high.

Experts also speculated that minocycline has potential to improve patient health and quality of life. As one clinical expert stated, “By providing a greater opportunity (time frame 6-24 hours) for the use

of tPA and the reversal of damage caused by a clot ... the patient has a far greater chance of survival as well as a decreasing the life-devastating disabilities caused by stroke.”⁶⁰ Additionally, “The patient would hopefully be able to return to their own home and decrease the need for long-term care in nursing homes.”⁶⁰

Experts generally thought that minocycline could be easily adopted into the current health care model for stroke, because it is readily available, inexpensive, administered as an intravenous formulation, and does not require much training on the part of the clinician.

Coronary Artery Disease Interventions

Intervention

Implantable cardiac monitor (Guardian system) for detection of impending myocardial infarction

When myocardial infarction (MI) occurs, physicians must rapidly remove arterial blockages and restore blood flow through the coronary arteries to limit damage to heart muscle tissue. However, many people do not immediately recognize MI symptoms and often fail to seek prompt medical attention. The longer treatment is delayed, the more likely the patient will incur greater—and potentially fatal—injury to the myocardium (i.e., heart muscle tissue). Delays in treatment can also increase the risk of potentially fatal arrhythmia, such as ventricular tachycardia or ventricular fibrillation (VF).⁶¹

Angel Medical Systems, Inc. (Shrewsbury, NJ), has developed an implantable electronic device designed to warn patients of an impending MI by measuring electrical changes in the heart. Oxygen levels decrease significantly in the myocardium during exercise, causing the heart to beat more rapidly to compensate for the increased demand for oxygen-rich blood. In the resting state, myocardial cells maintain a net negative electrical charge (polarized). During contraction, myocardial cells take on a net positive charge (depolarized). In the healthy heart, essentially all myocardial cells become depolarized and repolarized (return to resting state) according to a predictable pattern. However, in an infarcted heart, the section of myocardium that is deprived of oxygen by a blood clot or other occlusion usually does not follow the normal pattern, leading to a change in electrical signal during the ST segment of the electrocardiogram (ECG).^{62,63}

According to the manufacturer, the system can detect these rapid changes in the ST segment and warn the patient by vibrating under the skin. The implantable component detects, analyzes, and stores the patient's ECG waveforms and other heart data, while an external telemetry device (about the size of a pager) collects data wirelessly from the implanted component and issues alarms and alerts to the patient, if necessary. Based on the severity of the alert, the telemetry device can advise the patient to seek emergency treatment or to contact his or her physician for a followup appointment. By connecting a laptop computer to an external telemetry device, the physician can program the implantable component and download stored patient data for analysis.⁶³

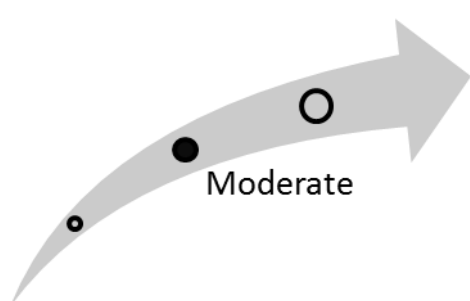
The system is intended to be implanted in a fashion similar to pacemaker implantation, but the technology is not intended for use in patients who currently have implanted pacemakers or other cardiac devices.⁶² In the U.S., Angel Medical Systems is evaluating the system in a phase II/III pivotal clinical trial under U.S. Food and Drug Administration (FDA) investigational device exemption status.⁶⁴⁻⁶⁶ According to the company, the AngelMed Guardian is commercially available in Brazil and received Conformité Européenne (CE) mark approval in Europe in September 2010.^{62,67}

In results from a 2010 clinical trial of 37 patients at high risk for acute coronary syndrome who received the implant, investigators reported, “During follow-up (median 1.52 years, range 126 to 974 days), 4 patients had ST-segment changes of <3 standard deviations (SDs) of their normal daily range, in the absence of an elevated heart rate. This in combination with immediate hospital monitoring led to angiogram and/or intravascular ultrasonography, which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 min (6, 18, 21, and 60 min, respectively). Alerting for demand-related ischemia at elevated heart rates, reflective of flow-limiting coronary obstructions, occurred in four patients. There were two false-positive ischemia alarms related to arrhythmias, and one alarm due to a programming error that did not prompt cardiac catheterization.”⁶⁸

Clinical Pathway at Point of This Intervention

For patients experiencing MI, thrombolytic drug therapy (e.g., tissue plasminogen activator) may be used if the patient arrives in the emergency department (ED) within 12 hours of the initial infarction event.⁶⁹ Percutaneous coronary intervention (PCI) using balloon angioplasty with or without coronary stenting is also widely used as a first-line treatment for acute MI.⁶⁹ Emergency physicians may refer patients with suspected MI to the cardiac catheterization laboratory to allow direct visualization of a coronary blockage under fluoroscopic guidance, after PCI.⁶⁹ If physicians detect multiple blockages, patients may undergo emergency coronary artery bypass graft surgery instead of PCI.⁶⁹ If approved for marketing, the Guardian system would likely be positioned as a warning system that allows patients to get to the hospital faster so that they may receive intervention in a timely fashion.

Figure 5. Overall High Impact Potential: Implantable cardiac monitor (Guardian system) for detection of impending myocardial infarction



Experts commenting on this topic offered strongly divergent opinions on many issues related to this technology, signaling much potential controversy for the technology. While some experts thought that the intervention has potential to reduce long-term costs and improve health outcomes by signaling patients with MI to seek timely care, other experts were highly skeptical about the proposed intervention's mechanism of action, high cost, invasive nature, and the unmet need it purports to address. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁷⁰⁻⁷⁶ One clinical expert is a member of a clinical events review committee that has adjudicated clinical events in patients receiving the AngelMed device in clinical trials, and this potential conflict of interest was balanced by the perspectives of the six experts who had no conflicts of interest.

Experts were divided on the importance of the unmet need this intervention purports to address. Some experts opined that a substantial unmet need exists in terms of helping patients recognize an impending MI, so they can seek prompt medical treatment, especially because positive outcomes are known to correlate with reduced time to treatment. Other experts noted that patients (particularly those who have had an MI in the past) are likely to recognize signs of an MI, citing national educational campaigns by the American Hospital Association, although another clinical expert pointed out that these public education efforts have not achieved their goal, because outcomes are still poor.

Furthermore, experts were divided on the validity of the theory underlying the device. Some stated that it seemed plausible, though they thought the available data do not yet conclusively show that the device would actually improve patient outcomes because the burden is still on the patient to get to the hospital in a timely fashion. Some experts were skeptical of the underlying science behind the intervention. As one health systems expert with ED experience stated, "The shift from a mechanical understanding to an electro-chemical one for early warning and detection is a stretch. It strikes me as a reach that depolarization of the myocardial cells will only occur when an MI is impending. I would think there would be a lot of false negatives and positives."⁷⁵

This group of experts agreed that the intervention has the potential for high controversy for additional reasons. Several pointed out that although this intervention is meant to be implanted in

patients “at high risk for MI,” determining who is at high risk is not easily discerned. The manufacturer suggests that patients who have experienced an MI are at highest risk, but some experts argued that these patients are likely being treated aggressively anyway, so they no longer are at highest risk, and they likely have a better understanding of what MI symptoms feel like and so are likely to get to the hospital in a timely fashion.

Several experts took issue with the potentially high cost of the intervention. Although some thought that the high initial cost might be offset by long-term cost savings that timely treatment offers, others thought that this intervention is too expensive to justify widespread use, especially because patients can be “trained” to recognize and act on MI symptoms without having an implanted device. Experts questioned the justification for subjecting a patient to an invasive surgical implant procedure in light of the issues of identifying appropriate patients and having sufficient outcomes data. Some experts also thought that this intervention could cause patients a great deal of anxiety, similar to the anxiety seen with an implantable cardioverter-defibrillator. As one clinical expert stated, patients may feel like a “ticking time bomb, especially if they’ve had a few false alarms [with their device].”⁷⁰

However, should the device be approved and diffuse, experts allowed for the possibility that the device might enable some patients to seek care in a more timely fashion, thereby improving morbidity and mortality. These experts also thought that patient throughput times might improve, because a clinician would have ECG data available (through the device) upon the patient’s arrival at the hospital. Lastly, experts thought that care setting and patient volume in the ED might be disrupted, because more patients would be likely to seek care.

Intervention

Apo-B synthesis inhibitor (mipomersen) for treatment of familial hypercholesterolemia

Despite the availability of lipid-lowering pharmacotherapies, many patients with familial hypercholesterolemia (FH) do not achieve acceptable lipid levels and remain at increased risk for early coronary events and sudden death.⁷⁷ Nonpharmacologic interventions, such as apheresis and liver transplantation, are costly, invasive, and not widely available. Thus, an unmet need exists for novel and effective pharmacologic therapies for this condition.

Mipomersen (ISIS Pharmaceuticals, Inc., Carlsbad, CA, and Genzyme Corp., now part of Sanofi-Aventis, Paris, France) is an antisense oligonucleotide inhibitor of apolipoprotein-B (apo-B) mRNA that is being investigated for the treatment of homozygous and heterozygous FH.⁷⁸ Apo-B provides the structural core for all atherogenic lipids (including low-density lipoprotein [LDL]) and is required for the release of cholesterol from the liver into the blood.^{77,79} Because excessive LDL in the blood plays a major role in the development of atherosclerosis and its associated risk factors, apo-B is a viable target for treatment of FH, the manufacturer believes.^{77,79} According to the manufacturer, the drug is intended to decrease production of apo-B, thereby reducing cholesterol's means of transportation into the blood.^{77,79} In clinical trials of mipomersen in patients with FH, the drug is being administered as a subcutaneous injection, administered once weekly in a dosage of 200 mg.⁸⁰ Patients weighing less than 50 kg receive a dosage of 160 mg every week.⁸⁰

According to the manufacturer, mipomersen has been evaluated in four phase III clinical trials, in which all primary, secondary, and tertiary outcomes were met.⁸¹ In a phase III trial of patients with homozygous FH, published results state, "45 patients completed the 26-week treatment period (28 mipomersen, 17 placebo). Mean concentrations of LDL cholesterol at baseline were 11.4 mmol/L (SD 3.6) in the mipomersen group and 10.4 mmol/L (3.7) in the placebo group. The mean percentage change in LDL cholesterol concentration was significantly greater with mipomersen (-24.7%, 95% CI -31.6 to -17.7) than with placebo (-3.3%, -12.1 to 5.5; $p = 0.0003$). The most common adverse events were injection-site reactions (26 [76%] patients in mipomersen group vs four [24%] in placebo group). Four (12%) patients in the mipomersen group but none in the placebo group had increases in concentrations of alanine aminotransferase of three times or more the upper limit of normal."⁸² In a clinical trial of patients with heterozygous FH, published results state, "Mipomersen produced significant reductions in LDL cholesterol and other atherogenic apolipoprotein B-containing lipoproteins. After 6 weeks of treatment, the LDL cholesterol level was reduced by 21% from baseline in the 200-mg/week dose group ($p < 0.05$) and 34% from baseline in the 300-mg/week dose group ($p < 0.01$), with a concomitant reduction in apolipoprotein B of 23% ($p < 0.05$) and 33% ($p < 0.01$), respectively. Injection site reactions were the most common adverse event. Elevations in liver transaminase levels ($> \text{or} = 3$ times the upper limit of normal) occurred in 4 (11%) of 36 patients assigned to active treatment; 3 of these patients were in the highest dose group."⁸³

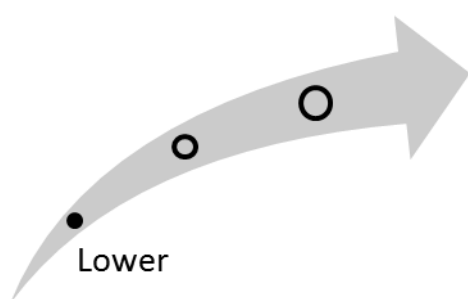
The manufacturer stated that it planned to file for marketing approval in the U.S for patients with homozygous FH in the fourth quarter of 2011.⁸¹ The manufacturer also plans to seek approval in the U.S. for patients with heterozygous FH, but states that, "Due to the larger size of the severe heFH [heterozygous FH] population, the FDA requested an additional 12 month clinical data before the mipomersen filing for severe heFH in the U.S."⁸¹ Should the drug be approved, the manufacturer states that it would be marketed under the brand name KynamroTM.⁸¹

Clinical Pathway at Point of This Intervention

According to the National Human Genome Research Institute, first-line treatment for patients with heterozygous FH includes lifestyle changes (e.g., diet, exercise) and drug therapy with cholesterol-lowering medications (e.g., bile acid sequestrants, ezetimibe, fenofibrate, gemfibrozil, niacin, statins).⁸⁴ For patients with homozygous FH, more aggressive therapies are often necessary and include apheresis or liver transplantation.⁸⁴

The manufacturers have stated that mipomersen is intended to be used in patients who are on maximally tolerated lipid-lowering therapies, but are not yet at their recommended LDL-cholesterol goal.⁷⁷ Thus, if approved for marketing, mipomersen would be positioned as a complementary (add-on) therapy to currently approved lipid modification drugs, such as bile acid sequestrants, ezetimibe, fenofibrate, gemfibrozil, niacin, and statins. For patients with homozygous FH, mipomersen might obviate or postpone the need for apheresis or liver transplantation. Thus, mipomersen may compete with these second-line options for patients who are not reaching their LDL cholesterol goals, despite use of available pharmacotherapies.

Figure 6. Overall High Impact Potential: Apo-B synthesis inhibitor (mipomersen) for treatment of familial hypercholesterolemia



Experts commenting on this intervention agreed that it would likely meet the important unmet need for improved therapies for patients with FH if proven effective, and they thought that this intervention, positioned as an add-on injectable therapy, would be easily adopted into the current health care infrastructure. Experts believe that questions remain about the agent's safety, and whether the LDL reductions seen in clinical trials will translate to improved clinical outcomes over time. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.⁸⁵⁻⁹¹ One expert disclosed a potential conflict of interest, stating that he consults on research with a manufacturer who makes antilipidemic agents. This potential conflict of interest was balanced by the perspectives of experts who did not report conflicts of interest.

Experts strongly agreed that the unmet need for novel, effective treatment for FH is extremely important, because of the significant risks for coronary events and sudden death associated with this condition. Experts also noted that existing treatments are either ineffective (pharmacotherapy) or “aggressive and costly” (apheresis and liver transplantation), thereby underscoring the importance of the unmet need.⁸⁷ The small patient population for this condition did not temper expert opinion on the importance of the unmet need.

Experts were optimistic about this agent's ability to improve patient health outcomes. As one research-based reviewer stated regarding the drug's mechanism of action, mipomersen “represents a very promising target for drug development.”⁸⁶ Most experts also noted that efficacy data from clinical trials are encouraging. However, one clinical expert was less optimistic, stating “The reduction in LDL cholesterol is relatively modest given the severe elevations that these patients exhibit. In addition, the frequency of elevation of liver enzymes is of significant concern with this agent.”⁹¹ This viewpoint was somewhat balanced by another clinical expert, who stated: “The initial studies also reveal safety of

mipomersen; only 11-12% of patients had elevation in some liver tests. Further studies will need to address if longer therapy will result in more patients with elevated liver function tests.”⁸⁵ Some reviewers noted that longer-term studies will be needed to determine whether the LDL reductions seen in clinical trials will translate to improved clinical outcomes over time.

Most experts suggested that this intervention would be easily incorporated into existing health care infrastructure and patient management models, mainly because the drug is likely to be positioned as an add-on therapy, and because it involves only a regular subcutaneous injection. While the injection may require visits to provider offices, this is a minor disruption to the existing system, experts noted, and additionally, patients might be trained to administer the injection themselves. The only potentially large disruption this agent may pose to patient management models is the possibility of reducing or postponing the need for more invasive treatments (e.g., apheresis or liver transplants). Similarly, experts thought that reducing or postponing the need for these costlier interventions might offset the ongoing costs of the injection.

Experts generally agreed that both clinicians and patients would accept this intervention, because it would likely offer improved outcomes and might reduce the need for apheresis or liver transplant. However, some reviewers noted that clinicians might want to see additional safety data before prescribing the drug and that patients might be reluctant to use a drug that requires injection.

Heart Failure Interventions

Intervention

Autologous mesenchymal stem cell transplantation (C-Cure) for treatment of heart failure

Current first-line treatments for heart failure (HF) are typically palliative and address only disease symptomology, rather than the underlying loss of cardiomyocytes that is the hallmark of the disease.⁹² In light of this, stem cells have been investigated as a means of improving the heart's capacity for self-repair.⁹² First-generation, "undifferentiated" stem-cell therapies for HF have shown limited clinical benefit in early clinical trials. Therefore, researchers are now suggesting pretreating cells with "activators" designed to improve the cells' cardiac homing ability and possible survival in cardiac tissue.⁹³

C-Cure® (Cardio3 Biosciences, Mont-Saint-Guibert, Belgium) is a bone-marrow-derived, cardiopoietic, mesenchymal stem cell therapy that is being investigated for treatment of heart failure.⁹⁴ The therapy involves harvesting mesenchymal cells from the patient's bone marrow, treating the cells with growth factors (a "cardiopoietic cocktail") and then injecting the cells into the patient's heart.⁹⁴ The cocktail includes transforming growth factor-beta1, bone morphogenetic protein-4, activin A, retinoic acid, insulin-like growth factor-1, fibroblast growth factor-2, alpha-thrombin, and interleukin-6.⁹⁵ The company claims that treatment with these proteins can transform mesenchymal (undifferentiated) stem cells into cardiac progenitor cells to replicate natural cardiogenesis, without modifying the genome of the cell.^{94,96} The cardiac progenitor cells are designed to behave identically to cells lost during progression of heart failure, and they potentially regenerate damaged heart muscle without risk of rejection.⁹⁷

In clinical trials, the stem cells have been initially collected from the patient's iliac crest. After cells are treated ex vivo, they are administered into the patient's left ventricle via 20 endomyocardial injections at sites bordering the damaged heart tissue. According to the company, this process takes place during a single surgical procedure, and cardiac electromechanical mapping is used to identify injection sites.^{95,96}

According to an April 2011 company press release, researchers reporting on a phase II clinical trial of 45 patients with severe HF of ischemic origin in Belgium and Serbia who were treated with optimal standard of care or optimal standard of care plus C-Cure concluded, "Patients receiving C-Cure saw an 18.1% increase in left ventricular ejection fraction (LVEF), a measure of heart function, over baseline, as measured by echocardiography, while the mean LVEF improved only marginally in patients enrolled in the control group. This difference in LVEF between the C-Cure treated and control patients was significant ($p < 0.01$) suggesting that C-Cure treatment leads to heart tissue repair."⁹⁸ In September 2011, the company reported that it planned to discuss the phase II results with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency before finalizing the protocol for the phase III trials.⁹⁹

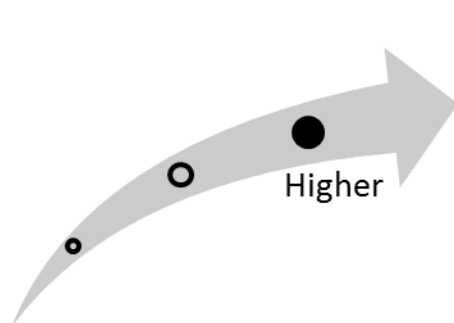
Clinical Pathway at Point of This Intervention

The Mayo Clinic states that first-line medical management of HF may include angiotensin-converting enzyme (ACE) inhibitors, beta blockers, angiotensin receptor blockers, digoxin, diuretics, or aldosterone antagonists.¹⁰⁰ In some cases, surgical intervention (e.g., coronary bypass surgery, heart valve repair or replacement, implantation of a ventricular assist device [VAD]) to treat the underlying cause of the HF may be indicated.¹⁰⁰ Patients with severe HF may require a heart transplant.¹⁰⁰

This stem cell therapy may reduce the need for pharmacotherapies that address symptoms of HF. However, it should be noted that in clinical trials investigating the use of guided stem cell therapy, patients receiving the intervention remained on a regimen of standard-of-care medical therapy. Thus,

the company may intend for the stem cell therapy to be used in conjunction with standard medical therapy. If approved for marketing, the stem cell therapy also has the potential to displace some of the need for other surgical interventions used as HF advances. The lifestyle changes (e.g., diet, exercise) that often accompany HF treatment would likely remain complementary interventions to stem cell therapy.

Figure 7. Overall High Impact Potential: Autologous mesenchymal stem cell transplantation (C-Cure) for treatment of heart failure



In general, although experts varied in their confidence about the potential efficacy of stem-cell-based interventions, experts agreed that this therapy has the potential to significantly affect many different parameters of the health care system. In particular, experts thought shifts in treatment paradigms and care models, care setting, staffing models, infrastructure needs, and cost would be seen. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health administration, and health systems backgrounds, provided perspectives on this topic.¹⁰¹⁻¹⁰⁷ Experts expressed the belief that an important need for disease-modifying treatments for HF exists, based on both the disease prevalence and its financial burden. However, experts had mixed opinions on whether this intervention would be capable of meeting that need. On one hand, some experts believe that stem-cell treatments are still unproven, citing the failure of first-generation stem cell therapies and the fact that “we don’t really understand stem cell homing and it probably makes more sense to understand the science before just injecting the heart.”¹⁰¹ On the other hand, two experts, one of whom has experience in tissue engineering, noted that this treatment contained sufficient growth factors to provide adequate cell homing.

Experts generally asserted that this treatment has the potential to significantly disrupt current care models, treatment pathways, and patient management models. First, they stated that focus of care would shift to regeneration and the underlying cause of HF, rather than on treatment of symptoms. Second, they indicated if this intervention were to be proven effective, it has the potential to obviate the need for expensive interventions (e.g., coronary bypass, heart transplantation) for patients with late-stage HF. Third, experts noted that this treatment requires a surgical procedure during a stage of HF that has previously been treated only with pharmacotherapy.

Although experts commenting on this topic did not expect a steep learning curve on the part of clinicians, they did think that the procedure would necessitate changes to hospital operations. First, care setting would shift from the primary or specialty clinician’s office to hospital-based surgery, which would likewise affect staffing requirements (e.g., surgeons to perform the injection, hematologists to perform the bone marrow harvest). Second, handling of stem cells is likely to require specialized laboratory services. However, some experts noted that despite these initial changes, the intervention might obviate the need for other invasive procedures or pharmacotherapy, thereby reducing demand for care over time.

Experts agreed that this procedure would be likely to be very expensive initially, based on the costs of the stem cell harvesting and treatment and surgical injection procedure, but that it could reduce costs over time. As one research-based expert put it, “The cost of the surgery would far exceed the standard medical treatment in the beginning, but over time the cost of the surgery may be less than the cost of the medical management that would continue for a person’s lifespan.”¹⁰⁵

Although experts generally thought that most patients and clinicians would accept this procedure, experts also thought that acceptance could be affected by controversy that might arise over this intervention. Although the procedure involves the use of a patient's own stem cells, the medical use of stem cells is subject to an ongoing public debate that may be a barrier to uptake, some experts stated. Another expert, speaking from a clinical perspective, asserted that the high cost and invasive nature of the intervention might be controversial. Experts noted that long-term efficacy data on the intervention's clinical benefit would be necessary for wide adoption.

Intervention

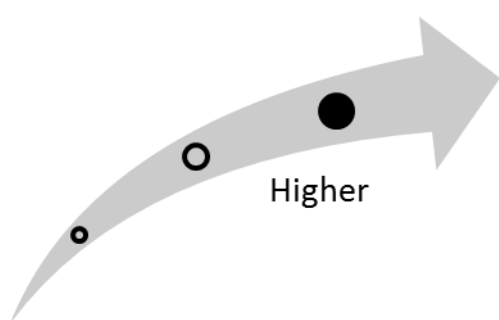
Portable driver system (Freedom Driver) for total artificial heart

The temporary Total Artificial Heart (TAH-t, SynCardia Systems, Inc., Tucson, AZ), is a pneumatic, biventricular, implantable device that functions in place of the two ventricles and four valves of a failing heart by pumping blood to both the pulmonary and systemic circulations.¹⁰⁸ The TAH-t, approved as a bridge-to-transplant by FDA in October 2004,¹⁰⁹ is indicated for use in cardiac transplant-eligible patients at risk of imminent death from nonreversible biventricular failure.¹⁰⁸ The TAH-t is powered by a conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart.¹¹⁰ A portable driver system that could allow patients to be discharged from the hospital while awaiting a suitable donor heart would address a significant unmet need for this small patient population.

The Freedom® Driver System, also developed by SynCardia Systems, is under development to address this need. It is a wearable pneumatic driver that powers the SynCardia TAH-t. The driver is intended to allow patients receiving the TAH-t to leave the hospital and live at home while awaiting a donor heart. The 13.5-lb pneumatic driver is carried in a backpack or shoulder bag. The driver is powered by two onboard batteries that can be recharged with an automobile adapter or a standard electrical outlet. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the skin in the left chest just below the ribs. The driver flashes a light or sounds an alarm when the system requires the user's attention.¹¹⁰

In March 2010, SynCardia received Conformité Européene (CE) mark approval to market the Freedom driver in the European Union for use with the SynCardia TAH-t.¹¹¹ The company is currently investigating the use of the portable driver system under an investigational device exemption clinical trial in the U.S.¹¹⁰ In November 2011, the company reported that 34 TAH patients had been enrolled in the clinical study, and 23 of these patients had been discharged from the hospital using the portable driver.¹¹⁰ Of those, the clinical experience of one patient has been published.¹¹² According to a July 2011 press release, a 41-year-old male, who received the TAH-t as a bridge to transplant, was discharged from the hospital using the portable driver system, which supported him for a total of 253 days, at which point he returned to the hospital to receive a dual heart and kidney transplant.¹¹²

Figure 8. Overall High Impact Potential: Portable driver system (Freedom Driver) for total artificial heart



Though the patient population for which this device is intended is small, and in-hospital driver systems already exist, a portable driver for the TAH-t system has the ability to dramatically improve patient quality of life and dramatically shift the care setting model by allowing patients to return home while awaiting transplant, experts commenting on this intervention agreed. Experts also thought that this device has the potential to dramatically reduce patient costs associated with lengthy hospital stays and that using the portable device would require training on the part of the home caregiver but is not likely to

affect many other health system parameters, such as treatment paradigms or current care models. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Clinical Pathway at Point of This Intervention

The American College of Cardiology/American Heart Association clinical guidelines identify cardiac transplantation or the implantation of a VAD as destination therapy as the only established surgical treatments for advanced, end-stage HF.¹¹³ The portable driver system is intended to complement TAH-t use.¹⁰⁸ As a bridge to transplantation, the TAH-t with the Freedom driver would complement heart transplantation. Some left VADs that are compatible with portable driver systems for in-home use could compete with the TAH-t and Freedom driver as a bridge to transplantation.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹¹⁴⁻¹¹⁹ Although experts noted that the patient population for which this device is intended is small, they generally agreed that an important unmet need exists for a driver system that would allow these patients to be discharged home while awaiting a heart transplant. Two of these experts stated that rather than closing a true gap in unmet need for health technology (because inpatient drivers are already available in the hospital setting) this device's greatest benefit is improving patient quality of life and affecting costs of care by shifting from inpatient to at-home care while awaiting a heart transplant.

In general, experts were confident that this device would work, but some concerns were raised about the potential for increased adverse events in an outpatient setting, especially because long-term trials have not been completed. As one expert with a health systems background noted, "Efficacy is assumed, but safety (especially in the event of device malfunction) has not been studied yet and is identified as a potential concern. Early failures seem likely to result in patient death."¹¹⁹ Several experts spoke to the potential safety issues that may arise in the home care setting should something go wrong with the patient or the device when the patient is no longer in the hospital, and emergency clinical staff are not nearby.

Experts agreed that one likely consequence of use of this device would be the additional burden of care that would fall to a patient's in-home caregiver and an in-home clinical care team. Because of these shifts, experts thought the following: (1) Families and others supporting the patient who have no clinical backgrounds would need extensive training to care for the patient at home and would need to understand how to operate the portable driver and respond to its alarms or potential malfunctions; (2) staffing mix would change for care of the patient, with more emphasis placed on home care nurses or home visit clinicians; (3) patients without access to a home caregiver support system would likely not be suitable to use this device.

Intervention

Vagus nerve stimulation (CardioFit) for treatment of heart failure

Patients with HF experience an increase in sympathetic nervous system activity and a decrease in parasympathetic nervous system activity.¹²⁰ However, the available interventions for treatment of HF address the sympathetic nervous system, and none are yet available to address the parasympathetic nervous system.¹²⁰ Recent studies in human clinical trials suggest that vagus nerve stimulation activates the parasympathetic nervous system, which can improve baroreflex sensitivity, improve cardiac function, and maintain a healthy heart rate. Vagus nerve stimulation is also purported to reduce levels of circulating inflammation markers in the bloodstream and to lower the risk of arrhythmia, ischemia, and tachycardia.¹²¹

The CardioFit® System (BioControl Medical, Yehud, Israel) is an investigational device that is being evaluated for the treatment of HF. It is intended to stimulate the vagus nerve to increase activity of the parasympathetic nervous system.¹²² The system consists of an implantable stimulator; a sensing lead, which passes through a vein into the right ventricle; and a stimulation lead, which transmits electrical signals from the stimulator to the vagus nerve.¹²² According to the manufacturer, the system can be programmed on and off using external wireless communication.¹²³

During device implantation, the physician positions a cuff electrode around the vagus nerve in the neck, and the pulse generator is placed in a pocket under the skin in the chest. The procedure is estimated to last about 50 to 90 minutes and requires general anesthesia. Sometimes a hospital stay of one night is required, though some patients are discharged on the same day. Three weeks after implantation, the physician progressively increases electrical stimulation of the right cervical vagus nerve to a maximum tolerable level. The system can be turned off or removed from the body at any time.¹²⁴

The system is being investigated in a phase III clinical trial in the U.S. and was granted CE mark approval in December 2008.^{123,125} Researchers giving results of a pilot clinical trial of 32 patients receiving the implant reported, “Study data showed that patients experienced sustained significant improvement across key clinical measures including left ventricular function and structure, heart rate variability, and resting heart rate. Patients also showed improvement in self-reported quality of life surveys and six-minute hall walk tests.”¹²³

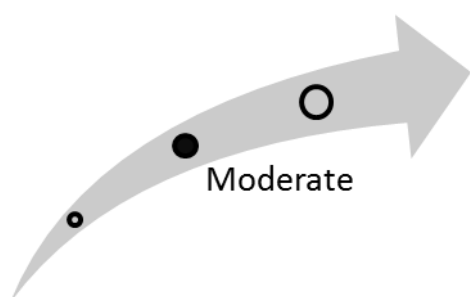
It appears that another company is also investigating the use of vagus nerve stimulation for the treatment of HF. Boston Scientific Corp. (Natick, MA) has registered a clinical trial investigating right vagal nerve stimulation in heart failure patients with a New York Heart Association (NYHA) Class III status with the National Clinical Trials database, but a search of the manufacturer’s Web site did not yield any additional information about the technology.¹²⁶

Clinical Pathway at Point of This Intervention

The Mayo Clinic states that first-line medical management of HF may include ACE inhibitors, beta blockers, angiotensin receptor blockers, digoxin, diuretics, or aldosterone antagonists.¹⁰⁰ In some cases, surgical intervention (e.g., coronary bypass surgery, heart valve repair or replacement, implantation of a VAD) to treat the underlying cause of the HF may be indicated.¹⁰⁰ Patients with severe HF may require a heart transplant.¹⁰⁰

Vagus nerve stimulation is intended for patients with functional NYHA Class II to IV HF status, in stable condition, with normal heart rhythm who fail to respond optimally to pharmacologic management of HF. The device may be used as an adjunct to drug therapy to enhance pump capacity.¹²⁷

Figure 9. Overall High Impact Potential: Vagus nerve stimulation (CardioFit) for treatment of heart failure



Despite the success of vagus nerve stimulation for other diseases and conditions, the intervention's ability to effect meaningful change in patient outcomes in HF was met with skepticism by experts commenting on this intervention. They suggested that, although this intervention would be easily incorporated into health care models, its high cost and invasiveness might be a barrier to uptake, especially until longer-term outcomes data are available. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹²⁸⁻¹³⁴ Most experts agreed that an important need exists for patients with HF that is not well controlled with pharmacotherapy. However, one clinical expert disagreed, stating that “Overall, for patients with HF and low EF [ejection fraction], the latest clinical trials show a very low mortality rate (less than 5% annually) with all appropriate drug and device use—this therapy is unlikely to improve clinical outcomes a whole lot more.”¹²⁹

Experts agreed that this intervention represents a departure from the way HF is currently treated, because neuromodulation has not yet been adopted for this disease. Experts were divided, however, on whether neurostimulation would actually improve outcomes in this population. On one hand, some experts suggested that vagus nerve stimulation's success in other diseases makes it a plausible option for HF. On the other hand, some experts opined that the data gathered so far are not particularly encouraging. Furthermore, the data available do not address long-term outcomes such as morbidity or mortality. Regardless of the potential efficacy of the intervention, this is a novel approach, experts agreed, and would add an additional pathway to the care model for HF. Furthermore, one expert suggested that if the intervention “gets patients out of acute care settings [by preventing complications of HF], it might have a large effect on the way patients are treated.”¹³¹

Experts were particularly concerned with both the high cost and invasiveness of the intervention. The device and implantation procedure are expected to be very expensive, and whether this cost would be offset by future savings attributable to improved outcomes is unclear. Similarly, the implantation procedure is invasive, which experts believe is not justified by efficacy data published thus far. One health systems expert noted that only a small subset of patients with HF might actually be able to undergo such an invasive procedure, stating “This intervention requires that a CHF [congestive heart failure] patient be in stable condition and be able to withstand a 50-90 minute procedure.”¹³³

Although the intervention would likely require the addition of a cardiac surgeon and a neurologist to the HF care team, experts generally thought that this intervention, if shown to be effective, could be easily incorporated into existing health care system infrastructure and staffing models, largely because of the diffusion of other cardiac implant devices.

Hypertension Interventions

Intervention

Baroreflex stimulation (Rheos Baroreflex System) for treatment-resistant hypertension

The human baroreceptor reflex (baroreflex) system is a network of natural blood-pressure sensors (baroreceptors) located throughout the arteries and veins that helps regulate blood pressure in concert with the central nervous system.¹³⁵ In chronic hypertensive conditions, the carotid baroreflex signal is often insufficient, and many patients with diffuse atherosclerosis have stiff vessels that are unable to respond to baroreflex signals. Physicians often prescribe various drugs to help maintain a safer blood pressure; however, some forms of hypertension do not respond well to pharmacotherapies. Furthermore, some patients find side effects of antihypertensive drugs intolerable, even at relatively low doses. The key role of carotid sinus baroreceptors in blood pressure regulation, therefore, makes them a potential target for the treatment of drug-resistant hypertension.¹³⁵

One intervention under study attempts to lower uncontrolled blood pressure by electrically stimulating the carotid baroreceptors.¹³⁵ The Rheos™ Baroreflex Hypertension Therapy System (CVRx, Inc., Minneapolis, MN) uses a pacemaker-like, implantable pulse generator, inserted subcutaneously near the clavicle, to deliver electrical signals to baroreceptors in both the left and right carotid arteries in the neck by means of two carotid sinus leads. Because a pressure-sensing switch that could turn on and off as needed would quickly wear out within the carotid arteries, the electrical pulse generator is always on when in the active mode. The system's external programming components allow physicians to noninvasively regulate the intensity of electrical stimulation and program the system according to individual patient needs. The device can deliver variable voltage to either or both carotid sinuses in a variety of modes. As with other implantable electronic devices, the Rheos system would likely require surgical replacement of the implantable pulse generator when the device's batteries have been depleted.¹³⁵⁻¹³⁷ Vascular surgeons, who are the most experienced at operating on carotid arteries, implant the device during a minimally invasive procedure. Patients typically require hospitalization overnight following device implantation.¹³⁵⁻¹³⁷

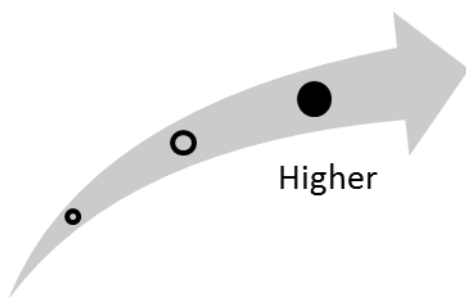
CVRx is conducting a phase II clinical trial of the Rheos system under investigational device exemption status from the U.S. Food and Drug Administration (FDA).¹³⁸ The company received Conformité Européene (CE) mark approval in October 2007 to market the Rheos system in the European Union for the treatment of hypertension.¹³⁹

In results of a 2010 trial of 45 patients with systolic blood pressure of 160 mmHg or higher or diastolic pressure of 90 mmHg or higher (despite three antihypertensive drugs), who were implanted with the Rheos system, investigators reported, "Baseline mean blood pressure was 179/105 mm Hg and heart rate was 80 beats/min, with a median of 5 antihypertensive drugs. After 3 months of device therapy, mean blood pressure was reduced by 21/12 mm Hg. This result was sustained in 17 subjects who completed 2 years of follow-up, with a mean reduction of 33/22 mm Hg. The device exhibited a favorable safety profile."¹⁴⁰

Clinical Pathway at Point of This Intervention

Electrical baroreflex stimulation therapy would be used as an adjunct to pharmacotherapy (e.g., beta blockers, angiotensin-converting enzyme [ACE] inhibitors) for treatment of severe hypertension. It is not expected to replace pharmacotherapy, although this technology may be an option for patients who cannot tolerate pharmacotherapy or adequate doses of pharmacotherapy.¹³⁵

Figure 10. Overall High Impact Potential: Baroreflex stimulation (Rheos Baroreflex System) for treatment-resistant hypertension



Experts commenting on this intervention agreed that an important unmet need exists for an intervention that can treat drug-resistant hypertension. Should baroreflex stimulation prove effective, experts thought, its high cost and invasive nature would cause some disruption to the health system because it would introduce a surgical procedure into a clinical pathway that previously included only drug therapy. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹⁴¹⁻¹⁴⁷ Experts agreed that the unmet need for interventions to effectively treat drug-resistant hypertension is important. As one clinical expert stated, “The overall number [of patients] may be small, but the potential benefit is large.”¹⁴¹ Additionally, a clinical expert stated, “Other than increasing [the] number of medications (with their own toxicity) there is no other solution to the problem of refractory hypertension at present.”¹⁴¹

Experts were supportive of the scientific theory underlying the proposed intervention and noted that clinical trials completed so far have shown significant reductions in patients’ blood pressure. However, several experts posed the question of whether this reduction in blood pressure would actually translate to improved clinical outcomes (e.g., morbidity, mortality) over time and were eager to see long-term clinical trial results. Despite this skepticism, some experts, particularly clinical experts, thought that if this intervention is shown to be efficacious, it has potential to make a significant impact on patient outcomes, including health prevention and promotion. As one clinical expert stated, “Uncontrolled hypertension is a silent killer. The research shows that some patients received as much as a 30-point drop in systolic blood pressure, which would help in the prevention of diseases that are associated with hypertension, such as coronary artery disease, stroke, and end organ damage.”¹⁴⁵

Although most experts did not anticipate that this intervention would disrupt the current care pathway and treatment models for most patients with hypertension, some thought that the addition of a novel, invasive, “end stage” intervention signaled a significant change to the treatment model for severe hypertension, which currently relies on pharmacotherapy only.

Experts suggested that the invasive nature of the implant procedure would shift the care setting from the physician’s office to an outpatient or inpatient surgery setting, a change that they anticipate would necessitate small changes to staffing and other hospital processes. Experts also expected that the implantation procedure and device would be very expensive, especially compared with the pharmacotherapy that is currently used. Whether this cost could be offset by future savings from potentially improved outcomes remains to be seen. Finally, some experts suggested that the invasive nature of the procedure might be a barrier to uptake for some patients. On the other hand, one clinical expert stated, “Many will have already had complications based on their hypertension and, having failed medical management, will likely be accepting of therapy.”¹⁴¹

Intervention

Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension

Lowering high blood pressure has been associated with significantly lower rates of stroke, heart attack, and heart failure.¹⁴⁸ For the majority of patients with hypertension, medical therapy with one or more antihypertensive drugs will continue to be the primary therapeutic approach. Nevertheless, inadequately controlled hypertension remains a problem for a growing number of people, especially as an aging population faces a greater risk of developing hypertension.¹⁴⁹ Strict adherence to recommended medical therapy can provide effective blood pressure control for most patients. However, even in highly motivated patients, the efficacy of antihypertensive therapy may be affected by several factors, including interaction with other prescription and over-the-counter medications as well as various foods, vitamins and/or herbal supplements.¹⁴⁹

Several case reports dating back to the 1950s suggested that radical surgery to block signals from the renal sympathetic nerves (renal sympathectomy) could significantly reduce hypertension and prolong life of hypertensive patients by counteracting the chronic activation of the sympathetic nervous system, which plays a central role in controlling blood pressure. However, the surgical procedure was associated with high rates of perioperative morbidity and mortality, as well as severe long-term complications (e.g., bowel, bladder, and erectile dysfunction and profound orthostatic hypotension), and later abandoned as hypertensive drug therapy improved.^{150,151} Additionally, research in kidney transplant patients, who experience renal denervation as part of transplant surgery, has shown that severing the renal nerves does not adversely affect normal kidney function, such as maintaining electrolyte levels and controlling fluid volume.¹⁵² Based on these findings, one manufacturer has investigated whether a minimally invasive, catheter-based approach could achieve similar results to renal sympathectomy surgery for controlling hypertension without the serious adverse effects of open surgery.¹⁵³

The Symplicity™ Catheter System (Ardian, Inc., which Medtronic, Inc., Minneapolis, MN, acquired in January 2011) allows a physician to apply radiofrequency (RF) energy to ablate the renal nerves from within the renal artery without adversely affecting other nerves in the abdomen, pelvis, or lower extremities.^{150,154} The minimally invasive procedure takes about 40 minutes to perform. The Symplicity system includes a proprietary low-profile catheter that delivers the RF energy and a portable, automated RF generator that powers the RF catheter.¹⁵³ According to the company, physicians perform the renal denervation procedure in a catheterization laboratory, using standard interventional techniques similar to those used for renal stent implantation.¹⁵⁵

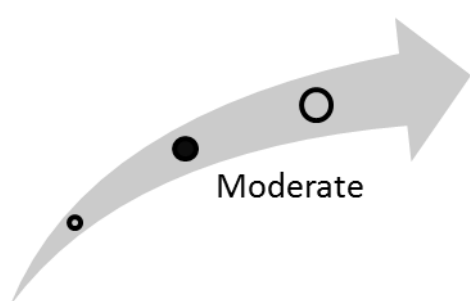
According to the manufacturer, the Symplicity Catheter System is approved for marketing in the European Union and Australia.¹⁵⁴ In July 2011, the company announced that it had received permission from FDA to begin the first randomized controlled trial in the U.S. to evaluate percutaneous renal denervation for treatment-resistant hypertension.¹⁵⁶ The Symplicity HTN-3 trial is scheduled to enroll about 530 patients at 60 U.S. sites. The primary endpoints will be change in baseline systolic blood pressure at 6-month followup and incidence of major adverse events within 1 month after randomization.¹⁵⁶

In a clinical trial of the intervention in 153 patients at 19 centers in Australia, Europe, and the U.S., published results state: "The median time from first to last radiofrequency energy ablation was 38 minutes. The procedure was without complication in 97% of patients (149 of 153). The 4 acute procedural complications included 3 groin pseudoaneurysms and 1 renal artery dissection, all managed without further sequelae. Postprocedure office BPs were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months, respectively."¹⁵⁷

Clinical Pathway at Point of This Intervention

Percutaneous renal denervation is expected to be used as an adjunct to pharmacotherapy (e.g., beta blockers, ACE inhibitors) for treatment of severe hypertension. At least initially, the procedure would most likely be reserved for patients with the most severe hypertension that has not responded to several drug regimens. Such patients who undergo percutaneous renal hypertension might still require some antihypertensive drug therapy, albeit at reduced levels. In patients with less-severe hypertension, percutaneous renal denervation could theoretically obviate the need for antihypertensive medication entirely. However, patients would need to consider the potential procedural risk compared with the potential freedom from long-term medical therapy for hypertension.

Figure 11. Overall High Impact Potential: Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension



Experts commenting on this intervention agreed that it has the potential to fill an important gap in treatment of hypertension and would likely be widely accepted by clinicians and patients. However, this intervention's potential impact is tempered by its lack of longer-term outcomes data, and the likelihood that it would be easily incorporated into existing health care infrastructure. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.¹⁵⁸⁻¹⁶⁴ One clinical expert disclosed a potential conflict of interest, stating that he is a member of the local investigative team for the Symplicity HTN-3 trial at the Medical University of South Carolina.¹⁵⁸ This potential conflict of interest was balanced by the perspectives of other experts who did not have a conflict of interest.

Experts agreed that the need for interventions for treatment-resistant hypertension is important, due to the size of the affected population, the morbidity and mortality associated with the condition, and the fact that no other treatments are available if pharmacotherapy fails to achieve desired outcomes. Although several experts noted that the data available for the intervention are limited, experts still thought that this intervention is likely to improve patient health, citing both the promising mechanism of action and efficacy data that have been collected to date. However, several experts noted that longer-term studies are necessary to determine whether the reduction in blood pressure that has been observed in trials translates to improved clinical outcomes.

Most experts suggested that this intervention would not be especially disruptive to health care infrastructure, because, as one expert wrote, "The procedure is very similar to procedures currently performed by interventional cardiologists," and the intervention would "leverage existing personnel and facilities."¹⁶² However, several experts agreed that this intervention would be likely to increase the volume of patients seeking services from catheter facilities, and would shift care from a pharmacotherapy-based to a procedural treatment regimen, a distinct departure from the current model of management.

Experts thought that should this intervention be approved, it would be broadly accepted by both clinicians and patients. According to experts, clinicians would be likely to adopt the technology because there are currently no alternative treatments for this population, and because the procedural technique required is similar to procedures that are already being performed. Experts believe that patients would be likely to accept the technology because it is minimally invasive, likely efficacious,

offers a “permanent fix,” and might reduce their need to take antihypertensive medication. Most experts thought this intervention would have a moderate effect on health care costs. Although the initial procedure will be associated with an initial upfront cost, some of this initial outlay could be offset by the potential for future savings, if the intervention is proven to reduce readmissions and costly events.

Thromboembolism Intervention

Intervention

Factor Xa inhibitors for prevention and treatment of thromboembolism

Anticoagulation therapy is regarded as an important and unavoidable component in the management of patients with (or at risk for) deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke.¹⁶⁵ However, the most-often used anticoagulation agent, warfarin, is characterized by many limitations including an unpredictable anticoagulation profile, the need for frequent monitoring of clotting parameters, and frequent dose adjustments.^{165,166} Unfractionated heparin, low-molecular-weight heparins, and fondaparinux, also used as anticoagulation agents, must be administered by injection, which hinder their feasibility for long-term use.¹⁶⁶ One recently approved, novel agent, dabigatran etexilate, might address some of these limitations in patients with atrial fibrillation (AF) who take the drug for prevention of stroke and blood clots.¹⁶⁵ A novel class of drugs called factor Xa inhibitors exert their effects via a different mechanism of action, and may have the potential to address some of the limitations described above.

Factor Xa (FXa) is a serine protease that converts prothrombin to thrombin and is one of the final elements in the coagulation cascade.^{165,167} Because of FXa's central location in the common coagulation pathway, it acts at both the intrinsic and extrinsic coagulation pathways.¹⁶⁸ Direct FXa inhibitors bind to the active site of FXa, preventing it from interacting with its substrates, thereby inhibiting clot formation.¹⁶⁵

Rivaroxaban (Janssen Pharmaceuticals, Inc., a unit of Johnson & Johnson, Inc., New Brunswick, NJ, and Bayer AG, Leverkusen, Germany) is an orally administered, direct and selective inhibitor of FXa that is intended to prevent venous thromboembolism (VTE).¹⁶⁶ Unlike existing anticoagulation therapies such as heparin and warfarin, rivaroxaban has shown a predictable pharmacologic profile and few interactions with other drugs or foods, researchers reported.¹⁶⁶ It also has produced a predictable anticoagulation effect thus far without the need for dose adjustments or ongoing monitoring of the International Normalized Ratio (INR) through prothrombin time tests (PTT).¹⁶⁶ In July 2011, the U.S. Food and Drug Association (FDA) approved rivaroxaban (brand name Xarelto®) for once-daily administration to prevent DVT that can lead to PE in patients undergoing knee or hip replacement surgery.¹⁶⁹ In November 2011, FDA approved rivaroxaban for reducing the risk of stroke in people who have nonvalvular AF.¹⁷⁰

Apixaban (Eliquis™, Bristol-Myers Squibb and Pfizer, Inc., both of New York, NY) is an orally administered direct and selective FXa inhibitor that is being investigated for the treatment and prevention of VTE, including DVT and PE, as well as for the prevention of stroke in patients with AF.¹⁶⁵ Because apixaban does not induce or inhibit cytochrome P450 enzymes, both researchers and the drug's codevelopers have suggested that the agent will have a low risk of drug-drug interactions, relative to currently used anticoagulants.^{171,172} Additionally, apixaban may be characterized by dose-dependent efficacy and a wider therapeutic index than currently prescribed agents. The manufacturers claim that routine monitoring of clotting parameters or frequent dose adjustments are not required during the treatment regimen.^{165,172} The manufacturers state that apixaban is intended to be administered orally, dosed twice daily.¹⁷² According to a November 2011 press release, the manufacturers intended to file for FDA approval for stroke prevention in patients with AF by the end of 2011.¹⁷³

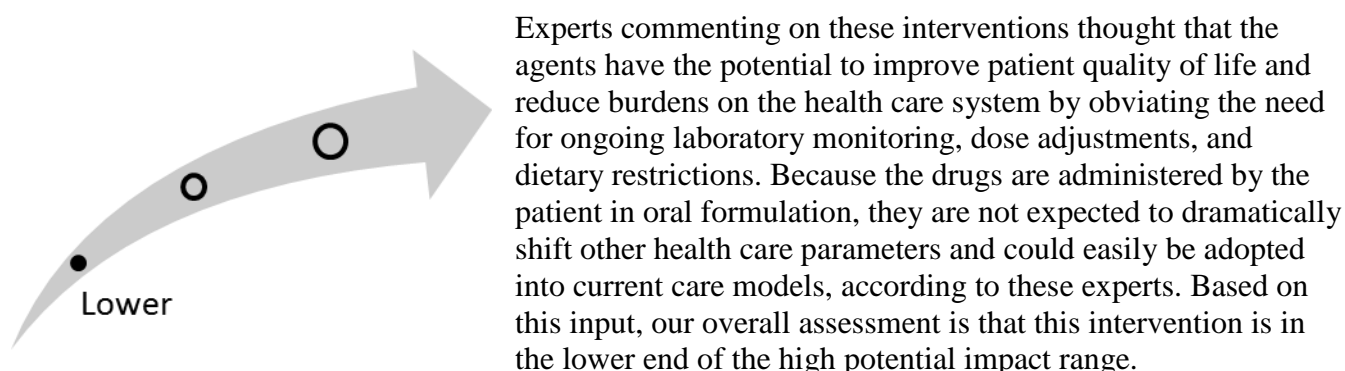
Edoxaban (Daiichi Sankyo Co., Ltd., Tokyo, Japan) is an orally administered direct FXa inhibitor that is being investigated for the prevention of venous thromboembolic events after major orthopedic surgery, prevention and treatment of recurrent VTE, and prevention of stroke in patients with AF.¹⁷⁴ According to its manufacturer, edoxaban is highly specific for FXa, which suggests that it would have

little effect on the enzymatic activities of other serine proteases.^{167,175} The manufacturer also states that the drug has a predictable pharmacokinetic and pharmacodynamic profile, which allows it to be dosed once daily.¹⁷⁵ The drug was approved in Japan in April 2011 for the prevention of VTE after major orthopedic surgery, but the company has stated that it does not intend to seek approval for this same indication in major markets such as the U.S. and Europe.¹⁷⁶ The company has stated that in these markets, it intends to concentrate its efforts on “completing phase III trials with the compound in the treatment of VTE and in AF.”¹⁷⁶

Clinical Pathway at Point of This Intervention

Patients undergoing orthopedic surgery are at a heightened risk for developing VTE, and because of this, it has become standard protocol to administer an anticoagulant (e.g., warfarin, heparin, low-molecular-weight heparin) to prevent VTE development.¹⁷⁷ Patients requiring chronic anticoagulation therapy for conditions such as AF are typically treated with oral anticoagulants, such as vitamin K antagonists (e.g., warfarin) or aspirin.¹⁷⁸ Recently, clinicians also gained the option of treating these patients with dabigatran, a direct thrombin inhibitor, or rivaroxaban, the first-approved FXa inhibitor.¹⁷⁹

Figure 12. Overall High Impact Potential: Factor Xa inhibitors for prevention and treatment of thromboembolism



Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on rivaroxaban.¹⁸⁰⁻¹⁸⁶ At the time of gathering expert comments, rivaroxaban was under consideration by FDA for approval, but had not yet been approved. Seven experts with similar backgrounds offered their perspectives on apixaban.¹⁸⁷⁻¹⁹³ Seven experts offered their perspectives on edoxaban.¹⁹⁴⁻²⁰⁰ Of the total pool of experts, two disclosed a potential conflict of interest, stating that they consult for several pharmaceutical companies that make anticoagulants. These potential conflicts of interest were balanced by the perspectives of other experts who did not report a conflict of interest.

Despite the availability of other anticoagulation agents, the limitations associated with these drugs represent an important unmet need, experts agreed. In particular, experts highlighted the current agents' unpredictable anticoagulation response, routine monitoring requirements, food and drug interactions, and impracticality for long-term use. Experts appeared to be confident that the new class of drugs has the potential to address these limitations. Their confidence was based on the well-understood mechanism of action through which these drugs exert their effects and on the extensive number of clinical trials that have been performed and reported on for the class. Though dabigatran's entrance to market somewhat tempered expert opinion on the importance of the unmet need, one research-based expert stated, “With the recent news of adverse events in elderly patients using dabigatran, there may be a particular need for another alternative to warfarin.”¹⁸⁹

Experts agreed that these agents have potential to affect several health system parameters, especially for those patients who are unable to take dabigatran for their conditions. Because the drug does not require the same ongoing laboratory monitoring that warfarin does, its infrastructure and testing needs (e.g., “Coumadin clinics”), staffing needs, and costs associated with monitoring would all be reduced if the agents become diffused, experts believe. If the class is associated with fewer adverse events or requires fewer dosing adjustments than existing agents, experts thought, this would reduce the number of physician visits patients require. Additionally, they did not expect that these drugs would require clinicians to take time to counsel patients on dietary restrictions, as they do for warfarin. Experts thought that these drugs would diffuse rapidly, because they could be easily incorporated into current health-system models. These experts were confident that both patients and clinicians would readily accept these agents, as one expert put it: “This would be a clear cut advantage over standard therapy: there would be a significant improvement in the quality of life of patients requiring chronic anticoagulation.”¹⁸⁵

Experts thought that the cost of taking one of these agents would be offset by a reduced need for ongoing monitoring and dose adjustments, although it is uncertain how this effect compares to the potential cost-benefit ratio of dabigatran. Some experts suggested that with the introduction of several new agents to the anticoagulation market, costs might be lowered to remain competitive within the market.

Valve Disorder Interventions

Intervention

Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation

Open surgical repair of the mitral valve—mitral annuloplasty—is considered the gold standard treatment for mitral valve disease. During mitral annuloplasty, the malformed portion of the valve leaflets is resected, and a rigid or semirigid ring is implanted to reinforce the annulus (a fibrous tissue ring around the mitral valve opening that supports the valve leaflets).²⁰¹ Percutaneous annuloplasty is a new, minimally invasive surgical approach intended to achieve the same therapeutic result as open surgery, but using catheter-based technique. Physicians implant catheters or rigid wires to reshape the mitral annulus from within the coronary sinus, a large vein located along the heart's outer wall between the left atrium and left ventricle and adjacent to the mitral valve.²⁰¹ In clinical trials, percutaneous annuloplasty procedures have typically been performed on patients under general anesthesia to facilitate the use of transesophageal echocardiography.²⁰¹

The Carillon® Mitral Contour System™, manufactured by Cardiac Dimensions, Inc. (Kirkland, WA), comprises a thin, flexible metal bridge or tether with a self-expanding anchor at each end.²⁰¹ The device is delivered to the coronary sinus by a catheter inserted in the jugular vein at the neck. After securing the distal anchor within the vein, the physician places tension on the delivery catheter to reshape the mitral annulus sufficiently to reduce the degree of mitral regurgitation (MR).²⁰¹ Typically, the device is not deployed if the application of tension does not sufficiently reduce MR. Then, the proximal anchor is released from the delivery catheter and secured in place, after which the delivery catheter is removed. This tension around the mitral valve annulus squeezes the mitral leaflets together to close the gap that may have developed due to heart enlargement.^{201,202}

In May 2011, Cardiac Dimensions announced the initiation of two new clinical trials using the Carillon Mitral Contour System.²⁰³ One trial will ascertain safety and efficacy of the device at 1, 3, 6, and 12 months by evaluating reduction in functional MR, heart size, and improvements in exercise capacity, and the other trial will be an extension of a recently completed trial.²⁰³

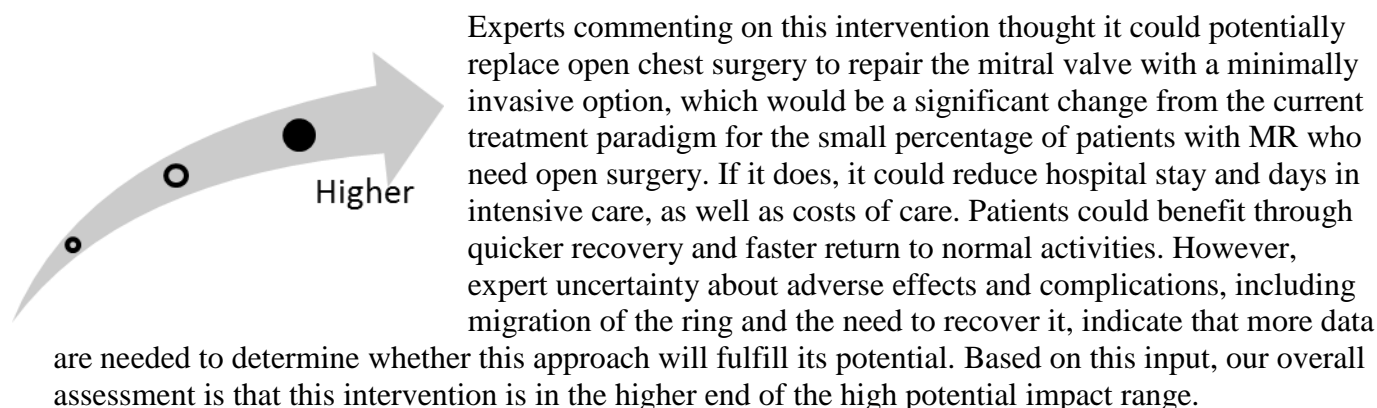
A 2009 trial of the Carillon device enrolled 48 patients, 30 of whom received the device. Eighteen patients did not receive the device because of access issues, insufficient acute functional mitral regurgitation (FMR) reduction, or coronary artery compromise. The major adverse event rate at 30 days was 13%; at 6 months, the degree of FMR reduction among five different quantitative echocardiographic measures ranged from 22% to 32%. Six-minute walk distance improved from a mean of 87 meters at baseline to 137 meters at 6 months after treatment ($p < 0.001$). Quality of life, measured by the Kansas City Cardiomyopathy Questionnaire, improved by more than 20 points from baseline to 6 months ($p < 0.001$).²⁰⁴

(Another company that had been developing a similar system, Viacor, Inc., Wilmington, MA, ended operations and suspended two phase II/III trials in spring 2011: NCT00815386 and NCT00787293.)

Clinical Pathway at Point of This Intervention

Current American College of Cardiology/American Heart Association (ACC/AHA) clinical guidelines recommend surgical mitral repair over mitral valve replacement in the majority of patients with severe chronic MR who require surgery. This is partly because surgical repair retains more natural tissue than total valve replacement and better preserves left ventricular function.²⁰⁵ Percutaneous annuloplasty would likely be used as an alternative to open surgical mitral annuloplasty in patients with dilated cardiomyopathy with a large annulus, especially patients at high risk of adverse events from open surgery.²⁰¹

Figure 13. Overall High Impact Potential: Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation



Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.²⁰⁶⁻²¹² Most experts agreed that the less invasive nature of this intervention and its potential application in patients who are not able to benefit from surgical repair of the mitral valve is important. Two clinical experts mentioned that the diversity in severity of MR and the fact that it differs from patient to patient limit the need for invasive surgery to a small percentage of patients, such as those with dilated cardiomyopathy and heart failure. So in terms of numbers, relatively few patients with MR need surgery.

A number of experts expressed concern about device implantation issues, potential adverse effects, and preliminary data that raise concerns about adverse events. One clinical expert indicated that in some patients, mitral valve repair is a transitory step, and its effect on the natural course of the disease process in dilated cardiomyopathy is not clear. However, the same expert also stated that for patients who need a second or third open-chest surgery, the proposed intervention is less invasive and may pose an advantage. An expert also indicated that if the device is approved and diffused, patients receiving it would need to be treated in facilities with specialized and “well trained” interventionalists capable of dealing with the problem of ring migration after intervention. Thus, adoption would be limited to specialized centers that could handle the technical challenge of the procedure and maintain proficiency given the small percentage of the patient population with MR who might be candidates.

Opinions about the cost per patient were divided among experts. Five experts commented that cost impact could be significant in terms of potential savings, but ultimately would depend on having good short-term and long-term outcomes, and being able to avoid open-chest surgery and reduce length of stay in hospitals. There was consensus among experts that this intervention could address the unmet need. Most agreed that the theoretical benefits of a less invasive valve repair procedure are very attractive but need to be balanced against adverse events and complications observed so far in trials. Experts also need more data to provide detailed answers of questions about health outcomes and efficacy.

Intervention

Transcatheter aortic valves (CoreValve and Sapien) implantation for treatment of severe aortic stenosis

The gold standard for treating aortic stenosis is open surgical replacement with a mechanical valve or a tissue valve obtained from cattle, pigs, or human cadavers.²¹³ However, open heart surgery requires cardiopulmonary bypass and is typically not an option for patients at high risk for surgical complications.²¹³ Thus, investigators have begun evaluating minimally invasive approaches to valve replacement to extend the therapeutic benefit of aortic valve replacement to high-risk surgical patients.²¹³

Medtronic, Inc. (Minneapolis, MN), developed the CoreValve® System, which is being investigated for the treatment of aortic stenosis in the U.S.²¹⁴ The system is intended for use in patients who are not surgical candidates or who are at high surgical risk.²¹³ The system features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame.²¹³ The bioprosthetic valve is deployed using an 18-French (Fr) delivery catheter with a set of disposable catheter-loading components.²¹³ According to the manufacturer, the implantation procedure lasts about 1 to 3 hours, and patients are typically sedated. The clinician guides a sheath into the heart, then threads a balloon catheter through the sheath into the heart. Once the balloon is positioned in the aortic valve, it is inflated, preparing the aortic valve for implantation of the CoreValve. Using imaging equipment, the clinician places the CoreValve over the diseased aortic valve. In some cases, the diseased valve is completely removed before placement of the CoreValve. The manufacturer claims that the CoreValve begins working immediately. The catheter is removed, and the incision is closed. The manufacturer states that the typical hospital stay following a transcatheter aortic valve Implantation (TAVI) procedure is 3 to 5 days.²¹⁵

CoreValve received Conformité Européenne (CE) mark for the CoreValve Percutaneous ReValving™ System for treatment of high-risk patients in May 2007.²¹⁶ In September 2010, Medtronic received the CE mark for the CoreValve delivery system with AccuTrak™ stability layer for TAVI.²¹⁶ Medtronic received an investigational device exemption for its CoreValve trial from the U.S. Food and Drug Administration (FDA) in October 2010 and has begun enrolling patients.^{216,217}

In a May 2011 press release, Medtronic stated the following, regarding results from a 2011 meta-analysis of data from 2,156 patients with severe aortic stenosis who were treated with the CoreValve System: “The results demonstrate positive patient outcomes based on procedural success rate (97.8 percent), vascular complication rate (2.9 percent), one-month stroke rate (1.9 percent), one-month survival rate (93.8 percent) and one-year all-cause mortality rate from five registries (17.1 percent).”²¹⁸

Edwards Lifesciences, LLC (Irvine, CA), developed the Sapien™ Transcatheter Heart Valve (THV) for potential use in patients with severe aortic stenosis who are at high surgical risk or who are not surgical candidates.²¹³ The bioprosthesis features a bovine pericardial tissue aortic valve affixed within a balloon-expandable cobalt-chromium alloy frame.²¹³ The bioprosthetic valves are available in 23 and 26 mm lengths.²¹³ The RetroFlex® and RetroFlex II™ delivery catheters are used to deploy the valve using femoral artery access, and the Ascendra™ delivery system is designed to implant the valve via minimally invasive surgery using a transapical approach.²¹³ Only the transfemoral approach has been evaluated by FDA for marketing approval at this time.²¹⁹

According to an informational guide published by the manufacturer, for implantation using the transfemoral approach, the patient is placed under general anesthesia. An incision is made in the patient's groin, where the physician places a sheath in the femoral artery. A balloon catheter is used to stretch the aortic valve opening. The replacement aortic valve is placed on the delivery system and crimped to allow insertion into the body through the sheath. Using fluoroscopy guidance, the valve and delivery system are inserted through the sheath and guided to the aortic valve. Once the new valve is positioned, the balloon is filled with liquid, expanding the new valve from its crimped mode to its functional mode. The valve is checked for proper function, the delivery system is removed, and the

incision is closed. The manufacturer states that the valve begins working immediately. The procedure is conducted in 1 to 3 hours, and the average hospital stay for a patient undergoing the TAVI procedure is 2 to 6 days.^{220,221}

In November 2011, the manufacturer announced that it had received approval from FDA for the transfemoral delivery of the Sapien transcatheter aortic heart valve for the treatment of inoperable patients with severe, symptomatic aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from correction of the aortic stenosis.²²² The company also stated the following conditions of approval: “As part of this approval, FDA has requested the implementation of two substantial post-approval studies. One study will follow patients already enrolled in The PARTNER Trial, and the second study will track new U.S. patients. The company anticipates the second study will be incorporated into a new national patient registry.”²²²

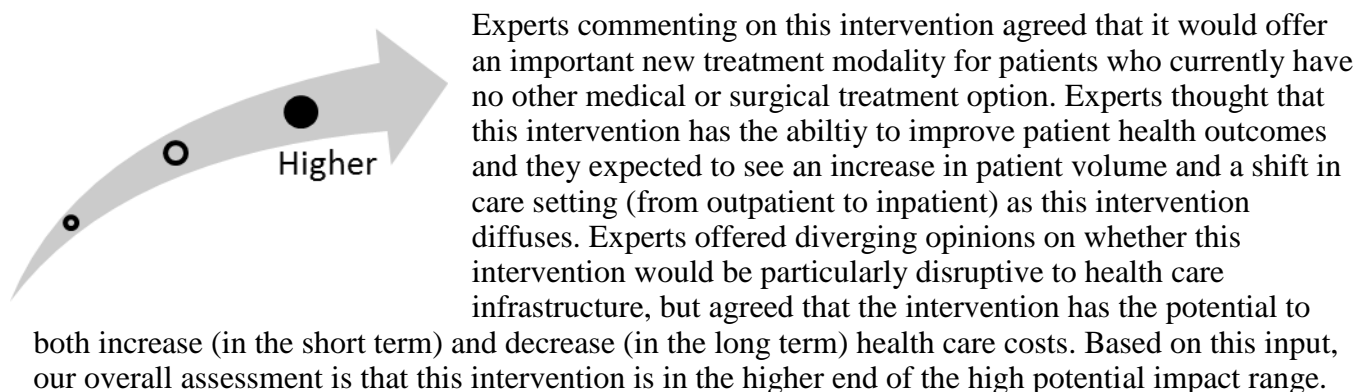
In an April 2011 press release, Edwards stated the following regarding results of the PARTNER trial, which were included in the FDA submission package:

In patients with aortic stenosis at high risk for surgery, transcatheter aortic valve replacement (TAVR) was non-inferior to surgical aortic valve replacement (AVR) for all-cause mortality at one year, 24.2 percent versus 26.8 percent, respectively. In addition, mortality at 30 days was lower than expected in both arms of the trial, with TAVR at 3.4 percent and AVR at 6.5 percent. The observed mortality in these AVR patients was lower than the thought risk of operative mortality of 11.8 percent... Both TAVR and AVR were associated with important but different peri-procedural hazards. The study demonstrated that major vascular complications and neurological events were more frequent with TAVR, while major bleeding and new onset atrial fibrillation were more frequent with AVR. Symptom improvement as measured by the New York Heart Association (NYHA) class and six-minute walk distance favored TAVR at 30 days and was similar to AVR at one year.²²³

Clinical Pathway at Point of This Intervention

In patients with aortic stenosis, medical therapy is prescribed to alleviate symptoms, which include chest pain, shortness of breath, and fainting.²¹⁶ According to 2006 guidelines by ACC/AHA, aortic valve replacement is considered the surgical treatment of choice for most adults with severe aortic stenosis.²²⁴ However, some patients are not candidates for surgical aortic valve replacement and therefore have a poor prognosis. TAVI is a new procedure intended to provide a less-invasive option for these patients, many of whom would have no treatment options otherwise.²¹⁶

Figure 14. Overall High Impact Potential: Transcatheter aortic valves (CoreValve and Sapien) implantation for treatment of severe aortic stenosis



Results and Discussion of Comments

Seven experts, with clinical, research, health system, and health administration backgrounds, offered perspectives on the CoreValve technology.²²⁵⁻²³¹ At the time of publication, expert comments on the Sapien technology had not been received. However, it is unlikely that expert opinion on the Sapien technology would differ dramatically from expert opinion on the CoreValve technology. One expert disclosed a potential conflict of interest, stating that he is assisting in implanting the CoreValve under an approved study protocol, but noted that he does not receive direct or indirect financial support for his participation.²²⁶ This expert's potential conflict of interest was balanced by the perspectives of other experts who did not have conflicts of interest.

Experts reached a firm consensus that the unmet need that this intervention purports to address is extremely important, in light of the large number of patients that will be affected, and the fact that no other therapies are available for this population. As one clinical expert stated: "There is no medical therapy for severe aortic stenosis. Those judged too high risk for surgical aortic valve replacement currently have no option other than repeated hospital admissions for heart failure or angina; their quality of life is dismal. TAVI offers the promise of improved quality of life and reduced hospital admissions."²²⁵

Experts were optimistic about this intervention's ability to meet the unmet need and improve patient health outcomes, mostly due to encouraging data from clinical trials, but also because no other options are available for this population. However, one clinical review cautioned that "The goal... is not to prolong life, but to improve the quality of life and reduce hospitalizations."²²⁵

Experts were divided in their opinion on whether this technology will markedly disrupt current health care infrastructure and patient management models. Nonclinical experts suggested, as one wrote, that "a large number of patients who were previously treated with medications would flow to the inpatient care settings and may put pressure on early adopters of the technology in terms of staff and facility."²³¹ However, clinical experts thought much less disruption would occur, with one writing: "The procedures will likely be done in the catheterization laboratory or a hybrid surgical OR, which are now quite common for a variety of reasons. The procedure is capable of being done under sedation and not general anesthesia; hospitalization is relatively short and the patient returns quicker to their own environment without needing long-term rehabilitation."²²⁶ Experts appear to agree that the greatest impact this intervention will have on patient management models is its potential to shift patients from the outpatient care setting to the inpatient setting.

Experts thought that clinicians who will perform this procedure would readily adopt this technology: "Despite increases in training required, clinicians would likely accept this intervention as an option for patients who previously did not have many options."²²⁷ Experts also generally expected patients to accept this procedure, because it offers a therapeutic option where previously none existed. As one clinical expert stated: "The chance to avoid hospitalization for heart failure and angina, and the chance to improve the quality of life of these patients makes acceptance and adoption of TAVI very likely."²²⁵ One expert, speaking from a systems perspective, offered a dissenting view, stating that "Patients may be reluctant to accept this as they have been told that they are high risk for surgery and may not fully appreciate the less invasive nature of this procedure, or may not be willing to risk subjecting themselves to any surgical procedure, no matter how minimally invasive."²²⁸

Expert opinion on how this intervention would affect health care costs is well summarized by the following comments: "Overall costs will increase as more patients elect to have this procedure," but "currently, this group of patients is often repeatedly hospitalized, particularly for heart failure or angina or syncope. There is a significant cost associated with that. TAVI will very likely reduce hospitalization. Further, TAVI will render patients more functional, perhaps delaying admission to nursing home or hospice facilities."^{225,227}

Intervention

Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation

Although open surgical repair of the mitral valve is considered the gold standard treatment for mitral valve disease, some patients are not candidates for surgery because of their high risk for complications. Thus, there is an unmet need for an intervention that offers an alternative to open surgical mitral valve repair.

Transcatheter mitral valve repair with the MitraClip® device (Abbott Laboratories, Abbott Park, IL) simulates the functional effects achieved by the Alfieri edge-to-edge surgical procedure, the standard open surgery repair procedure used for treatment of MR.²⁰¹ In the Alfieri procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening.²⁰¹ In a MitraClip procedure, the physician uses the MitraClip, a two-armed, flexible metal clip covered in polyester fabric, instead of sutures to help the mitral valve close more completely.²⁰¹

According to the manufacturer, the MitraClip system consists of a steerable guide catheter, including a clip delivery device, and the MitraClip implant.²³² To implant the MitraClip, a physician inserts the guide catheter into the femoral vein at the groin and threads it up to the heart and into the right atrium under fluoroscopic guidance in a cardiac catheterization lab.²⁰¹ To reach the mitral valve in the left atrium, the physician creates an opening in the septum, the wall that separates the right and left atrial chambers, with the needle-like dilator within the catheter. After transseptal puncture, the catheter is advanced into the left atrium and through the mitral valve as the clip is expanded. Using Doppler ultrasound to identify the optimal location for clip placement to correct valve leaks, the physician grasps and fastens the edges of the valve leaflets together with the MitraClip. Before releasing the implant from the clip delivery device for permanent placement, the physician confirms proper positioning of the MitraClip with further ultrasound scans. If the device positioning is acceptable, the physician releases the clip from the delivery device and removes the catheter.²⁰¹ In clinical trials of the device, patients were hospitalized for 1 to 2 days after the procedure for observation. Eventually, the procedure could be performed on an outpatient basis at experienced centers.^{233,234}

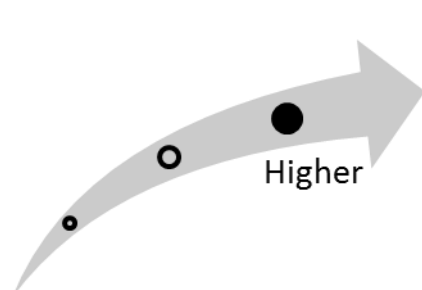
In March 2008, Evalve (acquired by Abbott) received CE mark approval to market the MitraClip system in the European Union for use as a nonsurgical option in patients with severe MR.²³⁵ The MitraClip is under evaluation in a phase III clinical trial in the U.S.²³⁶ In a April 2011 press release, the company reported the following data from the ongoing trial: “At two years after treatment, data from 279 patients from the EVEREST II trial demonstrated a clinical success rate of 51.7 percent for patients treated with the MitraClip device compared to a clinical success rate of 66.3 percent for surgery patients ($p = 0.04$) on an Intention-to-Treat (ITT) basis. These results compare with the one-year data, which demonstrated a clinical success rate of 55.2 percent for patients who received the MitraClip device, compared to a clinical success rate of 73.0 percent for surgery patients ($p = 0.0007$). The clinical success rate is defined as freedom from death, from surgery for valve dysfunction, and from moderate to severe MR (3+ or 4+).”²³⁷

Clinical Pathway at Point of This Intervention

Current ACC/AHA clinical guidelines recommend surgical mitral repair over mitral valve replacement in the majority of patients with severe chronic MR who require surgery. This is partly because surgical repair retains more natural tissue than total valve replacement and better preserves left ventricular function. Open surgical repair of the mitral valve is considered the gold standard treatment

for mitral valve disease, and use of the MitraClip device for catheter-based repair of the mitral valve would replace open surgical repair for treatment of MR in patients at high risk of complications from open surgery.

Figure 15. Overall High Impact Potential: Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation



Overall, experts commenting on this intervention thought that the MitraClip procedure has the potential to have a substantial impact on most parameters of the health care system, such as disrupting care models, increasing infrastructure and staffing requirements, shifting care setting, and requiring substantial clinician training; they were split on whether it would increase or decrease costs. Although several experts noted the need for longer-term safety data, experts generally believe this device has the potential to meet the need for minimally invasive interventions for treatment of MR. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this technology.²³⁸⁻²⁴⁴ One clinical expert stated that he has performed nonfunded research with the company that developed the MitraClip. This potential conflict of interest was balanced by the perspectives of the remaining six experts who had no conflicts of interest.

Experts strongly agreed that the unmet need for less invasive interventions for MR is important, based on both the prevalence of the disease and the risks that prevent some patients from undergoing open surgical repair. Although experts generally agreed that the underlying theory of replicating sutures with a device is sound, they were divided about whether this device would improve patient outcomes. Some experts, basing their opinions on early clinical data, posited that the device would be safer and offer a better quality of life for patients when compared with open surgery. However, several experts commented that the procedure might be associated with long-term risks, such as clotting or device malfunction, that will become clearer only after longer trials are completed. The clinical expert with research experience in this area stated, “The intervention can and does work, but in highly selected patients. Approximately 1/10 patients with MR are eligible for this procedure and approximately 70% of these selected patients will have a reasonably favorable outcome.”

Experts’ comments consistently concurred that the device has potential to affect the care model, treatment paradigm, and patient management. This intervention would be the first minimally invasive option for patients with MR and would provide an option for patients who are not candidates for open surgery. Second, because the procedure is minimally invasive and offers a faster recovery time, it has the potential to reduce the number of open surgeries performed, reduce use of cardiac care unit resources, and shorten hospital stays. Third, postoperative treatment plans are likely to be less complicated than for open surgeries.

Experts generally agreed that this intervention would affect care processes, including clinician training requirements, infrastructure needs, care setting, and staffing models. First, the transseptal puncture approach is considered to be a “high risk” technique that would require “substantial training” on the part of the interventional cardiologist. The clinical expert experienced in this procedure stated that it “requires a highly skilled team that communicates well. Not every interventional cardiologist or echocardiographer will be able to perform this procedure.” Second, staffing models would shift from surgical teams and the operating room to catheterization teams and the catheter and electrophysiology labs. Patient throughput would increase, and care associated with sternal incision and its subsequent

risks would decrease. In terms of cost, most experts thought that despite the initial high cost of the device (\$31,000), overall costs associated with the treatment of MR might ultimately decrease because of the device's potential to replace expensive open surgical procedures and reduce length of hospital stays.

Experts believe strongly that patients would accept this intervention, primarily because of its minimal invasiveness, faster recovery time, and reduced potential for adverse events. Experts noted that patients who are contraindicated for open surgery would welcome a treatment option when they had none before. While a couple of experts thought that clinicians would be open to accepting this procedure, most thought some reluctance from the medical community. First, some experts thought clinicians would be slow to adopt the intervention, because of the specialized training required to perform the procedure, especially until more and longer-term data become available. Second, because the device is “attempting to replace a gold standard, there may be resistance,” one expert wrote. One health-systems expert stated that this procedure is more likely to be adopted in “higher medical university centers and specialized surgery centers, because there will be appropriate skill sets and infrastructure available for this procedure. Smaller hospitals that do not have access to multiple cath labs and clinicians who do not have the skill set to perform this procedure might not be that inclined to adopt this intervention.”

Experts thought high potential for controversy exists, mainly because of the ongoing “turf wars” between interventional cardiologists and surgeons, but also because of the need for more clinical data and the risk associated with transseptal puncture.

Intervention

Transcatheter pulmonary valves (Melody and Sapien) for treatment of congenital pulmonary valve defects

Before the FDA approval of the Melody® Transcatheter Pulmonary Valve (Medtronic, Inc.) in January 2010 under humanitarian device exemption status, no minimally invasive alternatives to open surgical valve repair existed for patients with congenital pulmonary valve defects, and these patients had to undergo multiple open heart surgeries over their lifetimes to address the problem.²⁴⁵ Therefore, this intervention has the potential to address a significant unmet need.

The Melody valve is an artificial pulmonary valve that consists of a bovine jugular venous valve and a wire stent scaffold that supports the valve.²⁴⁶ A physician implants the artificial heart valve within the existing valve using a special delivery catheter that is inserted into the femoral vein and threaded up to the heart. The physician inflates the balloon catheter to expand the stent and place the valve, which begins functioning immediately. The procedure lasts about 1 to 2 hours and is performed under general anesthesia. Patients are typically hospitalized overnight after the procedure.²⁴⁵ According to the manufacturer, the Melody valve is designed to restore pulmonary valve function and delay (not replace) the need for invasive open heart surgery in patients with a dysfunctional right ventricular outflow tract (RVOT) conduit.²⁴⁷ The technology is indicated for use in pediatric and adult patients with a regurgitant or stenotic RVOT conduit that was at least 16 mm in diameter when originally implanted.²⁴⁷

The Melody valve is being investigated in clinical trials, including a postmarket surveillance study.²⁴⁸ In a 2011 clinical trial investigating the use of the Melody valve in 102 patients with RVOT dysfunction, researchers concluded, “The median peak systolic RVOT gradient decreased from 37 mmHg (29-46 mmHg) to 14 mmHg (9-17 mmHg, $p < 0.001$) and the ratio RV pressure/AoP decreased from 62% (53-76%) to 36% (30-42%, $p < 0.0001$). The median end-diastolic RV-volume index (MRI) decreased from 106 mL/m² (93-133 mL/m²) to 90 mL/m² (71-108 mL/m², $p = 0.001$). Pulmonary regurgitation was significantly reduced in all patients. One patient died due to compression of the left coronary artery. The incidence of stent fractures was 5 of 102 (5%). During follow-up [median: 352 days (99-390 days)] one percutaneous valve had to be removed surgically 6 months after implantation due to bacterial endocarditis. In 8 of 102 patients, a repeated dilatation of the valve was done due to a significant residual systolic pressure gradient, which resulted in a valve-in-valve procedure in four.”²⁴⁹

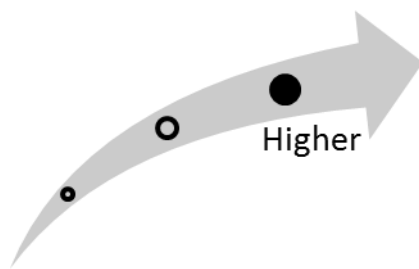
Another system, the Sapien Pulmonic Transcatheter Heart Valve (Edwards Lifesciences, LLC (Irvine, CA)), is commercially available only in Europe at this time, but late-phase clinical trials for purposes of achieving marketing approval in the U.S. are ongoing.²⁵⁰ The Sapien system consists of a bovine pericardial valve sutured to a stainless steel stent and is delivered using the RetroFlex transfemoral delivery system.²⁵⁰ The Sapien system serves a patient population with larger failed conduits because the valve (23 and 26 mm) and delivery systems (22 and 24 Fr diameter) are available in larger sizes than the Melody system.^{250,251}

Clinical Pathway at Point of This Intervention

In patients with congenital obstruction to the ventricular outflow tract (VOT), with severe pulmonary stenosis and an associated hypoplastic pulmonary annulus, severe pulmonary regurgitation, subvalvular pulmonary stenosis, or supravalvular pulmonary stenosis, surgery to replace the defective pulmonary valve is the recommended treatment. Surgical valve replacement is also preferred for most patients with dysplastic pulmonary valves who also have severe tricuspid regurgitation or who need a surgical maze procedure.^{252,253} The Melody valve procedure is intended to restore pulmonary valve

function and delay, not replace, the need for invasive open heart surgery in patients with a dysfunctional RVOT conduit.

Figure 16. Overall High Impact Potential: Transcatheter pulmonary valves (Melody and Sapien) for treatment of congenital pulmonary valve defects



Overall, experts commenting on this intervention were enthusiastic about the valve's ability to meet the need for a less invasive solution for patients with congenital pulmonary valve defects. The patient population affected is small, however. Because the intervention would reduce or delay the need for open heart surgeries, this device could have a significant impact on multiple health system parameters by enabling patients to avoid open heart surgery, moving a procedure from the surgical suite to catheter laboratory setting, reducing cost, and improving patient outcomes by reducing the number of open heart surgeries needed for these patients. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.²⁵⁴⁻²⁵⁹ One clinical expert has worked with Medtronic on trial design for an unrelated technology, and this potential conflict of interest was balanced by the perspectives of experts without conflicts of interest. The comments below relate only to the Melody valve and do not include perspectives on the Sapien valve.

Experts believe strongly that the need for minimally invasive pulmonary valve replacement is important, based on the risk associated with first-time or repeated open heart surgery. Furthermore, experts were somewhat confident that this implant would improve health outcomes, based on a sound underlying theory and trial data to date; however, some experts were eager to see the longer-term data that will come from the postmarket study to better understand the optimal use of this technology. Specifically, experts believe that this valve has the potential to both improve quality of life for patients and to delay the need for surgery for several years, which ultimately could reduce the number of surgeries a patient must undergo over a lifetime.

Experts believe that the device would have an impact on patient management and care models because it is minimally invasive. Two experts, however, pointed out that because surgical valve replacement would likely still eventually be required for these patients, the overall care model would remain unchanged, and this intervention would be added as an interim option for some patients within the existing treatment paradigm.

Experts thought that this intervention would result in significant changes in current health operations. Most experts anticipated a notable clinician learning curve in training and patient selection. One clinical expert noted that "threading percutaneously placed valves through the peripheral circulation seems to generally be difficult. The added difficulty of placing them into a venous conduit would seem to be nontrivial."

Second, the device would shift care from the surgical setting to the cardiac catheterization lab, although one clinical expert noted, "This is not a procedure that most adult cath labs are set up for." Similarly, interventional cardiologists would become a necessary addition to the care team. One clinical expert suggested that this intervention might promote the use of the hybrid catheterization/operating room models.

Third, experts generally agreed that health care processes would be affected, in that the procedure would likely decrease length of patient stay, which would enable an increased patient throughput and

volume (since patients who were too risky for surgery might now become treatable) and require less aftercare than open surgery.

Experts anticipated that this intervention would generally reduce costs of care associated with congenital pulmonary valve defects because it would likely be less expensive than open surgery, although this would be affected by the device price, and length of stay would be shorter than open surgery. If the valve significantly delays the need for repeated open heart surgeries, financial burden would also be reduced over the lifetime care of the patient. Because this intervention is less invasive and might be less risky than open surgery, most experts thought, clinicians would readily and rapidly accept the intervention as an option. Some experts thought a small amount of controversy would be generated, based on the ongoing “turf wars” between cardiac interventionalists and surgeons and the lack of long-term safety and durability data.

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