

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 03: Cardiovascular Disease

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA290-2010-00006-C

Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

December 2014

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. HHSA290-2010-00006-C). 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 close to diffusion into practice in the United States. 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 interventions that experts deemed, 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 6 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 horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 03: Cardiovascular. (Prepared by ECRI Institute under Contract No. HHSA290-2010-00006-C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2014. <http://effectivehealthcare.ahrq.gov/index.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 emerging technologies and innovations in health care and to create an inventory of interventions 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 analyzing 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 use 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 Interventions 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 email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

David Meyers, M.D.
Acting Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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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 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

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 a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) 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 information on topics and issuing topic 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 150 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

(COIs). 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 five to 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 designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential 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 having potentially 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 five topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for expert comment before November 4, 2014, in this priority area; *and* (3) we received five to seven sets of comments from experts between January 1, 2014, and November 13, 2014. (Fifty-six topics were being tracked in this priority area as of November 4, 2014.) We present four summaries on four topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts’ comments. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by interventions within that disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 03: Cardiovascular

Topic	High-Impact Potential
1. * Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia	Moderately high
2. * Percutaneous left atrial appendage occlusion (Watchman device) for prevention of atrial fibrillation–associated stroke	Moderately high
3. * Portable Freedom Driver for in-home support of the Total Artificial Heart	Lower end of the high-impact-potential range
4. Riociguat (Adempas) for treatment of pulmonary artery hypertension	No high-impact potential at this time; archived in horizon scanning system on basis of experts’ comments
5. * Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	Moderately high

Discussion

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, and affect costs and care delivery. Most of the innovations being tracked, as well as the innovations deemed by expert comments to have potential for high impact, pertain to cardiovascular devices that

provide support for end-stage heart failure (HF) or address valve problems, arrhythmias, stroke, and treatment-resistant hypertension. Only one pharmaceutical, lomitapide, was deemed as having potential for high impact.

Prior Potential High Impact Topics Archived

- **Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy:** In the June 2014 High-Impact Interventions report (and earlier high-impact reports), commenters were optimistic that this intervention has potential to improve patient health outcomes by reducing complications associated with lead-based ICDs that carry a high risk of morbidity and some mortality. Some experts suggested that this device's limited pacing capabilities could temper widespread diffusion and impact. FDA approved the S-ICD in September 2012. This intervention has been diffusing for more than 2 years and, therefore, no longer meets criteria for tracking and has been archived in the horizon scanning system.
- **Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis:** In the June 2014 High-Impact Interventions report (and earlier high-impact reports), commenters suggested that this device could offer an important and effective new treatment modality for patients who have no other effective medical options and are not candidates for open surgery. Experts generally agreed on a high potential for this intervention to disrupt health care infrastructure and patient management, citing the need for significant capital and operational support for centers not equipped to perform the procedure. FDA approved the first transcatheter aortic valve implantation (Sapien device, Edwards LifeSciences Corp., Irvine, CA) in November 2011. CoreValve became the second transcatheter aortic valve approved by FDA, which did so in January 2014; it initially had characteristics differentiating it from Sapien. However, the next-generation Sapien device emerged and the main factors differentiating CoreValve from its predecessor no longer exist. This procedure has been diffusing for more than 2 years and, therefore, no longer meets criteria for tracking and has been archived in the horizon scanning system.

Eligible Topic Deemed Not High-Impact

- **Riociguat (Adempas) for treatment of pulmonary artery hypertension:** Riociguat (Bayer AG, Leverkusen, Germany) is a soluble guanylate cyclase stimulator intended for treating patients who have pulmonary artery hypertension (PAH). Riociguat purportedly vasodilates pulmonary and systemic arterial vascular beds; it is intended for use as monotherapy or as an add-on therapy to endothelin-receptor antagonists. Experts commenting saw no potential for high impact because of its high cost and the availability of other pharmacotherapies to treat PAH. In light of experts' comments, this topic is being archived in the horizon scanning system.

Topics Deemed High-Impact

We present four interventions that experts who commented thought have potential for high impact. They are devices to treat atrial fibrillation-associated stroke, HF, cardiac valve disorders, and a drug to treat a genetic disorder.

Atrial Fibrillation–Associated Stroke

A serious complication of atrial fibrillation (AF) is ischemic stroke and patients with AF have a four to five times greater risk of stroke than other individuals, after all standard stroke risk factors are accounted for. Stroke risk is high in AF because thrombi form in the atria or, more commonly, in the left atrial appendage, and circulate systemically, traveling to the brain to cause stroke. These thrombi or clots can be prevented through pharmacologic therapy. Antithrombotic agents include vitamin K antagonists, aspirin, low-molecular-weight heparin, and oral anticoagulants. However, clinical experts estimate that from 14% to 44% of patients with AF have bleeding risks that preclude them from taking anticoagulants. Additionally, use of the standard and lowest cost anticoagulant therapy, warfarin, requires frequent monitoring, dosage adjustments, and dietary restrictions. Warfarin discontinuation rates are an estimated 32% per year. Although more recent, new anticoagulant alternatives exist (e.g., apixaban, dabigatran, rivaroxaban) that eliminate the need for routine monitoring and dietary restrictions, these therapies have other drawbacks. The drawbacks include nonhemorrhagic side effects, potential drug-drug interactions, and the fact that no antidote to the drugs is available in the event of uncontrolled bleeding. Therefore, an unmet need exists for better and safer treatments for AF-associated stroke.

Percutaneous Left Atrial Appendage Occlusion (Watchman) for Prevention of Atrial Fibrillation–Associated Stroke

- **Key Facts:** The Watchman[®] LAA Closure Technology is a device that is implanted in the patient's left atrial appendage (LAA) to occlude its opening and prevent thrombi from entering systemic circulation. The device may be an alternative to anticoagulant therapy in patients with AF. The device was developed by Atritech (Minneapolis, MN), which Boston Scientific Corp. (Natick, MA) acquired in 2011. In December 2013, the Circulatory System Devices Panel of the U.S. Food and Drug Administration's (FDA's) Medical Devices Advisory Committee voted 13-1 that the device's benefits outweigh its risks and recommended marketing approval for the device to reduce the risk of embolic stroke in patients with AF. It was the second time the device had been considered by an FDA panel. In mid-June 2014, the company announced at an investor conference that FDA had just required the device to go before a third FDA advisory panel before a final decision could be made. In October 2014, the Circulatory System Devices Panel voted 6-5 (with 1 abstention) that the benefits outweigh the potential risks. The panel also voted 12-0 on a reasonable assurance of safety, but 6-7 against on a reasonable assurance of effectiveness. A final FDA decision is pending. The device was Conformité Européenne (CE) marked in 2005.

In November 2014, Reddy and colleagues reported 4-year followup efficacy data from the PROTECT AF trial. Investigators observed primary efficacy event rates in the device and control groups of 2.3% and 3.8%, respectively. Investigators reported the most frequent adverse events were serious pericardial perfusion and major bleeding. In March 2013, the manufacturer reported results from a confirmatory study requested by FDA. The PREVAIL trial evaluated safety and efficacy of the device compared to warfarin therapy with three co-primary endpoints in 407 patients. In the first co-primary endpoint, the manufacturer reported the adverse event rate was 2.2%, which met the pre-established threshold for safety. The second co-primary endpoint did not meet prespecified criteria for efficacy of all stroke, cardiovascular death, and systemic embolism at 18 months. The third co-primary endpoint met prespecified criteria for occurrence of late ischemic stroke and systemic embolism at 18 months.

Costs associated with the Watchman device have not been established in the United States. Based on estimates from the United Kingdom, total costs at December 2014 exchange rates were approximately \$17,740, which included device cost of \$8,320 and \$9,420 for the implantation procedure.

- **Key Expert Comments:** Experts commenting on this intervention generally agreed that data showed it could reduce stroke incidence in patients with AF. However, several experts noted that it would not completely eliminate the need for long-term anticoagulant therapy. Given the lack of patient adherence to preventive anticoagulation therapy, experts suggested that the device has potential to reduce the need for anticoagulant therapy. Experts generally anticipated widespread adoption by both patients and clinicians. However, some experts noted insufficient information regarding long-term safety and efficacy. The initial cost of device implantation might be offset if it prevents stroke and obviates or decreases the need for anticoagulation therapy, experts commented. Overall, experts opined that this intervention has potential to fulfill the unmet need of safe and efficacious treatments for preventing stroke in patients with AF, but they desired longer-term outcomes data.
- **High-Impact Potential:** Moderately high

Genetic Disorder: Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder that causes accumulation of high levels of low-density lipoprotein (LDL) cholesterol (LDL-C) due to a defect on chromosome 19 that impairs the LDL receptor's ability to remove LDL from the bloodstream. According to the National Human Genome Research Institute, FH can cause premature onset of coronary artery disease, myocardial infarction, and cardiac-related death. FH is an autosomal dominant disorder, meaning a defect needs to be present on only one of two number 19 chromosomes for the person to be affected. Patients who have inherited only one defective LDL receptor gene are said to have heterozygous FH. In rare instances, the genetic defect is inherited from both parents, causing a genetic condition known as homozygous (Ho) FH, which is more severe than heterozygous FH. According to the Familial Hypercholesterolemia Foundation, heterozygous FH occurs in approximately 1 of every 500 persons and HoFH occurs in approximately 1 of every 1 million persons in the United States, or an estimated 360 persons. In individuals with HoFH, heart attack and death often occur before age 30; thus effective treatment is needed to prevent premature death.

Lomitapide (Juxtapid) for Treatment of Homozygous Familial Hypercholesterolemia

- **Key Facts:** Lomitapide (Juxtapid™) is a microsomal triglyceride transfer protein inhibitor that was FDA approved in December 2012 as a daily oral therapy for treating HoFH. In the trial (n=29) that served as the basis for the approval, Cuchel et al. (2013) reported that lomitapide at a median dose of 40 mg per day reduced LDL-C concentrations by a mean of 50% at 26 weeks from baseline. By week 56, LDL-C concentrations were reduced by 44% (95% confidence interval [CI], -57% to -31%; p<0.0001). At week 78, LDL-C concentrations were reduced by 38% (-52% to -24%; p<0.0001). The most commonly reported adverse events were gastrointestinal symptoms. Four patients had aminotransaminase levels measured at more than five times the upper limit of normal; the increase resolved after dose reduction or temporary halt of lomitapide therapy. No patient permanently stopped lomitapide because of liver abnormalities.

Retail prices for a 30-day lomitapide supply are more than \$29,000 (as of December 2014) with the use of a coupon. Thus, the annual per-patient cost is more than \$348,000.

The manufacturer offers a support program to help patients who require financial support. Representative, private, third-party payers that include lomitapide in their drug formularies typically have preauthorization and step-therapy policies in place that govern coverage of the drug. Some payers place quantity limits on the drug and require annual recertification and documentation of patients' positive clinical response from lomitapide before approving prescription renewals. The company reports continued quarterly U.S. market growth, with plans for further expansion in the international market. However, the initial annual sales projections were reduced because of patient discontinuation and lower-than-anticipated growth rates in the U.S. market.

- **Key Expert Comments:** Experts generally agreed that lomitapide has a moderate to high potential to fill the unmet need for effective treatment for HoFH, given that it may serve as a bridge between conventional lipid-lowering drugs, such as statins, and invasive treatments, such as apheresis, which is costly, labor-intensive, and may not be readily accessible to all patients with this rare condition. Experts agreed that lomitapide would likely be adopted widely by both patients and clinicians for the targeted population, but noted cost to be a major barrier to acceptance. Experts generally commented that this intervention could have a substantial impact in terms of cost, because of the long-term treatment requirements for patients with HoFH. Most experts noted that this drug has potential to reduce the need for invasive procedures if proved to be effective in the long term.
- **High-Impact Potential:** Moderately high

Heart Failure

HF adversely affects quality of life as well as life expectancy and can develop from any condition that overloads, damages, or reduces heart muscle efficiency, impairing the ventricles' ability to fill with or eject blood. In 2009, 1 in 9 death certificates mentioned HF, and it was the underlying cause in 56,410 deaths. Based on data from 2007 to 2010 from the National Health and Nutrition Examination Survey, 5.1 million people older than age 20 years in the United States have HF. Approximately 50% of people with HF die within 5 years of diagnosis. HF prevalence 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 of patients with coronary artery disease, an increasing population of aging patients, and significant advances in the control of other potentially lethal diseases. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030, and costs will increase 120%. The estimated cost of HF in the United States in 2013 was \$32 billion. Because of the clear unmet need for effective therapies for HF and its underlying causes, many new drugs, biologics, and devices are under study for treating patients who have the condition.

Portable Freedom Driver for In-Home Support of the Total Artificial Heart

- **Key Facts:** The Freedom[®] Driver System, made by SynCardia Systems, Inc., of Tucson, AZ, is a wearable, pneumatic, portable driver under development to enable at-home support for the company's temporary Total Artificial Heart (TAH-t) in patients awaiting a heart transplant. In October 2004, FDA approved the TAH-t as a bridge to transplantation with use of a traditionally powered conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart. It is indicated for use in cardiac transplant-eligible patients at risk of imminent death from nonreversible biventricular failure. A portable driver system that would enable patients

to be discharged to home care to await a suitable donor heart would address a significant unmet need for the relatively small number of people in this patient population.

The battery-powered Freedom Driver System is intended to serve this purpose. It weighs 13.5 lb and is carried by the patient in a backpack or shoulder bag. As with conventional, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the patient's 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. Literature searches have not identified any completed, published clinical trials using the Freedom Driver System as of November 2014; however the company submitted data to FDA from a premarket approval trial. In July 2014, a company press release reported results from 106 patients in that trial (the Freedom PMA trial). The company reported, "The SynCardia Total Artificial Heart with the Freedom Drive System allowed 75% of those patients to be discharged from the hospital, while 86% of the 106 patients either were bridged to heart transplants or were alive and supported by the SynCardia Total Artificial Heart and the Freedom driver as of June 30, 2014."

In June 2014, FDA approved the Freedom Driver "for use with the SynCardia temporary Total Artificial Heart as a bridge to transplantation in cardiac transplant candidates who are clinically stable." Costs for the Freedom Driver System have not been reported. The total cost of care for patients with artificial hearts using the portable driver might be lower than that of hospitalized patients with artificial hearts, because inpatient stay is shortened.

- **Key Expert Comments:** Although this intervention is expected to have a significant impact on quality of life for patients with a TAH-t and may reduce health care costs associated with lengthy hospital stays while awaiting a heart transplant, the patient population for which this device is intended is small, which tempers its overall potential impact on the health care system, experts thought. However, they also thought that shifting care from the inpatient to the outpatient setting would be a very important effect of this intervention. Several experts commented that a shift to home care could potentially reduce costs for patients awaiting heart transplantation. However, other experts thought that the cost of equipment and home nursing care would be similar to inpatient care.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Valve and Structural Disorders

Mitral regurgitation (MR) is defined broadly as a backward flow of blood from the heart's left ventricle into the left atrium during contraction. MR can be divided into two major categories: primary, or organic MR, and secondary, or functional MR (FMR). FMR is associated with poor long-term survival, and its presence in patients with ischemic and dilated cardiomyopathy is an independent risk factor for cardiovascular morbidity and mortality. According to Mayo Clinic investigators, without treatment, severe MR can lead to congestive HF or potentially life-threatening cardiac arrhythmias. Significant MR occurs in an estimated 1% to 2% (about 4 million) of the U.S. population. More than 250,000 cases of significant MR are diagnosed each year in the United States and about 50,000 people undergo some type of surgery for the disease, according to one manufacturer in the field.

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 standard open-surgery repair 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 deployed through a catheter, rather than using sutures during open surgery. In 2014, Kar and colleagues reported 5-year outcomes from 78 patients with severe MR and high risk for surgical mortality who received the MitraClip. Investigators reported a 5-year survival rate of 44% and reduced symptoms in 83% of surviving patients. In 2013, Pleger and collaborators reported 1-year outcomes from 59 patients with severe, symptomatic MR and reduced ejection fraction who received MitraClip. Procedural efficacy was measured by the reduction in MR and improvement in New York Heart Association (NYHA) functional classification. Investigators reported that device implantation was associated with reduced MR and improved NYHA functional class, translating into improved 6-minute walk test distance. Followup echocardiography suggested a reversal in heart enlargement, with reduced left atrial volume and left ventricular end-systolic diameter and increased left ventricular ejection fraction (LVEF). These results were consistent with outcomes of a subgroup of 25 patients with severely reduced LVEF ($23\pm 2\%$), suggesting that sicker patients also reaped a benefit from MitraClip. Investigators reported 30-day mortality of 2.9%.

In October 2013, FDA granted marketing approval for the MitraClip delivery system for treating significant symptomatic degenerative MR. After approval, Abbott requested a new technology add-on payment from the U.S. Centers for Medicare & Medicaid Services (CMS). In August 2014, CMS published a decision memo that outlines coverage of the device and procedure under its Coverage with Evidence Development process. Hospitals reporting device costs to ECRI Institute's PriceGuide database reported a cost range of \$25,000 to \$30,000 for the valve kit.

- **Key Expert Comments:** Experts commenting on this technology generally agreed this procedure addresses a considerable unmet need and has the potential to improve patient health. However, most experts opined that more data concerning safety and long-term outcomes are needed, citing the potential for adverse events and the technically difficult nature of the procedure. Experts were split on whether this technology would disrupt health care delivery. Some experts believe it would not because the infrastructure for transcatheter heart procedures is already in place, while other experts believe that an increase in case volume might disrupt health care delivery. The majority of experts believe use of the MitraClip will increase health care costs but were not sure if those costs could be offset by a reduced need for other therapy for this population. They said longer-term data are needed to determine this. Overall, experts opined that the benefits of this intervention outweigh the risks.
- **High-Impact Potential:** Moderately high

Atrial fibrillation–Associated Stroke Intervention

Percutaneous Left Atrial Appendage Occlusion (Watchman) for Prevention of Atrial Fibrillation–Associated Stroke

Unmet need: Patients with atrial fibrillation (AF) are at high risk of developing stroke due to thrombi forming in the left atrial appendage (LAA).¹⁻⁴ Anticoagulant therapy is used in an attempt to prevent stroke in patients with AF, but an estimated 14% to 44% of patients with AF have bleeding risks that preclude them from taking anticoagulants.^{1,5} Additionally, with standard warfarin therapy, the need for frequent monitoring, dosage adjustments, and dietary restrictions make it a less-than-optimal therapy and discontinuation rates are estimated to be about 32% per year.⁶ Although newly approved alternatives (e.g., apixaban, dabigatran, rivaroxaban) eliminate the need for routine monitoring and dietary restrictions required with warfarin, these therapies have other drawbacks, including nonhemorrhagic side effects, potential for drug-drug interactions, and no approved antidote in the event of uncontrolled bleeding.^{7,8}

Intervention: The Watchman device is a permanent implant that is placed in the LAA to prevent strokes in patients with AF. Stroke prevention is accomplished by occluding the LAA opening to prevent clots that have formed in the LAA from entering circulatory system.⁹ The Watchman LAA Closure Technology consists of three components: a delivery catheter and transseptal access sheath, which is used to access the LAA and serves as a conduit for the delivery catheter; a self-expanding nitinol frame with a permeable polyester fabric that is preloaded within the delivery catheter; and fixation barbs on the frame that allow the device to be secured in the LAA. Once the device is expanded, the fabric covers the atrium-facing surface of the device. The system is available in five sizes (i.e., 21, 24, 27, 30, and 33 mm).^{9,10} Transesophageal echocardiography performed before the procedure allows clinicians to assess the LAA anatomy to determine which of these sizes is appropriate for the patient.¹¹

Implantation is performed during a percutaneous catheterization procedure, using a standard transseptal technique and fluoroscopic guidance. According to the manufacturer, the implantation procedure lasts about 1 hour and can be done under local or general anesthesia. Patients can typically leave the hospital 24 hours after the procedure, but require anticoagulant therapy.¹¹ A minimum of 45 days of warfarin therapy after device implantation is required for patients in whom warfarin is not contraindicated. For patients who have contraindications to warfarin anticoagulation, the manufacturer recommends treatment with 75 mg clopidogrel and an adult aspirin dose daily for up to 6 months, followed by a once-daily adult aspirin dose indefinitely.¹⁰

Clinical trials: In November 2014, Reddy and colleagues reported results of a 4-year followup from the PROTECT AF trial. Investigators observed primary efficacy event rates in the device and control groups of 2.3% and 3.8%, respectively.¹² In patients in whom the Watchman device was implanted, investigators observed cardiovascular and all-cause mortality rates of 1.0% and 3.2%, respectively.¹² According to the manufacturer, additional 4-year safety results observed in patients who had received the Watchman device in the PROTECT AF trial include all-stroke (1.5%), hemorrhagic stroke (0.2%), and disabling stroke (0.5%).¹³ Investigators reported the most frequent adverse events to be serious pericardial perfusion and major bleeding in both the device and control groups.¹²

In March 2013, the manufacturer reported results from a confirmatory study requested by the U.S. Food and Drug Administration (FDA). The PREVAIL trial (n=407) evaluated safety and efficacy of the device compared with warfarin therapy for three co-primary endpoints. The manufacturer reported an adverse-event rate of 2.2%, with an upper bound on the confidence interval (CI) of 2.62% versus a prespecified threshold of 2.67%. The second endpoint did not meet prespecified criteria for efficacy of all stroke, cardiovascular death, and systemic embolism at 18

months. The third endpoint met pre-specified criteria for occurrence of late ischemic stroke and systemic embolism at 18 months. The observed adverse-event rate in the device group was 0.0253 per 100 patient years (CI upper bound 0.0268, vs. prespecified 0.0275).¹⁴ All patients are enrolled in a 5-year long-term followup analysis.

Manufacturer and regulatory status: The Watchman device was developed by Atritech, Inc. (Minneapolis, MN),¹⁵ which was acquired by Boston Scientific Corp. (Natick, MA) in 2011.¹⁶ The device is limited to investigational use in the United States.¹⁵ Atritech filed a premarket approval application (PMA) with FDA in 2008.¹⁷ In 2010, FDA “requested that a confirmatory study be conducted to further substantiate the safety and effectiveness of the Watchman LAA Closure Technology in patients with AF at risk of stroke and eligible for anticoagulation therapy.”¹⁸

Boston Scientific submitted an amended PMA to FDA, basing its application on the results of the PREVAIL trial and earlier trials. In December 2013, the Circulatory System Devices Panel of FDA’s Medical Devices Advisory Committee voted to recommend that FDA approve the Watchman device to reduce the risk of embolic stroke in patients with AF.¹⁹ The panel voted 13-1 in favor of approval for each of three criteria: (1) that Watchman’s benefits outweigh its risks, (2) that reasonable assurance of Watchman’s safety exists, and (3) that reasonable assurance of Watchman’s efficacy exists. On June 17, 2014, the company announced at an investor conference that FDA had just rendered a decision requiring the device to go before a third advisory panel for consideration before a final decision could be made.²⁰ In October 2014, the FDA advisory panel voted 6-5 (with 1 abstention) that the benefits outweigh the potential risks. The panel also voted 12-0 on a reasonable assurance of safety, but 6-7 against on a reasonable assurance of effectiveness.²¹ The company anticipates a decision in the first half of 2015.²²

The device received a Conformité Européenne (CE) mark, allowing marketing in Europe, in 2005, and was commercialized outside the United States in 2009. In 2012, the European Union expanded indications for Watchman to include use of the device in patients in whom warfarin therapy is contraindicated.^{10,23} Boston Scientific is also developing a next-generation Watchman device that purportedly reduces the potential for damage leading to pericardial effusion.²⁴

Diffusion: If approved for marketing, the device will likely compete with anticoagulant therapy. The Watchman device may also compete with surgical exclusion of the LAA or percutaneous LAA occlusion performed with the FDA-cleared Lariat® suture delivery device.^{25,26} Additionally, several investigational percutaneous LAA occlusion devices may compete with the Watchman device if approved in the United States. These devices include the Coherex Wavecrest™ LAA occluder system²⁷ and the Amplatzer™ cardiac plug.²⁸

Costs for LAA occlusion with the Watchman device have not been established in the United States. In the United Kingdom, total costs for the Watchman implantation procedure and device are estimated at about £11,400 with the device costing approximately £5,300, and the implantation procedure costing approximately £6,000.²⁹ At December 2014 currency exchange rates, those estimated total costs would be about \$17,909 including \$8,322 for the device and \$9,423 for the implantation procedure.³⁰ A 2012 Canadian economic evaluation comparing cost-effectiveness of LAA occlusion devices and anticoagulants cited the average cost of the Watchman device as \$8,500; the fees attributed to anesthesia, nursing, physician, a 1-night hospital stay, and transesophageal echocardiogram performed at time of procedure and twice during followup visits totaled \$5,246; thus, total cost estimated in Canada in 2012 for the procedure, including the device, was \$13,746.³¹

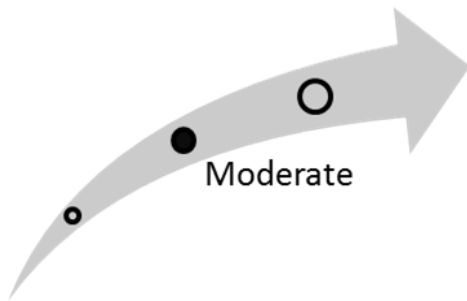
At this time, the U.S. Centers for Medicare & Medicaid Services (CMS) does not have a national coverage determination for other LAA occlusion devices, and no coverage determination is in process at this time for LAA occlusion with the Watchman device.

ECRI Institute routinely searches of a group of representative, private third-party payers that publish their coverage policies online and found a number of payers that consider percutaneous or transcatheter LAA occlusion with the Watchman and/or other similar devices to be investigational or experimental and, therefore, deny coverage for the procedure. Payers that deny coverage include Aetna,³² Anthem,³³ Blue Cross Blue Shield (BCBS) of Alabama,³⁴ BCBS of Massachusetts,³⁵ BCBS and BlueCare Network of Michigan,³⁶ BCBS of North Carolina,³⁷ BCBS of Tennessee,³⁸ CIGNA,³⁹ Empire BCBS,⁴⁰ HealthNet,⁴¹ Regence,⁴² and UnitedHealthcare.⁴³

Clinical Pathway at Point of This Intervention

A serious complication of AF is ischemic stroke.^{1,2} Risks for ischemic stroke after all standard stroke risk factors are accounted for are four to five times greater in patients with AF than other individuals.² Stroke risk is high in AF because thrombi form in the atria or, more commonly, in the LAA, enter circulation, and can travel to the brain.^{3,4} Thromboembolism is prevented through antithrombotic pharmacologic therapy. Guidelines recommend that the choice of antithrombotic drug be based on the absolute stroke and bleeding risks and the patient's relative risks and benefits.¹ Antithrombotic agents include vitamin K antagonists, aspirin, low-molecular-weight heparin, and the oral anticoagulants apixaban, dabigatran, and rivaroxaban.^{1,8,44} The Watchman may potentially be positioned as an alternative to anticoagulant therapy for stroke prevention in patients with AF.⁹

Figure 1. Overall high-impact potential: percutaneous left atrial appendage occlusion (Watchman) for prevention of atrial fibrillation–associated stroke



Overall, experts commenting on this topic agreed that it could reduce stroke incidence in patients with AF. However, experts noted that it would not eliminate, but might reduce the need for long-term anticoagulant therapy. Experts thought lack of long-term safety and efficacy data was the most significant barrier to otherwise anticipated widespread patient and clinician adoption. Experts generally agreed that initial costs associated with this intervention could be alleviated if the device improves patient medication adherence and reduces incidence of stroke. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.⁴⁵⁻⁵⁰ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Overall, the experts agreed that AF treatment options are limited to prevent and reduce stroke incidence. The Watchman device has the potential to improve patient health outcomes, experts agreed. Several cited the device's potential to reduce dependency on anticoagulant therapy.^{47,49,50} However, they also noted that it would not completely eliminate the need for long-term anticoagulant therapy. One expert with a health systems perspective opined,

“The intervention is really more of a supplemental treatment option as it does not eliminate the need for warfarin therapy (current standard of care) but rather acts as a fail-safe should clots persist despite the treatment option.”⁵⁰

Acceptance and adoption: Experts generally anticipated widespread adoption by both patients and clinicians. However, some noted insufficient information regarding long-term safety and efficacy. One clinical expert anticipated wide clinical acceptance, but also listed cost and eligibility as potential barriers.⁴⁵ An expert representing a research perspective commented, “Long-term follow-up data that support the safety and efficacy of Watchman is still insufficient. Non-inferiority design and the composite outcome measures used in the trials did not provide firm evidence to show Watchman is better than current standard of care.”⁴⁹ Patients would be willing to accept this as a minimally invasive procedure, the experts thought, but listed safety, efficacy, and cost as potential barriers.

Health care delivery infrastructure and patient management: Most experts commenting on this intervention did not anticipate a major disruption to health care delivery infrastructure. They generally agreed that device implantation could be performed in existing infrastructures, but that some training would be required. One expert with a health systems perspective commented, “The Watchman device will need specific training and experience for successful and safe implantation. Such catheter-guided procedures may impact cath lab utilization.”⁴⁶ Another expert with a research perspective noted a potential increase in case volume.⁴⁹

Health disparities: Experts did not think this technology would affect health disparities, other than being unaffordable for patients without health insurance or with high co-pays. One expert representing a clinical perspective commented, “This will be an expensive device therapy. Uninsured patients and those with less-generous health plans may find these high-cost device therapies out of reach. This may in fact worsen the health disparities in the overall population.”⁴⁵

Genetic Disorder Intervention

Lomitapide (Juxtapid) for Treatment of Homozygous Familial Hypercholesterolemia

Unmet need: Homozygous familial hypercholesterolemia (HoFH) occurs in 1 of every 1 million people in the United States, or about 360 individuals and is, thus, a very rare disease.⁵¹ These individuals are at high risk of cardiac morbidity and mortality before age 30 years. Despite the availability of lipid-lowering pharmacotherapies used in the general population, many patients with HoFH do not achieve target lipid levels and remain at increased risk of having early coronary events and sudden death.⁵² Nonpharmacologic interventions, such as apheresis and liver transplantation, are costly, invasive, and not widely available. One other drug, mipomersen sodium (Kynamro®), is available for patients with HoFH as a weekly subcutaneous injection as an adjunct to lipid-lowering drugs and diet to reduce low-density lipoprotein cholesterol (LDL-C), apolipoprotein-B (apo-B), total cholesterol, and non-high-density lipoprotein cholesterol (non-HDL-C).^{53,54} Effective oral, self-administered therapy is needed. Lomitapide (Juxtapid™) was intended to address this need.

Intervention: Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor that is indicated as a daily oral therapy for treating HoFH.⁵⁵ MTP is a lipid transfer protein that assists in assembling two lipoproteins: chylomicrons and very-low-density lipoproteins (VLDLs). MTP assists in the assembly by transferring triglycerides onto apo-B, an essential component of chylomicrons and VLDL.^{56,57} In essence, MTP binds and shuttles individual lipid molecules from the site of their synthesis (in either the intestine or the liver) to an emerging apo-B molecule, which then forms a chylomicron in the intestine or VLDL in the liver.^{56,57} Lomitapide prescribing information advises to begin treatment at 5 mg once daily and to escalate dosage gradually based on acceptable safety and tolerability to 10 mg daily after at least 2 weeks; dosage may be increased at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily.⁵⁸

The manufacturer claims that “if insufficient lipid is transferred to the apo-B molecule, the emerging apo-B is destroyed and lipoprotein secretion is inhibited;” therefore, “inhibition of MTP activity prevents both hepatic VLDL and intestinal chylomicron secretion, and consequently lowers plasma lipids.”⁵⁶ Lomitapide is self-administered orally, once daily, without food.⁵⁹

Clinical trials: FDA approval of lomitapide was based on review of a trial that evaluated the drug in 29 patients with HoFH.^{60,61} The median dose was 40 mg per day. Lomitapide reduced LDL-C concentrations by a mean of 50% at 26 weeks from baseline. By week 56, LDL-C concentrations remained reduced by 44% (95% confidence interval [CI], -57 to -31; $p < 0.0001$). At week 78, LDL-C concentrations were reduced by 38% (-52 to -24; $p < 0.0001$). In the trial, the most commonly reported adverse events were gastrointestinal symptoms. Four patients had aminotransaminase levels measured at more than five times the upper limit of normal; the increase in aminotransaminase levels resolved after dose reduction or temporary halt of lomitapide therapy, but remains a concern for patients on therapy. During the trial, researchers reported that no patient permanently stopped lomitapide because of liver abnormalities.^{60,61}

In November 2013, the manufacturer reported results from a phase III extension study of 19 patients with HoFH. At week 126, mean LDL-C concentrations were reduced from baseline by 45.5% (356 ± 127 mg/dL vs. 189 ± 120 mg/dL; $p < 0.001$).⁶²

Manufacturer and regulatory status: Lomitapide is manufactured by Aegerion Pharmaceuticals, Inc. (Cambridge, MA).⁵⁵ In December 2012, FDA approved lomitapide capsules as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, total cholesterol, apo-B, and non-HDL-C in patients with HoFH.⁶¹ Lomitapide has boxed warnings on its product label advising of a risk of severe liver toxicity (as

does the injectable drug for HoFH, mipomersen sodium).^{53,58,63} Likewise, it (and mipomersen) is available only in concert with a Risk Evaluation and Mitigation Strategy (REMS) program.^{53,58,63} The REMS program requires the manufacturer to certify prescribing physicians and dispensing pharmacies to use the drug and to document safe-use conditions, including a prescription authorization form for each new prescription.⁵³ For lomitapide, the program also requires that liver function tests be performed in patients before administration and at intervals during and after administration.

The company must also conduct three postmarketing studies for lomitapide: an animal study to evaluate potential drug toxicity in pediatric patients; a long-term patient registry to determine long-term safety; and an enhanced pharmacovigilance program to monitor reports of malignancy, teratogenicity, and hepatic abnormalities.⁶¹

In May 2013, Aegerion announced that the European Committee for Medicinal Products for Human Use had adopted a positive opinion with a unanimous vote recommending a marketing authorization in the European Union for lomitapide (to be marketed as Lojuxta™) capsules for a similar indication.⁶⁴ In August 2013, Aegerion announced that it had received approval from the European Commission.⁶⁵

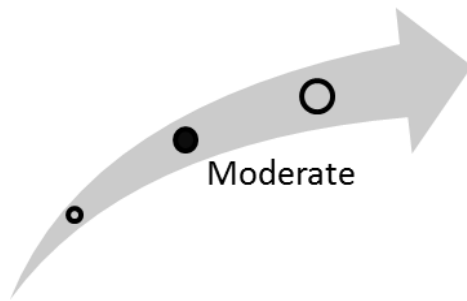
Diffusion: In October 2014, the company reported an 18% quarterly growth in net product sales in the United States. The company anticipated annual net lomitapide sales would reach between \$150 and \$160 million in 2014 after reducing initial estimates from a range of \$180 million to \$200 million because of patient discontinuation and lower-than-anticipated U.S. growth rates.⁶⁶ The company had previously announced that it had initiated a phase III trial in Japan and expected continued market-share growth in the United States and Brazil.⁶⁷

CMS does not have a national coverage determination for lomitapide, so coverage is at the discretion of local Medicare D prescription drug plans. Representative, private, third-party payers that include lomitapide in their drug formularies have precertification and step-therapy policies in place that govern coverage of the drug.⁶⁸⁻⁷⁴ Some of these payers place quantity limits on the drug and require annual recertification and documentation of patients' positive clinical response from lomitapide before allowing prescription renewals.^{68,73} According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, a 30-day supply of lomitapide cost more than \$29,000 with the use of a coupon (as of December 2014).⁷⁵ Thus, the annual per-patient retail cost is more than \$348,000. The manufacturer offers support services through its COMPASS program, which can help patients who require financial support advocate for their needs and guide them through financial obstacles to treatment.⁷⁶

Clinical Pathway at Point of This Intervention

According to the National Human Genome Research Institute, first-line treatment for patients with HoFH includes lifestyle changes (e.g., diet, exercise) and drug therapy with cholesterol-lowering medications (e.g., statins, bile acid sequestrants, ezetimibe, niacin, gemfibrozil, fenofibrate).⁷⁷ For these patients, these therapies are often insufficient, and more aggressive treatment is needed, including periodic apheresis or, possibly, a liver transplant.⁷⁷ The FDA-approved indication for lomitapide is as an adjunct to a low-fat diet and other lipid-lowering treatments to reduce LDL-C, total cholesterol, apo-B, and non-HDL-C in patients with HoFH.⁶¹

Figure 2. Overall high-impact potential: lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia



Overall, experts agreed that for the relatively small number of patients affected by HoFH, lomitapide has moderate to strong potential to fill the treatment gap between conventional lipid-lowering drugs (e.g., statins) and invasive, resource-intensive treatments such as apheresis and, in rare instances, liver transplantation. Experts agreed that lomitapide would likely be adopted widely by both patients and clinicians for the target population, but noted cost to be a major barrier to acceptance. Most experts commented that this intervention has the potential to reduce the need for invasive procedures if proved to be effective in the long term. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this technology.⁷⁸⁻⁸⁴ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: For the small population of patients with HoFH, no effective oral pharmacologic therapy has been available to bridge the gap between conventional lipid-lowering drugs (e.g., statins) and the need for apheresis or, in rare instances, a liver transplant, the experts noted. Experts generally agreed that lomitapide holds potential to improve patient health, citing the potential of the drug to significantly reduce LDL. However, some experts cited the potential for adverse events and agreed on the need for more long-term clinical data. One clinical expert commented, “Drug lowers LDL cholesterol by about 50%. However, there is significant side effect of hepatic steatosis in nearly every treated patient. This is a major limiting factor.”⁷⁸

Acceptance and adoption: Experts generally agreed on the potential for this intervention to be widely adopted by affected patients and clinicians. Because this drug is an adjunct to a low-fat diet and other lipid-lowering treatments to reduce LDL-C, total cholesterol, apo-B, and non-HDL-C, clinicians are likely to prescribe it, according to the experts. Most experts noted the ease of self-administering an oral medication to be attractive to both patients and clinicians. Several experts listed cost as a major barrier for patient and clinician acceptance, but noted that it would more likely affect patients. A health systems expert opined that the high drug cost could be potentially equal to the cost of treating HoFH as it progresses, “Expensive pharma medications are widespread in the healthcare system. The high cost of this medication is comparable to the costly surgical interventions a patient can likely expect with uncontrolled disease progression.”⁸³

Health care delivery infrastructure and patient management: Overall, most of the experts thought that using lomitapide would create little to no disruption to the health care delivery infrastructure or disease management practices for this patient population.

Lomitapide has the potential to reduce the need for apheresis or liver transplantation, noted one expert representing research perspective.⁸¹ Another research expert commented that liver function testing of patients for the duration of their lomitapide treatment would affect patient management.⁸²

One health systems expert thought the therapy would not present major disruptions to patient care, noting that “preauthorizations are very common for cardiac medications given the expense and intensity of patient education that go hand in hand, so even the REMS criteria will not present a significant disruption.”⁸³

Health disparities: Several experts cited cost as a major barrier for patients without insurance coverage and even for patients with insurance who could have significant copayments. One expert representing a health systems perspective opined, “The cost of this treatment is exceptionally high, which may lead to a health disparity between economic classes. It will almost be a certainty that without insurance, patients will not be able to receive this treatment.... This will create a noticeable divide between patients with insurance and those without.”⁷⁹

Heart Failure Intervention

Portable Freedom Driver for In-Home Support of the Total Artificial Heart

Unmet need: HF adversely affects quality of life as well as life expectancy and can develop from any condition that overloads, damages, or reduces heart muscle efficiency, impairing the ventricles' ability to fill with or eject blood. In 2009, 1 in 9 death certificates mentioned HF, and it was the underlying cause in 56,410 deaths. Based on data from 2007 to 2010 from the National Health and Nutrition Examination Survey, 5.1 million people older than age 20 years in the United States have HF. Approximately 50% of people with HF die within 5 years of diagnosis. HF prevalence 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 of patients with coronary artery disease, an increasing population of aging patients, and significant advances in the control of other potentially lethal diseases.

Ventricular assist device implantation and cardiac transplantation are the only established surgical treatments for end-stage HF.⁹⁷ Historically, artificial heart technology has involved using large, hospital-based pneumatic driver systems that require patients to be hospitalized and tethered to a driver console. The standard, 400-pound console powers the implantable components while patients await availability of a suitable donor heart.^{85,86} An option that would allow these patients to leave the hospital and receive artificial-heart support at home while awaiting a donor heart has the potential to lower treatment costs and improve quality of life.⁸⁷

Intervention: The temporary Total Artificial Heart (TAH-t) is a 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 via a conventional external pneumatic driver system.^{88,89} The driver system is large and cumbersome and requires patients to remain hospitalized while awaiting a donor heart.⁸⁷ To enable patients to leave the hospital and await a suitable donor heart at home, the TAH-t manufacturer has developed the 13.5 lb Freedom® Driver System. The portable driver is a wearable pneumatic device that powers the existing SynCardia TAH-t, which is indicated for use as a bridge to heart transplantation.⁸⁵

To implant the TAH-t, a surgeon first removes the left and right ventricles and the four native valves of the failing heart. The surgeon then replaces the excised heart chambers and valves with the TAH-t, which replicates their function, in a procedure similar to heart transplantation.⁹⁰

As with conventional hospital-based pneumatic driver systems, the Freedom Driver connects to the implantable TAH-t by a flexible pneumatic driveline that enters the body through the skin in the left chest just below the ribs. The driver sounds an alarm and/or flashes a light when it requires the user's attention. Two onboard batteries, which can be recharged using either a standard electrical outlet or automobile charger, power the portable Freedom Driver. The pneumatic driver is designed for patients to wear in a backpack or shoulder bag.⁸⁷

Clinical trials: Literature searches have not identified any completed, published clinical trials using the Freedom Driver System as of November 2014, although the device is mentioned in a three publications: a review article and two case reports. However the company submitted data to FDA from a premarket approval trial and those data were highlighted in a July 2014 company press release. The release reported results from 106 patients in the Freedom PMA (FDA premarket approval) trial. The company reported, "The SynCardia Total Artificial Heart with the Freedom Drive System allowed 75% of those patients to be discharged from the hospital, while 86% of the 106 patients either were bridged to heart transplants or were alive and supported by the SynCardia Total Artificial Heart and the Freedom driver as of June 30, 2014."⁹¹

Manufacturer and regulatory status: SynCardia Systems, Inc. (Tucson, AZ), makes the TAH-t and Freedom Driver. In June 2014, FDA approved the Freedom Driver “for use with the SynCardia temporary Total Artificial Heart as a bridge to transplantation in cardiac transplant candidates who are clinically stable.”⁹¹ In March 2010, SynCardia received CE mark approval to market the Freedom driver in the European Union for use with the SynCardia TAH-t.⁹² The TAH-t as a bridge to transplant had been approved by FDA in October 2004.⁹³

Diffusion and cost: The company reported that as of December 2014, about 1,350 SynCardia TAH-t devices had been implanted worldwide; more than 200 patients have used the Freedom driver.⁹¹

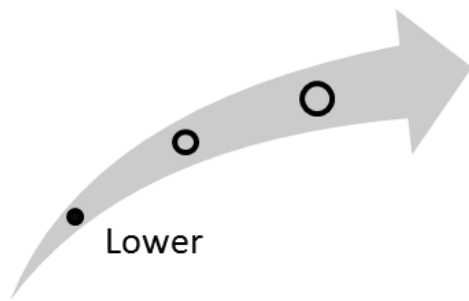
Costs for the Freedom Driver System have not yet been reported in the United States. Total cost of care for patients with artificial hearts using the portable driver at home presumably might be lower than that of hospitalized patients with artificial hearts, because the inpatient stay is shortened. However, the change in care setting may result in more of a cost shift than a significant cost reduction. Ambulatory patients would continue to need regular visits from specially trained nurses at home as well as followup office visits with specialist physicians to monitor device function. Furthermore, as with hospital-based pneumatic drivers, home use of the portable driver would require the immediate availability of a backup driver in case the primary unit fails and that someone (e.g., family member) be available to assist the patient. Thus, driver acquisition and maintenance costs might be comparable between portable and hospital-based drivers. The majority of the overall treatment costs for these patients will continue to include the costs of the artificial heart itself and surgical implantation, regardless of whether patients are supported in the hospital with a conventional driver or at home with a portable driver.

The following available cost information is based on inpatient use of the SynCardia TAH-t. Reported costs for a SynCardia TAH-t kit are approximately \$124,700, which includes a patient simulator (for training), tubing, and surgical disposables in addition to the device itself.⁹⁴ Staff training costs to meet manufacturer’s device-related certification requirements are approximately \$98,000, plus \$58,590 for a new center startup kit, in addition to device costs. SynCardia will loan a hospital the necessary driver units if the center remains certified to implant the TAH-t and maintains an inventory of two TAH-t kits and a spare kit.⁹⁴ Annual maintenance costs for the TAH-t are estimated at \$18,000.^{95,96} Additional costs related to inpatient care of patients in whom the TAH-t has been implanted include those for ancillary services, such as operating room use and attendant overhead; surgical team fees; charges for clinical staff; radiology, laboratory, and intensive care unit services; blood products; drugs; rehabilitation; and other professional payments.

Clinical Pathway at Point of This Intervention

American College of Cardiology Foundation (ACC)/American Heart Association (AHA) clinical guidelines identify ventricular assist device implantation and cardiac transplantation as the only established surgical treatments for end-stage HF.⁹⁷ The portable driver system is intended to complement TAH-t use.⁸⁷ As a bridge to transplantation, the TAH-t with the Freedom driver would complement heart transplantation. Some left ventricular assist devices 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.

Figure 3. Overall high-impact potential: Portable Freedom Driver for in-home support of the temporary Total Artificial Heart



Although the intended patient population for this device is few in number, the portable Freedom Driver system has the potential to dramatically improve patient quality of life while awaiting a transplant and to dramatically shift the care setting from inpatient to outpatient, experts commenting on this intervention agreed. Experts also thought that this device has potential to reduce costs associated with lengthy hospital stays, although its outpatient use would require resources, such as training for staff and home caregivers/family members. The experts noted that the intended patient population for this device is very small in number. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁹⁸⁻¹⁰³ One of these experts declared a potential conflict of interest (COI), because the expert is an active investigator in a trial studying a portable ventricular assist device, a possible competitor.⁹⁸ This potential COI is balanced by the perspectives of other experts who reported having no COIs. We have organized the following discussion of expert comments according to the parameters on which they commented. Note: expert comments were received before FDA granted marketing approval for the Freedom Driver.

Unmet need and health outcomes: Although experts noted that the intended patient population for this device is small, they generally agreed that an important unmet need exists for a driver system that would allow patients to be discharged home while awaiting a heart transplant. Experts viewed this device's greatest potential benefits to be improving patient quality of life and decreasing costs of care by enabling patients awaiting a heart transplant to be discharged to home.

Use of this device could provide psychological benefits (increased independence, mobility, and quality of life), the experts generally thought. Some experts suggested a further health benefit might be realized by reducing risk of health care-acquired infections by getting patients out of the hospital sooner. Some experts likened this technology's potential to that of ventilators and ventricular assist devices, which have migrated from inpatient care to outpatient care and a home setting with positive results.

Acceptance and adoption: If good outcomes are demonstrated from the ongoing trial, both clinicians and patients would readily adopt this technology because of its potential for lower costs and improved quality of life and health status, the experts thought. Although several experts also noted that extensive training (on the part of both hospital staff and patients' home caregivers) would be required for use of this device, they did not think this would be a barrier to uptake.

Health care delivery infrastructure and patient management: Experts noted that shifting care from an inpatient setting to the home is important and would likely lower costs significantly, given the expense of continuous, long-term inpatient care. However, some experts anticipated that

moving these patients home may simply shift costs and would increase the need for home-care personnel with experience in caring for patients who have received artificial hearts.

One health systems expert opined, “Ambulatory patients would continue to need regular visits from specially trained nurses at home as well as follow-up office visits with specialist physicians to monitor device function. Furthermore home use of the portable driver would require the immediate availability of someone (e.g., family member) be available to assist the patient.”¹⁰⁰

Health disparities: Experts generally agreed that the portable Freedom driver is likely to have minimal effect on health disparities. But some thought cost could be a factor, and one clinical expert opined, “This will be very costly and will have all the issues related to insurance status disparities.”⁹⁸

Valve and Structural Disorder Intervention

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

Unmet need: Significant mitral regurgitation (MR) occurs in an estimated 1% to 2% (about 4 million) of the U.S. population. More than 250,000 cases of significant MR are diagnosed each year in the United States, and each year, about 50,000 people undergo some type of surgery for the disease.¹⁰⁴ Although surgical intervention (i.e., valve repair or replacement) is the preferred treatment for severe MR, many patients are not candidates for these procedures because of a high surgical risk that stems from advanced age or extensive comorbidities.^{105,106} Up to one-half of candidates with symptomatic, severe MR may not receive surgical intervention for this reason.¹⁰⁵ In light of this unmet need, investigators and manufacturers have developed less-invasive approaches to mitral valve repair. The MitraClip[®] Mitral Valve Repair System is a recently approved catheter-based approach to repairing the mitral valve that may offer a treatment option for patients at high risk for complications from surgery.¹⁰⁷

Intervention: The MitraClip device is intended to simulate the functional effects achieved by the Alfieri edge-to-edge open surgical procedure used for treating MR.¹⁰⁶ 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.¹⁰⁸ The MitraClip device mimics this procedure by “clipping together” the mitral valve leaflets, rather than using sutures.^{106,109}

To implant the MitraClip, a physician inserts a guide catheter into the femoral vein at the patient’s groin and threads it up to the heart into the right atrium under fluoroscopic guidance in a cardiac catheterization lab.¹¹⁰ To reach the mitral valve in the left atrium, the physician performs a transseptal puncture to create an opening in the septum, the wall that separates the right and left atrial chambers, with the needle-like dilator within the catheter.^{110,111} Use of transseptal atrial puncture, a difficult procedure, has traditionally been limited to large interventional cardiac care programs staffed with electrophysiologists who are well-experienced in the technique.¹¹²

As the procedure continues, the operator advances the catheter into the left atrium and through the mitral valve as the clip is expanded. Using Doppler ultrasound to assess the optimal clip placement, the physician grasps and fastens the edges of the valve leaflets together with the MitraClip.^{110,111} Before releasing the implant from the clip delivery device for permanent placement, the physician confirms proper positioning with further ultrasound scans. If the device positioning is acceptable, the physician releases the clip from the delivery device and removes the catheter.^{107,110}

The MitraClip device will most likely be used for patients with degenerative mitral valve disease with prolapse (backward collapse) originating mainly from the center of the valve, a fairly well-defined population that would not necessarily require additional types of cardiac intervention.^{113,114}

Clinical trials: In 2014, Kar and colleagues reported 5-year outcomes from 78 patients with grade 3+ or 4+ MR considered at high risk of surgical mortality who received MitraClip therapy. Investigators reported a 5-year survival rate of 44% and occurrence of reduced symptoms in 83% of surviving patients. At 5 years, 70% of surviving patients experienced MR reduction to 2+ or less. The authors also reported a sustained reduction in left ventricular end-diastolic volume and left ventricular end-systolic volume throughout the study duration.¹¹⁵

In 2013, Lim and colleagues published outcomes from 127 patients with severe, degenerative MR at a prohibitive risk for mitral valve surgery who were treated with MitraClip therapy. Investigators reported implantation success of 95.3% and a hospital stay of 2.9±3.1 days. Major

adverse events reported at 30 days included death in 6.3%, stroke in 2.4%, and myocardial infarction in 0.8%. At 1 year, 30 patients (23.6%) had died, with no survival difference between patients discharged with primary or secondary MR.¹¹⁶

In 2013, investigators reported 1-year outcomes from 59 patients with severe, symptomatic MR and reduced ejection fraction who received MitraClip therapy.¹¹⁷ The primary outcomes evaluated were procedural efficacy measured by reduction in MR and improvement in New York Heart Association (NYHA) functional classification. Investigators found that device implantation was associated with reduced MR and improved NYHA functional class, translating into improved 6-minute walk test distance. Followup echocardiography suggested a reversal in heart enlargement, with reduced left atrial volume and left ventricular end-systolic diameter and increased left ventricular ejection fraction (LVEF). These results were consistent with outcomes in a subgroup of 25 patients with severely reduced LVEF (ejection fraction $23\pm 2\%$), suggesting that sicker patients also benefitted from MitraClip therapy. Investigators reported 30-day mortality of 2.9%.¹¹⁷

The manufacturer is recruiting for a U.S. based trial to evaluate the safety and effectiveness of MitraClip therapy in patients with functional mitral regurgitation who are considered extremely high-risk for mitral valve surgery.¹¹⁸

Manufacturer and regulatory status: The MitraClip is manufactured by the Abbott Vascular division of Abbott Laboratories (Abbott Park, IL). Abbott obtained the MitraClip technology through its acquisition of Evalve, Inc. (Menlo Park, CA), in November 2009.¹¹⁹ In October 2013, FDA approved the device for treating patients who have received a diagnosis of “significant symptomatic degenerative MR who are at prohibitive risk for mitral valve surgery.”¹²⁰

MitraClip’s approval process took several years to complete. Originally, the device was anticipated to be reviewed by FDA in 2011. In May 2011, the manufacturer issued a voluntary device recall—because of issues with the delivery catheter’s tip—in Europe, Australia, Singapore, and other countries where the device had been approved. Although the company resolved the issue and reintroduced the device in those countries, the recall prompted FDA to request additional information and analysis regarding the MitraClip, which the company provided in an amended premarket approval (PMA) application.¹²¹

In March 2013, the Circulatory System Devices Panel of FDA’s Medical Devices Advisory Committee voted on three questions (safety, effectiveness, risk-benefit ratio) pertaining to the PMA application. The panel voted 5-3 that MitraClip’s benefits outweigh the risks for use in patients who meet the criteria specified in the proposed indication. The panel voted 8-0 that available data “show reasonable assurance” that MitraClip implantation would be safe when used for the proposed indication. However, the panel voted 5-4, with the chairman voting as tie breaker, that available trial data did not provide “reasonable assurance” that the MitraClip procedure would be effective for its proposed indication.¹²²

After the panel meeting, Abbott and FDA determined “that patients with primary MR etiology ([degenerative MR]) at prohibitive risk of surgery were the appropriate patient population to evaluate the risks and benefits of the MitraClip device.” As opposed to functional MR, patients with degenerative MR are not amenable to medical therapy and, therefore, the subset of patients with degenerative MR who are at prohibitive surgical risk lacks effective treatment options. A retrospective study of patients with degenerative MR at prohibitive surgical risk was performed (see Lim et al. 2013),¹¹⁶ and MitraClip’s premarket approval application approval was based on this patient population.¹²³

Diffusion and costs: In Europe, the MitraClip device’s list price is about \$26,200.¹²⁴ Hospitals reporting device costs to ECRI Institute’s PriceGuide database reported a costs ranging from \$25,000 to \$30,000 for the Mitral valve kit,¹²⁵ which concurs with prices reported from other sources.^{126,127} Procedural costs to implant MitraClip might be somewhat higher than those of other

interventions performed in a cardiac catheterization lab, such as percutaneous transluminal coronary angioplasty with stenting of the coronary arteries, because transseptal puncture is required to implant the MitraClip in the left heart. MitraClip therapy would be expected to substantially increase short-term treatment costs compared with medical management alone in patients who are ineligible for open mitral valve repair.

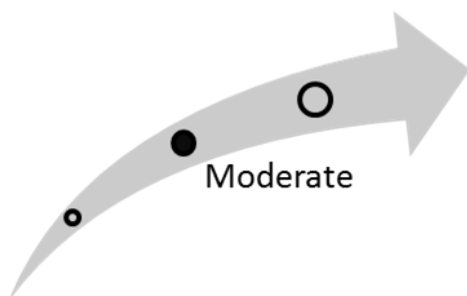
The device is just beginning to diffuse, given the recency of its approval. Its adoption may be slow initially because of safety alerts in 2013 and product recalls in 2011 that could affect physician and patient acceptance. According to one U.S. consulting firm, 20,000–30,000 U.S. patients with degenerative MR disease are candidates for the procedure each year.¹²⁸ At this time, six representative, private, third-party payers (i.e., Anthem, CIGNA, Humana, Medica, United Healthcare, Regence) consider transcatheter mitral valve replacement investigational and deny coverage for the procedure.^{129–134} Aetna, however, recently issued a medical coverage policy that considers the procedure “medically necessary for persons with grade 3+ to 4+ symptomatic degenerative mitral regurgitation and at high-risk for traditional open-heart mitral valve surgery.”¹³⁵

As requested by Abbott, CMS approved the MitraClip System for a new technology add-on payment in fiscal year 2015. New technology add-on payments are limited to the lesser of 50% of the average cost of the device or 50% of the costs in excess of the Medicare Severity–Diagnosis Related Group (MS-DRG) payment for the case. The maximum add-on payment for the MitraClip procedure will be \$15,000 per case.¹³⁶ In August 2014, CMS announced that the agency will cover transcatheter mitral valve repair under its Coverage with Evidence Development program under specific conditions described in its decision memo.¹³⁷ These include independent preprocedure assessment of each patient by a cardiothoracic surgeon and a cardiologist, hospital care provided by a multidisciplinary heart team, infrastructure requirements, case volume requirements, and mandatory participation in a national registry.¹³⁷

Clinical Pathway at Point of This Intervention

The preferred treatment for severe MR is open surgery for valve repair or replacement.^{105,106} ACC/AHA clinical guidelines recommend surgical mitral repair over mitral valve replacement in most patients because the “valve is suitable for repair and appropriate surgical skill and expertise are available.”¹³⁸ MitraClip may potentially be positioned as a catheter-based (transcatheter) alternative to surgical valve repair.^{105,106}

Figure 4. Overall high-impact potential: transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation



Overall, experts agreed this procedure addresses a considerable unmet need and has the potential to improve patient health. However, most experts opined that more data concerning safety and long-term outcomes are needed. Experts’ opinions differed somewhat about how much this intervention would disrupt health care delivery for this condition. Some experts believe the disruption to health care delivery would be limited, because the infrastructure to perform the

procedure is already in place at many health care facilities offering minimally invasive transcatheter valve procedures; other experts believe that the potential increase in the number of patients seeking treatment for functional MR has potential to cause a large disruption to health care delivery. The majority of experts thought the MitraClip would increase health care costs, but they wanted to see more long-term data to assess whether the device would reduce long-term costs of care for this patient population. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this technology.¹³⁹⁻¹⁴⁴ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for less-invasive interventions to treat MR is important, the majority of experts generally agreed, citing the large number of patients with MR who are not candidates for surgical repair and the ineffectiveness of pharmacotherapy. One expert with a health systems perspective noted that pharmacological treatments act as a “Band-Aid” instead of an effective cure.¹⁴⁴

Experts generally agreed this intervention has potential to improve patient health outcomes, citing decreased mortality and morbidity in patients who are not good surgical candidates. However, several experts commented about the lack of randomized controlled trial data. One expert representing a research perspective commented, “Limited evidence suggests that MitraClip may be a reasonable option in patients who have no other good treatment options.”¹⁴²

Experts also expressed concerns about device and procedure safety and believe that the numerous comorbidities seen in these patients would present risk and preclude some patients from achieving greatly improved outcomes. One expert representing a research perspective opined, “Transseptal puncture required to access the left heart chambers is technically challenging and carries risk of life-threatening complications. Due to the complexity of procedure, the procedure would likely be performed in centers with established interventional cardiac programs.”¹⁴¹

Acceptance and adoption: Although most experts agreed that the MitraClip implant would entail a significant learning curve and training for clinicians, they agreed that if clinical trial data continue to demonstrate benefits and safety, clinical acceptance would follow. Several experts listed the difficulty of the procedure and limited reimbursement to be potential barriers to clinician acceptance. One clinical expert commented, “This is a technically challenging procedure for multiple reasons: 1. Transseptal puncture - usually performed by electrophysiologists and less frequently by interventionalists so will need extra training. 2. Extra training on actual deployment of mitral clip - again not usually performed by interventionalists. However, given the potential number of patients who may meet criteria for this procedure, I believe that it will be embraced by clinicians.”¹⁴³

Experts generally agreed on the potential for wide patient acceptance of this intervention, citing the limited number of treatment options and relatively less-invasive nature of the procedure compared with surgery.

Health care delivery infrastructure and patient management: Experts offered varied perspectives about this intervention’s potential impact on the health care system. Some experts commented that little disruption to health care delivery would occur, because the infrastructure is already in place, while other experts noted that an increase in case volume might cause a large disruption to health care delivery. One clinical expert stated that this intervention would likely be offered only in facilities that already have equipment and staffing in place to perform the

procedure.¹⁴³ Conversely, some experts attributed the potential for disruption to significant training requirements.

The device and its related procedure would be expensive and affect overall health care costs, the experts generally agreed. The importance of long-term studies in determining overall impact on health care costs was noted by most experts. But a few experts thought that the MitraClip would affect health care costs only minimally, reasoning that this procedure would be less costly than surgical treatment or long-term care of patients who are not eligible for surgery.

Health disparities: Experts all agreed that this device would have minimal impact on health care disparities. However, several experts cited cost, reimbursement, and limited access to centers with established interventional cardiac programs to be potential factors that could affect health disparities.

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