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

Priority Area 03: Cardiovascular Disease

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U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

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Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

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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. HHSA290201000006C). 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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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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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.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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

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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 identifying 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 4 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 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 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 annually. Topics eligible for inclusion are those interventions expected to be within 0–4 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 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

(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 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 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 17 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 May 16, 2013, in this priority area; *and* (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Forty-seven topics were being tracked in this priority area as of May 18, 2013.)

Since the last report in December 2012, the horizon scanning criteria for inclusion changed (i.e., were narrowed slightly), and two topics that had been included as having high-impact potential were removed from consideration. These topics are: "Vagus nerve stimulation (CardioFit) for treatment of heart failure," removed because it is too early in development, and "Percutaneous annuloplasty (Carillon Mitral Contour System) for treatment of functional mitral regurgitation," removed because the developer has decided to stop pursuing development for the U.S. market, although the device is now marketed in Europe.

For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present eight summaries on nine 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. *Catheter-based renal denervation (Symplicity System) for treatment-resistant hypertension	Moderate
2. Catheter-based ventricular restoration implant (Parachute) for treatment of heart failure	No high-impact potential at this time
3. Extra-aortic balloon counter-pulsation heart assist device (C-Pulse) for treatment of heart failure	No high-impact potential at this time
4. Imatinib (Gleevec) for treatment of pulmonary artery hypertension	No high-impact potential at this time

Topic	High-Impact Potential
5. Implantable cardiac monitor (AngelMed Guardian System) for detecting myocardial infarction	No high-impact potential at this time
6. *Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia	Moderate
7. Off-label minocycline with tPA for treatment of stroke	No high-impact potential at this time
8. *Pediatric ventricular assist device (Excor) for pediatric end-stage heart failure	Moderate
9. Percutaneous left atrial appendage occlusion (Watchman) for prevention of atrial fibrillation–associated stroke	No high-impact potential at this time
10. Point-of-care genetic testing to determine antiplatelet regimen after percutaneous coronary intervention	No high-impact potential at this time
11. *Portable Freedom Driver for in-home support of the Total Artificial Heart	Lower end of the high-impact-potential range
12. Recombinant human relaxin-2 (serelaxin) for treatment of acute heart failure	No high-impact potential at this time
13. *Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevation myocardial infarction	High
14. *Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for treatment of life-threatening ventricular tachyarrhythmias	Lower end of the high-impact-potential range
15. *Transcatheter aortic valve implantation (CoreValve) for treatment of severe aortic stenosis	High
16. *Transcatheter aortic valve implantation (Sapien) for treatment of severe aortic stenosis	High
17. *Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	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 or address valve problems, arrhythmias, and treatment-resistant hypertension. Only one pharmaceutical was deemed as having potential for high impact.

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 that occur in the United States 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 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 forms of cardiac arrhythmia. Experts highlighted one device that could be of potentially high impact in treating arrhythmia.

Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Treatment of Life-Threatening Ventricular Tachyarrhythmias

- **Key Facts**: The standard available implantable cardioverter-defibrillators (ICDs) that are intended to prevent sudden cardiac death by treating ventricular tachyarrhythmias require implanting a transvenous lead in the heart. Complications that arise from ICD implantation are often related to the lead-implantation portion of the procedure. Additionally, lead failure is a major limitation with ICD implantation, and procedures to remove these faulty leads are often associated with morbidity and mortality. The Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD®) System (Boston Scientific Corp., Natick, MA) 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. Further, the device does not require imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks. The S-ICD was approved by the U.S. Food and Drug Administration (FDA) in September 2012. According to FDA, the device is approved for use only in patients who do not require a pacemaker or pacing therapy.

  In February 2013, Jarman and colleagues reported on clinical experience using the S-ICD in the United Kingdom. Investigators surveyed all UK hospitals implanting the S-ICD; 76% (19 of 25) of hospitals responded with data on 111 patients. Patients had a median age of 33 years (range 10–87 years). Underlying pathologies included primary electrical disease, 43%; hypertrophic cardiomyopathy, 20%; ischemic cardiomyopathy, 14%; congenital heart disease, 12%; idiopathic dilated cardiomyopathy, 5%; and other cardiomyopathies, 6%. Overall, 17% of patients (19 of 111) required 20 repeat operations related to S-ICD placement, including 9% of patients (10 of 111) in whom the device was permanently removed. During the study period, S-ICDs delivered 24 appropriate shocks in 13 of 111 patients. Investigators found no instances of the device failing to detect or treat (defibrillate) ventricular arrhythmias above the programmed detection rate. Devices delivered 51 inappropriate shocks in 17 of 111 patients. Among 51 inappropriate shocks, 41 were due to T-wave over-sensing.

  In policies addressing conventional ICDs, several private third-party payers describe the S-ICD as investigational or experimental and, therefore, deny coverage for the technology. However, many of these policies predated the FDA approval and might change when updated. The U.S. Centers for Medicare & Medicaid Services (CMS) has a national coverage determination for ICDs and criteria for coverage, but does not specifically mention the S-ICD system. The cost of the device is reported to be similar to that of conventional ICDs; however, the procedure purportedly takes less time to perform because it can be performed in an outpatient setting with no need for fluoroscopy, imaging, or an electrophysiology laboratory.
- **Key Expert Comments**: Experts were optimistic that this intervention has some 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. This optimism was diluted partially by a couple of experts who suggested that this device's limited pacing capabilities would temper widespread diffusion and impact. 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 result in shorter hospital stays than for conventional ICD implantation and possibly lower costs associated with the procedure.
- **Potential for High Impact**: Lower end of the potential high-impact range

Genetic Disorder

The section on genetic disorders includes a topic that purportedly addresses an unmet need for an inherited disorder that affects the cardiovascular system. Familial hypercholesterolemia (FH) is an inherited genetic 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 U.S. National Human Genome Research Institute, FH can cause premature onset of coronary artery disease, myocardial infarction (MI), 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 exhibits increased severity compared with 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.

Experts commenting on topics in this area identified one pharmaceutical agent that they thought could have high impact.

Lomitapide (Juxtapid) for Treatment of Homozygous Familial Hypercholesterolemia

- **Key Facts**: Lomitapide is a microsomal triglyceride transfer protein inhibitor that is indicated as a daily oral therapy for treating HoFH. In December 2102, FDA approved lomitapide (Juxtapid™) for marketing. In the trial that served as the basis for the approval, investigators reported that the median dose was 40 mg per day and that lomitapide 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 in aminotransaminase levels resolved after dose reduction or temporary halt of lomitapide therapy. No patient permanently stopped lomitapide because of liver abnormalities. Retail prices for a 28-day supply of lomitapide range from more than $21,000 for 5 mg tablets to more than $27,000 for 20 mg tablets (as of June 2013). Representative, private, third-party payers that include lomitapide in their drug formularies typically have precertification and step-therapy policies in place that govern coverage of the drug. These payers generally place quantity limits on the drug and require annual recertification and documentation of patients' positive clinical response from lomitapide before extending coverage to renewed prescriptions for the drug.
- **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 physicians for the targeted population of patients with HoFH. The experts also thought that a majority of patients would likely accept lomitapide as long as out-of-pocket costs for lomitapide therapy were not cost-prohibitive.
- **Potential for High Impact**: Moderate

Heart Failure

Heart failure, 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 ventricles' ability to fill with or eject blood. According to AHA, about 5.7 million U.S. adults aged 20 years or older were living with heart failure 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 heart failure is about 10 per 1,000 people. Nearly 550,000 new cases of heart failure occur each year. In 2005 (the most recent year for which mortality statistics are available), more than 292,000 patients died in the United States with a prior diagnosis of heart failure; it was listed as the underlying cause in nearly 59,000 deaths and a contributing (secondary) factor in the remaining cases. Heart failure prevalence has increased during the past 20 years, and the number of patients who progress to end-stage heart failure is expected to grow because of increased survival in patients with coronary artery disease, 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 heart failure and its underlying cause, many new drugs, biologics, and devices are under study for treating patients with heart failure. Experts commenting on topics on heart failure identified two devices they thought have potential for high impact.

Pediatric Ventricular Assist Device (Excor) for Pediatric End-Stage Heart Failure

- **Key Facts**: Ventricular assist devices (VADs) are an established therapy for adults with end-stage heart failure awaiting a donor heart for transplantation; however, adult VADs are too large and generally unsuitable for use in pediatric patients, especially infants and newborns. One pediatric VAD was approved for use only in (larger) children aged 5 years or older. Extracorporeal membrane oxygenation (ECMO) has often been used off label to provide mechanical circulatory support to treat end-stage heart failure in infants and children, but ECMO is unsuitable for moderate-to-longer-term use in pediatric patients because it can cause serious and potentially life-threatening complications. In December 2011, FDA granted manufacturer Berlin Heart GmbH, of Berlin, Germany, marketing approval for its Excor Pediatric VAD under humanitarian device exemption status for use in pediatric patients with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support. As a condition of approval, FDA required the company to conduct a postapproval study to evaluate whether safety and outcomes of Excor used in general clinical practice are comparable to the safety and outcomes reported in an investigational device exemption (IDE) trial. In August 2012, investigators reported results from 48 pediatric patients aged 16 years or younger awaiting heart transplantation who received ventricular support with either the Excor or ECMO. Patients were divided into one of two 24-patient cohorts based on body size (Cohort 1, <0.7 m^2, median age, 1 year, median weight 9 kg; Cohort 2, 0.7 to <1.5 m^2, median age 9 years, median weight, 31 kg). The primary efficacy endpoint for the Excor groups was time to death or device withdrawal due to unacceptable neurological outcome. For the ECMO control groups, the primary endpoint was only time to death, because neurologic status was unavailable. For Cohort 1, the median length of support was 28 days compared with a median of 5 days in the matched ECMO control group ($p<0.001$). The longest Excor duration of support in Cohort 1 was 174 days compared with 21 days with ECMO. For Cohort 2, the Excor median length of support was 43 days compared with 5 days in the matched ECMO control group ($p<0.001$). The longest Excor duration of support in Cohort 2

was 192 days compared with 28 days with ECMO. Overall, Excor use led to 88% survival of Cohort 1 patients and 92% survival of Cohort 2 patients (either heart transplantation or weaning due to recovery).

- **Key Expert Comments**: Experts noted that this technology would fill a large unmet need for very young pediatric patients (i.e., infants to age 5 years) who have severe heart failure and are poorly served by traditional options for mechanical cardiac support. However, experts cautioned that although this technology has great potential to improve patient outcomes by extending the length of time that pediatric transplant candidates could wait for a donor heart, the technology's benefit would be tempered by the limited availability of donor organs for this population.
- **Potential for High Impact**: Moderate

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. 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 traditionally 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 the relatively small number of people in this patient population. The battery-powered Freedom Driver System weighs 13.5 lb and is carried by the patient in a backpack or shoulder bag. 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 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. A clinical trial of the driver is ongoing. As of November 2012 (the latest company update), the company had reported that 41 of 55 patients supported with the Freedom driver in an IDE clinical trial in the United States had been discharged from the hospital using the portable driver. Completion of the SynCardia Freedom Driver System Study is expected in September 2013.
- **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, the patient population for which this device is intended is small, which tempers its overall potential impact on the health care system. However, experts thought that shifting care from the inpatient to the outpatient setting would be a very important effect of this intervention, if approved for marketing.
- **Potential for High Impact**: Lower end of the high-impact-potential range

Hypertension

Hypertension, or high blood pressure, affects about one-third of the adult population in the United States and has long been described as the "silent killer" because it often shows no specific symptoms. However, more pronounced symptoms are associated with severe or long-term hypertension and include severe headache, dizziness or confusion, nausea, fatigue, blurred vision, chest pain, difficulty breathing, irregular heartbeat, and blood in the urine. According to AHA,

about 76.4 million people in the United States have hypertension. National health surveys from both highly industrialized and developing nations suggest that hypertension is effectively managed in only 11.2% of cases. Hypertension was the primary cause of 61,762 deaths in the United States in 2009, the most recent year for which statistics were available, according to AHA and the American Stroke Association. Experts commenting on hypertension topics identified a new approach they thought has potential for high impact that uses a device under development for treatment-resistant hypertension.

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

- **Key Facts**: Lowering high blood pressure has been associated with significantly lower rates of stroke, heart attack, and heart failure. However, inadequately controlled hypertension remains a problem for a growing number of people. The Symplicity™ Catheter System (Medtronic, Inc., Minneapolis, MN) is in development for treatment-refractory hypertension. The device is intended to enable a physician to apply radiofrequency energy to ablate renal nerves from within the renal artery without adversely affecting other nerves in the abdomen, pelvis, or lower extremities. In clinical trials, the minimally invasive procedure has taken about 40 minutes to perform. In March 2013, investigators reported 24-month results from Symplicity HTN-2, the first randomized trial investigating renal denervation. Among 40 patients who received Symplicity renal denervation, blood pressure at 24 months dropped by -29/-10 mm Hg from 178/97 mm Hg at baseline ($p<0.01$). Among 26 control group patients who crossed over to receive renal denervation after 6-month primary endpoint assessment (crossover group), average blood pressure at 24 months dropped by -35/-13 mm Hg from 178/98 mm Hg at baseline ($p<0.01$). Further, investigators observed no device-related serious adverse events, no late vascular complications, and no significant declines in kidney function compared with baseline values through 24 months. According to the company, physicians perform the procedure in a catheterization laboratory using standard interventional techniques similar to those used for renal stent implantation. In May 2013, Medtronic completed patient enrollment in the Symplicity HTN-3 trial, a phase III randomized controlled trial intended to support a U.S. marketing approval application. The company also announced that the Symplicity device would be one of the first medical devices evaluated under the FDA-CMS parallel review program, which enables CMS to begin a national coverage determination while FDA completes its safety and efficacy review.
- **Key Expert Comments**: Experts commenting on this intervention agreed that it has the potential to fill an important gap in treating refractory hypertension and would likely be accepted by clinicians and patients. However, this intervention's potential impact is tempered by its lack of long-term outcomes data and the fact that although it can be easily accommodated in a catheterization laboratory, it introduces a surgical procedure into a treatment paradigm that previously was limited to medical management. Thus, it could shift the care paradigm from medical management to a procedure and increase demand on catheterization laboratory infrastructure.
- **Potential for High Impact**: Moderate

Myocardial Infarction

MI, also known as heart attack, is caused by blockage of one or both of the coronary arteries or their major branches, leading to ischemia (oxygen insufficiency) in heart muscle tissue. MI can

result in irreparable damage to heart muscle as cells cease functioning properly. Successful MI treatment involves restoring coronary circulation by clearing or bypassing the blockage promptly. According to AHA, about 600,000 new and 320,000 recurrent MIs occur each year in the United States. Of these, approximately 157,000 MIs are fatal. Experts commenting on cardiovascular topics identified a novel collaborative approach they thought has potential for high impact intended to improve treatment for acute MI.

Standardized Protocol and Integrated System (RACE Project) for Treatment and Transfer of Patients with ST-Segment Elevated Myocardial Infarction

- **Key Facts**: The Reperfusion of Acute Myocardial Infarction in Carolina Emergency Departments (RACE) project was developed in North Carolina to reduce systemic barriers to timely treatment for patients with ST-segment elevated myocardial infarction (STEMI) and improve care for these patients statewide. Among the RACE Project's goals are decreasing delays in administration of reperfusion therapy, increasing the frequency with which reperfusion is provided to eligible patients, and improving care processes. The project seeks to achieve these goals by aligning physicians, nurses, hospitals, emergency medical service (EMS) personnel, professional societies, payers, and government entities in a regionally organized, collaborative initiative. In 2011, investigators reported "door-in-door-out" times before and after implementation of the RACE program for 436 patients treated for STEMI at 55 North Carolina hospitals without primary percutaneous coronary intervention capability. Investigators found that median door-in-door-out times improved from 97 minutes at baseline (interquartile range, 56–160 minutes) to 58 minutes after RACE program intervention (interquartile range, 35–90 minutes; $P<0.0001$). Adopting all RACE-recommended EMS processes was associated with the shortest median time to treatment (44 minutes vs. 138 minutes for hospitals that adopted none of the RACE recommendations to revise EMS processes). As of June 2013, program developers had expanded the project's focus to include expedited emergency care for patients who experience cardiac arrest and stroke. As a result, they have redefined the RACE acronym as "Regional Approach to Cardiovascular Emergencies" from its original title. RACE Project developers have also been collaborating with professional medical specialty societies on a national demonstration project intended to establish similar cardiac care improvement programs in 20 regions across the United States.
- **Key Expert Comments**: Overall, the experts concluded that the RACE Project represented great potential to fill an unmet need by providing a good model on which other States could pattern their own initiatives to improve patient access to timely STEMI treatment. Experts generally agreed that if effectively implemented in a State, the RACE Project has substantial potential to reduce health care disparities by trying to provide the most effective, recommended care to STEMI patients, regardless of their location. However, several experts suggested that some physicians and smaller health care facilities might resist implementation out of concerns that participating in this type of initiative could decrease their revenues by lowering their case volumes.
- **Potential for High Impact**: High

Valve and Structural Disorders

This section includes topics that purport to address unmet needs for certain disorders of heart valves.

Mitral regurgitation (MR): 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 heart failure 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.

Aortic valve stenosis: This condition is a narrowing that affects primarily the elderly and obstructs normal blood flow through the aortic valve, the most likely of the heart's four valves to fail because of disease. Severe, untreated aortic valve stenosis can eventually lead to heart failure or sudden cardiac arrest. According to researchers, in the United States, about 29% of people aged 65 years or older and 37% of people aged 75 years or older have aortic sclerosis, a precursor condition to aortic stenosis characterized by mild thickening or calcification of the aortic valve without restricted leaflet motion. About 1% to 2% of the population is living with a bicuspid aortic valve, a congenital defect in which the aortic valve develops two instead of three normal valve leaflets. According to Novaro (2011), half of this population will develop aortic stenosis.

Experts commenting on topics in this area identified two technologies that they thought could have high impact.

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

- **Key Facts**: New minimally invasive approaches are making the therapeutic benefit of aortic valve replacement an option for patients with severe aortic stenosis who are not candidates for open-heart valve surgery or who are at high risk of complications from open-heart surgery. One system (Sapien®) was FDA approved in November 2011; another system (CoreValve®) is approved only for investigational use in the United States.

  Edwards Lifesciences Corp., of Irvine, CA, developed the Sapien Transcatheter Heart Valve system, which features a bovine pericardial tissue aortic valve affixed within a balloon-expandable, cobalt-chromium alloy frame. The company developed delivery systems for implanting the valve using either a transfemoral or transapical approach. The procedure takes up to 4 hours, including about half an hour for fluoroscopy, with an average hospital stay of 2–6 days. In November 2011, FDA approved the Sapien for transfemoral delivery for treating severe, symptomatic, aortic stenosis in patients who have been determined by two cardiac surgeons to be ineligible for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from the procedure. In October 2012, FDA expanded the labeling to include patients with severe aortic stenosis who are at high risk of experiencing surgical complications. FDA requested, as a condition of the initial 2011 approval, two substantial postapproval studies.

  The CoreValve System (Medtronic) 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-French diameter delivery catheter with a set of disposable catheter-

loading components in a procedure that lasts up to 4 hours and requires, on average, a 3–5 day hospital stay. Medtronic received an IDE designation for its CoreValve trial from FDA in October 2010, and trials are under way.

In May 2012, CMS released a national coverage determination stating that CMS "covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)" when the procedure is used for "the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication" and when numerous conditions are met, including the required credentials and experience of the facilities and surgeons who perform the procedure.

The Sapien valve device costs a reported $32,500. The technology requires significant and costly infrastructure investments (hybrid operating room costing $3 million to $4 million to build); a new type of interdisciplinary cardiac care team in which the interventionalist and surgeon work together with technologists, cardiac nurses, and an anesthesiologist; a special recovery room; the ability to convert to open surgery if needed; and extensive training of the entire team.

- **Key Expert Comments**: Experts commenting on this intervention agreed that it would 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 thought that this intervention would improve patient health outcomes and that an increase in patient volume and a shift in care setting (from outpatient to inpatient) would occur as this intervention diffuses. Expert opinions diverged about whether and how much this intervention would disrupt health care infrastructure, but agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs associated with this patient population.
- **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 treating 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. In 2013, investigators 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±2%), suggesting that sicker patients also reaped a benefit from MitraClip. Investigators reported 30-day mortality of 2.9%. Also in 2013, investigators reported outcomes from 117 patients in the GRASP Registry. Investigators

reported acute procedural success in all patients and no procedure-related mortality. Outside the United States, the manufacturer issued a product recall in 2011 and a safety advisory in early 2013. Both issues were related to potential problems with the MitraClip delivery system that could malfunction and require emergency open-heart surgery to correct. FDA is reviewing a marketing application for the device and is expected to issue a final decision by the end of 2013. MitraClip received the Conformité Européene (CE) mark for marketing in Europe in 2008 for use as a nonsurgical option in patients with severe MR.

- **Key Expert Comments**: Overall, experts commenting on this technology agreed this procedure addresses a considerable unmet need and has the potential to improve patient health, although some experts thought more data concerning safety and long-term outcomes are needed. Experts were split on whether this technology would disrupt health care delivery. Some experts believe that little disruption to health care delivery would occur because the infrastructure is already in place, while other experts believe that the increase in patient volume might cause a large disruption to health care delivery. The majority of experts believe the MitraClip would increase health care costs, but more long-term data are needed to determine whether it would decrease long-term costs by reducing the need for standard therapy for this population.
- **Potential for High Impact**: High

Arrhythmia Intervention

Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Treatment of Life-Threatening Ventricular Tachyarrhythmias

Unmet need: Implantable cardioverter-defibrillators (ICDs) are an established therapy to prevent sudden cardiac arrest from ventricular arrhythmias. Conventional ICDs have a transvenous lead that is placed in the heart for cardiac sensing and defibrillation.[1] This transvenous lead, however, can cause serious complications, both during and after implantation. Complications such as cardiac tamponade, pneumothorax, and hemothorax can occur during the lead implantation, and lead failure can occur after implantation, which is a major limitation of this therapy.[1] Lead failure can generate unnecessary shocks or fail to provide necessary shocks. Removal of faulty leads is often associated with significant morbidity and mortality. Lead problems have occurred in up to an estimated 40% of cases for some lead models. This has prompted development of an ICD system that replaces conventional transvenous leads with a single subcutaneous lead in the chest.[1-3]

Intervention: The Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD®) System is indicated "to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing" (i.e., the device is approved only for patients who do not require a pacemaker or pacing therapy).[4,5] The S-ICD System components consist of the SQ-RX® pulse generator, the Q-Trak® subcutaneous electrode, the Q-Guide™ electrode insertion tool, and the Q-Tech™ programming system.[6] The battery-powered, computer-controlled pulse generator is intended to detect cardiac activity and provide defibrillation energy to the heart through the single subcutaneous electrode; the manufacturer states that the battery lasts 5.1 years.[6,7] The external programmer is designed to allow clinicians to set parameters for the pulse generator and retrieve data.[6]

According to the manufacturer, a physician typically implants the S-ICD during an outpatient procedure using anatomic landmarks rather than fluoroscopic imaging guidance to position the device.[7-9] To implant the device, a physician creates a pouch for the pulse generator beneath the skin under the left arm using an incision along the rib cage around the fifth and sixth intercostal spaces at the mid-axillary line.[7] Two small incisions to the left of the sternum are used to thread the subcutaneous electrode under the skin and connect it to the pulse generator.[7] Before closing the incisions, the physician tests and adjusts the system using the external programmer.[7,8]

Clinical trials: In February 2013, Jarman and colleagues reported on the early phase clinical experience using the S-ICD in the United Kingdom.[10] Investigators surveyed all UK hospitals implanting the S-ICD, of which 76% (19 of 25) of hospitals responded with data on 111 patients. Patients had a median age of 33 years (range 10–87 years). Underlying pathologies treated with the S-ICD included: primary electrical disease, 43%; hypertrophic cardiomyopathy, 20%; ischemic cardiomyopathy, 14%; congenital heart disease, 12%; idiopathic dilated cardiomyopathy, 5%; and other cardiomyopathies, 6%.[10] Overall, 17% of patients (19 of 111) required 20 repeat operations related to S-ICD placement, including 9% of patients (10 of 111) in whom the device was permanently removed.

During the study period, S-ICDs delivered 24 appropriate shocks, including 10 shocks for ventricular fibrillation, in 12% of patients (13 of 111). One patient died from a cardiac arrhythmia, but investigators found no instances of the device failing to detect or treat (defibrillate) ventricular arrhythmias above the programmed detection rate. Devices delivered 51 inappropriate shocks in 15% of patients (17 of 111). Among inappropriate shocks, 80% (41 of 51) were due to T-wave

over-sensing. Patients who received inappropriate shocks due to T-wave over-sensing were significantly younger than patients who did not (24±10 vs. 37±19 years; p=0.02).[10]

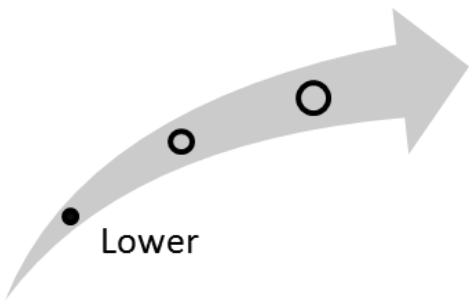
Manufacturer and regulatory status: Boston Scientific Corp., of Natick, MA, makes the S-ICD; Boston Scientific acquired the device's originator, Cameron Health, in 2012.[11] According to the company, the device has been commercially available in Europe and New Zealand since 2009.[8] In the United States, the U.S. Food and Drug Administration (FDA) approved the S-ICD in September 2012.[5] As part of the approval, FDA is requiring Boston Scientific to conduct a 5-year, 1,600-patient postmarket study to assess the device's long-term safety and performance and to assess differences in effectiveness across sexes.[5]

Diffusion: After FDA approval, Boston Scientific planned a phased launch of the system in the United States to ensure that clinicians were trained to use the system in a safe and effective way.[4] As of September 2012 (the latest figures reported), the company stated that more than 1,400 S-ICD systems had been implanted in patients around the world.[4] The device's cost is reported to be similar to costs of conventional transvenous-lead ICDs; however, the procedure may cost less than conventional ICD implantation because it can be performed in an outpatient setting with no need for fluoroscopy or an electrophysiology laboratory, taking less time.[9] The U.S. Centers for Medicare & Medicaid Services (CMS) national coverage determination on ICDs does not mention the S-ICD specifically, but ICDs that are FDA approved are covered as medically necessary when a beneficiary meets certain eligibility criteria.[12] In their coverage policies addressing ICDs (generally updated or revised after FDA approval of the S-ICD), several private, third-party payers that publish their coverage policies online define the S-ICD as investigational or experimental and, therefore, deny coverage for the technology. Third-party payers that deny coverage for S-ICD therapy include Aetna,[13] Anthem,[14] Blue Cross Blue Shield (BCBS) of Arizona,[15] BCBS of Kansas City,[16] BCBS of North Carolina,[17] CIGNA,[18] Empire BCBS,[19] Humana,[20] and United HealthCare.[21]

Clinical Pathway at Point of This Intervention

According to the American College of Cardiology (ACC) and the American Heart Association (AHA), prophylactic ICDs are the preferred treatment for patients with ventricular fibrillation who are at risk of sudden cardiac arrest. For patients who do not meet criteria for an ICD, beta blockers are considered first-line therapy, and radiofrequency ablation might be indicated. For patients with ventricular fibrillation refractory to ICD, drug therapy and radiofrequency catheter ablation or antiarrhythmic surgery might be warranted.[22] The S-ICD system competes directly with standard ICD systems that require a transvenous electrode in the heart. Clinicians might prefer the S-ICD System to other ICD systems because it offers the potential to reduce procedure-related complications and lead-related adverse events, and it does not require imaging during placement.

Figure 1. Overall high-impact potential: Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for treatment of life-threatening ventricular tachyarrhythmias



Overall, experts commenting on this topic thought that this intervention might have some 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 bring about shorter hospital stays. However, some experts suggested that this device's limited capabilities, compared with other ICDs, might temper its diffusion and impact on patient health outcomes. 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, health systems, and health administration backgrounds, commented on this intervention.[23-28] One of these experts declared a potential conflict of interest (COI) because the expert is an electrophysiologist who acts as a consultant to original developer Cameron Health and was an investigator in the S-ICD investigational device exemption (IDE) study.[25] This potential COI is balanced by the perspectives of other experts who reported having no COIs. We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need this intervention purportedly addresses is important and the intervention has potential to meet that need, the experts generally agreed, basing their opinions on both the "high incidence of lead failure in conventional ICDs and the high morbidity and mortality associated with lead failure and replacement in these devices,"[23] as one expert put it. They generally thought that the S-ICD would improve patient outcomes, because of the soundness of the theory underlying the technology and also on the data collected thus far.

Acceptance and adoption: Both patients and clinicians would likely adopt this device if it shows good efficacy relative to existing ICDs, the experts agreed; however a few experts suggested that longer-term data will be necessary before clinicians fully embrace the technology and thought that diffusion might be constrained by the device's limited pacing capabilities. One expert, speaking from a clinical perspective, stated: "The main advantage of the system is its degree of invasiveness, which is much less [than currently available ICDs]. However, there are substantial weaknesses with a device that does not have a [transvenous] lead…does not advocate [the] ability [to perform] event tachycardia pacing or bradycardia pacing …[and] is large and placed in the axilla."[27]

Health care delivery infrastructure and patient management: Because ICD placements are common, this intervention is unlikely to significantly disrupt current care models or operational processes, with a few exceptions, experts noted. First, because the device does not use transvenous leads and can be placed using only anatomic landmarks, specialized cardiac procedure rooms and fluoroscopy or other imaging techniques might be used less, the experts commented. Second, experts commented, the device can be implanted in an outpatient setting, which would shift care from the inpatient to outpatient setting now associated with conventional ICDs. Finally, they noted that physicians implanting the device might require some initial S-ICD-specific training. Although the S-ICD's cost is similar to that of other ICD systems, experts thought that by avoiding lead complications and shifting the setting from inpatient to outpatient surgery, this intervention has the potential to reduce some financial burden.

Health disparities: All experts generally agreed that the S-ICD has minimal potential to affect health disparities among patients who might be candidates for ICD therapy. One expert with a research background suggested that the S-ICD might provide a therapeutic option for a subset of patients who are ineligible to receive a conventional transvenous-lead ICD and for whom medical therapy is not an option.[26]

Genetic Disorder Intervention

Lomitapide (Juxtapid) for Treatment of Homozygous Familial Hypercholesterolemia

Unmet need: Despite the availability of lipid-lowering pharmacotherapies, many patients with homozygous familial hypercholesterolemia (HoFH) do not achieve acceptable lipid levels and remain at increased risk for early coronary events and sudden death.[29] 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).[30,31]

Intervention: Lomitapide (Juxtapid™) is a microsomal triglyceride transfer protein (MTP) inhibitor that is indicated as a daily oral therapy for treating HoFH.[32-34] 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.[35] 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.[35,36] 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.[37]

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."[35]

Clinical trials: FDA approval of lomitapide was based on review of a trial that evaluated the drug in 29 patients with HoFH.[38,39] 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. No patient permanently stopped lomitapide because of liver abnormalities.[38,39]

Manufacturer and regulatory status: Lomitapide is manufactured by Aegerion Pharmaceuticals, Inc., of Cambridge, MA.[35] In December 2012, FDA approved lomitapide capsules for marketing 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.[39] As a condition of approval, FDA required the company to conduct three postmarketing studies: 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.[39]

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.[40]

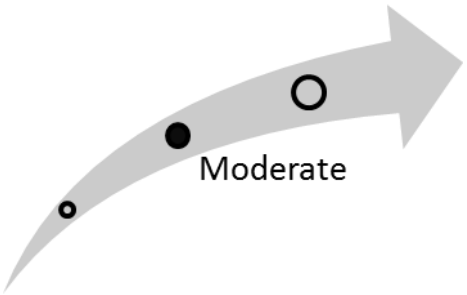
Diffusion: Both lomitapide and mipomersen have boxed warnings on their product labels advising of a risk of severe liver toxicity.[30,37,41] Likewise, both drugs are available only through a Risk Evaluation and Mitigation Strategy (REMS).[30,37,41] A REMS program requires the manufacturer to certify prescribing physicians and dispensing pharmacies to use the drug and documentation of safe-use conditions, including a prescription authorization form for each new prescription.[30] However, lomitapide is administered daily as an oral pill, which could improve patient satisfaction and adherence to therapy. Thus, lomitapide may provide physicians with another treatment option for patients with HoFH.

CMS does not have a national coverage determination for lomitapide, so coverage is at the discretion of local Medicare contractors. Representative, private, third-party payers that include lomitapide in their drug formularies typically have precertification and step-therapy policies in place that govern coverage of the drug.[42-44] These payers generally place quantity limits on the drug and require annual recertification and documentation of patients' positive clinical response from lomitapide before extending coverage to renewed prescriptions for the drug.[42-44] Online pharmacy RxUSA.com listed retail prices for a 28-day supply of lomitapide that range from $21,636 for 5 mg tablets to $27,156 for 20 mg tablets (as of June 5, 2013).[45]

Clinical Pathway at Point of This Intervention

According to the National Human Genome Research Institute, first-line treatment for patients with heterozygous familial hypercholesterolemia includes lifestyle changes (e.g., diet, exercise) and drug therapy with cholesterol-lowering medications (e.g., statins, bile acid sequestrants, ezetimibe, niacin, gemfibrozil, fenofibrate).[46] For patients with HoFH, these therapies are often insufficient, and more aggressive therapies are necessary, including periodic apheresis or, possibly, a liver transplant.[46] 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.[39]

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 with HoFH, lomitapide has moderate to strong potential to fill the current treatment gap between conventional lipid-lowering drugs (e.g., statins) and invasive, resource-intensive treatments like apheresis and, in rare instances, liver transplantation. As an oral rather than injectable drug, lomitapide would likely be adopted widely by physicians for the target population, experts agreed, and they thought that a majority of patients would likely accept the drug as long as their out-of-pocket costs were not cost-prohibitive. Experts generally believe that lomitapide use would be unlikely to cause disruption to the current health care delivery infrastructure or current disease management practices 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.[47-52] One clinical expert reported treating patients with familial hypercholesterolemia but no direct COIs, such as consulting for drug manufacturers.[52] Another clinical expert reported a potential COI as a consultant for drug developers and a clinical trial investigator in the field of lipid lowering, although not specifically related to patients with HoFH.[50] These potential conflicts of interest are balanced by experts who reported no COIs. Expert reviews were collected before the FDA approval of lomitapide in December 2012. We organized the following discussion of expert comments according to the parameters on which experts commented.

Unmet need and health outcomes: For the small population of patients with HoFH, no effective pharmacologic therapy exists to bridge conventional lipid-lowering drugs (e.g., statins) and apheresis, and in rare instances, liver transplantation, the experts agreed. Four experts suggested that lomitapide holds potential to improve patient health, at least moderately, especially given the lack of other effective drug therapies when conventional drugs do not manage the disease. But two experts believe that insufficient data were available to estimate the drug's potential health benefit, with one expert noting that available data suggested a gradual drop in potential efficacy in cholesterol reduction from about 50% at 6 months to 38% at 1.5 years after therapy initiation.

Nevertheless, despite these reservations, all experts agreed that lomitapide has moderate to strong potential to fill the unmet need in effective treatments for HoFH, given that it may represent a bridge between conventional lipid-lowering drugs, such as statins, and invasive treatments, such as apheresis, that are costly, labor-intensive, and may not be readily accessible to all patients with this rare condition.

Acceptance and adoption: Physicians would be likely to widely adopt lomitapide for the targeted population of patients with HoFH, the experts agreed. One clinical expert cautioned against inappropriate overuse of the drug among the broader population of patients with elevated cholesterol not due to a genetic defect as in HoFH, because lomitapide has been associated with an increased risk of liver-related adverse effects.[50] A majority of patients would likely accept lomitapide if their physicians advise it, as long as the (out-of-pocket) cost to patients of lomitapide therapy is not cost-prohibitive, the experts thought.

Health care delivery infrastructure and patient management: Overall, most experts thought that using lomitapide would create little to no disruption to the health care delivery infrastructure or current disease management practices for this patient population. But two experts with clinical and health systems backgrounds anticipated that lomitapide would have a larger, albeit positive, disruptive effect on HoFH patient management. It would do so, they thought, by supplanting labor- and resource-intensive apheresis care and, less commonly, liver transplantation, with outpatient care involving patient self-administration and office-based physician followup to monitor treatment efficacy and identify possible treatment-related liver problems.[50,51]

In evaluating lomitapide's potential impact on treatment costs, expert opinion was divided. Three experts thought that lomitapide might cost substantially more than conventional lipid-lowering drugs but would still most likely cost less than apheresis or liver transplantation in the long-term. Other experts anticipated that adding lomitapide would represent a moderate, incremental increase in treatment costs for this population. One expert with a health systems background expected that third-party payers would require prior authorization to use lomitapide to help control overuse in lower-risk populations with elevated cholesterol levels.[51]

Health disparities: Lomitapide use would have limited potential to affect health care disparities in the treatment of patients with HoFH, according to the opinions of four experts. But two experts,

with clinical and systems backgrounds, suggested that if lomitapide could replace resource-intensive, clinic-based treatment (apheresis) with a self-administered, oral drug therapy, it might reduce disparities by affording more patients access to treatment for HoFH, assuming they have prescription drug insurance and that third-party payers provide coverage.[50,51,53]

Heart Failure Interventions

Pediatric Ventricular Assist Device (Excor) for Pediatric End-Stage Heart Failure

Unmet need: Available forms of mechanical circulatory support to treat end-stage heart failure in infants and children (e.g., off-label use of extracorporeal membrane oxygenation [ECMO]) who are awaiting a heart transplant are inadequate for moderate-to-longer-term use in pediatric patients.[54] Ventricular assist devices (VADs) are an established therapy for adults with end-stage heart failure awaiting a donor heart for transplantation; however, adult VADs are too large and, thus, generally unsuitable for use in pediatric patients.[55] A VAD designed for use in newborns and young children could fill the technology gap that exists for moderate-to-long-term mechanical circulatory support in pediatric patients with end-stage heart failure who are awaiting a suitable donor heart.

Intervention: The Excor Pediatric VAD is a miniaturized pneumatic pump system designed to provide mid- to long-term mechanical circulatory support for infants and children with severe heart failure.[56] According to the manufacturer, the Excor pediatric device is the first VAD designed specifically for use in infants, children, and adolescents.[57] Components of the Excor system are available in a wide range of sizes to accommodate use in pediatric patients from newborn to adolescent age and with various anatomical requirements.[58]

The paracorporeal (i.e., attached to the body) system consists of one or two external blood pumps (depending on single- or two-chamber support) that are connected to the left and/or right ventricular chamber(s) and major arteries through several silicone cannulas that divert blood from the heart and great arteries. Surgeons use conventional open-heart surgical techniques to place the cannulas and connect the Excor Pediatric VAD.[59]

A stationary Ikus driving unit powers the pneumatic pumps with alternating air pressure to pump blood through the external blood chambers via a series of unidirectional polyurethane valves. The Ikus also houses the battery backup system and the computerized components used to monitor and adjust pulse rate, systolic drive pressure, diastolic suction pressure, and relative systolic duration.[56] The Ikus is intended primarily for stationary use operating on main power in a hospital setting; reliance on backup battery power should be restricted to moving a patient within a health care facility or in instances of main power failure.[56]

Clinical trials: In August 2012, Fraser and colleagues reported results from the IDE trial that included 48 pediatric patients, aged 16 years or younger, awaiting heart transplantation who received ventricular support with the Excor device.[60] Patients were divided into one of two 24-patient cohorts based on body size (Cohort 1, <0.7 m^2, median age, 1 year, median weight 9 kg; Cohort 2, 0.7 to <1.5 m^2, median age 9 years, median weight, 31 kg). Investigators compared survival data, with data censored at the time of transplantation or device weaning due to recovery, among the Excor patients with survival data in two propensity-score-matched historical control groups that received ECMO while awaiting transplantation.

In the trial, the primary efficacy endpoint was defined differently for the Excor groups and ECMO control groups. For Excor patients, primary endpoint was time to death or device withdrawal due to unacceptable neurological outcome, defined as either coma or presence of profound sensory, motor, language, or cognitive impairment assessed on the Pediatric Stroke Outcome Measure. For ECMO patients, primary endpoint was only time to death because neurologic status was unavailable from the ELSO (Extracorporeal Life Support Organization) database.

For Cohort 1, the median length of support was 28 days compared with a median of 5 days in the matched ECMO control group ($p<0.001$). The longest duration of support in Cohort 1 was 174

days with Excor compared with 21 days with ECMO. The median time to the primary endpoint (i.e., death or support withdrawal) had not yet been reached at 174 days for Cohort 1 patients, although the median time to the primary endpoint for matched ECMO patients was 13 days ($p<0.001$).

For Cohort 2, the median length of support was 43 days compared with a median of 5 days in the matched ECMO control group ($p<0.001$). The longest duration of support in Cohort 2 was 192 days with Excor compared with 28 days with ECMO. The median time to the primary endpoint for Cohort 2 was 144 days compared with 10 days for matched ECMO patients ($p<0.001$).

Overall, 88% of Cohort 1 patients and 92% of Cohort 2 patients survived to either heart transplantation or weaning because of recovery with the use of the Excor device.[60]

Manufacturer and regulatory status: Berlin Heart GmbH, of Berlin, Germany, makes the Excor Pediatric VAD. In December 2011, FDA granted Berlin Heart marketing approval for the Excor Pediatric VAD under Humanitarian Device Exemption (HDE) status for use in pediatric patients with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support.[61] The HDE regulatory category applies to devices expected to benefit fewer than 4,000 patients per year. The approval process is similar to that for premarket approval (PMA), except that the device is exempt from PMA effectiveness requirements.

As a condition of approval, FDA required the company to conduct a postapproval study to evaluate whether safety and outcomes of Excor use in general clinical practice are comparable to the safety and outcomes reported in the IDE trial.[61,62] According to the company, the Excor Pediatric VAD also has marketing approval in Europe and Canada.[63,64]

Diffusion: CMS provides coverage for VAD therapy as a bridge to heart transplantation under its inpatient procedure payment system when an FDA-approved VAD is used according to FDA-approved, labeled instructions.[65] Private, third-party payers generally cover VAD procedures, including pediatric VADs, as a bridge to heart transplantation when FDA-approved devices are used for FDA-approved labeled indications for patients listed as or under evaluation to become transplant candidates and who are at imminent risk of death without mechanical support.[66-76]

The Excor Pediatric VAD costs about $37,400 and the driver unit costs about $117,000 (as of June 2013).[77,78] The pneumatic drive lines that connect the device to the Ikus driver unit cost about $500 each.[78] The cannulas that transport blood between the heart and great arteries to the external pumping components range in price from about $2,400 to $4,100.[78] Total device cost would depend on the need for single- or dual-chamber pumping support and device configuration.

Clinical Pathway at Point of This Intervention

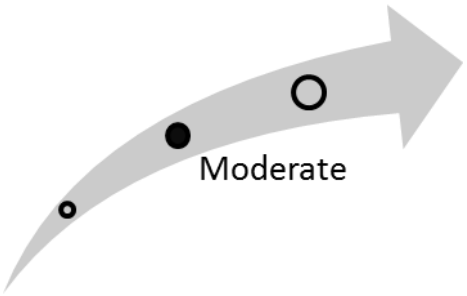
Pediatric heart failure (PHF) is diagnosed using a number of tests to determine the nature of the heart failure. Testing may include chest radiographs, electrocardiograms to monitor heart rhythm, and cardiac ultrasound (echocardiography) to evaluate heart function. In children older than 4 years of age, a physician might also use an exercise stress test to evaluate the patient's cardiac and respiratory function.[79]

PHF can be difficult to manage appropriately if the underlying cause is unknown. When the underlying cause is known, appropriate therapy is prescribed that may include medical and/or surgical management. The main goals of medical therapy for PHF are reducing preload or afterload fluid volume, enhancing cardiac contractility, improving oxygen delivery, and enhancing nutrition.[80] For the majority of PHF cases related to congenital heart defects, physicians may prescribe digitalis, diuretics, and angiotensin-converting enzyme inhibitors to help eliminate excess fluid, lower blood pressure resistance, and improve the heart's pumping capacity. Effective reconstructive surgery (e.g., valve repair or replacement) may be available for appropriate surgical

candidates.[79,81] For PHF related to cardiomyopathy, specific drug treatments are lacking, although symptom management with digitalis, diuretics, or afterload reduction therapy may be used. PHF-related acute myocarditis has broader treatment options, and generally accepted treatment options include supportive therapy with inotropic agents, mechanical ventilation, antiarrhythmic drugs, and antithrombotics.[81]

If heart function continues to deteriorate despite therapy, a patient may be assessed for suitability to undergo heart transplantation.[79] Mechanical circulatory support, including ECMO or VADs suitable for older children, may be used as bridge therapy for patients awaiting a suitable donor heart.[55] However, ECMO generally does not provide safe and effective support for longer than about 3 weeks, especially in newborns. Most available adult VADs are inappropriate for use in infants and smaller children.[54] The Excor Pediatric Ventricular Assist Device is indicated for longer-term use as a bridge to heart transplantation in pediatric patients with severe left ventricular or biventricular dysfunction who are transplant candidates and require circulatory support.

Figure 3. Overall high-impact potential: pediatric ventricular assist device (Excor) for pediatric end-stage heart failure



Experts noted that this technology would fill a large unmet need for very young pediatric patients (i.e., infants to age 5 years) who have severe heart failure and are awaiting heart transplantation. However, experts cautioned that although this technology might help extend the length of time that pediatric transplant candidates could wait for a donor heart, the availability of donor organs for this population would ultimately determine the impact on long-term health outcomes. Experts anticipated wide acceptance of this technology at pediatric heart transplant centers and did not expect it to cause significant disruption at these centers, which are experienced in staff- and resource-intensive patient care. Pediatric VADs were unlikely to alter health care disparities for this patient population, experts concurred. 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, and health systems backgrounds, offered perspectives on this intervention.[82-87] One clinical expert reported participation in clinical trials of other VADs designed for adult patients (Thoratec and WorldHeart devices).[86] These potential COIs are balanced by experts who reported having no COIs. We organized the following discussion of expert comments according to the parameters on which the experts commented.

Unmet need and health outcomes: Expert opinions varied on the importance of the unmet need this device addresses. Half thought the need was moderately important, given the relatively small number of infants and children affected in the PHF population and the availability of one other pediatric VAD (DeBakey HeartAssist) for patients older than 5 years of age. However, other experts thought the unmet need was very important because of the current lack of VADs suitable for long-term bridge to heart transplantation in newborns and children up to the age of 5 years.

Patient health has moderate potential to improve with use of the technology because it extends the waiting period for an appropriate donor heart, the experts generally thought. However, experts concurred that many of these patients would continue to face severe health issues, such as infection and thrombotic events, with or without the new technology. Thus, this technology would likely have a moderate potential for improving patient health in this population because of the severity of the condition and the very shallow organ-donor pool available for heart transplant in this population. One expert with a research background downplayed the technology's potential impact even further, believing outcomes reported so far indicate the technology's potential impact will be minimal.[82]

Acceptance and adoption: Clinicians and children's families would demonstrate moderate to wide acceptance of the Excor device, the experts surmised. They thought family acceptance would be higher than clinician acceptance overall, given the lack of options for severe PHF in infants and small children. One expert with a research background thought an initial clinician learning curve in using the device would be seen.[87] Clinician acceptance of this technology could be broadened, two experts thought, by applying lessons learned from VAD experience in adult patients to the pediatric VAD population.[86,87]

Health care delivery infrastructure and patient management: The use of the Excor pediatric VAD is unlikely to cause significant disruption to health delivery infrastructure at hospitals that adopt the technology, the experts agreed. Although the technology requires a highly trained, experienced team of PHF specialists, centers most likely to use the Excor already have teams experienced in ECMO and other labor-intensive, invasive technologies, including pediatric VADs intended for use in older children. Similarly, patient management is unlikely to change substantially with addition of the Excor, the experts agreed, because these patients already requires substantial monitoring and clinician intervention because of their high-risk status as patients with PHF.

Health disparities: Experts generally anticipated minimal to no change in health disparities with the use of the Excor. One clinical expert surmised that a patient's insurance coverage status could affect disparities by determining access to advanced care for PHF, whether or not the Excor device was used, because of the substantial costs involved.[86]

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

Unmet need: Traditionally, artificial heart technology has involved using large, hospital-based pneumatic driver systems. This technology requires patients to be hospitalized and tethered to a driver console that powers the implantable components while they wait for a donor heart to become available.[88,89] A therapeutic option that would allow these patients to leave the hospital and receive artificial-heart support at home while awaiting a donor heart conceivably has the potential to lower treatment costs and improve quality of life.[90]

Intervention: The temporary Total Artificial Heart (TAH-t) is a biventricular, implantable device that functions in place of the two failing 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.[91,92] The system is large and cumbersome and requires patients to remain hospitalized while awaiting a donor heart.[93] The Freedom Driver is a wearable pneumatic driver designed to power the TAH-t and is intended to allow patients receiving the TAH-t to leave the hospital and live at home while awaiting a donor heart. The patient wears/carries the 13.5 lb pneumatic driver 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 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.[93]

Clinical trials: Literature searches have not identified any completed published clinical trials using the Freedom driver, although the company has reported some preliminary results for 41 patients in the Freedom Driver IDE trial. The clinical experience of one individual patient has been published as a case summary.[94]

A 60-patient SynCardia Freedom Driver System Study, an FDA-approved IDE trial, is in progress and is scheduled for completion in September 2013.[89] The company has reported on its Web site that as of November 19, 2012 (the most recent posted update as of June 11, 2013), 55 TAH-t patients had been enrolled in the Freedom driver clinical study (including two patients under compassionate use).[90] Of these patients, 41 had been discharged home using the Freedom portable driver. The Freedom Driver IDE trial requires a minimum of 30 discharges with the portable driver.[90]

Manufacturer and regulatory status: SynCardia Systems, Inc., of Tucson, AZ, makes the TAH-t and Freedom Driver. In October 2004, FDA approved the TAH-t as a bridge to transplant.[95] The portable Freedom Driver is under evaluation in an FDA-approved IDE trial.[93] 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.[96]

Diffusion: The device is available only through the IDE trial or under compassionate use at this time in the United States.

SynCardia has publicly reported on its Web site that as of October 2012 (latest posted information), 100 patients had been supported with the Freedom driver worldwide.[93] The company has periodically distributed limited, anecdotal information in press releases. The most recent press release (May 30, 2013) stated that a 35-year-old man treated at the University of Arizona Medical Center was discharged home and supported for approximately 62 days with the Freedom driver before he underwent heart transplantation.[97] SynCardia issued three other press releases in 2013 relating limited information about three other men who were supported with the Freedom driver: a

31-year-old man treated at Intermountain Medical Center (Salt Lake City, UT; March 21, 2013),[98] a 74-year-old man treated at Penn State Hershey Medical Center (Hershey, PA; January 15, 2013),[99] and another 35-year-old man treated at Ronald Reagan UCLA Medical Center (Los Angeles, CA).[99] However, these news releases did not specify how long the men had been supported with the Freedom portable driver.

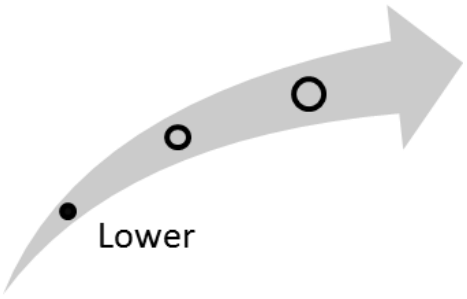
Costs for the portable driver system have not been established in the United States. Total cost of care for patients with artificial hearts using the portable driver at home would be expected to be considerably lower than those of hospitalized patients with artificial hearts. However, ambulatory patients would need regular home visits from nurses trained in use of the device as well as followup clinic visits with specialist physicians to monitor device function and patient health status. Further, 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.

Reported costs for TAH-t kit are about $124,700; the kit includes a patient simulator for physician training, tubing, and surgical disposables in addition to the device itself. The external control console costs about $92,000. Hospitals must also maintain a continuously available backup control console. Hospitals may be able to rent the control consoles as part of an annual service agreement with the manufacturer. Staff training costs to meet manufacturer's device-related certification requirements are an estimated $98,000 in addition to device costs.[100,101]

Clinical Pathway at Point of This Intervention

ACC/AHA clinical guidelines identify VAD implantation and cardiac transplantation as the only established surgical treatments for end-stage heart failure.[102] The portable driver system is intended to complement TAH-t use.[93] As a bridge to transplantation, the TAH-t with the Freedom driver would complement heart transplantation. Some left ventricular assist devices (LVADs) 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 4. Overall high-impact potential: Portable Freedom Driver for in-home support of the temporary Total Artificial Heart



Although the patient population for which this device is intended is small and in-hospital driver systems already exist to support patients with a TAH-t, a portable driver for the TAH-t system has the ability to improve patient quality of life and dramatically shift the care setting 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 reduce costs associated with lengthy hospital stays and that using the portable device would require additional resources, such as training for staff and family members. 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

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[103-109] We organized the following discussion of expert comments according to the parameters on which experts commented.

Unmet need and health outcomes: Although they noted that the patient population for which this device is intended is small, experts 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. 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 allowing patients awaiting a heart transplant to do so at home.

Because patients using this device can return home to live, it could provide a psychological benefit of improved quality of life, the experts generally thought. They also believe a potential health benefit would arise from increased mobility. Some experts suggested a further health benefit may be realized in getting patients out of the inpatient hospital setting with its associated risk of nosocomial infections. Some experts likened this technology's potential to that of ventilators and VADs, which have been moved from the hospital setting to the home-care realm with positive results.

Acceptance and adoption: Both clinicians and patients would readily adopt this technology because of its potential for lower costs and improvements in patient quality of life and health status, the experts thought, provided long-term data are positive. Although several experts also noted that extensive training (on the part of both hospital staff and patient home caregivers) would be required for diffusion 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 patient 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. Experts noted, however, that few data are available to illustrate this presumption. Some experts anticipated that moving these patients home may simply shift care, and consequently costs, and increase the need for home-care personnel with experience in treating patients who have received artificial hearts.

The shift in care setting has potential to change case management. The shift could "substantially impact the aftercare community and require additional collaboration and coordination between inpatient and outpatient facilities," said one expert with a health systems background, reflecting others' opinions as well.[106] A clinical expert expected a larger disruption in current management of patients who have artificial hearts, noting, "This [device] will require patients and families to learn and take ownership – and in turn family knowledge, attitudes, availability, and dynamics all have to be evaluated for implant suitability."[105]

Experts generally expected disruptions to the way these patients are currently managed, with moderate overall disruption to clinical patient management, and larger disruption for patients and their home caregivers/families who would need to play a more active role in caring for these patients at home than if the patient remained in hospital.

Health disparities: Experts generally agreed that the portable Freedom driver was likely to have minimal effect on health disparities. One expert with a research background suggested that the technology might potentially decrease access to care "due to the need for extensive caregiver support and training, [and] proximity to facilities that could handle this level of care.[107]

Hypertension Intervention

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

Unmet need: Lowering high blood pressure has been associated with lower rates of stroke, heart attack, and heart failure,[110] and many pharmacotherapies are available for treating hypertension.[111] Strict adherence to recommended medical therapy can provide effective blood pressure control for most patients.[112] However, even in highly motivated patients, several factors may affect the efficacy of antihypertensive therapy, including interaction with other prescription and over-the-counter medications as well as various foods, vitamins, and herbal supplements.[112] Because uncontrolled hypertension is associated with high morbidity and mortality, novel interventions for treating this condition are needed.[111]

Intervention: The sympathetic nervous system contributes to increases in blood pressure.[113,114] Afferent renal sensory nerves, which carry signals from the kidneys to the central nervous system, also play a role in promoting sympathetic outflow and are considered additional contributors to hypertension.[115] Surgical disruption of renal sympathetic nerves has been explored for decades as a potential therapeutic intervention for hypertension.[116]

Earlier approaches usually involved radical sympathetic denervation, which reduced blood pressure but was not sufficiently targeted to avoid perioperative and long-term complications (e.g., bowel, bladder, erectile dysfunction; postural hypotension).[116] The Symplicity® Renal Denervation System™ is intended to replicate the blood pressure improvements seen with radical sympathetic denervation, but avoid its associated side effects.[116]

The Symplicity system uses radiofrequency energy delivered via catheter technology to selectively ablate afferent and efferent renal nerves located in the adventitia of the renal arteries.[115] The manufacturer purports that bilaterally denervating the renal nerves with the Symplicity system can achieve a sustainable decrease in blood pressure.[117] According to the manufacturer, the system comprises two components: a generator that automatically controls the radiofrequency energy delivery and is activated by a hands-free switch and a catheter that applies the radiofrequency energy to the renal artery and is compatible with 6 French (Fr) diameter guide catheters.[118-120]

The denervation procedure is performed in a catheterization laboratory with the patient under conscious sedation; the procedure takes about 40 minutes to complete.[118,121,122] The manufacturer states that to perform the procedure, a physician introduces the catheter through the femoral artery via a guide catheter and threads it to the renal artery. The catheter's tip is placed against the arterial wall, and clinicians deliver radiofrequency energy to the surrounding sympathetic nerves; the energy is managed via a computer-controlled algorithm.[118] The physician may apply up to six ablations, lasting up to 2 minutes each, within each renal artery.[122] The manufacturer states that because the one-time procedure does not involve a permanent implant, patients recover and return to their activities of daily living quickly.[117]

Clinical trials: In March 2013, investigators reported 24-month results from Symplicity HTN-2, the first randomized, controlled, crossover trial investigating renal denervation.[123] Among 40 patients randomly assigned to receive Symplicity renal denervation, blood pressure dropped significantly at 24 months by -29/-10 mm Hg from 178/97 mm Hg at baseline ($p<0.01$). Among 26 randomly assigned control group patients who later crossed over to receive renal denervation after 6-month primary endpoint assessment (crossover group), average blood pressure dropped at 24 months by -35/-13 mm Hg from 178/98 mm Hg at baseline ($p<0.01$). Investigators noted that average blood pressure reductions at 24 months had been preserved compared with reductions achieved for both groups at 6, 12, and 18-month followup. Further, investigators observed no device-related serious adverse events, no late vascular complications, and no significant declines in

kidney function at 24 months compared with patients' baseline values. Investigators also observed that pulse pressure improved significantly by -18.5 mm Hg from baseline for the initial treatment group ($p<0.01$) and by -22.5 mm Hg from baseline for the crossover group ($p<0.01$). Pulse pressure is the numeric difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP); higher pulse pressures have been associated with increased cardiovascular complications, especially in older patients.[123]

Also in May 2013, Symplicity's manufacturer announced 6-month safety results from 617 patients in the Global Symplicity Registry (which includes patients outside the United States).[124] Investigators reported no major complications or serious adverse events related to Symplicity renal denervation. Two patients experienced vascular complications at the catheter access site immediately after the procedure. Angiography revealed a renal vessel irregularity in 9% of patients after the procedure due to the application of radiofrequency energy to the vessel wall. However, no detected vessel irregularities interfered with brisk renal blood flow. Investigators surmised that all vessel irregularities had resolved shortly after the procedure.[124]

Besides the registry's primary safety analysis, analysis of available data for the secondary efficacy endpoint at 6 months showed renal denervation significantly reduced both office and ambulatory blood pressure measurements compared with baseline measurements. Patients with SBP of more than 180 mm Hg and DBP of more than 100 mm Hg (n=17) showed an average reduction of -30/-16 mm Hg from baseline at 6 months (SBP $p<0.0002$; DBP $p<0.0008$). Among patients with SBP of more than 160 mm Hg (or more than 150 mm Hg in diabetic patients) (n=114), blood pressure dropped by an average of -18/-9 mm Hg from baseline at 6 months ($p<0.0001$). Among 29 patients who also had 24-hour ambulatory blood pressure measurement (n=29), blood pressure fell by an average of -11/-4 mm Hg from baseline ($p<0.0001$).[124]

A 2012 health economics study reported that catheter-based renal denervation is cost-effective and may lower cardiovascular morbidity and mortality in patients with treatment-resistant hypertension.[125]

Manufacturer and regulatory status: Medtronic makes the Symplicity system, which it acquired when it bought developer Ardian, Inc., in 2011. The system is available only for investigational use in the United States but is approved for marketing in the European Union and Australia.[126] Other renal denervation systems are in development. St. Jude Medical, Inc. (St. Paul, MN), received European marketing approval for its EnligHTN™ renal denervation system in May 2012.[127] Boston Scientific is developing its Vessix™ Renal Denervation System, which is under evaluation in early phase clinical trials in Europe.[128]

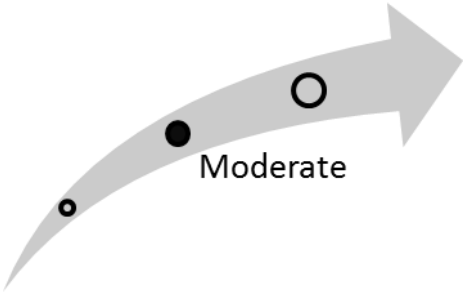
Diffusion: On May 23, 2013, Medtronic announced it had completed patient random assignment for Symplicity HTN-3, a 530-patient, phase III trial intended to support a PMA application to FDA for its Symplicity renal denervation system.[129] The company also announced that the Symplicity device would be evaluated under the relatively new FDA-CMS parallel review program, which enables CMS to begin a national coverage determination process for an intervention while FDA conducts its safety and efficacy review. Medtronic reported that Symplicity HTN-3 trial data would comprise a substantial component of the parallel review.[129] U.S. pricing of the Symplicity technology has not been reported yet.

Clinical Pathway at Point of This Intervention

According to the most recent report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, lifestyle modifications (e.g., weight and diet management) are the initial interventions used in patients with hypertension. If lifestyle changes do not result in satisfactorily controlled blood pressure, pharmacotherapy is indicated.[110] Medical

management of hypertension includes thiazide-type diuretics, used alone or in combination with one of several classes of antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, or calcium channel blockers).[110] If the Symplicity Renal Denervation System is approved for use in the United States, it is likely to be positioned for use in treatment-resistant hypertension that has not adequately responded to three or more antihypertensive medications. These medical therapies are likely to be used in conjunction with the renal denervation procedure.[118,130]

Figure 5. Overall high-impact potential: catheter-based radiofrequency ablation (Symplicity System) renal denervation for treatment-resistant hypertension



Experts commenting on this intervention agreed that it has potential to fill an important gap in treating hypertension and would likely be accepted by clinicians and patients. However, this intervention's potential impact is tempered by the need for longer-term outcomes data. The procedure is expected to be easily incorporated into the existing health care infrastructure (i.e., using a catheterization laboratory). Several experts agreed that the intervention would likely increase the number of patients treated in catheterization labs and would represent a shift in patient management away from medical therapy to a procedure. 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.[131-136] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The need for effective interventions for treatment-resistant hypertension is important, experts agreed, because of the size of the affected population, the morbidity and mortality associated with the condition, and the dearth of available treatments once pharmacotherapy fails to achieve desired outcomes. The experts were cautiously optimistic that this intervention is likely to improve patient health, citing the promising efficacy data that have been collected to date. However, several experts noted that the available data are limited, and several experts want to see longer-term studies to determine whether the reduction in blood pressure observed in trials translates to improved clinical outcomes and to further clarify the safety profile of the intervention.

Acceptance and adoption: Expert opinions varied regarding the degree of acceptance of this intervention by both clinicians and patients. Some experts thought that clinicians would likely adopt the technology because alternative treatments do not exist for this population and because the intervention requires only a one-time procedure. On the other hand, some experts suggested that the invasiveness of the procedure might pose a barrier to acceptance by some patients. Additional data anticipated by the phase III U.S. pivotal trial and the ongoing global registry are eagerly anticipated.

Health care delivery infrastructure and patient management: Most experts suggested that this intervention would not especially disrupt health care infrastructure because the procedure will be performed in a catheterization laboratory, which as one clinical expert stated, "could accommodate patient volume, assuming it is an outpatient procedure, is not associated with significant complication, and requires a single sitting application."[131] However, several experts agreed that this intervention would likely increase the volume of patients seeking services from catheterization labs and would represent a shift in patient management away from office-prescribed medical therapy over the long term should this intervention be shown to reduce the need for ongoing hypertension pharmacotherapy.

Most experts expected 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 proved to improve patient health.

Health disparities: Experts were about evenly divided regarding renal denervation's potential to affect health disparities. Experts who thought the technology would have minimal to no impact on changing disparities anticipated that the technology would be likely expensive and, thus, could increase disparities among patient populations with less access to care, particularly African Americans. One clinical expert added that the expensive therapy may not be covered by some health plans, at least initially, potentially creating further disparities among patients without health insurance; however, "it may help those without prescription drug coverage if it decreases the number of medications they need."[135] Another clinical expert surmised that if this technology shows long-term effectiveness, it could potentially have a large effect on reducing disparities if poor patients have access to it because "poor patients often have trouble getting medications and are often noncompliant."[131]

Myocardial Infarction Intervention

Standardized Protocol and Integrated System (RACE Project) for Treatment and Transfer of Patients with ST-Segment Elevated Myocardial Infarction

Unmet need: Despite the substantial amount of evidence that supports the effectiveness of rapid reperfusion therapy in patients with ST-segment elevation myocardial infarction (STEMI), an estimated 18% to 50% of patients eligible for therapy do not receive it. Further, fewer than half of patients in the United States receive reperfusion treatment within the timeframes recommended by current treatment guidelines.[137] Systemic barriers to providing timely reperfusion for patients with STEMI include the following:[137]

- Administration issues (e.g., bed availability)
- Ambiguous leadership
- Competition among health care facilities for patients
- Inconsistent use of prehospital electrocardiogram (ECG) and fibrinolysis
- Lack of integrated health care and coordination
- Lack of standardized protocols and feedback
- Legislative issues (e.g., the Emergency Medical Transfer and Active Labor Act)
- Reimbursement issues
- Transportation and transfer issues among facilities

Intervention: The Reperfusion of Acute Myocardial Infarction in Carolina Emergency Departments (RACE) project was developed in North Carolina to address some of the barriers to timely STEMI treatment by aligning physicians, nurses, hospitals, emergency medical service (EMS) personnel, professional societies, payers, and government entities in a regionally organized, collaborative, statewide initiative.[137,138] The program developers have stated their desire to "establish a statewide system for reperfusion, as exists for trauma care, to overcome systemic barriers."[139] Among the RACE Project's goals are decreasing delays in administration of reperfusion therapy, increasing the frequency with which reperfusion is provided to eligible patients, and improving care processes (e.g., improving the proportion of patients presenting via EMS who arrive with prehospital 12-lead ECGs).[137,138]

For each hospital participating in the project, the RACE team works with appropriate administrators, nurses, physicians, and technicians to devise a unique "coronary reperfusion plan," based on medical evidence, published guidelines, available resources, and regional and local practice patterns.[139] Even though the resulting systemic changes vary from hospital to hospital, the RACE team provides an overall set of recommendations to each hospital in the form of an operations manual.[139]

Specific recommendations may include the following:[137]

- For EMS-level interventions, prehospital ECGs, a statewide training program for ECG interpretation, and preferential transport to primary percutaneous coronary intervention (PCI) for certain patients.
- For emergency departments lacking primary PCI capacity, an algorithm for fibrinolytic therapy rather than transfer for primary PCI, based on ACC/AHA guidelines.
- For improving inter-hospital transportation, an algorithm for preferred transportation method for each PCI center and standards for rapid assessment (10 minutes from landing to takeoff time) and transfer with helicopter transport.
- For primary PCI center catheterization laboratories, a plan for "thirty minutes from contact to catheterization laboratory readiness, 24 hours a day, seven days a week," and immediate

feedback, including recording and reporting first door-to-balloon time to the referring emergency department.

Clinical trials: In 2011, investigators reported "door-in-door-out" times before and after implementation of the RACE program for 436 patients treated for STEMI at 55 North Carolina hospitals without primary PCI capability.[138] Investigators found that median door-in-door-out times improved significantly after RACE program intervention, from 97 minutes at baseline (interquartile range, 56–160 minutes) to 58 minutes after RACE program intervention (interquartile range, 35–90 minutes; $p<0.0001$).

Changes resulting from the RACE program reduced door-in-door-out times independently for care processes in the hospital (-17.7 minutes [95% CI, -27.5 to -7.9]), emergency department (-10.1 minutes [95% CI, -19.0 to -1.1]), and emergency medical services (-7.3 minutes [95% CI, -13.0 to -1.5]). Adopting all RACE-recommended EMS processes was associated with the shortest median time to treatment (44 minutes vs. 138 minutes for hospitals that adopted none of the RACE recommendations to revise EMS processes).[138]

In 2010, investigators reported on 2,023 patients treated for STEMI before and after RACE program implementation, including 1,140 patients treated at primary PCI-capable hospitals and 923 patients treated at non-PCI hospitals.[140] The team found that RACE-recommended interventions were associated with statistically significant improvements in treatment times in women and the elderly, for each of the following measures: door-to-ECG time ($p<0.05$), door-to-device ($p<0.05$), door-in-door-out ($p<0.05$), and door-to-needle (for intravenous thrombolysis) ($p<0.05$). Investigators found no significant differences in treatment times between African Americans and white patients at PCI-capable hospitals. RACE program changes suggested a 4.4-minute reduction in the baseline time-to-treatment disparity between women and men for door-to-ECG times (95% CI, -8.1 to -0.4; $p=0.03$). However, investigators noted that after RACE program interventions, an age-related time-to-treatment gap persisted in the elderly, relative to younger patients.[140]

Program developers and funding: The RACE project was developed by a consortium of North Carolina health care providers, the Duke Clinical Research Institute of Duke University Medical Center (Durham, NC), the North Carolina chapter of ACC (Raleigh, NC), and Blue Cross and Blue Shield of North Carolina (Durham, NC).[141] A literature search did not yield information on the costs associated with the RACE project. In a presentation on the project, the program's executive director has listed several funding sources, including the Medicare Quality Improvement Organization, AHA, third-party payers such as the Blue Cross Blue Shield Foundation, hospitals, State government, and other foundations and philanthropic sources.[142]

Diffusion: In mid-2012, the Duke University Center of Clinical Excellence and AHA announced the start of a national effort modeled in part on the RACE program, titled the Regional Systems of Care Demonstration Project – Mission: Lifeline® STEMI Systems Accelerator.[143] The national demonstration project planned to enroll 20 regional sites across the United States for comprehensive implementation of regional emergency cardiac care systems. The national project identified five target objectives, as outlined in its project manual:[144]

- Increase the rate and speed of reperfusion for STEMI cases
- Establish a predetermined plan for identification of STEMI, acute treatment, and timely disposition to the most appropriate hospital
- Empower the EMS and non-PCI emergency departments to determine the best reperfusion plan and most appropriate destination protocol
- Improve the care of high-risk STEMI patients

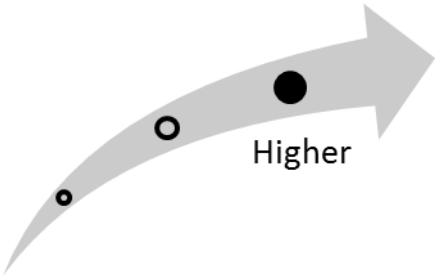
- Perform a baseline assessment to create an ideal plan for system improvements, and implement these improvements through ongoing data assessment and feedback at quarterly intervals for at least 1 year

As of June 2013, the RACE Project involved 119 hospitals and 540 emergency medical agencies across North Carolina. The newest phase of the program is called RACE CARS (Cardiac Arrest Resuscitation System), which focuses on improving care for patients who experience out-of-hospital cardiac arrest.[145] Additionally, program developers in North Carolina redefined the RACE acronym as "Regional Approach to Cardiovascular Emergencies" to encompass a broader overall mission that will expand the model to include expedited emergency care for patients who experience cardiac arrest and stroke.[146]

Clinical Pathway at Point of This Intervention

ACC and AHA recommend in their clinical guidelines that patients with STEMI be treated with fibrinolysis within 30 minutes from symptom onset, or primary PCI within 90 minutes from onset.[137] However, various health care system factors present challenges in meeting these recommended treatment goals.[137] The RACE model was developed to address some of these factors and challenges on a systems level. In particular, the RACE model aims to reduce the time to primary PCI for patients transferred from hospitals that are not primary PCI-equipped to hospitals that are able to perform primary PCI.[139] Currently, only 4% of these patients are treated within the 90-minute treatment window.[137]

Figure 6. Overall high-impact potential: standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-segment elevated myocardial infarction



Experts commenting on this intervention agreed that increasing the number of patients who receive timely access to recommended STEMI treatment could fill a large unmet need and could make a substantial contribution to improving patient outcomes. Given the success in reducing time to treatment demonstrated in clinical trials, experts concluded that the RACE project provided a good model for other States to follow in establishing their own programs to expedite and expand access to guideline-directed STEMI care. However, effective implantation of regional programs to improve STEMI treatment would require acceptance and participation from all parties involved in patient care, including paramedics and emergency medical technicians and medical transportation teams, hospital administrators, and clinicians in emergency departments and cardiac catheterization laboratories. Several experts also believe that if effectively implemented, programs designed to expedite guideline-directed STEMI care have substantial potential to reduce health care disparities by overcoming geographic and other barriers that currently affect how patients with STEMI are treated. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this program.[53,147-151] One expert with a background in health systems and administration reported being a director at the ACC with responsibility for overseeing the national "Door-to-Balloon" project at the same time the RACE Project was in progress. However, the expert reported no input on the administration, development, or operation of the Door-to-Balloon project, although some individuals were involved with both projects.[151] These potential COIs of interest are balanced by experts who did not claim COIs. We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Increasing the share of patients who receive timely access to STEMI treatment, as recommended in clinical guidelines, continues to represent a substantial unmet need throughout the U.S. health care system, all experts agreed. Basing their opinions on the RACE Project's reported success in reducing time and barriers to STEMI treatment in North Carolina, all experts concurred that the project has substantial potential to improve patient health. One expert suggested that the RACE Project could potentially improve patient health further by adding education elements for patients and primary care physicians that stress the urgency of seeking medical help when severe chest pain develops.[150] Overall, the experts concluded that the RACE Project represents great potential to fill an unmet need by providing a good model on which other States could pattern their own initiatives to improve patient access to timely STEMI treatment.

Acceptance and adoption: The experts agreed that most physicians would be likely to accept the systemic changes necessary to implement the RACE Project because of the potential improvement in patient outcomes. However, five experts suggested that some physicians and smaller health care facilities could resist implementation because of concerns that participating in this type of initiative could decrease their revenues by lowering their volumes of STEMI cases.[53,147,148,150,151] One expert noted that because roughly one-third of eligible hospitals did not participate in the RACE Project [at the time of the published study], investigators should continue to analyze and address potential barriers to project participation.[151] The experts generally agreed that most patients would overcome their perceived preferences for familiar local hospitals and physicians in favor of transfer to another facility better equipped to treat STEMI when they are taught about the project's goal of potentially improving their outcomes.[53,147-151]

Health care delivery infrastructure and patient management: Implementing a program like RACE has substantial potential to disrupt the current health care delivery infrastructure for STEMI patients at several levels, five of six experts responded.[53,147-149,151] Successful implementation would probably require extensive communication and coordination among stakeholders in the chain of STEMI care, especially EMS, medical transportation, emergency departments, and cardiac catheterization laboratories. But the sixth expert thought that implementing a program like the RACE Project would produce a smaller disruption to the current health care delivery infrastructure. This expert suggested that State government involvement might be required to improve the success of this kind of project in cases in which some hospitals decline to participate because of concerns about lost revenue from transferred STEMI patients, and that nonparticipating hospitals might experience bad media coverage and a smaller patient base as a result of their nonparticipation in the care-improvement program.[150]

Patient management changes were seen as being related to infrastructure changes. Experts generally agreed that the largest change to how STEMI patients are managed would be timely performance of emergency PCI in all appropriate patients by redirecting emergency transport of STEMI patients to the nearest PCI-capable hospital or rapidly transferring them from their local non–PCI-capable facilities.

Overall, experts suggested that implementing the RACE Project could have a moderate to large impact on health care costs.[53,147-151] Implementing a RACE Project would likely involve high start-up costs; however, the program has the potential to reduce some long-term costs by avoiding morbidity and mortality in patients who previously may not have received timely STEMI care, as recommended in clinical guidelines. One expert concluded that the RACE Project would increase cost-effectiveness of STEMI care, although total treatment costs and "who pays what" for STEMI care would be unlikely to change substantially.[150] Another expert suggested the lack of reimbursement for transferring hospitals could be a major factor in several hospitals' decision to decline participation in the RACE Project. This expert also cited the potential for a large increase in transportation costs, especially helicopter transport, to send all STEMI patients to a PCI-capable hospital; these costs would need to be taken into consideration when planning a RACE Project.[151]

Health disparities: Five experts generally agreed that if effectively implemented in a State, the RACE Project has substantial potential to reduce health care disparities by trying to provide the most effective, recommended care to STEMI patients, regardless of their location.[53,147-150] One expert stated the program would have the most potential effect on reducing disparities if it also included patient education on STEMI and efforts to increase program participation by all eligible hospitals.[150] Another expert believes that although more STEMI patients were receiving more effective and more appropriate care, the RACE Project was not specifically designed to address overall health care disparities.[151]

Valve and Structural Disorder Interventions

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

Unmet need: The gold standard for treating aortic stenosis has been open surgical replacement of the valve with a mechanical valve or a bioprosthetic valve.[152-154] However, open-heart surgery is typically not an option for patients at high risk of surgical complications.[152,153,155] Medical therapy is typically the only therapeutic option for these patients; however, medical therapy is often ineffective in this population, and mortality tends to be high.[156-158]

Intervention: Manufacturers have developed a catheter-based valve implantation technology that allows clinicians to implant diseased aortic valves using minimally invasive techniques. Transcatheter aortic valve implantation (TAVI; also known as transcatheter aortic valve replacement [TAVR]) is intended to extend the therapeutic benefit of surgical aortic valve implantation to patients ineligible for surgery or at high risk of surgical complications.[153,155,159-161]

The Sapien™ Transcatheter Heart Valve is intended for use in patients with severe aortic stenosis who are not surgical candidates or who are at high risk of developing surgical complications.[155] The bioprosthesis features a bovine pericardial tissue aortic valve affixed within a balloon-expandable stainless-steel frame.[162] The valve is available in 23 and 26 mm sizes to accommodate different aortic annulus sizes.[162] 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 using a minimally invasive transapical approach.[163,164]

According to Sapien's manufacturer, for TAVI by the transfemoral approach, the patient is placed under general anesthesia and an incision is made in the patient's groin, where the physician places a catheter in the femoral artery. A balloon catheter is used to stretch the aortic valve opening. A member of the operating team places the valve on the delivery system and crimps it to allow insertion into the body through the sheath. Using fluoroscopic guidance, the surgeon inserts the valve and delivery system through the catheter and guides it to the aortic valve. Once the new valve is positioned, the balloon is filled with liquid, expanding the new valve from its crimped state to its functional mode. The implant is checked for proper function, the delivery system is removed, and the incision is closed. The procedure takes up to 4 hours, and the average hospital stay for a patient undergoing TAVI is 2–6 days.[165]

The CoreValve® System is being investigated in IDE trials in the United States, also for treating severe aortic stenosis.[166] The system is intended for use in patients who are not surgical candidates or who are at high risk of developing surgical complications. The system 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 diameter delivery catheter with a set of disposable catheter-loading components.[167,168]

According to CoreValve's manufacturer, typical implantation procedures last about 1–3 hours, and patients are sedated. The clinician guides a catheter into the heart, then threads a balloon catheter through the guide catheter into the heart. Once the balloon is positioned in the aortic valve, it is inflated to prepare for implanting the CoreValve. Using imaging equipment to direct placement, the clinician situates the CoreValve over the diseased aortic valve. In some cases, the diseased valve is completely removed before the CoreValve is placed. The catheter is removed, and the incision is closed. The manufacturer states that the typical hospital stay following a TAVI procedure is 3–5 days.[169]

One of three other, more direct access routes can be used when the transfemoral route is impractical or undesirable because of severe, systemic vascular disease that impedes catheter navigation from the femoral artery. In the transapical approach, the physician makes a small

incision between the ribs to access the heart apex (bottom) and advances the delivery catheter through the apex into the left ventricle to reach the aortic valve.[170,171] In the subclavian approach, the physician inserts a catheter under the collarbone into the subclavian artery to deploy the aortic valve.[169] The transaortic approach allows a physician to insert the delivery catheter into the aorta through the ribs using either a mini-thoracotomy in the second intercostal space or an upper hemisternotomy.[172,173] Valve deployment with alternate access routes is similar to that in the transfemoral approach, once the delivery catheter is positioned.

Clinical trials: In March 2013, Sapien's manufacturer announced 3-year results from patients at high risk of surgical complications (Cohort A) in the PARTNER trial that suggested comparable outcomes for TAVI and open surgery.[174] Cohort A patients were randomly assigned to receive conventional open-surgical aortic valve replacement or TAVI performed via transfemoral or transapical access. Investigators observed no significant differences between groups in all-cause mortality or stroke incidence. At 3 years after intervention, all-cause mortality for TAVI patients was 44.2% compared with 44.8% for surgical patients (p=0.483).[174] Earlier outcomes showed a similar trend, with the following outcomes:[174]

- All-cause mortality at 1 year of 24.3% for TAVI and 26.8% for surgery (p=0.45)
- All-cause mortality at 2 years of 33.9% for TAVI and 35% for surgery (p=0.78)

No statistically significant differences in stroke incidence were observed between TAVI and surgery groups, respectively, with results as follows:[174]

- At 3 years, 8.2% for TAVI versus 9.3% for surgery (p=0.763)
- At 2 years, 7.7% for TAVI versus 4.9% for surgery (p=0.17)
- At 1 year, 6.0% for TAVI versus 3.2% for surgery (p=0.08)

Investigators also reported that symptom improvement and valve performance were similar in both groups and were maintained through the 3 years of patient followup.[174]

In May 2013, Medtronic reported 1-year results from the CoreValve ADVANCE Study that suggested TAVI had low rates of mortality and stroke, and improved hemodynamics (blood flow) in patients with severe aortic stenosis considered to be at high risk of surgical complications.[175] The CoreValve Advance International Post Market Study (CoreValve is approved in Europe) is a prospective, observational study intended to evaluate CoreValve TAVI procedures in patients outside of a clinical trial setting. Among the 996 treated patients overall, investigators reported on 806 of 824 patients (97.8%) for whom 1-year followup data were available. At 1 year, the all-cause mortality rate was 17.9%, the cardiovascular mortality rate was 11.7%, and the combined stroke rate was 4.5%, including a 2.3% minor stroke rate and a 2.3% major stroke rate.

In the study, investigators also observed substantial improvement in disease symptoms. At baseline, only 20% of patients were classified as class I or class II on the New York Heart Association (NYHA) scale of functional limitations due to heart failure. However, 30 days after TAVI, 85% of patients were classified as NYHA class I or II, and at 1 year, 87% of patients were classified as NYHA class I or II.[175]

Manufacturer and regulatory status: Edwards Lifesciences Corp. of Irvine, CA, makes the Sapien Transcatheter Heart Valve. FDA approved the Sapien device in November 2011 for transfemoral delivery in patients who have severe, symptomatic aortic stenosis and 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 the procedure.[176] In October 2012, FDA expanded the Sapien labeling to include patients with severe aortic stenosis who are high risk of experiencing complications from open-heart valve surgery. This approval was for both transfemoral and transapical delivery of the Sapien valve in this patient population.[177,178]

Medtronic makes the CoreValve System. The valve is not yet approved for marketing in the United States but CoreValve received CE mark in May 2007 for the CoreValve Percutaneous ReValving™ System for treating patients at high risk of experiencing complications with surgery.[179] Medtronic received a CE mark in September 2012 for the newest valve addition to the system, the CoreValve Evolut, a 23 mm valve that can fit an aortic annulus size of 18 mm. The CoreValve System now has four valve sizes (23, 26, 29, and 31 mm) to fit aortic annulus sizes that range from 18 mm to 29 mm.[179] FDA granted Medtronic an IDE for its U.S.-based CoreValve trial in October 2010.[180]

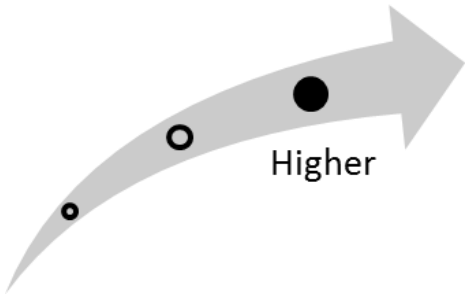
Diffusion: In May 2012, CMS released a national coverage determination for TAVI, stating that CMS "covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)" when the procedure is used for "the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication" and when certain conditions are met.[181] The coverage determination listed criteria for the required infrastructure, interdisciplinary team members, number of procedures to achieve and maintain proficiency, and other requirements. The determination covers the approved Sapien valves and the CoreValve devices given in the context of the IDE trial.

As of June 2013, representative, private, third-party payers generally covered TAVI procedures for patients who are not surgical candidates and have adopted requirements that are similar to or the same as Medicare's requirements; however, some of these payers have not followed the Medicare policy and have not yet expanded their coverage policies to include patients who are eligible for open surgery but at high risk of complications.[182-187]

Clinical Pathway at Point of This Intervention

According to 2006 guidelines by ACC/AHA, aortic valve replacement is considered the surgical treatment of choice for most adults with severe aortic stenosis who are candidates for open heart surgery.[188] For patients who are not candidates for open surgery and have a poor prognosis, medical management or aortic balloon valvuloplasty were the only options. However, these options do not provide full relief of aortic stenosis symptoms; the only definitive treatment is aortic valve replacement.[152,153,189] The advent of TAVI provides a new option for patients with severe aortic stenosis who are not candidates for surgery or who are at high risk of complications if they undergo surgery, and would otherwise have no treatment options.[155,178,190,191]

Figure 7. Overall high-impact potential: transcatheter aortic valve implantation (Sapien; CoreValve) for treatment of severe aortic stenosis



Experts commenting on this intervention agreed that it offers an important new treatment modality for patients who have no other medical or surgical treatment option. Experts thought that this intervention would improve patient health outcomes, and they thought an increase in patient volume and a shift in care setting (from outpatient to inpatient) would be seen as this intervention diffuses. Experts experienced in the procedure pointed out that establishing a program puts a

significant strain on conventional resources and requires additional infrastructure to evaluate potential patients and perform the procedure. Others were less familiar with how disruptive the intervention would be to health care infrastructure, but agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs. 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, and health system backgrounds, offered perspectives on the Sapien technology.[192-197] Seven experts, with similar backgrounds, offered perspectives on the CoreValve technology.[198-204] Two experts reported having a potential COI because both are involved in implanting these valves in patients at their respective medical centers. These potential COIs are balanced by experts who reported having no potential COIs.[192,197] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need addressed by this intervention is extremely important, the experts concurred, citing the large number of patients who would be affected and the fact that no other effective therapies are available for this population. As one clinical expert stated: "There is a large gap for certain patient populations. Patients currently deemed too high a risk for surgery have only a medical option [and] medical therapy has no impact on the natural history of the disease, thus mortality is high."[197] Further, experts asserted that this patient population is growing as the U.S. population ages and as better techniques for identifying patients with aortic stenosis are developed.

In supporting this intervention's ability to meet the unmet need and improve patient health outcomes, experts were optimistic mostly because of encouraging data from clinical trials but also because it provides an option to a population that has no other effective options available. Further, some experts suggested that over time, this intervention may be extended to patients who are "less ill," although data on safety and durability of the procedure are needed for this expanded patient population.

Acceptance and adoption: Clinicians who treat these patients would readily accept this technology, the experts thought, considering that no other interventions are available for this patient population. But they thought actual adoption might be relatively slow for centers outside of those that participated in the clinical trials, given the conditions of coverage, infrastructure requirements, and required multidisciplinary teams. Experts also generally thought that patients would accept this procedure because it offers a therapeutic option where previously none existed and because the intervention is considered minimally invasive.

Health care delivery infrastructure and patient management: Experts had differing perspectives about the extent to which this technology will disrupt health care infrastructure and patient management models. Some experts stated that this intervention could be conducted in existing facilities that have hybrid operating rooms and the necessary interdisciplinary clinical staff, thereby not markedly disrupting current infrastructure. However one clinical expert with experience in the technology stated that for facilities without existing infrastructure, "Starting a TAVR program…is a huge undertaking. It is not just adding another procedure, it is adding a whole new program to a medical center. The resource utilization is considerable. The program will put a significant strain on conventional resources and require an additional infrastructure to evaluate potential patients."[202] One notable consequence of this intervention is the shift in care setting for patients who typically would have been treated only with medical therapy. Case volume at centers offering TAVI is expected to rise accordingly, and even if patients referred for evaluation are not

candidates for TAVI, the referrals alone are expected to increase patient case load on heart teams that evaluate patients for TAVI eligibility.

Experts were confident that this intervention would a have significant impact on health care costs for payers and hospitals. Costs of care for patients previously treated with medical therapy who are eligible for and undergo TAVI will increase. Experts noted the Sapien device cost as $32,500, and costs for the deployment procedure are added to that, even though the hospital stay might be shorter than for open surgery. Also, some experts noted that Medicare reimbursement rates might not cover device and procedure costs, so hospitals might lose revenue on the procedure, although such a loss might be offset by an increase in referrals that end up receiving other non-TAVI treatment (such as open surgery). Several experts noted that some costs associated with medically managed patients with end-stage disease (e.g., hospitalizations) might decrease after patients undergo TAVI because they would not be expected to need pharmaceutical treatment and because hospitalizations could decrease for complications in patients previously on medical therapy.

Health disparities: Experts generally anticipated that TAVI would not alter health disparities significantly, in part because of the high device and procedure cost as well as the limited availability, at least initially, to centers of excellence with clinical trial experience in TAVI. However, one clinical expert concluded that TAVI might greatly alter disparities in care for very elderly patients with newly discovered severe aortic stenosis, who were essentially "written off" before TAVI became available because of the ineffectiveness of medical therapy.[202]

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

Unmet need: Although open surgical repair of the mitral valve is the gold standard treatment for mitral regurgitation (MR), some patients are ineligible for surgery or are poor surgical candidates because of their high risk of developing complications.[205,206] Left untreated, severe MR can lead to congestive heart failure or potentially life-threatening cardiac arrhythmias.[207] For these patients, a treatment gap exists for an intervention that approximates the therapeutic benefit of open surgical mitral valve repair while minimizing the procedural risks.

Intervention: The MitraClip device is intended to simulate the functional effects achieved by the Alfieri edge-to-edge surgical procedure, an open surgery repair technique used for treating MR.[206] 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.[208] The MitraClip device mimics this procedure by "clipping together" the mitral valve leaflets, rather than using sutures.[206,209]

The MitraClip is an implantable, two-armed, flexible metal clip made of cobalt and chromium and covered in polyester fabric. It is intended to help the mitral valve close more completely, thereby potentially reducing MR.[210] The MitraClip system consists of the clip device, a clip-delivery system, and a steerable guide catheter. To implant the device, the patient is placed under general anesthesia (but no heart-lung machine is required), and the clinician inserts the guide catheter through the femoral vein into the heart and, using the catheter and the clip-delivery systems, delivers and deploys the clip device.[211]

The device is placed by advancing the guide catheter into the left atrium and positioning the opened clip over the mitral valve. The surgeon advances the clip to the left ventricle and closes its arms, clamping the mitral valve leaflets together. At this point, MR is assessed; if the change in MR is not satisfactory, the clip is repositioned.

The implantation procedure requires a trans-septal puncture, which has been called a "crucial early step" in the procedure. The procedure is performed in a catheterization laboratory using fluoroscopic and transesophageal echocardiographic guidance.[206] The manufacturer states that recovery typically lasts 1–3 days.[211]

Clinical trials: In 2013, investigators reported 1-year outcomes from 59 patients with severe, symptomatic MR and reduced ejection fraction who received MitraClip therapy.[212] The primary outcomes evaluated were procedural efficacy measured by reduction in MR and improvement in 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. Patients also demonstrated reductions in certain cardiac markers: high-sensitive troponin T ($p<0.05$) and NT-proBNP (nonsignificant). Followup echocardiography suggested a reversal in heart enlargement, with reduced left atrial volume, left ventricular end-systolic diameter, and an increase in left ventricular ejection fraction (LVEF). These results were consistent with outcomes of a subgroup of 25 patients with severely reduced LVEF (EF 23±2%; n=25), suggesting that sicker patients also benefitted from MitraClip therapy. Investigators reported 30-day mortality of 2.9%.[212]

Also in 2013, investigators reported outcomes from 117 patients in the GRASP Registry.[213] The primary outcome measures were the rate of major adverse events at 30 days, freedom from death, surgery for mitral valve dysfunction, or grade 3+ or greater MR at 30 days and 1 year. Investigators reported acute procedural success, defined as residual MR grade 2+ or less after MitraClip implantation, in all patients and no procedure-related mortality.

With experience, physicians substantially reduced their procedural times. Procedure times varied widely among cases involving implantation of a single clip and multiple clips.

Major adverse events were reported for four patients at 30 days (4.3%). Thirteen patients experienced increased MR to MR grade 3+ or more at 1 year. At 1 year, no patients required surgery for mitral valve dysfunction. Freedom from death, freedom from surgery for mitral valve dysfunction, or freedom from grade 3+ or more MR was 96.4% at 30 days and 75.8% at 1 year.[213]

Manufacturer and regulatory status: Abbott Laboratories, of Abbott Park, IL, makes the MitraClip. The PMA for the MitraClip device is under review at FDA. The company expects an FDA decision on the MitraClip PMA by the end of 2013.[214,215]

In March 2013, an FDA advisory panel voted on the safety, effectiveness, and risk-benefit ratio of the MitraClip system as part of a review of the MitraClip PMA. 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: to reduce significant symptomatic mitral regurgitation (MR of 3+ or more) in patients at high risk of complications with open surgery and in whom existing comorbidities would not preclude the expected benefit from treatment. The panel voted 8-0 that available data show MitraClip to be safe when used for the proposed indication. However, the panel voted 5-4, with the chairperson voting as tie breaker, that there was not "reasonable assurance" from available trial data that the MitraClip procedure would be effective for its proposed indication.[216]

In March 2013, the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) issued a medical device alert advising interventional cardiologists and cardiothoracic surgeons of a "risk of death or serious harm" during MitraClip implantation.[217] The MHRA alert advises, "if the Actuator Knob on the Clip Delivery System (CDS) is turned in the wrong direction, this can prevent successful deployment of the clip, leading to the need for open surgical repair."[217]

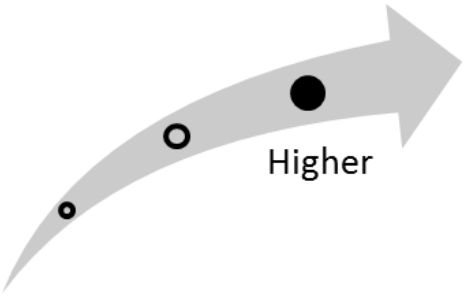
In May 2011 (before the 2013 safety advisory), the manufacturer issued a voluntary device recall in Australia, Europe, Singapore and other countries where the device had been approved because of issues with the delivery catheter's tip. Although the company resolved the issue and reintroduced the device in those countries, the recall prompted FDA to request additional information and analysis regarding the MitraClip, which the company provided.[218]

Diffusion: The device is not yet commercially available in the United States. The safety alerts in 2013 and product recalls in 2011 might potentially affect physician acceptance of the device if and when MitraClip becomes commercially available in the United States. Should MitraClip receive FDA approval, the availability of reimbursement for the device and procedure also could affect physician acceptance and diffusion. Two representative, private, third-party payers (Humana, United Healthcare) consider MitraClip therapy investigational at this time and deny coverage for the procedure.[186,219] Payers, including those with existing noncoverage policies for MitraClip procedures, may revise their coverage policies should FDA approve the device, given the unmet need in this patient population.

Clinical Pathway at Point of This Intervention

The preferred treatment for severe MR is open surgery for valve repair or valve replacement.[205,206] 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."[188] If approved for marketing in the United States, the MitraClip would be positioned as a catheter-based (transcatheter) alternative to surgical valve repair.[205,206]

Figure 8. 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, although some experts agreed that more data concerning safety and long-term outcomes are needed. Experts' opinions differed somewhat about how much this intervention would disrupt current 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 valve surgery, although other experts believe that the potential increase in numbers 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 wanted to see more long-term data to assess whether it 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 higher end of the 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.[220-226] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The majority of experts agreed that the unmet need for less-invasive interventions to treat MR is important because of the large number of patients with MR who are not candidates for surgical repair. One expert also noted that patients with secondary MR and significant left ventricular dysfunction would be good candidates for this procedure.[220]

But opinions diverged about the device's potential to fulfill the unmet need. Two experts thought this device has relatively low overall potential to fulfill the unmet need, with one stating that this is just another treatment option for patients with MR.[221] Another expert believes that the procedure is highly risky and that more data demonstrating safe and reliable outcomes would be needed for the device to have a greater potential in fulfilling the unmet need. Conversely, other experts thought that this device holds promise, especially for patients at high risk of developing surgical complications.

Health outcomes could improve with this intervention, most of the experts believe, although they expressed a desire to see more and longer-term clinical data. One expert believes that the MitraClip has great potential to improve health outcomes in both patients with primary MR that originates from the center of the valve and patients with relatively normal valve tissue who have secondary MR due to chamber enlargement or dysfunction.[220] This expert also thought MitraClip might serve as an intermediate treatment for patients with severe dilated cardiomyopathy. But concerns about device and procedure safety were raised by some experts who believe that the numerous comorbidities seen in these patients would present risk and preclude some patients from achieving greatly improved outcomes.

Acceptance and adoption: Although most experts agreed that the MitraClip implant would entail significant training and a significant learning curve for clinicians, they agreed that if clinical trial data continue to demonstrate benefits and safety of the device, clinical acceptance would follow.

Patients would likely accept this minimally invasive therapeutic option for MR if sufficient data of safety and effectiveness is developed, because they lack other options, the experts all agreed. But one expert noted that this procedure is not intended to completely repair mitral valves; therefore, patients who are eligible for open surgery might prefer that option to achieve a complete, rather than partial, repair.[220]

Patient acceptance could also be influenced by cost, two experts suggested, but they differed. One expert believes cost could have a positive effect on acceptance because of decreased treatment costs[221] and the other believes that acceptance would be limited if insurance does not cover the procedure.[225]

Health care delivery infrastructure and patient management: The experts offered three perspectives about this intervention's potential impact on the health care system. First, the majority of experts believe availability of this device could increase the number of patients coming to the hospital for a procedure and shift care from outpatient medical management to inpatient care, thus, having a large potential to disrupt the health care delivery system. Second, other experts believe that the infrastructure to carry out this procedure is already in place in most cardiac intervention facilities and so it should not greatly disrupt the health care delivery infrastructure, although these experts agreed that increased case volume was a potential disruption. Finally, one expert thought any change in patient management would be gradual and, therefore, would not significantly disrupt the current care pathway.[220]

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. One clinical expert noted, "It's unclear if access to this procedure would be any better than any other interventional procedure…. One benefit might be for patients with poor social circumstances that have to be eliminated [i.e., addressed] as either left ventricular assist device candidates or heart transplant candidates when they become [end]stage because of severe lack of social support or ability to afford or care for themselves."[220]

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