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

Priority Area 03: Cardiovascular Disease

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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. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

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

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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 National Academy of Medicine (formerly 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.

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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 identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 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 a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

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

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

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

Results

The table below lists the 15 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 8, 2015, in this priority area; *and* (3) we received five to seven sets of comments from experts between July 1, 2014, and May 8, 2015. (Fifty-seven topics were being tracked in this priority area as of May 8, 2015.) We present 12 summaries on 15 topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts' comments (we discuss two PCSK9 inhibitors in one summary and three percutaneous left atrial appendage occlusion devices in one summary). 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. * Alirocumab (Praluent; PCSK9 inhibitor) for treatment of familial hypercholesterolemia and statin-resistant hypercholesterolemia	Moderately high
2. * Andexanet alpha for reversal of factor Xa inhibitors	Moderately high
3. * Combination valsartan/sacubitril (LCZ696) for treatment of heart failure	High
4. * Evolocumab (Repatha; PCSK9 inhibitor) for treatment of familial hypercholesterolemia and statin-resistant hypercholesterolemia	Moderately high
5. Endovascular aneurysm sealing system (Nellix) for treatment of infrarenal abdominal aortic aneurysms	No high-impact potential; archived on basis of experts' comments
6. * Ivabradine (Corlanor) for treatment of heart failure	Lower end of the high-impact-potential range
7. * Percutaneous left atrial appendage occlusion (Lariat Suture Delivery Device) for prevention of atrial fibrillation–associated stroke	Lower end of the high-impact-potential range
8. * Percutaneous left atrial appendage occlusion (Watchman) for prevention of atrial fibrillation–associated stroke	Lower end of the high-impact-potential range
9. * Percutaneous left atrial appendage occlusion (Wavecrest) for prevention of atrial fibrillation–associated stroke	Lower end of the high-impact-potential range

Topic	High-Impact Potential
10. * Portable Freedom Driver for in-home support of the Total Artificial Heart	Lower end of the high-impact-potential range
11. * Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation	Moderately high
12. Riociguat (Adempas) for treatment of pulmonary artery hypertension	No high-impact potential at this time; archived on basis of experts' comments
13. * Selexipag (Uptravi) for treatment of pulmonary artery hypertension	Lower end of the high-impact-potential range
14. Silk Road procedure for prevention of stroke during carotid artery stenting	No high-impact potential; archived on basis of experts' comments
15. * Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	Moderately high

Discussion

Research activity in all disease areas of the cardiovascular priority area is robust and addresses both novel and incremental innovations that could affect patient outcomes, shift care models, and affect costs and care delivery. Many of the innovations being tracked, as well as the innovations deemed by expert comments to have potential for high impact, pertain to cardiovascular devices that provide support for end-stage heart failure (HF) or address valve problems and stroke prevention in patients with arrhythmias. Pharmaceuticals deemed as having high-impact potential include drugs to treat HF, familial hypercholesterolemia (FH) and statin-resistant hypercholesterolemia, and a reversal agent targeting new anticoagulants used to reduce the risk of ischemic stroke.

Prior Potential High Impact Topics Archived

- **Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia**: In the December 2014 High-Impact Interventions report (and earlier high-impact reports), commenters were optimistic that lomitapide (Aegerion Pharmaceuticals, Inc., Cambridge, MA) has potential to improve patient health outcomes by providing an orally administered alternative to injected drugs that might prevent the need for more invasive treatments, such as apheresis or liver transplantation. The trial used to support U.S. Food and Drug Administration (FDA) approval demonstrated a 38% reduction in low-density lipoprotein cholesterol (LDL-C) concentrations after 18 months, and no patients halted therapy because of liver abnormalities. FDA approved lomitapide in December 2012. This intervention has been diffusing for more than 2 years and, therefore, no longer meets criteria for tracking and was archived in the horizon scanning system in January 2015.

Eligible Topics Deemed Not High-Impact

- **Endovascular aneurysm sealing system (Nellix) for treatment of infrarenal abdominal aortic aneurysms:** The Nellix® EndoVascular Aneurysm Sealing System (Endologix, Inc., Irvine, CA) is intended to seal off abdominal aortic aneurysms by creating two blood-flow channels within the aneurysm, using two balloon-expandable stents, placed bilaterally. The stents are surrounded by a fast-curing polymer that fills the aneurysm sac around the device, with the goal of preventing endoleaks. Experts commenting on this device viewed it as only a marginal improvement to existing devices and noted the lack of data comparing Nellix to other commercially available stent-graft devices used for endovascular treatment of

abdominal aortic aneurysms. Based on experts' comments, this topic was archived in May 2015 in the horizon scanning system.

- **Riociguat (Adempas) for treatment of pulmonary artery hypertension:** Riociguat (Bayer AG, Leverkusen, Germany) is a soluble guanylate cyclase stimulator intended for treating patients who have pulmonary artery hypertension (PAH). Riociguat purportedly vasodilates pulmonary and systemic arterial vascular beds; it is intended for use as monotherapy or as an add-on therapy to endothelin-receptor antagonists. Experts commenting saw no potential for high impact because of its high cost and the availability of other pharmacotherapies to treat PAH. Based on experts' comments, this topic was archived in May 2015 in the horizon scanning system.
- **Silk Road procedure for prevention of stroke during carotid artery stenting:** The Enroute® Transcarotid Stent and Enroute Transcarotid Neuroprotection System (Silk Road Medical, Inc., Sunnyvale, CA) are intended to allow physicians to implant a carotid stent via direct carotid artery access rather than femoral artery access in the groin. According to the manufacturer, the Silk Road procedure may reduce the risk of periprocedural stroke by temporarily reversing blood flow through the target carotid artery to prevent the release of emboli to the brain during carotid stent implantation. The rerouted blood is filtered externally and returned through the femoral vein. FDA approved the carotid stent in May 2015, and cleared the embolic filtering device in February 2015. Experts reviewing this technology cited little potential for high impact because several other carotid stents and catheter-based embolic protection systems are available for carotid stenting procedures. Further, experts anticipated that use of the technology would likely be limited to vascular surgeons, because of their experience in carotid surgery, and that many other interventional physicians (i.e., who are not vascular surgeons) would be unlikely to adopt and learn this alternative approach without comparative data demonstrating superiority over other embolic protection devices and techniques. Based on experts' comments, this topic was archived in May 2015 in the horizon scanning system.

Topics Deemed High-Impact

We present 12 interventions that experts who commented thought have potential for high impact. They are devices to treat atrial fibrillation–associated stroke, HF, and cardiac valve disorders and drugs to treat statin-resistant hypercholesterolemia, a genetic disorder, HF and to reverse the effect of factor Xa anticoagulant drugs.

Atrial Fibrillation–Associated Stroke

A serious complication of atrial fibrillation (AF) is ischemic stroke, and patients with AF have a four to five times greater risk of stroke than other individuals, after all standard stroke risk factors are accounted for. Stroke risk is high in AF because thrombi form in the atria or, more commonly, in the left atrial appendage (LAA), and circulate systemically, traveling to the brain to cause stroke. These thrombi or clots can be prevented through pharmacologic therapy. Antithrombotic agents include aspirin, low-molecular-weight heparin, and oral anticoagulants, including vitamin K antagonists and factor Xa inhibitors. However, clinical experts estimate that from 14% to 44% of patients with AF have bleeding risks that preclude them from taking oral anticoagulants. Additionally, use of the standard and lowest-cost oral anticoagulant therapy, warfarin, requires frequent monitoring, dosage adjustments, and dietary restrictions. Warfarin discontinuation rates are an estimated 32% per year. Newer anticoagulant alternatives (e.g., apixaban, edoxaban, rivaroxaban) eliminate the need for routine monitoring and dietary restrictions. However, these

therapies have other drawbacks, including nonhemorrhagic side effects, potential drug-drug interactions, and the fact that no antidote is available in the event of uncontrolled bleeding. Therefore, an unmet need exists for better and safer treatments for AF-associated stroke.

Andexanet Alfa for Reversal of Factor Xa Inhibitors

- **Key Facts:** Factor Xa inhibitors (apixaban [Eliquis®], edoxaban [Savaysa™], rivaroxaban [Xarelto®]) are a class of rapidly acting, target-specific anticoagulants and are broadly prescribed for indications including for preventing stroke and venous thromboembolism. Unfortunately, up to 5% of patients prescribed factor Xa inhibitors can experience potentially fatal uncontrolled bleeding episodes or may require emergency surgery. These patients have an urgent need for effective agents to reverse factor Xa inhibitor activity and facilitate normal hemostatic restoration.

  Andexanet alfa is a novel investigational medication developed as a universal reversal agent for factor Xa inhibitors. As a modified recombinant factor Xa derivative, andexanet alfa functions as a highly specific decoy that rapidly reverses the activity of direct and indirect factor Xa inhibitors. Results from completed clinical trials demonstrate that, in healthy patients, intravenously infused andexanet alfa successfully reverses the activity of commonly prescribed factor Xa inhibitors apixaban, edoxaban, and rivaroxaban. An ongoing phase IV trial is investigating andexanet alfa's effectiveness for reversing factor Xa inhibitor activity in patients experiencing acute major bleeds.

  In November 2013, FDA granted andexanet alfa breakthrough therapy designation for reversing the effects of factor Xa inhibitors in patients who suffer a major bleeding episode or who require emergency surgery (with its risk of bleeding). Andexanet alfa's manufacturer has announced plans to file a biologics license application (BLA) by late 2015, supported by data from a series of completed phase III studies and the ongoing phase IV trial. As of June 2015, no pricing estimates were available.
- **Key Expert Comments:** Experts evaluating andexanet alfa's high-impact potential universally agreed that this drug both addresses a significant unmet need and is likely to be widely adopted by clinicians and patients. Experts also stated that andexanet alfa would be easily integrated into health care systems because it is an intravenous drug that showed high efficacy and a solid safety profile in completed clinical trials. However, these experts reserved some support for andexanet alfa's high-impact potential because of a lack of efficacy data from patients prescribed factor Xa inhibitors. Overall, experts offered a positive assessment of andexanet alfa and its potential to reverse factor Xa inhibitor activity.
- **High-Impact Potential:** Moderately high

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

- **Key Facts:** Catheter-based procedures to occlude the LAA are intended to remove a potential source of blood clots that increase stroke risk. Devices used to occlude the LAA include the Lariat, Watchman, and WaveCrest. These devices may be an alternative to anticoagulant therapy in patients with AF. FDA approved Boston Scientific Corp.'s Watchman in March 2015, making it the first available device in the United States with a labeled indication for reducing stroke risk in patients with nonvalvular AF. The Watchman approval took 6 years and 3 FDA advisory panels, plus an additional phase III trial requested by FDA. Although the U.S. Centers for Medicare & Medicaid Services (CMS) does not have a national coverage determination for LAA occlusion devices, it has accepted a request

from Boston Scientific to initiate a national coverage analysis "for percutaneous, transcatheter, intraluminal left atrial appendage (LAA) closure using an implanted device." According to CMS, "the scope of this national coverage analysis does not include surgical techniques used to achieve LAA closure." CMS anticipated completing a proposed decision memo by November 21, 2015.

In March 2015, Pillarisetti and colleagues reported on 478 patients with nonvalvular AF who underwent LAA closure using either the Watchman or Lariat devices. At 1 year, 17% of patients had a detectable leak from the LAA. Leaks occurred in 21% of the Watchman group and 14% of the Lariat group. Adverse events in the Watchman group included one device embolization requiring surgery and two pericardial effusions requiring pericardiocentesis. Adverse events in the Lariat group included cardiac tamponade requiring urgent surgical repair in four patients. Three patients in each group had a cerebrovascular accident judged to be unassociated with device leaks.

The devices are expected to cost about $8,000 in the United States; procedure costs are not yet apparent. In the United Kingdom, total procedural costs are reportedly about $17,300, which includes device costs of about $8,100 and implantation procedure costs of about $9,200.

- **Key Expert Comments:** Experts concluded that LAA occlusion devices would likely have a role in treating patients who cannot tolerate long-term oral anticoagulation rather than the larger population of patients with AF who are well managed with oral anticoagulants. Several experts commented that the potential of LAA occlusion devices as an alternative to long-term warfarin therapy has been lessened in the last couple of years because new drug competitors to warfarin are purportedly safer and much easier to use because they do not require frequent blood tests or have as many dietary interactions or restrictions as warfarin.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Heart Failure

HF adversely affects quality of life as well as life expectancy and can develop from any condition that overloads, damages, or reduces heart muscle efficiency, impairing the ventricles' ability to fill with or eject blood. In 2011, 1 in 9 death certificates mentioned HF, and it was the underlying cause in 58,309 deaths. Based on data from 2009 to 2012 from the National Health and Nutrition Examination Survey, 5.7 million people older than 20 years in the United States have HF. Approximately 50% of people with HF die within 5 years of diagnosis. HF prevalence has increased in the past 20 years, and projections show that HF prevalence will increase 46% between 2012 and 2030, resulting in more than 8 million people aged 18 years or older with HF. The expected increase in disease burden is due to the improved survival of patients with coronary artery disease, an increasing population of aging patients, and significant advances in the control of other potentially lethal diseases. The estimated cost of HF in the United States in 2013 was $32 billion. Projected estimates indicate that by 2030, the total annual cost of HF will increase to $69.7 billion. Because of the clear unmet need for effective therapies for HF and its myriad underlying causes, new drugs, biologics, and devices are under study for treatment.

Combination Valsartan/Sacubitril (LCZ696) for Treatment of Heart Failure

- **Key Facts:** Combination valsartan/sacubitril, also known as LCZ696, is an oral angiotensin receptor neprilysin inhibitor primarily comprising two active antihypertensives, valsartan

and sacubitril. The drug has a novel mechanism of action, with both active components inhibiting the renin-angiotensin-aldosterone system (RAAS) and enhancing endogenous natriuretic peptide activity. These functions reportedly enable the drug to relieve cardiovascular system strain, resulting in improvements in HF and other cardiovascular health outcomes.

In the pivotal PARADIGM-HF phase III trial, daily therapy was reported to have reduced mortality and hospitalization rates and reduced or preserved patients' ejection fractions. A separate analysis reported that treatment also improved biomarkers of cardiac stress to a greater extent than valsartan monotherapy.

Currently, valsartan/sacubitril is being given in trials up to a maximum daily dose of 400 mg (administered as two 200 mg doses). Dosages are being titrated across a treatment course and may be prescribed as a monotherapy or adjunct for treating HF. Few severe treatment-related adverse events have been observed in clinical trials, but recent research suggests that the sacubitril component of the therapy may be associated with increased Alzheimer's disease risk when administered as a monotherapy. Ongoing long-term trials may help determine whether sacubitril, as formulated in LCZ696, has similar side effects.

The manufacturer initiated a rolling new drug application (NDA) in 2014 and, in February 2015, FDA announced that it would evaluate the application under its priority review program. An FDA decision on combination valsartan and sacubitril is expected by August 2015. Official retail pricing has not been reported, but industry observers have projected annual costs of $2,000 to $2,500 per patient.

- **Key Expert Comments:** Overall, experts commenting on this intervention agreed that HF is a serious health issue and stated that valsartan/sacubitril has considerable potential to address HF and severe HF-related outcomes. Several experts favorably noted valsartan/sacubitril's efficacy for decreasing hospitalizations and emergency department visits, reducing disease progression leading to secondary treatment, and improving all-cause mortality rates. Although some experts acknowledged the potential Alzheimer's disease risk posed by the sacubitril component, they thought that ongoing long-term trials might resolve this issue and still concluded that this intervention has significant high-impact potential.
- **High-Impact Potential:** High

Ivabradine (Corlanor) for Treatment of Heart Failure

- **Key Facts:** Ivabradine is an oral antianginal medication that reportedly treats HF by reducing heart rate, a suspected key factor in HF pathophysiology. Unlike previously approved HF drugs, ivabradine's heart rate-lowering activity is derived by selective inhibition of the funny channel (I_f) current, a primary pacemaker modulator. Due to its high specificity and selective binding, ivabradine is classified as a "pure" heart rate-reducing drug, and has shown a more favorable safety profile than other HF medications.

  Before its development for the American market, ivabradine was widely used in other countries in multiple generic and branded formulations for treating HF and chronic stable angina pectoris. Although several international studies suggest that ivabradine is a cost-effective drug for treating HF, other researchers reported that it is not superior to optimized beta-blocker therapy, a standard of care for treating HF. In completed and ongoing clinical trials, long-term adjunct ivabradine administration is associated with reduced HF symptoms, decreased physiological markers of HF, and improved patient quality of life.

  In April 2015, FDA approved ivabradine, branded as Corlanor®, for treating chronic HF. Corlanor's approval was primarily based on data from the international, multicenter SHIfT

(Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial) study, which monitored long-term ivabradine administration efficacy and safety. For U.S. marketing, Corlanor is explicitly indicated for patients with stable HF symptoms, a normal heartbeat with a minimum resting heart rate of 70 beats per minute, and who are receiving optimized beta blocker therapy. As of June 2015, Corlanor retailed for about $200 per 30-day supply, or about $2,400 per patient per year.

- **Key Expert Comments:** Experts commenting on this intervention acknowledged that HF, ivabradine's approved indication, is a paramount national health issue, but were hesitant to suggest that ivabradine would significantly improve patient health outcomes. Multiple experts considered ivabradine to lack superiority to other available HF medications. These experts were also critical of purported pivotal trial data, which was judged to have design flaws that hindered favorable evaluation. Overall, considering ivabradine's cost, limited efficacy, and adjunct indication, experts did not enthusiastically support this intervention's high-impact potential.
- **High-Impact Potential:** Lower end of the high-impact-potential range

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

- **Key Facts:** The Freedom® Driver System is a wearable, pneumatic, portable driver designed to enable at-home support for the system manufacturer's temporary Total Artificial Heart (TAH-t) in patients awaiting a heart transplant. In October 2004, FDA approved the TAH-t as a bridge to transplantation with use of a traditionally powered conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart. It is indicated for use in cardiac transplant–eligible patients at risk of imminent death from nonreversible biventricular failure. A portable driver system that allows patients to be discharged to home care to await a suitable donor heart, the recently approved Freedom Driver could 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, 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.

  Available data on the Freedom driver are limited and generally come from small single-center reports. In 2014, Arabia and colleagues reported on 11 patients discharged home with the Freedom driver. All patients were alive at 3-month followup, but 45% of patients were readmitted within 3 months of the initial discharge. The average time from discharge to rehospitalization was 56 days. Reasons for readmission included driver alarm, suspected driveline infections, small bowel obstruction, and nausea and diarrhea. In July 2014, a company press release reported results from 106 patients in the Freedom PMA trial. The company reported, "The SynCardia Total Artificial Heart with the Freedom Driver System allowed 75% of those patients to be discharged from the hospital, while 86% of the 106 patients either were bridged to heart transplants or were alive and supported by the SynCardia Total Artificial Heart and the Freedom driver as of June 30, 2014."

  In June 2014, FDA approved the Freedom Driver "for use with the SynCardia temporary Total Artificial Heart as a bridge to transplantation in cardiac transplant candidates who are clinically stable." Costs for the Freedom Driver System have not been reported. The total

cost of care for patients with a total artificial heart using the portable driver might be lower than that of hospitalized patients with artificial hearts, because inpatient stay is shortened.

- **Key Expert Comments:** Experts thought that the greatest potential of this intervention is to improve quality of life and psychological well-being for patients with a TAH-t, although few published data are available to support this premise. However, fundamental care of patients with artificial hearts is unlikely to change whether they receive care at home or in a hospital. Further, the patient population for which this device is intended is small, which tempers its overall potential impact on the health care system, experts thought. Several experts commented that a shift to home care could potentially reduce costs for patients awaiting heart transplantation. However, other experts thought that the cost of equipment and home nursing care would be similar to inpatient care.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Portable Warm Blood Perfusion System (Organ Care System) for Living Heart Transplantation

- **Key Facts:** The Organ Care System™ (OCS) Heart is intended to better preserve donated hearts in transit by simulating the organ's natural environment and perfusing it with warm blood to maintain organ function. The technology uses an internal oxygen supply and pulsatile pumping system to circulate a proprietary solution containing donor blood through the heart to provide oxygen and replenish essential nutrients. The self-contained perfusion module maintains the proper temperature and humidity, protects the organ from external contaminants, and allows sterile ultrasound scans to measure heart function and sterile blood sampling for laboratory analysis. According to the manufacturer, the technology may potentially expand the pool of donor organs and allow more transplant candidates to receive a suitable donor heart by preserving heart function, extending the time window for safe organ transport, and providing real-time ex vivo organ monitoring. In April 2015, Dhital and colleagues reported the first use of the warm blood perfusion system to allow clinicians to procure donor hearts after circulatory death in donors at extended geographic distances. Donor hearts are traditionally harvested from donors after brain death while the heart is still beating. Use of donor hearts after circulatory death could expand the potential donor pool. The manufacturer has filed a premarket notification application with FDA for 510(k) marketing clearance and expects to receive clearance in 2015. Cost information is not yet available; however the OCS Lung System which is also under development to preserve donor lungs was stated by the manufacturer to cost about $250,000, and a single-use lung perfusion set was priced at $45,000. The company expects the OCS Heart to cost the same.
- **Key Expert Comments:** Experts were generally optimistic about the OCS Heart's potential to improve donor heart preservation, although several noted the scarcity of published data documenting the technology's possible benefit. Experts anticipated that large heart-transplant programs would likely adopt the warm blood perfusion technology quickly if it receives marketing clearance in the United States and that candidates for heart transplantation would be very interested in the technology. Although the OCS Heart has the potential to expand the pool of donor hearts available to transplant candidates, most experts did not expect the technology to substantially alter health care disparities present in the heart transplantation setting.
- **High-Impact Potential:** Moderately high

Hypercholesterolemia

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

Although statins have long been the gold standard for medically managing various hypercholesterolemia indications, and drugs in this class are relatively inexpensive and effectively lower LDL-C levels in a majority of patients, experts estimate that up to 20% of patients cannot tolerate clinically required statin doses or have forms of hypercholesterolemia (both FH and non FH forms) that are resistant to statin therapy. Nationwide, as many as 6 million Americans may meet diagnostic criteria for statin-resistant hypercholesterolemia.

Alirocumab (Praluent) and Evolocumab (Repatha) PCSK9 Inhibitors for Treatment of Familial Hypercholesterolemia and Statin-Resistant Hypercholesterolemia

- **Key Facts:** Alirocumab (Praluent™) and evolocumab (Repatha™) are investigational, subcutaneously injected pharmacotherapies developed to treat familial and statin-resistant hypercholesterolemia. In contrast to traditional statin-based therapy, these two monoclonal antibodies treat hypercholesterolemia by inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme discovered to hinder LDL-C clearance. In clinical trials thus far, treatment with PCSK9 inhibitor drugs has been reported to improve patient health outcomes by significantly increasing the rate at which LDL-C levels are lowered. In trials, PCSK9-inhibitor administration also reduced LDL-C levels in patients whose disease failed to adequately respond to statin therapy. If approved, PCSK9 inhibitors may be positioned as monotherapies as well as adjuncts to statins. Both alirocumab and evolocumab are designed for biweekly injections at various dosages, although alirocumab also has a monthly injection dosing option.

  Official pricing information for PCSK9 inhibitors has not been announced because the drugs are not yet FDA approved. However, industry analysts predict that, initially, higher-end treatment estimates could range from $7,000 to $12,000 annually, per patient, which may be two to three times the annual cost of statins (about $3,000 per year for name brand statin at 10 mg/day dosage). If used as an adjunct with statins, therapy costs would be even higher. Due to this significant potential financial impact, particularly if approved indications are expanded or if used off-label, leading pharmacy benefits managers have stated plans to moderate PCSK9 drug prices. In June 2015, FDA an advisory committee met to evaluate the BLAs for alirocumab and evolocumab and voted to recommend approval of both drugs;

although the panel expressed concern about the short-term of the evolocumab studies (i.e., 12 weeks). FDA set a decision date (Prescription Drug User Fee Act date) of July 24, 2015, for alirocumab and August 27, 2015, for evolocumab.

- **Key Expert Comments:** Experts commenting on both PCSK9 inhibitors thought that these drugs have considerable promise for treating statin-resistant hypercholesterolemia indications, and would be widely accepted by patients and clinicians. Several experts reserved complete support for alirocumab's and evolocumab's high-impact potential, though, pending outcomes of long-term clinical trials evaluating these drugs' effect on patient morbidity and mortality. Experts were also concerned about the high, recurring cost of alirocumab and evolocumab compared with the cost of generic statins and how it could impact disparities in health care and market diffusion; however, multiple experts stated that PCSK9 inhibitors' health benefits could outweigh pricing issues. Overall, experts assessed alirocumab and evolocumab positively and perceived both drugs to have significant potential to address a growing health issue.
- **High-Impact Potential:** Moderately high

Pulmonary Artery Hypertension

PAH is a progressive, life-threating condition characterized by hypertension and narrowed vessels in the lungs, placing significant strain on the heart's right ventricle and often leading to HF. About 1,000 new PAH cases are diagnosed in the United States each year. Women are twice as likely as men to develop PAH. Since 1980, the numbers of hospitalizations and deaths related to PAH have increased, especially among women and older adults, and are believed to reflect increased physician awareness and changes in diagnosis and reporting. Between 1980 and 2002, annual deaths linked to PAH increased from 10,922 to 15,668, although an increase in rate was observed only among women. Several PAH treatments are available; but, they have limited effectiveness in many patients. Thus, effective new treatments could benefit patients with PAH.

Selexipag (Uptravi) for Treatment of Pulmonary Artery Hypertension

- **Key Facts:** Selexipag (Uptravi®) is an orally available selective prostacyclin receptor agonist that activates the prostacyclin receptor (IP receptor). This action reportedly dilates pulmonary vessels to reduce PAH symptoms. According to the manufacturer, selexipag differs from other prostacyclin analogs because of its selectivity for the IP receptor over other prostanoid receptors, which could limit systemic side effects compared with traditional prostacyclins. In March 2015, McLaughlin and colleagues in the GRIPHON study reported that selexipag reduced morbidity and mortality by 40% compared with placebo.

  Investigators noted that the GRIPHON study was the first large randomized controlled trial of PAH drugs to report on morbidity and mortality rather than other measures, such as exercise tolerance and walking distance. In December 2014, the manufacturer submitted an NDA to FDA supported by data from the GRIPHON study. A decision is expected in December 2015.
- **Key Expert Comments:** Experts thought that physicians and patients would welcome another oral prostacyclin therapy that purportedly has more selective action with fewer systemic side effects than other drugs in this class. All experts noted that selexipag is the first drug targeting PAH to demonstrate a substantial benefit, 40%, in reducing morbidity and mortality for the disease. One expert thought the drug has potential to be a "game changer," provided that benefits demonstrated in the GRIPHON study can be replicated.
- **High-Impact Potential:** Lower end of the high-impact range

Valve and Structural Disorders

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

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

- **Key Facts:** Transcatheter mitral valve repair with the MitraClip® device is intended to simulate the functional effects achieved by standard open-surgery repair of MR. In the standard procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening. In a MitraClip procedure, the physician uses a transcatheter approach in which a two-armed, flexible metal clip covered in polyester fabric is deployed through a catheter, rather than using sutures during open surgery.

  In March 2015, at the American College of Cardiology conference, Sorajja and colleagues reported in a conference abstract that MitraClip valve repair was successful, defined as reduction in MR grade to moderate or lower, for 91.8% of patients enrolled in the American College of Cardiology and Society of Thoracic Surgeons Transcatheter Valve Therapy registry. Investigators noted that institutional experience with and case volume of MitraClip procedures had a bearing on procedural success but not on major adverse outcomes, complications, or device-related events. In-hospital mortality was 2.3%, and 4 of the 13 patient deaths were from heart-related causes. At 30-day followup, the stroke rate was 1.6%, 5.8% of patients had died, and 8% of patients were hospitalized for HF. In 2015, Feldman and colleagues reported 1-year outcomes for "real world" patients with average or high risk of surgical complications who underwent MitraClip implantation for severe MR. Thirty-day mortality was 4.2% in high-risk patients and 1.5% in average-risk patients. Despite age and comorbidities including AF, coronary artery disease, and diabetes, 89% of all patients achieved MR reduction to grade 2+ or less, and 90% were discharged home. At 1 year, mortality was 23% in the high-risk group and 10% in the average-risk group, and freedom from MR of more than grade 2+ was 83% among surviving patients in both groups. The share of patients with New York Heart Association functional class III or IV HF fell from 81% at baseline to 15% at 1 year in the high-risk group and from 51% to 9% in the average-risk group.

  In October 2013, FDA approved the MitraClip delivery system for treating significant symptomatic degenerative MR. After approval, Abbott requested and subsequently received a new technology add-on payment code from CMS. In August 2014, CMS published a decision memo that outlines coverage of the device and procedure under its Coverage with Evidence Development process. Hospitals reporting device costs to ECRI Institute's PriceGuide database reported an average price paid of $30,000 for the MitraClip kit.

- **Key Expert Comments:** Experts commenting on this technology generally agreed this procedure addresses a considerable unmet need and has the potential to improve patient health for patients who are not eligible for mitral valve surgery. However, most experts opined that more data concerning safety and long-term outcomes are needed, citing the potential for adverse events and the technically difficult nature of the procedure. Experts were split on whether this technology would disrupt health care delivery. Some experts believe it would not, because the infrastructure for transcatheter heart procedures is already in place. However, other experts believe that an increase in case volume might disrupt health care delivery. Some experts anticipated that patient demand for minimally invasive procedures may ultimately expand use of the MitraClip procedure to include patients who are good candidates for open mitral valve repair and reduce the number of mitral valve surgeries. The majority of experts believe use of the MitraClip will increase health care costs but were not sure if those costs could be offset by a reduced need for other therapy for this population. They said longer-term data are needed to determine this.
- **High-Impact Potential:** Moderately high

Atrial Fibrillation–Associated Stroke Interventions

Andexanet Alpha for Reversal of Factor Xa Inhibitors

Unmet need: Direct and indirect factor Xa inhibitors (i.e., apixaban [Eliquis®], edoxaban [Savaysa™], rivaroxaban [Xarelto®], unfractionated and low-molecular-weight heparins) are target-specific anticoagulants prescribed for indications including preventing stroke in patients with AF and treating venous thromboembolism.[1,2] Oral factor Xa inhibitor use is widespread because drugs in this are known to have class have high efficacy and require less monitoring than comparable vitamin K antagonist anticoagulants (primarily warfarin).[1] While factor Xa inhibitors reportedly have solid overall safety profiles, up to 5% of patients taking these medications experience potentially fatal uncontrolled bleeding episodes or require emergency surgery in which bleeding is an issue.[3] An urgent need exists for safe, effective interventions to reverse factor Xa inhibition and allow normal hemostatic restoration during emergency events.[3]

Intervention: Andexanet alfa is a novel factor Xa derivative, developed via recombinant DNA technology in a Chinese hamster ovary cell line, intended to reverse factor Xa inhibitors.[2] Biochemically, andexanet alfa differs from native factor Xa in three primary aspects. Andexanet alfa lacks native factor Xa's membrane-binding domain, so andexanet alfa does not interfere with native factor Xa's prothrombinase complex activity. Andexanet is also manufactured with a serine-to-alanine substitution and a deletion of the heavy-chain-activation peptide; these modifications result in the drug having no endogenous pro- or anticoagulant properties.[2,4] Rather, andexanet alfa acts as a factor Xa decoy, binding highly selectively to factor Xa inhibitors. Selective binding sequesters factor Xa inhibitor molecules, rapidly decreasing free plasma factor Xa inhibitor concentrations and subsequently neutralizing inhibitors' anticoagulant activity.[2,4]

Andexanet alfa is administered intravenously and has been investigated in clinical trials with two protocols: (1) a single infusion, at dosages up to 420 mg, and (2) an intravenous bolus followed by continuous infusion for up to 2 hours.[5,6] Successful reversal results from these trials suggest that andexanet alfa can be employed as either a rapid (emergency) or prolonged universal factor Xa inhibitor reversal agent.

Clinical trials: In four completed phase II trials enrolling healthy patients, the activity of commonly prescribed direct and indirect factor Xa inhibitors (apixaban, edoxaban, rivaroxaban, and enoxaparin low-molecular-weight heparin) was rapidly reversed after bolus infusion of 210 or 420 mg of andexanet alfa.[5,7] Andexanet alfa was well tolerated, and the most frequently observed adverse event was mild infusion-related reaction.[7]

Two ongoing pivotal phase III trials, ANNEXA-A™ and ANNEXA-R™, are investigating andexanet alfa's sustained efficacy for reversing apixaban and rivaroxaban activity in healthy patients. Evaluating a primary study endpoint, preliminary data demonstrated that within 5 minutes of infusion, andexanet alfa bolus led to rapid, near complete reversal (94% reversal; $p<0.0001$) compared with placebo.[8] The study also met secondary endpoints, with statistically significant reductions ($p<0.0001$) in unbound factor Xa inhibitor molecules and restored thrombin generation, as measured by endogenous thrombin potential (ETP) in blood.[8] Additionally, no adverse events were associated with andexanet alfa infusion.[8]

An ongoing phase IV trial is investigating andexanet alfa's efficacy for reversing factor Xa inhibitor activity in patients presenting with acute major bleeds. As of June 2015, no data were available from this study.

Manufacturer and regulatory status: Portola Pharmaceuticals, Inc. (South San Francisco, CA), is developing andexanet alfa with supplemental commercial manufacturing support from CMC Biologics, Inc. (Copenhagen, Denmark), and Lonza Group AG (Basel, Switzerland).[9] Portola also established late-phase clinical trial partnership agreements with manufacturers of leading factor

Xa inhibitors, including Bristol-Myers Squibb and Pfizer, Inc. (both of New York, NY); Bayer AG (Leverkusen, Germany) and Janssen Pharmaceuticals (unit of Johnson & Johnson, New Brunswick, NJ); and Daiichi Sankyo Co., Ltd. (Tokyo, Japan).[4]

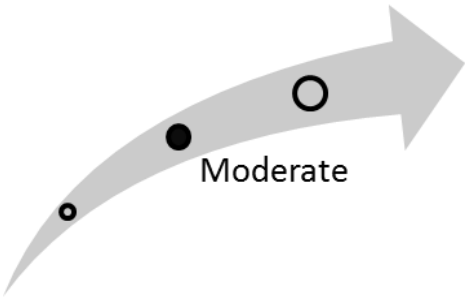
In November 2013, the U.S. Food and Drug Administration (FDA) granted breakthrough therapy status to andexanet alfa for reversing effects of factor Xa inhibitors in patients who experience a major bleeding episode or who require emergency surgery (with its risk of bleeding).[10] Portola plans to pursue an accelerated approval pathway.[11] In a recent pipeline-update presentation, Portola executives indicated intentions to file a biologics license application (BLA) by late 2015.[12]

Diffusion: As of June 2015, andexanet alfa is available only through clinical trials. Portola has not announced anticipated per-unit or per-patient pricing.

Clinical Pathway at Point of This Intervention

For emergency reversal of factor Xa inhibitors, first-line standard of care is administration of nonspecific procoagulants,[13,14] with a recent expert clinical panel (the working group on perioperative haemostasis) explicitly recommending either 30 to 50 U/kg of activated prothrombin complex concentrate (PCC), or 50 U/kg of nonactivated PCC for emergency indications.[13] Andexanet alfa is intended as a universal reversal agent for all direct and indirect factor Xa inhibitors. If approved, andexanet alfa could replace present guideline-directed therapy and become a new standard for this indication.

Figure 1. Overall high-impact potential: andexanet alpha for reversal of factor Xa inhibitors



Most experts commenting on this intervention agreed that andexanet alfa addresses a significant unmet need, providing an effective emergency reversal agent without affecting health care delivery methods or infrastructure. These experts also noted that this intervention has significant potential to improve patient health outcomes, but, at the time of their reviews, were concerned about a lack of available data supporting andexanet alfa's efficacy for treating its proposed indication. Experts generally anticipated that, if approved, andexanet alfa would be widely accepted by patients and clinicians. Based on this input, our 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 anticoagulant-reversal treatment.[15-20] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: All consulted experts commented that given the broad, and increasing, prescription of factor Xa inhibitors, an unmet need exists for a specific, effective emergency reversal agent of factor Xa inhibitor activity. These experts also agreed that andexanet alfa has high potential to address this need.

Acceptance and adoption: The majority of experts predicted that, as an emergency intervention, andexanet alfa would be accepted and adopted by clinicians and patients. Several experts also concluded that andexanet alfa's high anticipated adoption could have a secondary effect of increasing factor Xa inhibitor prescription, because the lack of specific reversal agents might contribute to limited use.[16,17,19,20]

Health care delivery infrastructure and patient management: Experts' consensus was that, as an infused medication, andexanet alfa would have a negligible impact on health care delivery infrastructure and patient management. Experts noted that present standard of care employs an identical administration route, so andexanet alfa use would not require dramatic changes; one clinical expert and one health systems expert expected that this drug would be widely stocked and seamlessly integrated into emergency care settings.[19,20]

Health disparities: Overall, experts anticipated that andexanet alfa would have minimal effect on health disparities. One clinical expert speculated that, compared with warfarin, factor Xa inhibitors' higher costs would limit their use by socioeconomic level; subsequently andexanet alfa might display similar stratification.[19]

Percutaneous (i.e., Transcatheter) Left Atrial Appendage Occlusion (Lariat, Watchman, WaveCrest) for Prevention of Atrial Fibrillation–Associated Stroke

Unmet need: About 87% of all strokes are ischemic (i.e., caused by a blood clot or other obstruction that blocks an artery supplying blood to the brain).[21] Estimates suggest that up to 90% of blood clots that form in the hearts of individuals with atrial fibrillation (AF) may originate in the left atrial appendage (LAA), a small pouch on the heart's left side.[22,23] Physicians typically prescribe oral anticoagulant drugs to patients with AF to reduce their risk of clot formation and ischemic stroke. Warfarin therapy has traditionally been the most widely used oral anticoagulant in this population, and it is the only oral anticoagulant recommended for use in patients with mechanical heart valves.[24] However, the need for frequent monitoring, dosage adjustments, and dietary restrictions make it a less-than-optimal therapy, and some investigators have reported that more than 60% of patients in general clinical practice may discontinue warfarin within 5 years of starting the drug.[25,26] Newer oral anticoagulants (i.e., apixaban, dabigatran, edoxaban, rivaroxaban) are available and reportedly safer and easier-to-use warfarin alternatives. However, no reversal agents are yet available for these newer oral anticoagulants, although some are in development.[2] Further, newer oral anticoagulant retail prices are as much as 75 times higher than warfarin for a 1-month supply, a factor that might present an access barrier for patients without adequate insurance coverage for pharmaceuticals.[27-29] Even with these options, some patients may be at increased bleeding risk and thus, ineligible for long-term oral anticoagulant therapy.[30,31] Further, patient adherence to recommended oral anticoagulation may be affected by factors including patient preference, convenience, age, cost, health insurance coverage, educational level, and perceived benefit.[24,32,33] For several years, clinical researchers and manufacturers have been evaluating whether a catheter-based intervention to seal the LAA would be a safe and effective alternative to long-term oral anticoagulation therapy to reduce stroke risk in patients with nonvalvular AF.

Intervention: Several manufacturers are developing similar implantable devices intended to seal off, or occlude, the LAA as a stroke-prevention strategy in patients with AF. The therapeutic goal is to prevent blood clots from escaping into general circulation and potentially blocking arteries in the neck or brain, thereby causing ischemic stroke.[34,35] The implantable devices typically are constructed from a nitinol frame that may be covered with a synthetic fabric. To implant a device, a physician inserts the delivery catheter in the femoral vein at the groin and advances it to the heart using a transseptal puncture to reach the left atrium.[36-38] Physicians place the implants within the LAA opening; fixation barbs on the frame are designed to anchor the implants in place.[35,39] Physicians perform transcatheter LAA occlusion in a catheterization laboratory using fluoroscopic guidance and transesophageal echocardiography to measure LAA dimensions with patients under general anesthesia.[34,36,38] LAA occlusion devices in development include the Watchman™ Left Atrial Appendage Closure Device and the WaveCrest™ LAA occlusion device. The Amplatzer™ Cardiac Plug is another LAA occlusion device that is being tracked in the AHRQ Horizon Scanning System, and is in a pivotal investigational device exemption trial that enrolled its first patient in March 2013, according to the company.

A related intervention for stroke prevention is transcatheter LAA ligation or exclusion using the Lariat® Suture Delivery Device, which is also performed in a catheterization lab under fluoroscopic and transesophageal echocardiographic guidance with patients under general anesthesia.[40,41] The Lariat procedure begins with two magnet-tipped guide wires placed inside and outside the patient's heart. One guide wire is advanced into the LAA from inside the left atrium via transseptal puncture,

beginning at the femoral vein in the groin. The other guide wire is advanced through the chest below the sternum (breastbone) into the epicardial space via epicardial puncture to access the anterior surface of the heart. Physicians use a proprietary balloon catheter placed inside the LAA to guide delivery of the Lariat snare-type suture loop over the apex (bottom) of the LAA and into position, before closing the loop at the LAA opening with a proprietary suture tightening device that eliminates operator variability during tightening. The operator uses a proprietary suture cutter to release the suture from the delivery device.[30,40,41] Some investigators reported placing a pericardial catheter from several hours to overnight to drain any periprocedural pericardial effusions.[41]

Clinical trials: *Watchman device.* In March 2015, Pillarisetti and colleagues reported endoleak and stroke risk in 478 patients with nonvalvular AF who underwent LAA closure using either the Watchman or Lariat devices. At 1 year, 17% (79 of 478) of patients had a detectable leak from the LAA. More leaks occurred in the Watchman group, 21% (46 of 219), than in the Lariat group, 13% (33 of 259; p=0.019). All Watchman leaks were termed eccentric (edge effect). All Lariat leaks were termed concentric (gunny sack effect). Watchman leaks were larger than Lariat leaks (3.10 ±1.5 mm vs. 2.15 ±1.3 mm; p=0.001). Adverse events in the Watchman group included one device embolization requiring surgery and two pericardial effusions requiring pericardiocentesis. Adverse events in the Lariat group included cardiac tamponade requiring urgent surgical repair in four patients. Three patients in each group had a cerebrovascular accident judged to be unassociated with device leaks.[42]

In November 2014, Reddy and colleagues reported long-term mortality and safety results of a 4-year followup from the PROTECT AF trial. Investigators observed primary efficacy event rates in the device and control groups of 2.3% and 3.8%, respectively.[43] In patients in whom the Watchman device was implanted, investigators observed cardiovascular and all-cause mortality rates of 1.0% and 3.2%, respectively.[43] According to the manufacturer, additional 4-year safety results observed in patients who had received the Watchman device in the PROTECT AF trial included all stroke (1.5%), hemorrhagic stroke (0.2%), and disabling stroke (0.5%).[44] Investigators reported the most frequent adverse events to be serious pericardial perfusion and major bleeding in both the device and control groups.[43]

In July 2014, Holmes and colleagues reported short- and long-term safety in 407 patients with AF who underwent Watchman implantation or continued oral warfarin anticoagulation. At 18-month followup, the first coprimary efficacy endpoint (composite of stroke, systemic embolism, and cardiovascular/unexplained death) did not achieve the prespecified criteria for noninferiority. The second coprimary efficacy endpoint (stroke or systemic embolism more than 7 days after enrollment) achieved noninferiority. Early safety events occurred in 2.2% of the Watchman arm, which was significantly lower than in the PROTECT AF trial, thus satisfying the prespecified safety performance goal. Using a broader, more inclusive definition of adverse effects, adverse events were still lower in the PREVAIL trial than in the PROTECT AF trial (4.2% vs. 8.7%; p=0.004). The comparative rate of pericardial effusions that required surgical repair decreased from 1.6% to 0.4% (p=0.027), and pericardial effusions requiring pericardiocentesis decreased from 2.9% to 1.5% (p=0.36), although the number of events was small.[45]

WaveCrest device. In January 2014, Aryana and colleagues reported preliminary data on procedural success in 60 patients with nonvalvular AF who underwent LAA occlusion with the WaveCrest device. Investigators reported that LAA occlusion was successful in 58 of 60 patients at 45 days. Success was defined as residual flow around the implant of 3 mm or less, with no total residual leak greater than 5 mm. After device implantation, all patients received dual antiplatelet therapy for 90 days and continued on lifelong aspirin therapy.[36]

Lariat device. In May 2015, Chatterjee and colleagues reported on the safety and procedural success of off-label LAA exclusion using the Lariat device in a systematic review of published

reports and analytic review of FDA's MAUDE database, which compiles, but does not verify device adverse-event and failure reports. Investigators identified five publish articles detailing LAA exclusion with the Lariat device in 309 patients. Procedural success, defined as complete LAA closure, was achieved in 90.3% of cases (279 of 309 procedures). Specific complications that were weighted for inverse of variance of individual studies included an urgent need for cardiac surgery (2.3%; 7 of 309 procedures) and death (0.3%; 1 of 309). The MAUDE database analysis identified 35 unique reports of adverse events associated with Lariat device. Of the 35 reports, investigators identified 5 that noted pericardial effusion and death and an additional 23 reports of urgent cardiac surgery without mention of death.[46]

Also in May 2015, Gianni and colleagues reported device efficacy in 99 patients who underwent the Lariat procedure at 4 institutions. No periprocedural deaths or strokes occurred. The rate of major bleeding was 9.3%. At 12-month follow-up, 5 late reopenings of the LAA were detected. Two patients with small reopenings developed stroke and transient ischemic attack. Investigators found that 22.4% of patients developed leaks after LAA closure with the Lariat device, sometimes more than 6 months after the procedure. They noted that leaks smaller than 5 mm that are considered safe in patients implanted with the Watchman device can lead to neurological events in patients treated with the Lariat device.[47]

In May 2014, Kanmanthareddy and colleagues reported AF burden and LAA reopening in 68 patients with AF and an electronic cardiac implant (pacemaker, implantable cardioverter-defibrillator [ICD], cardiac resynchronization device) who underwent LAA ligation with the Lariat device. Three months after the Lariat procedure, the cumulative atrial arrhythmia burden (time spent in atrial arrhythmias) decreased from 75% to 48% ($p<0.01$). In 14% of these patients, AF burden decreased from 100% to 0%. Complete LAA closure was achieved in 89% of patients. LAA reopening from 1 to 3 mm occurred in 6% of patients. Reopening from 3 to 5 mm occurred in 5% of patients. Patients who had LAA reopening greater than 3 mm showed no reduction in arrhythmia burden.[48]

Manufacturer and regulatory status: SentreHeart, Inc. (Redwood City, CA), manufactures the Lariat suture delivery device. FDA cleared the Lariat III Suture Delivery Device in September 2014 through the 510(k) pathway, but not specifically for use to treat AF, and thus its use for this indication is off-label. The indication is for facilitating "suture placement and knot tying for use in surgical applications where soft tissues are being approximated and/or ligated with a pre-tied polyester suture."[49] FDA granted the first-generation Lariat Suture Delivery Device 510(k) marketing clearance in June 2006 for the same indication.[50] The company states that the Lariat device also has regulatory clearance for soft tissue ligation and approximation in Europe, Canada, and Australia.[51,52]

Boston Scientific Corp. (Marlborough, MA) has developed the Watchman device (after acquiring the original developer, Atritech, Inc., Plymouth, MN, in 2011).[53] In March 2015, FDA approved Boston Scientific's Watchman device through the premarket approval (PMA) process.[54] The device is indicated for use in patients with nonvalvular AF who are at increased risk for stroke and systemic embolism based on stroke-risk score, for whom oral anticoagulation therapy is recommended, and who "are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin."[55] The Watchman's lengthy review process lasted more than 6 years and involved three FDA advisory panels and an FDA request for an additional phase III trial (PREVAIL) to confirm the device's long-term safety and efficacy before approval could be granted. As conditions of approval, FDA is also requiring the company to conduct a postapproval study to measure three primary endpoints that "must be met separately per the pre-specified performance goals in order to declare study success, where the upper bound of the

95% confidence interval for the event rates for the first, second, and third primary endpoints must be lower than 9.6%, 6.6% and 2.66%, respectively."[55] The device received a CE mark, allowing marketing in Europe, in 2005. In 2012, the European Union expanded indications for Watchman to include use of the device in patients in whom warfarin therapy is contraindicated.[34,56]

Coherex Medical, Inc. (Salt Lake City, UT), manufactures the WaveCrest left atrial appendage occluder. The company anticipates conducting clinical trials to support applications for approval in the United States and Japan; it has completed and published European studies of the device.[35] In November 2014, the WaveCrest device received regulatory approval in Australia, where the device is intended for use in LAA occlusion in patients with nonvalvular AF, LAA anatomy amenable to percutaneous treatment, and risk factors for potential thrombus formation in the LAA.[57] In September 2013, the WaveCrest device received CE mark in the European Union for use in LAA occlusion.[58]

St. Jude Medical, Inc. (St. Paul, MN), manufactures the Amplatzer Cardiac Plug (ACP) and Amplatzer Amulet™ Left Atrial Appendage Occluder. The devices are not available in the United States, but the ACP is in a pivotal FDA-approved investigational device exemption trial in the U.S. and Canada intended to enroll 400 to 3,000 patients to support marketing applications in those countries; the first patient was reportedly enrolled in March 2013.[59] In January 2013, St. Jude Medical received a CE mark for its next-generation Amplatzer Amulet LAA Occluder.[60] The company received a CE mark for its first-generation ACP device for transcatheter LAA occlusion in 2008.[60]

Diffusion: LAA occlusion devices will likely compete with oral anticoagulants, including generic warfarin and the newer agents (i.e., apixaban, dabigatran, edoxaban, rivaroxaban). Devices in this class are likely to also compete with each other, if devices other than the Watchman become commercially available in the United States.

According to ECRI Institute's PriceGuide database, the average quoted price of the Lariat suture delivery device as reported by U.S. hospitals is about $5,000 each. The total cost of the accessory devices required to perform a Lariat ligation procedure, including the proprietary occlusion balloon catheter, guide wire, and suture cutter, is about $2,690.[61]

According to PriceGuide, the average price paid for the Watchman device was $8,000.[62] In the United Kingdom, total costs for the Watchman implantation procedure and device are estimated at about £11,400 with the device costing approximately £5,300, and the implantation procedure costing approximately £6,000.[63] At May 2015 currency exchange rates, those estimated total costs would be approximately $17,500, including $8,137 for the device and $9,210 for the implantation procedure.[64] A 2012 Canadian economic evaluation comparing cost-effectiveness of LAA occlusion devices and anticoagulants cited the average cost of the Watchman device as $8,500; the fees attributed to anesthesia, nursing, physician, a 1-night hospital stay, and transesophageal echocardiogram performed at time of procedure and twice during followup visits totaled $5,246; thus, total cost estimated in Canada in 2012 for the procedure, including the device, was $13,746.[65] If they became commercially available in the United States, the WaveCrest, Amplatzer ACP or Amulet devices would likely be priced comparably to the Watchman device, given the similar design and implantation techniques.

At this time, the U.S. Centers for Medicare & Medicaid Services (CMS) does not have a national coverage determination for LAA occlusion devices. However, CMS has accepted a request from Boston Scientific to initiate a national coverage analysis "for percutaneous, transcatheter, intraluminal left atrial appendage (LAA) closure using an implanted device."[66] According to CMS, "the scope of this national coverage analysis does not include surgical techniques used to achieve LAA closure." CMS anticipates completing a proposed decision memo by November 21, 2015.[66] Boston Scientific applied to CMS for a new technology add-on payment for its Watchman device

under the Acute Inpatient Prospective Payment System for Federal fiscal year 2015 but withdrew the application after FDA failed to grant the device marketing approval by CMS's add-on payment deadline.[67]

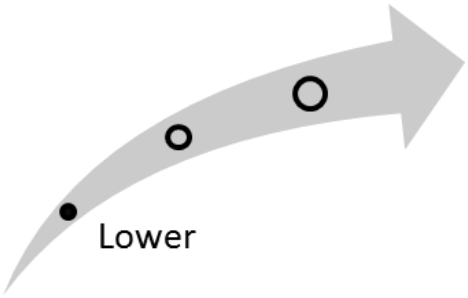
ECRI Institute searches of a representative group of private third-party payers that post their coverage policies online found several payers that consider percutaneous or transcatheter LAA occlusion with the Watchman and/or other similar devices to be investigational or experimental and therefore deny coverage for the procedure. As of May 2015, payers that deny coverage for percutaneous or transcatheter LAA occlusion procedures include Aetna,[68] Anthem,[69] Blue Cross Blue Shield (BCBS) of Alabama,[70] BCBS of Massachusetts,[71] BCBS of Tennessee,[72] CIGNA,[73] Empire BCBS,[74] and Regence.[75] UnitedHealthcare also considers transcatheter LAA occlusion experimental, but its coverage policy states, "However, depending on the enrollee-specific benefit document, coverage may be available through participation in an eligible clinical trial."[76] As they periodically review their coverage policies, payers may adjust their noncoverage policies in light of the recent FDA approval of the Watchman device.

Boston Scientific has published reimbursement advice for health care providers on its corporate Web site. The company suggests coding Watchman procedures using ICD-9 procedure code 37.90 (insertion of a left atrial appendage device, transseptal catheter technique) and CPT III code 0281T (percutaneous transcatheter closure of the left atrial appendage with implant, including fluoroscopy, transseptal puncture, catheter placement(s) left atrial angiography, left atrial appendage angiography, radiological supervision and interpretation).[77] The company anticipates that Watchman implantation would likely be reimbursed under MS-DRG 250 (percutaneous cardiovascular procedure without coronary artery stent with MCC [major complications or comorbidities], fiscal year 2015 national average Medicare base payment, $17,529) or MS-DRG 251 (percutaneous cardiovascular procedure without coronary artery stent without MCC, fiscal year 2015 national average Medicare base payment, $11,965).[77]

Clinical Pathway at Point of This Intervention

A serious complication of AF is ischemic stroke.[24,78] Risks for ischemic stroke after all standard stroke risk factors are accounted for are four to five times greater in patients with AF than in other individuals.[78] Stroke risk is high in AF because thrombi form in the atria or, more commonly, in the LAA, enter circulation, and can travel to the brain.[79,80] Thromboembolism is prevented primarily through antithrombotic pharmacologic therapy. Guidelines recommend that the choice of antithrombotic drug be based on the absolute stroke and bleeding risks and the patient's relative risks and benefits. Guidelines also advise that "selection of an antithrombotic agent should be based on shared decision making that takes into account risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics."[24] Anticoagulants include vitamin K antagonists, aspirin, low-molecular-weight heparin, and the newer oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban.[24] Catheter-delivered implantable devices may potentially be positioned as an alternative to anticoagulant therapy for stroke prevention in patients with nonvalvular AF.[40,81]

Figure 2. Overall high-impact potential: percutaneous left atrial appendage occlusion (Lariat, Watchman, WaveCrest) for prevention of atrial fibrillation–associated stroke



Overall, experts commenting on this technology class agreed that it holds some potential to reduce stroke incidence in patients with AF who cannot tolerate long-term oral anticoagulation. However, some experts noted that the perceived benefit of this technology has become muted with the relatively recent availability of newer alternatives to warfarin, such as apixaban, dabigatran, edoxaban, and rivaroxaban. Several experts were concerned about the incidence of device-related adverse events and a history of recalls with some products in this class. Experts also noted the lack of trial data comparing the efficacy of these devices to newer oral anticoagulants in addition to generic warfarin. 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

Experts with clinical, research, health systems, and health administration backgrounds offered perspectives on these three interventions.[82-102] The number of commenters on these devices is as follows:

- Two experts commented on all three devices.[82-84,100-102]
- Five experts commented on two of the devices.[85-90,96-99]
- Five experts commented on one of the devices.[91-95]

One expert reported a potential conflict of interest as a speaker on an unrelated product for the manufacturer of one device.[87,88] This was balanced by the perspectives of the other experts, who reported no conflicts. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts differed in their opinions about the potential unmet need that this technology class purports to address. Several noted the high incidence of AF in the aging population and the proportion of that population that might face an unacceptable bleeding risk from long-term oral anticoagulation. One clinical expert noted, "Stroke prevention in atrial fibrillation is a huge problem requiring anticoagulation to treat, but many are also at significant risk of bleeding, and effectiveness of treatment, especially Coumadin, is compromised by difficulty [in maintaining] appropriate INRs [international normalized ratios, a measure of anticoagulation]. Eliminating this with left atrial appendage occlusion offers promise for these patients and frees them from the burden of frequent blood testing and dietary constraints, etc. The novel oral anticoagulants are very expensive for some patients, limiting this as an option."[88]Another clinical expert stated, "Atrial fibrillation is a huge problem, and with our aging population, the percentage of people who have concomitant significant bleeding risks is quite high. This leads to a large percentage of patients who are at high risk of stroke but cannot be on anticoagulation because of too high a bleeding risk (14-44%). Therefore, the implications of a device that can 'cure,' or

dramatically reduce the risk of cerebrovascular accident with the eventual ability to be off anticoagulants is huge."[93]

However, other experts disagreed about the magnitude of the unmet need. One clinical expert noted, "The greatest advantage of such devices was to avoid the use of Coumadin [warfarin]. But now with newer oral anticoagulants, that advantage is muted."[84] Another clinical expert concurred: "In clinical practice, the number of patients who cannot tolerate anticoagulation is not as large as 44% of patients with atrial fibrillation. Those who cannot tolerate anticoagulation are those most likely to benefit, but the data in the population are scarce. At present, the Watchman is not clearly non-inferior to therapy with anticoagulation, and both warfarin and the novel anticoagulants are generally very well tolerated. So there is not a huge unmet need."[92]

Experts were also divided on the likelihood that these interventions would substantially improve health outcomes. One research expert noted, "Chronic anticoagulant therapy is associated with its own challenges and complications, so devices like the Watchman could potentially improve health in eligible atrial fibrillation patients."[89] A clinical expert stated, "Based on data from the Watchman device, this type of therapy holds significant promise."[88] On the other hand, one clinical expert noted, "More evidence is needed to demonstrate the effectiveness of the device in preventing stroke. Device-related adverse events are also concerning."[100] Another clinical expert stated, "The only real advantage of such devices is to avoid anticoagulant medications. This is offset by the invasiveness of the procedure."[83] A research expert observed, "Most studies are small, reporting on fewer than 100 patients, and most studies report data at less than 6-month follow-up."[85]

Acceptance and adoption: Generally, most of the experts did not anticipate that clinicians would widely adopt LAA occlusion devices as first-line AF therapy. Clinical experts cited the lack of definitive data demonstrating the superiority of this technology to long-term warfarin and even less data comparing it to newer oral anticoagulants, such as apixaban, dabigatran, edoxaban, and rivaroxaban. One clinical expert stated, "Without a large trial showing these devices reduce stroke as well or better than the newer anticoagulants, there will be minimal acceptance."[84] Another clinical expert noted, "I can't see this gaining wide acceptance because of the inconvenience of the procedure, slow learning curve and limited availability of proceduralists with adequate skills (interventionalists/electrophysiologist doctors) and invasiveness of procedure."[93]

Experts suspected that patients might be somewhat more accepting of LAA occlusion than physicians because the prospect of ending lifelong anticoagulation is appealing. However, the risk of device-related complications, the modest acceptance by many physicians, and unlikely insurance coverage could dissuade many patients from undergoing the procedure. One clinical expert stated, "From a patient perspective, I think many would rather have a procedure done than take anticoagulation for life. However, given the invasive nature, it will never gain wide acceptance."[93] A research expert concurred, stating "For atrial fibrillation patients who have concerns about chronic anticoagulant therapy, a solution like the Watchman might look attractive. However, some patients might be concerned about serious adverse events and might be hesitant about undergoing the procedure."[89]

Health care delivery infrastructure and patient management: Experts generally expected this technology to have a small disruptive on health care infrastructure because the implantation procedures are similar to established techniques used by experienced interventional teams in large catheterization laboratories. Several experts thought that patient demand for the procedure could have a larger infrastructure impact; however, they doubted that substantial patient demand would develop for the procedure. One health systems expert commented, "This intervention would be performed by interventional cardiologists in existing cardiac catheterization labs, both of which are plentiful. If this intervention was widely accepted and utilized, there would be a small impact as the patients would not require outpatient blood testing for INR."[99] A clinical expert stated, "At present

the lack of evidence showing substantial benefit of the Watchman in patients who can take other anticoagulants means it is unlikely to disrupt current health care delivery systems. If efficacy is demonstrated among those too high risk to take oral anticoagulants, there may be more of a market."[92] Yet another clinical expert stated, "If this became a high volume procedure, it would be a major disruption to hospitals' delivery infrastructure. Currently only a few laboratories in the area perform the procedure. If it became ubiquitous, many more hospitals would need to develop the training of the physicians/staff as well as the required cath lab space/time to accommodate these patients."[93]

The experts were divided on the extent to which LAA occlusion would alter patient management. One health systems expert stated, "If widely adopted, the intervention could shift the delivery of care from the outpatient setting with weekly visits and high demand on physician attention and decision making to the inpatient setting in the interventional labs. Patients would no longer be required to have weekly follow up for INR management."[97] A clinical expert noted, "The biggest potential [change] is to decrease the risk of stroke, which would cause a large disruption in patient care, as it is such a huge burden on the patient and health care system. It would also likely decrease hospitalizations for gastrointestinal bleeds, etc. One could expect more admissions for complications and a brief hospital admission for the procedure (overnight observation)."[93] Yet another clinical expert stated, "Perhaps some patients will be treated with these devices in the future, but I would suspect that most patients will still get anticoagulant medications."[83]

Health disparities: The experts generally agreed that LAA occlusion devices would be unlikely to change disparities in care for patients with AF. Some experts thought that the lack of reimbursement from large private insurance companies could prevent lower-income populations from access to the treatment, although they did not expect the technology to be widely used in any subpopulation. One clinical expert noted, "I don't see a large impact to health disparities here. The same issues that would create under-utilization of anticoagulation in patients with elevated CHADS scores in atrial fibrillation will also lead to under-utilization of this technology."[93]

Hypercholesterolemia Interventions

Alirocumab (Praluent) and Evolocumab (Repatha) PCSK9 Inhibitors for Treatment of Familial Hypercholesterolemia and Statin-Resistant Hypercholesterolemia

Unmet need: Along with dietary and lifestyle modifications, statins are widely prescribed to treat various dyslipidemias, including hypercholesterolemia. Although statin-class drugs are valued for their treatment and cost efficacy, experts estimate that 10% to 20% of patients cannot tolerate the high doses required to manage symptoms, or patients have clinical indications, such as familial hypercholesterolemia (FH), that are resistant to statin administration.[103,104] In total, more than 6 million Americans (nearly 2% of the population) may have statin-resistant hypercholesterolemia indications. For these patients, treatment alternatives, like the second-generation cholesterol-lowering drug ezetimibe (Zetia®), have limited efficacy. Accordingly, a significant need exists for effective treatments for patients with statin-resistant hypercholesterolemias.[105]

Intervention: Alirocumab and evolocumab are members of a new class of medications known as PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. Candidate drugs in this class share a mechanism of action, preventing normal PCSK9 binding to low-density lipoprotein receptor (LDLR) and subsequent hepatic LDLR degradation.[106] Hindering LDLR degradation is hypothesized to lower plasma low-density lipoprotein cholesterol (LDL-C) levels and improve health outcomes for patients with hypercholesterolemia indications.[107] By extension, PCSK9 inhibitors could enhance the efficacy of cholesterol-lowering drugs, such as statins, and also offer an effective alternative monotherapy for patients resistant to standard hypercholesterolemia therapies.[107-109]

Alirocumab and evolocumab are both fully humanized monoclonal antibodies to PCSK9, developed as PCSK9 inhibitors for treating heritable and statin-resistant hypercholesterolemias.[109] Both are subcutaneously injectable medications.[110,111] Alirocumab is designed for biweekly injections at 75 or 150 mg doses;[112,113] in contrast, evolocumab can be injected biweekly, at a dose of 140 mg, or monthly, at a dose of 420 mg.[114,115]

Clinical trials: Both PCSK9 inhibitors have been investigated in pivotal clinical trials to form the basis of submissions to FDA for marketing approval. Alirocumab's pivotal trial data are being collected from the ODYSSEY study program, a series of short- and long-term studies enrolling patients with primary, heritable, and treatment-resistant hypercholesterolemias.

Across these patient populations, completed ODYSSEY studies have reported that chronic alirocumab administration is associated with sustained, significantly improved cholesterol-lowering efficacy for up to 2 years.[116] For example, in the ODYSSEY Combo I study (n=316), patients with primary hypercholesterolemia and increased coronary artery disease risk demonstrated statistically significant reduction in LDL-C levels when administered alirocumab injections compared with placebo (alirocumab, 48.2±1.9% reduction; placebo, 2.3±2.7% reduction; $p<0.0001$).[117] Similar statistical superiority for alirocumab compared with placebo was observed in the ODYSSEY FH I, FH II, High FH, and Long Term studies, which enrolled patients with primary or heritable hypercholesterolemia.[110,116,118]

Additionally, ODYSSEY studies, including ODYSSEY Alternatives, Options I, and Options II, have found that alirocumab is superior to statins and other standard therapies for lowering hypercholesterolemic patients' LDL-C levels.[119,120] In the most recently published data from the ODYSSEY Combo II study (n=720), after 24 weeks, alirocumab injections were superior to daily oral ezetimibe (alirocumab, 50.6±1.4%; ezetimibe, 20.7±1.9%; difference, 29.8±2.3%; $p<0.0001$) at reducing LDL-C.[121] Additionally, the study's conclusion stated that almost twice as many patients

receiving alirocumab reached clinically healthy LDL-C levels as did patients receiving ezetimibe (77% vs. 45.6%).[121]

Evolocumab's treatment efficacy has been evaluated in several small, short-term (12-week) studies enrolling patients with heritable hypercholesterolemia and across a series of large trials that enrolled patients with broad hypercholesterolemia indications. In the RUTHERFORD (n=147), RUTHERFORD-2 (n=331), and TAUSSIG (n=37) studies, researchers found that within 12 weeks, biweekly or monthly evolocumab injections effectively lowered LDL-C levels in patients with heritable hypercholesterolemia.[114,122,123] Similarly, in trials including the DESCARTES, MENDEL-2, OSLER, and OSLER-2 studies, evolocumab was superior to statin or ezetimibe therapy for reducing LDL-C levels in patients with primary hypercholesterolemia.[124-126] In the largest analysis, combining OSLER and OSLER-2 data sets (n=4,465), biweekly or monthly evolocumab injections reduced LDL-C by 61% compared with LDL-C levels under standard therapy ($P<0.001$).[126]

Overall, both PCSK9 inhibitors have been well tolerated; the most commonly observed adverse events across all studies are influenza, injection-site reactions, and nasopharyngitis.[114,127-129] Serious treatment-related adverse events were infrequent and, in most trials, occurred at rates similar those observed for placebo or comparator drugs.[126,129] Ongoing trials are examining both alirocumab's and evolocumab's long-term safety and efficacy, in part to evaluate potential PCSK9 inhibitor-related neurocognitive risks.[116,130,131]

Manufacturer and regulatory status: Alirocumab was originally identified by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY), and is being developed and manufactured in collaboration with Sanofi (Paris, France).[132,133] In August 2014, alirocumab's manufacturers announced intentions to pursue an expedited 6-month FDA review, using a purchased rare pediatric disease priority review voucher.[133] Regeneron and Sanofi subsequently filed a BLA for alirocumab, branded as Praluent, based on data from 10 pivotal phase III studies (i.e., the ODYSSEY clinical trial program); the application was accepted in January 2015, and an FDA advisory committee voted on June 9, 2015 to recommend approval with an FDA decision expected by July 24, 2015.[134]

Evolocumab, branded as Repatha, is being developed and manufactured by Amgen, Inc. (Thousand Oaks, CA).[135] FDA accepted Amgen's BLA in August 2014, based on data from nearly 7,000 patients, including more than 4,500 patients with hypercholesterolemia enrolled in phase III trials.[135] An FDA advisory committee voted on June 10, 2015 to recommend approval with an FDA decision date expected August 27, 2015; although the committee expressed reservations about the short duration (12 weeks) of the studies.[135]

Diffusion: As of June 2015, access to these drugs is limited to patients enrolled in clinical trials. Manufacturers of these drugs, along with leading industry analysts, expect both drugs to be approved by their stated review deadlines and available for prescription shortly thereafter.[136] Initial FDA-approved labeling may be limited to heritable hypercholesterolemia indications; however, pending safety and efficacy data are anticipated to result in expanded indications covering patients with primary statin-resistant hypercholesterolemia.[137]

Neither alirocumab's nor evolocumab's manufacturers have announced retail costs for their drugs. However, the pending approvals and "blockbuster" sales potentials have led to pricing speculation among industry observers and preemptive cost-control declarations by pharmacy benefits managers (PBMs).[136-138] Analysts have predicted that PCSK9 inhibitors will be widely adopted and, at estimates of $7,000 to $12,000 annually per patient, which would cost significantly more (two to three times more) than standard hypercholesterolemia medications.[137] Recently, observers have speculated that manufacturers may present tiered pricing models, with lower-dose options retailing for 50% to 60% of higher-dose prescriptions.[136]

PCSK9 inhibitors are positioned as chronic medications for all studied hypercholesterolemia indications, compounding patient treatment costs. Realizing the prospective economic strain that

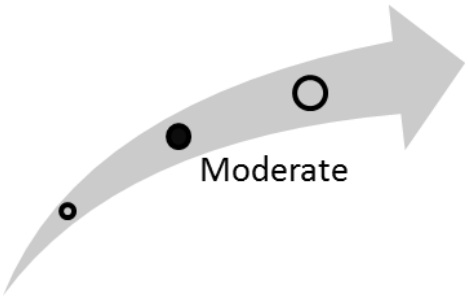
these drugs could place on the health care system, PBM executives have stated plans to moderate PCSK9 inhibitor prices, with contrasting manufacturer's statements suggesting that pricing might be set by perceived treatment value and market tolerance.[134,138] Industry observers note that pending PCSK9-inhibitor cost-control measures could be similar to those employed for recently approved hepatitis C drugs; in those cases, PBMs established preferential formulary inclusions and omissions for competing drugs, based on manufacturer agreements to offer price discounts.[134] For more information on hepatitis C medication pricing, please refer to Chapter 9 of this report ("Infectious Disease Including HIV/AIDS").

Clinical Pathway at Point of This Intervention

Patients with hypercholesterolemia intolerant to initial statin therapy are often prescribed higher-dose statins, potentially in conjunction with ezetimibe (Zetia®); fibrates; niacin; omega-3 fatty acid ethyl esters or marine-derived omega-3 polyunsaturated fatty acids; or various bile acid sequestrants, to more effectively reduce patients' LDL-C levels.[139] Surgical procedures including LDL apheresis and portacaval anastomosis (for homozygous familial hypercholesterolemia) may also be indicated as later-line therapies for certain treatment-resistant patients.[139] Alirocumab and evolocumab are intended as alternative pharmacotherapies for these patients.

In 2013, FDA approved two medications, the adjunct drug lomitapide (Juxtapid®; Lojuxta®) and monotherapy mipomersen (Kynamro®), for treating heritable hypercholesterolemia.[140-142] Alirocumab and evolocumab, as developed, could also be positioned as alternate medications for patients with heritable hypercholesterolemia indications.

Figure 3. Overall high-impact potential: Alirocumab (Praluent) and Evolocumab (Repatha) PCSK9 Inhibitors for Treatment of Familial Hypercholesterolemia and Statin-Resistant Hypercholesterolemia



Experts commenting on these interventions agreed that PCSK9 inhibitors address a large public health issue, given the substantial and growing population of patients with statin-resistant hypercholesterolemia. Although available clinical trial data indicate alirocumab's and evolocumab's potential to address an unmet need, experts support was tempered by the paucity of long-term safety and patient health outcome data for both drugs. Experts did, however, note that some of these concerns may be adequately resolved by larger ongoing safety and efficacy studies. The majority of experts acknowledged PCSK9 inhibitors' significant potential economic impact, but considered potential cost-controlling measures and improved patient health outcomes in evaluating anticipated widespread patient and clinician acceptance of these drugs. Based on this input, our assessment is that these interventions are in the moderate high-impact-potential range.

Results and Discussion of Comments

Nine experts, with clinical, research, and health systems backgrounds, offered perspectives on alirocumab and/or evolocumab.[143-154] Of these, three provided opinions for both

interventions.[144,146,148,149,153,154] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Overall, these experts acknowledged that hypercholesterolemia indications represent a major health issue and thought that both PCSK9 inhibitors have high potential to address an unmet need for novel, effective therapies for patients with these indications. One expert with a research background commented solely on evolocumab and was guardedly optimistic in evaluating PCSK9 inhibitors; this expert reasoned that while the entire class of new drugs might significantly improve patient health outcomes, when evaluated individually, single PCSK9 inhibitors may not distinguish themselves as particularly impactful.[152]

Acceptance and adoption: Experts' consensus predicted that PCSK9 inhibitors, bolstered by reported safety and efficacy data, would be widely accepted by both clinicians and patients. Multiple experts, however, noted that because alirocumab and evolocumab are subcutaneously injected, some patients may be hesitant to adopt them when competing oral therapies are available.[149,150] Other experts also suggested that the expected high cost of PCSK9 inhibitors could also prevent adoption of these interventions, especially if health insurance coverage is not available or if co-pays are high.[143,147]

Health care delivery infrastructure and patient management: Expert consensus was that although alirocumab and evolocumab require subcutaneous injection, in contrast to statins and other orally administered drugs, these two interventions would have minimal impact on health care delivery infrastructure and patient management.

Health disparities: The majority of experts expected these drugs to have minimal impact on health disparities. However, three experts opined that, primarily due to the anticipated high cost, health disparities could be adversely affected if low-income individuals are unable to afford them.[145,151,154] One clinical expert who evaluated alirocumab also noted that, because hypercholesterolemia indications disproportionately affect racial minorities, expensive, new drugs could worsen health disparities along those lines.[145]

Heart Failure Interventions

Combination Valsartan/Sacubitril (LCZ696) for Treatment of Heart Failure

Unmet need: Standard heart failure (HF) monotherapies and combination therapies attempt to reduce prominent symptoms and delay disease progression. Expert clinical panel–recommended HF pharmacotherapies include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), digoxin (Lanoxin), beta blockers, diuretics, and aldosterone antagonists. Clinicians may also prescribe nitrates for chest pain, statins to lower cholesterol, and blood thinners to prevent blood clots.[155,156] In ideal cases, these interventions improve patients' quality of life and reduce mortality rates; however, many patients have HF that fails to respond adequately to these treatment options.[156,157] A significant unmet need exists for alternative, effective medications for treating HF.

Intervention: Combination valsartan/sacubitril (LCZ696) is a novel oral angiotensin receptor neprilysin inhibitor; its active components are valsartan, an approved angiotensin receptor blocker, and sacubitril, a prodrug inhibitor of neprilysin, an enzyme that normally counteracts blood pressure-lowering atrial and brain natriuretic peptides.[158,159] In a crystalline complex combination, valsartan and sacubitril are hypothesized to both inhibit the renin-angiotensin-aldosterone system (RAAS), which normally regulates blood volume and systemic vascular resistance, and enhance endogenous natriuretic peptide activity.[158] Purportedly, these actions result in reduced cardiovascular system strain, alleviating HF symptoms and other cardiovascular outcomes.[158]

Preliminary clinical results indicate that valsartan/sacubitril is superior to valsartan monotherapy for improving biomarkers of cardiac stress.[160,161] Additionally, in an animal model of HF, valsartan/sacubitril administration was associated with attenuated cardiac remodeling, potentially due to the drug's inhibition of cardiac fibrosis and hypertrophy.[162]

Based on completed studies, valsartan/sacubitril could be prescribed as a monotherapy or adjunct to standard HF medications. Unlike standard approved HF medications, primarily used to treat patients with reduced ejection fraction, valsartan/sacubitril's demonstrated ability to relieve cardiovascular strain also makes it a candidate drug for treating HF patients with preserved ejection fraction. This added property potentially affords valsartan/sacubitril expanded indication over available HF medications.[163,164]

Clinical trials: PARADIGM-HF (n=8,442) was a pivotal clinical trial designed to compare valsartan/sacubitril to enalapril, an ACE inhibitor, for reducing all-cause mortality and hospitalization rates in patients with HF. The pivotal trial opened in 2009 and was concluded early, based on recommendations of a data monitoring committee positively evaluating the strength of interim trial results.[165]

Measured over 4 years, patients receiving daily valsartan/sacubitril demonstrated the following improved patient health outcomes relative to enalapril:[166,167]

- Fewer patients required intensification of HF medical treatment (520 vs. 604; hazard ratio, 0.84; 95% CI, 0.74 to 0.94; p=0.003)
- Twenty-three percent fewer hospitalizations for worsening HF (851 vs. 1,079; p<0.001)
- Fewer patients required intensive care (768 vs. 879; 18% rate reduction; p=0.005)
- Fewer patients required HF device implantation or cardiac transplantation (22% risk reduction; p=0.07)

Researchers also noted that valsartan/sacubitril showed superiority for reducing hospitalization within 30 days of starting treatment.[167]

Overall, valsartan/sacubitril has been reportedly well tolerated; few side effects and no serious treatment-related adverse events have been reported in phase II or III trials. In the concluded

PARADIGM-HF pivotal trial, cough, hyperkalemia, renal dysfunction, and symptomatic hypotension were the most common valsartan/sacubitril treatment-related adverse events.[166] Investigators also noted that valsartan/sacubitril treatment-related adverse events led to fewer study-participant discontinuations than did enalapril treatment (10.72% vs. 12.25%).[166,167] A January 2015 study by an independent French research group proposed that sacubitril was inconclusively linked to accelerated Alzheimer's disease risk; no increased neurocognitive risk has been observed in valsartan/sacubitril trials, but ongoing trials may resolve any potential associations.[168]

In larger clinical trials, valsartan/sacubitril is orally administered at daily doses up to 400 mg.[166,167,169] Valsartan/sacubitril doses are commonly titrated up to this maximum dose over the treatment course; however, no official titration protocol is available.[163,169]

Manufacturer and regulatory status: Novartis International AG (Basel, Switzerland) is developing valsartan/sacubitril.[165] FDA granted valsartan/sacubitril fast-track status for treating HF, allowing Novartis to submit a rolling application for approval. Novartis submitted a new drug application (NDA) to FDA in 2014, and in February 2015, FDA announced that it would review the application under its priority review program. A decision is expected in August 2015.[165]

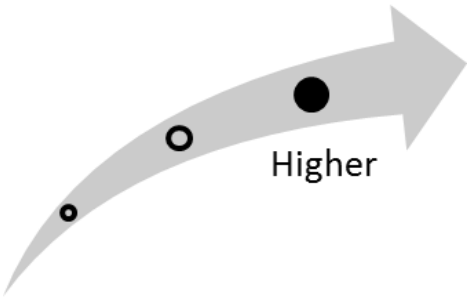
Diffusion and cost: To date, Novartis has not announced retail costs for valsartan/sacubitril. However, industry observers have projected valsartan/sacubitril annual cost at $2,000 to $2,500 per patient.[170] Comparatively, per-patient standard generic HF medications are as low as 13 cents to 20 cents per daily dose, equivalent to less than $75 annually.[170,171]

Clinical Pathway at Point of This Intervention

Expert clinical panel–recommended HF pharmacotherapies include ACE inhibitors, ARBs, digoxin, beta blockers, diuretics, and aldosterone antagonists. Clinicians may also prescribe nitrates for chest pain, statins to lower cholesterol, and blood thinners to prevent blood clots.[155,156] Additionally, surgical interventions such as coronary artery bypass graft surgery, heart valve repair or replacement, ICDs, cardiac resynchronization therapy (CRT) or biventricular pacing, heart pumps, and heart transplants can also be indicated.[155,172]

If approved for treating HF, valsartan/sacubitril could be prescribed as a monotherapy or adjunct to standard HF medications because recent pharmacokinetic studies suggest that valsartan/sacubitril has limited interactions with drugs commonly prescribed for HF and comorbid conditions and does not interfere with the activities of these drugs.[173-175]

Figure 4. Overall high-impact potential: Valsartan/sacubitril (LCZ696) for treatment of heart failure



Experts commenting on this intervention acknowledged that HF is a significant health issue with severe patient outcomes that are inadequately addressed by present therapies. Experts thought valsartan/sacubitril could dramatically improve patient health outcomes. This intervention has favorable safety profiles in clinical trials, and although there is an unconfirmed link to increased adverse neurocognitive risk, experts stated that this concern would not limit valsartan/sacubitril's potential acceptance and use. The majority of experts also favorably cited valsartan/sacubitril's

significant efficacy for improving mortality, hospitalization rates, and advanced-treatment rates. Based on this input, our 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, and health systems backgrounds, offered comments on valsartan/sacubitril.[176-181] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Overall, experts stated that HF and related health outcomes were a prominent health issue that is inadequately controlled by available therapies. Concurrently, these experts also agreed that valsartan/sacubitril has high potential to address an unmet need for novel, effective therapies for patients with HF, noting the drug's strong comparative efficacy and safety profile and potentially expanded patient base.

Acceptance and adoption: Experts' consensus was that valsartan/sacubitril would be broadly diffused among clinicians. Additionally, they concluded that, as a new medication with superior efficacy for improving key health outcomes, this intervention would appeal to patients, with safety and cost concerns presenting minimal barriers to adoption.[176,177,179]

Health care delivery infrastructure and patient management: Most experts thought that, as an oral HF medication, valsartan/sacubitril would not significantly affect health care delivery infrastructure or patient management. However, one health systems expert noted that widespread use of valsartan/sacubitril might dramatically decrease emergency department visits and hospital admissions, shifting care from the inpatient to the outpatient setting.[180] One clinical expert anticipated that broad use of valsartan/sacubitril would require many patients to adjust treatment regimens, a process that could require several office visits per patient, consuming substantial management resources.[181]

Health disparities: Five of six experts thought that valsartan/sacubitril would have little to no impact on health disparities. In contrast, one clinical expert thought that valsartan/sacubitril's comparatively high anticipated cost could prevent uninsured or economically disadvantaged patients from accessing this intervention, subsequently increasing health disparities.[176]

Ivabradine (Corlanor) for Treatment of Heart Failure

Unmet need: Standard of care for treating HF includes ACE inhibitors, ARBs, digoxin, beta blockers, diuretics, and aldosterone antagonists.[155,156] These medications are reasonably priced and often achieve sufficient clinical improvements. However, standard drugs are not universally effective, and an unmet need exists for additional medications that can further improve patient health outcomes when administered as monotherapy or adjunctively to other available treatments.[156,157]

Intervention: Ivabradine is a novel, antianginal, heart-rate-lowering medication, originally developed for treating chronic stable angina pectoris.[182,183] Ivabradine directly lowers heart rate by selectively inhibiting the funny channel (I_f) pacemaker current and reducing the diastolic depolarization rate.[182,184] Purportedly, this action addresses a key aspect of HF pathophysiology: researchers hypothesize a connection between HF-related diminished cardiac function, increased heart rate, and cardiac muscle overexertion, leading to increased severe HF symptoms.[182,185] Ivabradine's heart rate–reducing activity is cardioprotective and relieves this systemic response cycle, potentially improving health outcomes.[186]

As a selective, highly specific binding agent, ivabradine is considered to be a "pure" heart rate–reducing medication.[182,185] Accordingly, ivabradine has no direct effects on myocardial contraction, ventricular repolarization, or intracardiac conduction, and has a more favorable safety profile than alternative HF drugs.[182,183]

Ivabradine is administered orally for treating HF and is prescribed at daily doses of up to 7.5 mg.[187] This dosing schedule is recommended by ivabradine's manufacturer, as well as by international clinical experts, including the United Kingdom's National Institute for Health and Care Excellence (NICE) and the European Medicines Agency's Committee for Medicinal Product for Human Use (CHMP).[188-190]

Clinical trials: Ivabradine's pivotal international clinical trial was the SHIfT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial), which concluded in 2010.[187] In this study, researchers compared chronic ivabradine therapy—at doses between 2.5 mg and 7.5 mg—to placebo for treating Asian and European patients with chronic HF and reduced ejection fraction. Analyses of all enrolled patients (n=6,505) found that daily ivabradine treatment reduced a composite HF-related mortality and hospitalization rate endpoint in patients whose baseline heart rate was 75 beats per minute or higher (hazard ratio, 0.76; 95% CI, 0.68 to 0.85; $p<0.0001$).[191,192] Additional subanalyses also indicated that ivabradine administration was associated with improved quality of life.[193] Ivabradine was well-tolerated among patients, even when evaluating patients with severe comorbid indications.[192,194]

In other large completed European-based trials, including the CORVET, LINCOR, and REALITY HF studies, ivabradine, when administered adjunct to ACE inhibitors, beta blockers, or other standard of care, reportedly lowered patient heart rates and frequency of angina attacks, and improved general health outcomes.[195-197]

An aggregate survey of ivabradine clinical data from more than 44,000 patients with HF determined that adverse event–related trial dropout rates were less than 1% in most major trials, and that reversible luminous visual phenomena symptoms were the only adverse events reported in at least 10% of clinical trial participants.[185,198] In contrast, the German INTENSIfY study (n=1,956), enrolling patients with coronary artery disease, found that 10 mg daily ivabradine was associated with significantly increased combined risk of cardiovascular death or nonfatal heart attack among patients with stable angina.[199,200] The applicability of this finding to patients with HF is unknown.

Manufacturer and regulatory status: Ivabradine was developed and originally manufactured by Les Laboratoires Servier (Suresnes, France).[198] Before FDA approval, ivabradine was available internationally in several branded and generic forms.[187]

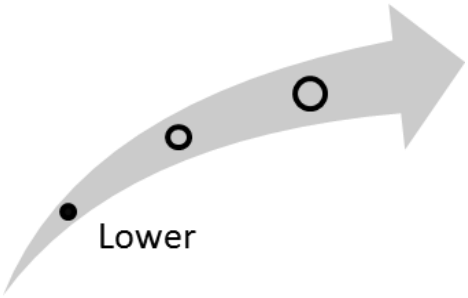
Amgen, Inc. (Thousand Oaks, CA), holds ivabradine's U.S. commercialization rights.[201] In April 2015, FDA approved ivabradine, branded as Corlanor®, for treating patients who have stable HF symptoms, a normal heartbeat with a resting heart rate of at least 70 beats per minute, and who are also taking optimized beta blockers therapy.[202] This approval was based on results from the SHIfT study.[187,203]

Diffusion and cost: Amgen has not released any information on ivabradine sales data. According to a U.S.-based, online aggregator of prescription-drug prices, GoodRx, as of June 2015, one month's supply (30 tablets) of ivabradine retailed for approximately $200. This price is comparable to branded beta blockers.[204] Ivabradine will likely be covered by many third-party payers; however, as a recently approved drug, some payers have yet to add it to their formularies.

Clinical Pathway at Point of This Intervention

Second-line standard of care for treating HF includes ACE inhibitors, ARBs, digoxin (Lanoxin), beta blockers, diuretics, and aldosterone antagonists. Clinicians may also prescribe nitrates for chest pain, statins to lower cholesterol, and blood thinners to prevent blood clots.[155,156] Ivabradine is approved as an adjunct to optimized beta blocker therapy for certain patients with HF.[202]

Figure 5. Overall high-impact potential: ivabradine (Corlanor) for treatment of heart failure



Experts commenting on this intervention acknowledged that HF is a significant health issue, and some thought that ivabradine might provide patient health outcome benefits; however, no experts concluded that ivabradine was superior to other available HF therapies. Most experts evaluating ivabradine's published clinical data found some evidence of the drug's efficacy for improving primary health outcomes, but others criticized aspects of the pivotal trial design that supported ivabradine's approval. These experts also noted that as a relatively expensive adjunct therapy, ivabradine could suffer limited adoption and corresponding high-impact potential. Based on this input, our assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided evaluations of ivabradine's high impact potential.[205-210] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most consulted experts acknowledged that HF is a significant health issue and that an unmet need exists for new interventions for treating patients whose disease is resistant to available medications. However, several experts with medical or research backgrounds expressed reservations regarding ivabradine's ability to address this unmet

need, citing ivabradine's limited demonstrated efficacy and its restricted initial indication as an adjunct therapy.[206,207,210]

Acceptance and adoption: Citing some positive results from the SHIfT trial as a supporting factor, most consulted experts opined that ivabradine would be accepted by clinicians and patients and used as a second-line HF therapy. One clinical expert, however, noted that some clinicians may hesitate to adopt ivabradine because of concerns raised by the SIGNIfY study [including an increased incidence of bradycardia and atrial fibrillation among patients with stable coronary artery disease without HF taking ivabradine].[206]

Health care delivery infrastructure and patient management: All experts agreed that ivabradine, as an orally administered HF drug, would not disrupt health care delivery infrastructure or patient management.

Health disparities: As a group, experts concluded that ivabradine would have little effect on health disparities.

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

Unmet need: HF adversely affects quality of life as well as life expectancy and can develop from any condition that overloads, damages, or reduces heart muscle efficiency, impairing the ventricles' ability to fill with or eject blood. In 2011, 1 in 9 death certificates mentioned HF, and it was the underlying cause in 58,309 deaths. Based on data from 2009 to 2012 from the National Health and Nutrition Examination Survey, 5.7 million people older than age 20 years in the United States have HF. Approximately 50% of people with HF die within 5 years of diagnosis.[78] Projections show that HF prevalence will increase 46% from 2012 to 2030, affecting more than 8 million people age 18 years or older. The expected increase in disease burden is due to the increased survival of patients with coronary artery disease, an increasing population of aging patients, and significant advances in the control of other potentially lethal diseases.[78]

Ventricular-assist device implantation and cardiac transplantation are the only established surgical treatments for end-stage HF.[211] Historically, artificial heart technology has involved using large, hospital-based pneumatic driver systems that require patients to be hospitalized and tethered to a driver console. The standard, 400-pound console powers the implantable components while patients await availability of a suitable donor heart.[212,213] An option that would allow these patients to leave the hospital and receive artificial-heart support at home while awaiting a donor heart has the potential to lower treatment costs and improve quality of life.[214]

Intervention: The temporary SynCardia Total Artificial Heart (TAH-t) is a biventricular, implantable device that functions in place of the two ventricles and four valves of a failing heart by pumping blood to both the pulmonary and systemic circulations via a conventional external pneumatic driver system.[215,216] The device replaces the patient's native heart. The driver system is large and cumbersome and requires patients to remain hospitalized while awaiting a donor heart.[214] To enable patients to leave the hospital and await a suitable donor heart at home, the TAH-t manufacturer has developed the 13.5 lb Freedom® Driver System. The portable driver is a wearable pneumatic device that powers the existing TAH-t, which is indicated for use as a bridge to heart transplantation.[212]

To implant the TAH-t, a surgeon first removes the heart's left and right ventricles and the four native valves. The surgeon then replaces the excised heart chambers and valves with the TAH-t, which replicates their function, in a procedure similar to heart transplantation.[217]

As with conventional hospital-based pneumatic driver systems, the Freedom Driver connects to the implantable TAH-t by a flexible pneumatic driveline that enters the body through the skin in the left chest just below the ribs. The driver sounds an alarm and/or flashes a light when it requires the user's attention. Two onboard batteries, which can be recharged using either a standard electrical outlet or automobile charger, power the portable Freedom Driver. The pneumatic driver is designed for patients to wear in a backpack or shoulder bag.[214]

Clinical trials: In July 2014, Arabia and colleagues reported in an abstract at the World Transplant Congress a single-center experience of 11 patients discharged home with the Freedom driver. The post-discharge 3-month survival was 100%. Five of 11 patients (45%) were readmitted within 3 months of the initial discharge with the portable driver. The average time from discharge to re-hospitalization for readmitted patients was 56±17 days. Reasons for readmission included driver alarm in two patients; body rash from sulfamethoxazole-trimethoprim applied for possible driveline infection in one patient; nausea, vomiting, and diarrhea in one patient; and small bowel obstruction in one patient.[218]

In a July 2014 press release, SynCardia highlighted data it submitted to FDA from a premarket approval trial. The release reported results from 106 patients in the Freedom PMA (FDA premarket

approval) trial. The company reported, "The SynCardia Total Artificial Heart with the Freedom Drive System allowed 75% of those patients to be discharged from the hospital, while 86% of the 106 patients either were bridged to heart transplants or were alive and supported by the SynCardia Total Artificial Heart and the Freedom driver as of June 30, 2014."[219]

In November 2013, Demondion and colleagues reported a single-center experience on 12 patients with an artificial heart who were discharged home with a portable driver. Patients were discharged home within a median of 88 days (range, 35–152) after device implantation. The mean rehospitalization rate was 1.2 patients. Readmissions were due to device infection in seven patients, technical problems with the console in three patients, and other causes, including neurologic dysfunction and hemolysis, in four patients. All patients discharged home subsequently underwent heart transplantation, and one patient died after receiving a transplant. Between discharge home and heart transplantation, patients using a portable driver spent 87% of their cardiac support time out of the hospital.[220]

In April 2013, Shah and colleagues reported on 66 patients who received an artificial heart, including 16 patients who were discharged home using a portable driver. Patients in both groups were similar in age and size, but patients with portable drivers had longer median duration of artificial heart support than patients on hospital-based drivers (range, 216 days [73–694] vs. 75 [1–379], $p<0.001$). Five discharged patients on portable drivers (31%) experienced driveline fracture requiring repair. Two patients with driveline fracture reported fault alarms from the portable driver. The other three patients noticed a hissing sound from the driveline at the fracture point. No hospitalized patients with conventional drivers experienced driveline fractures. Fractures were repaired with mechanical excision in two patients and covered with vulcanizing tape in the other three patients. Patients with driveline fracture had longer times on artificial heart support than those without such fractures (483 days [271–694] vs. 89 [1–460]; $p<0.001$). Five of seven patients on artificial heart support for more than 9 months required driveline repair. None of the fractures resulted in patient death.[221]

Manufacturer and regulatory status: SynCardia Systems, Inc. (Tucson, AZ), makes the TAH-t and Freedom Driver system. In June 2014, FDA approved the Freedom Driver "for use with the SynCardia temporary Total Artificial Heart as a bridge to transplantation in cardiac transplant candidates who are clinically stable."[219] In March 2010, SynCardia received a CE mark for the Freedom driver, allowing its use with the SynCardia TAH-t in Europe.[222] The TAH-t as a bridge to transplant had been approved by FDA in October 2004.[223]

Diffusion and cost: The company reported that as of May 2015, more than 1,440 SynCardia TAH-t devices had been implanted worldwide, and more than 200 patients have used the Freedom driver.[219]

Costs for the Freedom Driver System have not been widely reported in the United States. According to ECRI Institute's PricePaid database, hospitals may be able to lease the Freedom driver for $24,900 per year or $2,500 per month.[224] Total cost of care for patients with artificial hearts using the portable driver at home presumably might be lower than that of hospitalized patients with artificial hearts, because the inpatient stay is shortened. However, the change in care setting may result in more of a cost shift than a significant cost reduction. Ambulatory patients would continue to need regular visits from specially trained nurses at home as well as followup office visits with specialist physicians to monitor device function. Furthermore, as with hospital-based pneumatic drivers, home use of the portable driver would require the immediate availability of a backup driver in case the primary unit fails and that someone (e.g., a family member) be available to assist the patient. Thus, driver acquisition and maintenance costs might be comparable between portable and hospital-based drivers. The majority of the overall treatment costs for these patients will continue to

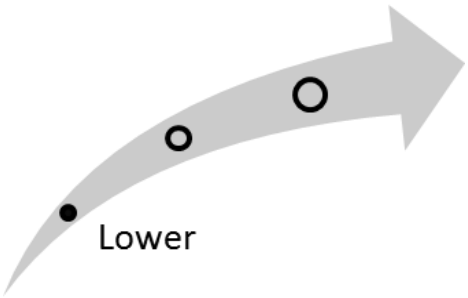
include the costs of the artificial heart itself and surgical implantation, regardless of whether patients are supported in the hospital with a conventional driver or at home with a portable driver.

The following available cost information is based on inpatient use of the SynCardia TAH-t. Reported costs for a SynCardia TAH-t kit are approximately $124,700, which includes a patient simulator (for training), tubing, and surgical disposables in addition to the device itself.[225] Staff training costs to meet the manufacturer's device-related certification requirements are approximately $98,000, plus $58,590 for a new-center startup kit, in addition to device costs. SynCardia will loan a hospital the necessary driver units if the center remains certified to implant the TAH-t and maintains an inventory of two TAH-t kits and a spare kit.[225] Annual maintenance costs for the TAH-t are estimated at $18,000.[226,227] Additional costs related to inpatient care of patients in whom the TAH-t has been implanted include those for ancillary services, such as operating room use and attendant overhead; surgical team fees; charges for clinical staff; radiology, laboratory, and intensive care unit services; blood products; drugs; rehabilitation; and other professional payments.

Clinical Pathway at Point of This Intervention

American College of Cardiology (ACC)/American Heart Association (AHA) clinical guidelines identify ventricular assist device implantation and cardiac transplantation as the only established surgical treatments for end-stage HF.[211] The portable driver system is intended to complement TAH-t use.[214] As a bridge to transplantation, the TAH-t with the Freedom driver would complement heart transplantation. Some left ventricular assist devices that are compatible with portable driver systems for in-home use could compete with the TAH-t and Freedom driver as a bridge to transplantation.

Figure 6. Overall high-impact potential: Portable Freedom Driver for in-home support of the temporary Total Artificial Heart



Although the intended patient population for this device is few in number, experts commenting on this intervention noted the portable Freedom Driver system has the potential to markedly improve patient quality of life while awaiting a transplant and to shift the care setting from inpatient to outpatient. The experts also thought that this device has potential to reduce costs associated with lengthy hospital stays, although its outpatient use would require resources, such as training for staff and home caregivers or 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

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[228-233] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Although experts noted that the intended patient population for this device is small, they generally agreed that an important unmet need exists for a driver system that would allow patients to be discharged home while awaiting a heart transplant. One clinical expert noted, "In these patients, the option to go home, albeit with extensive support, prior to their transplant (or if they never receive a transplant) is a significant benefit."[232] Experts viewed this device's greatest potential benefit to be improving patient quality of life by enabling patients awaiting a heart transplant to be discharged to home. One clinical expert noted, "The Freedom driver does have moderate potential to improve quality of life and theoretically some complications such as nosocomial infections. That said, the limited data to date is mixed if not somewhat underwhelming. It does appear that Freedom patients do manage to spend a significant portion of their time to transplant/death outside of the hospital, which cannot be minimized. That needs to be balanced by what may be an increased risk of line fractures."[232] Another clinical expert stated, "There is no particular improvement in patients' primary heart failure, but [they are] likely to have better mental health being at home."[228] Experts generally cited a lack of data supporting the potential benefit of allowing patients to await heart transplantation at home. One clinical expert stated, "…The key word is potential. It is certainly possible that improvements in care processes and technology may reduce the risk of fractures and allow the system to extract savings from the shift of care to an outpatient setting."[232]

Acceptance and adoption: Experts generally expected moderate acceptance from clinicians at artificial heart programs, who would need to balance pressure to go home from patients and families while weighing concerns of increased risk to patients from possible device failures without access to immediate clinical support. One clinical expert noted, "The desire to get patients out of the hospital will put significant pressure on clinicians to adopt the Freedom driver. They will likely counter that with concern regarding the risk of line fracture. Clinicians may also find that having the patient at home without the full infrastructure and personnel of a hospital may actually generate more work for them, in more off-hours calls, etc."[232]

Regarding patient acceptance, the experts generally expected it would be somewhat higher—patients would likely look forward to waiting at home. One clinical expert noted, "Unlike physicians, patients tend to be more willing to accept certain increased risks in exchange for improved quality of life, including spending time at home with family. I suspect patients will pressure their physicians to use the Freedom driver."[232] However, an expert with a research background noted that "some patients [and their family] caregivers might be resistant to home care due to anxiety" about correctly responding to potential device alarms or emergencies.[231]

Health care delivery infrastructure and patient management: Although the Freedom driver might allow some patients with artificial hearts to go home, experts did not anticipate major changes to health care infrastructure from this change. One clinical expert noted, "Personnel and infrastructure at major centers will already be in place."[228] Other experts anticipated a major shift in how patients are managed by allowing some patients to be supported at home. Some experts anticipated that safely discharging patients home would require extensive training for home care nurses and education for patients and their family caregivers. However, other experts stated that the location of care delivery would not substantially alter actual patient management. One clinical expert opined, "Shifting a portion of the patient's care to the outpatient setting clearly occurs but the extensive resources that must follow the patient and high readmission rate mitigates many of the usual benefits of such a shift, such as lower costs, lower physical and staffing resources. Perhaps with increasing experience, the system will be able to extract greater care delivery benefits to match the quality of life benefits of spending some time at home."[232]

Experts noted potential cost savings by allowing some artificial heart recipients to wait at home, although no data are available to validate that theory. Rather, several experts anticipated that

moving these patients home may simply shift costs and would increase the need for home-care personnel with experience in caring for patients who have received artificial hearts. One clinical expert noted, "Although initially one might think that there would be significant cost saving by allowing the patient to go home, the data are equivocal and most likely indicate that costs are shifted, not reduced, for an individual patient."[232] However, one expert with a research background noted, "Although home care would also be costly, if a patient requires a long duration of total artificial heart support, the cost differential between at home care and in-hospital care could be substantial."[231]

Health disparities: Experts generally agreed that the portable Freedom driver is likely to have minimal effect on health disparities. One clinical expert noted, "The small number of patients who receive total artificial hearts are highly selected and even screened," therefore, "access to underserved populations is unlikely to be affected by the portable driver option."[232] Another clinical expert stated, "This will be an expensive niche therapy for a minority of patients and has no impact on bridging disparities. This will remain a therapy for patients with good insurance plans."[228]

Portable Warm Blood Perfusion System (Organ Care System) for Living Heart Transplantation

Unmet need: According to the Organ Procurement and Transplantation Network (OPTN), the number of heart transplant candidates awaiting a suitable donor heart continues to grow, while heart donation rates remain flat. In 2012 in the United States, 3.5 hearts were donated for every 1,000 deaths.[234,235] Between 2010 and 2012, an average of 3,000 candidates remained on the waiting list for a donor heart at the end of each year. During each of those years, about 2,000 candidates underwent heart transplantation while about 400 patients died while waiting and another 100 patients became too ill to undergo transplantation and were removed from the list.[235] As of May 25, 2015, OPTN had registered 4,191 transplant candidates as waiting for a suitable donor heart.[236] Other challenges to increasing heart transplantation rates include wide regional variation in donation rates, waiting times, and access to transplant centers, which tend to be concentrated near urban population centers.[235]

Static cold storage, also called cold ischemic storage, is the standard of care for preserving donor hearts in transit to recipient patients.[237-239] Cold storage can adequately preserve donor hearts for about 4–6 hours.[238] However, the process of organ matching and obtaining consent from next of kin must be completed before heart transplantation can proceed.[240] Additionally, static cold storage can damage grafts and negatively affect heart transplantation outcomes.[238] New graft preservation methods could potentially help more patients undergo heart transplantation by expanding the pool of acceptable donor organs and improving the quality of transplanted hearts.

Intervention: The Organ Care System™ (OCS) is intended to improve the preservation of donated organs in transit, including hearts, lungs, and livers, by simulating the organs' natural environment and perfusing organs with warm blood to maintain organ function.[241] The OCS Heart is optimized for preserving donor hearts.[242] The system uses an internal oxygen supply and pulsatile pumping system to circulate a proprietary solution containing donor blood through the donor heart to provide oxygen and replenish essential nutrients.[243] A portable console houses all the system components, including the Perfusion Module, the oxygen supply, interchangeable batteries, and a wireless monitor.[244,245] When physicians harvest the donor heart, they place it in the perfusion module and revive it to a beating state.[244] The self-contained perfusion module maintains the proper temperature and humidity, protects the organ from external contaminants, and allows sterile ultrasound assessment of heart function and sterile blood sampling for laboratory analysis.[239,244] The wireless monitor allows clinicians to assess the organ's status and control system functions.[239,244]

According to the manufacturer, the OCS may provide several advantages over cold ischemic storage. Perfusing the donor heart with blood during transport may reduce time-dependent cold ischemic injury to donor hearts.[242,242] The ability to monitor a metabolically active heart outside the body could give physicians more clinical data to assess the donor heart's suitability before transplantation, by possibly identifying hidden pathology and improving tissue matching by evaluating a functioning organ.[237,242,245,246] Preserving heart function, extending the time window for safe organ transport, and providing real-time ex vivo organ monitoring purportedly could expand the pool of potential organ donors and increase use of available donor hearts.[237,243,245] Expanding the donor heart pool and permitting more transplant candidates to receive a suitable donor heart could improve health outcomes of heart transplant candidates.[237,247] Increasing the number of successful heart transplants could potentially reduce overall treatment costs in this population by reducing the volume of expensive care before and after transplantation and shortening average post-transplant lengths of stay.[245,247]

Clinical trials: In April 2015, Ardehali and colleagues reported short-term patient and graft survival for 130 adults who underwent heart transplantation at 10 U.S. and European transplant

centers using standard cold storage (n=63) or the OCS Heart (n=67) in the PROCEED II trial. Patient and graft survival at 30 days, the primary endpoint with a 10% noninferiority margin, was 94% in the OCS Heart group and 97% in the standard cold storage group (difference, 2.8%; one-sided 95% upper confidence bound, 8.8; p=0.45), thus meeting the primary efficacy endpoint. Cardiac-related serious adverse events occurred in 13% of the OCS Heart group and 14% of the cold storage group. Investigators noted that further research is needed to evaluate the OCS Heart's metabolic assessment capability.[248]

In April 2015, Dhital and colleagues reported procedure parameters and cardiac function for the first three patients who underwent heart transplantation using the OCS Heart with distant procurement of donor hearts after circulatory death. Donor heart warm ischemic times were 28 minutes, 25 minutes and 22 minutes; OCS Heart perfusion times were 260 minutes, 257 minutes, and 254 minutes. Two patients needed temporary mechanical cardiac support after transplantation. All patients regained normal cardiac function within 1 week of heart transplantation and were progressing normally at 77–176 days of followup.[249]

In July 2014, Esmalian and colleagues reported antibody development and freedom from major cardiac adverse events for 38 candidates for heart transplantation who were randomly assigned to standard cold storage or OCS Heart graft preservation. The OCS group had significantly longer total ischemic time but significantly shorter cold ischemic time. Investigators observed no significant difference between preservation methods in the development of antibodies to donor organs or antibody-related graft rejection or freedom from nonfatal major cardiac adverse events. Administrative difficulties prevented two patients who were assigned to undergo OCS preservation from receiving it.[250]

In June 2014, Koerner and colleagues reported survival, graft rejection, and renal failure for 159 candidates for heart transplantation who received OCS preservation (n=29) or standard cold storage (n=130). Survival rates in the OCS group and standard care groups, respectively, were 96% and 95% at 30 days, 89% and 81% 1 year, and 89% and 79% at 2 years. Primary graft failure was less frequent in the OCS group than in the standard care group, (6.89% vs. 15.3%; p=0.20). The OCS group had less severe acute graft rejection (17.2% vs. 23.0%; p=0.73) and acute renal failure requiring hemodialysis (10.0% vs. 25.3%; p=0.05) than did the standard care group. Length of hospital stay did not differ significantly between groups (26 days vs. 28 days; p = 0.80).[251]

Manufacturer and regulatory status: TransMedics, Inc. (Andover, MA), manufactures the OCS Heart. The company has filed a premarket notification with FDA for 510(k) marketing clearance for the OCS Heart.[252] TransMedics has a CE mark allowing marketing of the OCS in the European Union for use in heart transplantation.[241]

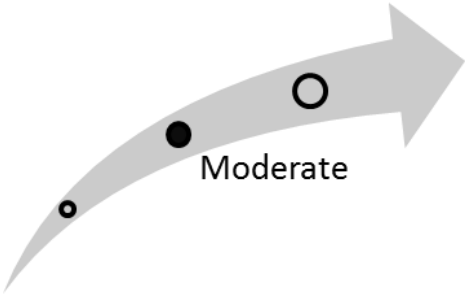
Diffusion and cost: The OCS Heart is expected to cost about $250,000 for the portable console plus about $45,000 for each single-use perfusion module.[253] Other associated costs would be expected to be similar to those for the OCS Lung, a closely related technology designed to preserve and transport donor lungs for transplantation. According to an ECRI Institute PricePaid analysis, the cost of hands-on clinical training for the OCS Lung was $100,000, and clinical field support 24 hours a day, 7 days a week, for 1 month costs $120,000. TransMedics indicated that the OCS Lung preservation capital equipment could be loaned to the hospital at no cost if the facility agreed to purchase 10 perfusion sets at $45,000 each.[254] A comparable arrangement for use of the OCS Heart could be anticipated.

Harvesting a donor heart for transplantation using conventional cold storage methods is estimated to cost about $70,000.[240]

Clinical Pathway at Point of This Intervention

ACC/AHA clinical guidelines identify ventricular assist device implantation and cardiac transplantation as the only established surgical treatments for end-stage HF.[211] The OCS Heart system would be used in place of standard cold storage to preserve donor hearts from the time of explantation from donors to implantation in transplant candidates. Acceptability of transplant grafts has traditionally been limited to donors who suffer brain death but still have a beating heart. Use of the OCS Heart could potentially increase the availability of donor hearts by expanding the donor pool.[246,255] In April 2015, Dhital and colleagues reported the first three cases of successful heart transplantation using donor hearts obtained after circulatory death.[249]

Figure 7. Overall high-impact potential: portable warm blood perfusion system (Organ Care System) for living heart transplantation



Although the intended patient population for this intervention is small, experts noted the importance of finding alternatives to static cold storage, which has important limitations in preserving donor hearts during transport. Experts cited the potential of portable warm blood perfusion technology for increasing the number of donor hearts available to the growing list of candidates for heart transplantation. However, experts thought that larger, randomized studies would be helpful to more clearly demonstrate the benefit of the technology compared with the standard of care for preserving donor hearts. 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.[256-261] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts were generally optimistic about the OCS Heart's potential to improve donor heart preservation, although several wanted to see additional data documenting the potential benefit. One expert with a health systems background noted, "The intervention has a chance to meet the unmet needs if it is proven to provide all the benefits" highlighted in some studies, "such as increased organ donor pool, better survival rate, better transportation with reduced risk in ischemic injuries."[259] One research expert stated, "Use of the OCS may be able to increase the percentage of viable hearts and potentially make hearts available for recipients at a greater distance from donors than is currently practical with cooling preservation."[256] The research expert continued, "Early evidence seems to show that OCS preserved hearts have a higher viability compared with chilled preservation. For the patients receiving the OCS heart [graft preservation], this should significantly improve their health."[256] The three clinical experts wanted to see more published data from larger trials before fully embracing the technology. One clinical expert noted, "If this system works, it could improve patient health moderately.

Unfortunately, there are few data supporting its efficacy."[260] Another clinical expert stated, "The system did not provide substantially improved outcomes in transplanted patients, when measured by survival, hospital stay, rejection episodes etc. It will likely have some effect on patients who may have not received a heart due to the small donor pool, which may increase with the normothermic heart transplantation system."[261]

Acceptance and adoption: Experts anticipated that most large heart transplant programs would likely adopt the OCS Heart system if it becomes commercially available in the United States. "Large transplant centers will quickly adopt this strategy in order to increase the number of transplants by increasing the number of donor hearts," noted one clinical expert, who continued, "however, the system is expensive and requires training. I am not sure if smaller transplant centers will be able to afford it and to have the transplant teams trained on the system, at least in the early years."[261] Patient acceptance of the OCS Heart system would be high, the experts agreed. One clinical expert noted, "Patients waiting for a heart transplant would welcome anything that might shorten their wait times."[260]

Health care delivery infrastructure and patient management: Implementing the OCS Heart system will require transplant teams to have additional training to use the technology, the experts thought. However, they did not anticipate that the new technology would cause major disruptions to the health care delivery infrastructure at established heart transplant programs. One clinical expert noted, "If this system is shown to be successful, it may cause a small disruption…by slightly increasing the number of annual heart transplants."[260] Another clinical expert added, "This may increase hospital utilization initially with the greater number of transplants, but may ultimately decrease hospitalizations since these patients who undergo transplantation should improve from a heart failure standpoint and therefore, ultimately use less health care resources."[261]

In terms of patient management, the experts did not anticipate that use of the OCS Heart system would cause much change to how patients are managed after undergoing heart transplantation, although it might shorten transplant wait times for some patients. One clinical expert noted, "If the system allows 25% more transplants to occur due to the greater use of less desired organs that might not be used with the current cold system, patients would transition from using health care resources as post-transplant patients rather than heart failure patients."[261]

Health disparities: Experts generally did not expect use of the OCS Heart system to substantially alter health disparities. One health systems expert stated, "With a better survival rate and no potential safety issue, and the possibility of increasing the pool of donor hearts and decreasing the risk of hypoxic injuries, there is a good chance it will be accepted."[259] One clinical expert noted, "I doubt that even a doubling of the number of donor hearts, which I doubt will occur with this new system, would change the profile of transplanted patients."[261] Two research experts noted that the potentially longer transit time afforded by the OCS system might somewhat reduce geographic barriers to getting a heart transplant that some patients might face. One health systems expert noted, "The intervention will allow access to more donor hearts; however transplants are very expensive, and groups with low income, inadequate insurance coverage, etc., may have a hard time getting on the transplant list."[259]

Pulmonary Artery Hypertension Intervention

Selexipag (Uptravi) for Treatment of Pulmonary Artery Hypertension

Unmet need: Pulmonary arterial hypertension (PAH) is a progressive, incurable, life-threatening condition characterized by hypertension in the pulmonary artery and arterial system, which places significant strain on the heart's right ventricle, often leading to HF. Hypertension results from the narrowing of small arteries throughout the lungs, which increases resistance to blood flow.[262] About 1,000 new PAH cases are diagnosed in the United States each year. Since 1980, the numbers of hospitalizations and deaths related to PAH have increased, especially among women and older adults.[262] Prostacyclins are an established class of drug for treating patients who have PAH; however, traditional intravenous and inhaled prostacyclin formulations have substantial shortcomings because of their burdensome administration requirements.[263] An oral drug with a novel mechanism of action could provide these patients with an effective alternative to traditional medications.

Intervention: Administration of prostacyclins via continuous infusion, frequent injection, or inhalation is a long-standing approach to treating PAH. However, traditional prostacyclin administration routes are burdensome to patients and limit these drugs' utility. Additionally, prostacyclins can have adverse systemic effects (e.g., headache, flushing, diarrhea, jaw pain) in some patients.[263] Selexipag (Uptravi®) is an orally available, selective prostacyclin receptor agonist that activates the prostacyclin receptor (IP receptor), one of five prostanoid receptors. This action purportedly induces vasodilation and inhibits the proliferation of vascular smooth muscle cells, potentially reducing symptoms of PAH. According to the manufacturer, selexipag differs from other prostacyclin analogues because of its selectivity for the IP receptor over other prostanoid receptors, which could limit off-target effects compared with effects of traditional prostacyclins.[263,264] In clinical trials, selexipag was administered as oral tablets at dosages between 200 mcg and 1,600 mcg per day.[263,265]

Clinical trials: In March 2015, McLaughlin and colleagues reported morbidity, mortality, and adverse events for 1,156 patients who received selexipag (n=574) or placebo (n=582) to treat PAH in the GRIPHON study.[265] At baseline, 20% of patients had previously untreated PAH, 47% were on monotherapy with endothelin receptor antagonists or phosphodiesterase type-5 (PDE-5) inhibitors, and 33% were on combination therapy with endothelin receptor antagonists and PDE-5 inhibitors. Mean treatment duration was 76.4±50.45 weeks for selexipag and 71.2±48.32 weeks for placebo. Selexipag reduced the risk of morbidity and mortality versus placebo (log-rank $p<0.0001$) by 40% (hazard ratio 0.60; 99% CI, 0.46 to 0.78). The treatment effect was consistent across age, gender, etiology, baseline functional class, and background PAH-therapy subgroups. The most frequent adverse events that had more than 3% greater incidence in the selexipag group were headache, diarrhea, nausea, jaw pain, myalgias, pain in extremity, flushing, and arthralgia, which were consistent with prostacyclin therapy effects.[265]

Manufacturer and regulatory status: Actelion Pharmaceuticals, Ltd. (Allschwil, Switzerland), has global development and commercialization rights for selexipag. Actelion acquired the rights from Nippon Shinyaku Co., Ltd., (Kyoto, Japan), which developed selexipag for treating PAH. In December 2014, Actelion submitted an NDA to FDA for selexipag to treat PAH, supported by data from the GRIPHON study. The company anticipates an FDA decision in December 2015.[264] Actelion also submitted a marketing authorization application to the European Medicines Agency, in December 2014.[264]

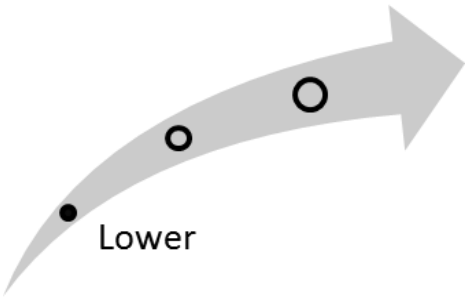
Diffusion and costs: If approved for use, selexipag would likely see at least moderate diffusion as the second oral prostacyclin drug available. Reliable cost estimates for selexipag are unavailable.

However, selexipag treatment costs could be similar to other recently approved PAH medications. According to GoodRx, the retail cost for one recently approved oral PAH treatment, riociguat (Adempas®), can range up to $8,900 for 90 tablets (i.e., a typical 30-day supply) of each available dosage.[266] Reported costs for treprostinil (Orenitram™), the first FDA-approved oral prostacyclin to treat PAH, can range up to $6,300 for 60 tablets (i.e., a typical 30-day supply) at a dose of 2.5 mg.[267] Costs for inhaled prostacyclin treatment can range up to about $100,000 per year. Injected prostacyclin treatments (Remodulin®, Flolan®, and Veletri®) can also cost upwards of $100,000 annually.[268]

Clinical Pathway at Point of This Intervention

PAH is typically treated with medication, although surgery may also be considered. Physicians prescribe several types of medications to reduce symptoms, including anticoagulants, calcium channel blockers, digoxin, diuretics, endothelin receptor antagonists, inhaled oxygen, PDE-5 inhibitors, and prostacyclins. Some physicians prescribe a combination of these medications. In cases that have progressed significantly, physicians may use surgical treatment, including heart or heart-lung transplantation and atrial septostomy (in which a hole is created between the heart's top two chambers).[269] Physicians would use selexipag as another oral prostaglandin option in managing patients with PAH.

Figure 8. Overall high-impact potential: selexipag (Uptravi) for treatment of pulmonary artery hypertension



Experts commenting on this intervention thought that selexipag could fulfill an unmet need for a more effective PAH treatment, although several other medications are available. Experts noted that the clinical trial used to support FDA approval for selexipag was the first to demonstrate a substantial morbidity and mortality benefit, whereas data of other PAH treatments generally report on measures such as improved walking distance. Experts also thought that the availability of a second oral prostacyclin drug with a purportedly more selective treatment target would give physicians another tool for treating PAH. 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 technology.[270-276] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Although other therapeutic options exist to treat PAH, these options are often not effective in many patients, the experts generally agreed. One clinical expert noted that "current therapies have shown only marginal benefit."[276] Another clinical expert stated, "While several different therapies exist, prostacyclin analogues are some of the most

efficient medications to treat this disease. However, prostacyclin analogs are generally difficult to use as they need to either be injected [or inhaled]. Inhaled prostacyclins are less efficacious than injectable forms."[270] A third clinical expert noted, "There is a subgroup of patients with pulmonary artery hypertension who are already on endothelin receptor antagonists and/or phosphodiesterase type-5 inhibitors who need an additional oral drug and especially with a unique mechanism of action. This drug will fit in that niche."[271] Most experts expected selexipag to offer improved outcomes because of the endpoints reported in the GRIPHON study. One clinical expert cited the lack of "data on 'hard' clinical endpoints such as death or hospitalizations in the other orally available prostacyclin analog (oral treprostinil [Orenitram]). Selexipag, on the other hand, does have clinical data showing a significant improvement in morbidity and mortality when compared to placebo."[270]

All experts cited the 40% decrease in morbidity and mortality reported in the GRIPHON study as a key differentiator for selexipag. One clinical expert noted, "This magnitude of benefit has not been seen in prior studies of other pulmonary artery hypertension therapies."[276] Another clinical expert stated, "Because it is looking at other health outcomes, this is a definite plus for this drug."[271] This clinical expert added, "This drug could be a game changer if it could delay the addition of other pulmonary hypertension drugs, and hence lower the cost. If it were able to delay or cancel the use of an IV prostacyclin, that would be an even 'huger' advantage!"[271] Another clinical expert added the following perspective, "While the decrease in morbidity and mortality is impressive, it would be interesting to see the breakdown in decrease in hospitalizations and all-cause mortality. If the majority of the improvement in morbidity and mortality is in disease progression, this is still valuable but less so than a decrease in hospitalizations or decrease in death rates."[270]

Acceptance and adoption: Wide acceptance by physicians is likely because of its perceived improved efficacy and ease of use, all of the experts thought. Factors that might reduce enthusiasm could be costs or administrative obstacles that restrict access to some patients, they noted. One clinical expert stated, "Physicians will be enthusiastic about this medication, given the fact that it is one of only two prostacyclin analogs that can be taken orally and the only one with significant morbidity and mortality benefit. Long-term safety data are still not available, but overall the drug appears to be relatively safe with few significant complications."[270] Another clinical expert noted, "It being an oral drug with a unique receptor binding of prostacyclins and being sponsored by a very well respected company in the field of pulmonary artery hypertension, there should be quick and wide acceptance."[271]

Likewise, patients would welcome selexipag, provided they can access the drug, the experts thought. One clinical expert stated, "The injectable forms of prostacyclin analogs are painful, expensive, and cumbersome to use. In addition, there are side effects of the device injection apparatus including pain, infections and bleeding at the injection site. Given the problems associated with the injectable prostacyclins, patients will be very eager to try an orally administered alternative."[270] A research expert added, "If the findings of the GRIPHON trial are reproducible in non-trial clinical settings, the efficacy is high enough, and the adverse events reasonable enough," most patients would likely accept this drug.[273] Experts anticipated that selexipag would be costly, although likely comparable to other available PAH treatments. Thus, selexipag might have a moderate impact on treatment costs. One clinical expert surmised, "There may be a decrease in costs associated with fewer hospitalizations; therefore, overall costs to the healthcare system will go down somewhat."[270]

Health care delivery infrastructure and patient management: Experts expected that selexipag would likely have a small impact on health care delivery infrastructure because it is a self-administered oral drug. One clinical expert anticipated fewer patients on injectable prostacyclins, "which take up a lot of nursing resources, in terms of teaching patients how to administer the drug,

dealing with complications of drug delivery system, etc.," adding "this will actually free up some nursing resources that can be dedicated to other patient care issues in pulmonary hypertension clinics."[270]

Likewise, most experts did not expect the use of selexipag to substantially change the way PAH is managed in most patients. One clinical expert noted, "Prior authorization will be needed, but this is part of normal workflow for practices using this and similar medications."[276] Another clinical expert stated, "Other than the expense, there should be no disruption in patients being managed. It may actually improve the throughput by requiring less labor-intensive therapies such as inhaled or IV medications."[271] However, one research expert anticipated that "patients may be more likely to receive treatment regularly and consistently, and may be less likely to receive surgical treatment as a result of selexipag."[272]

Health disparities: Experts thought that the availability of another oral prostacyclin drug could theoretically improve access to treatment compared to intravenous prostacyclins for some patients. At the same time, however, the anticipated high drug cost could simultaneously restrict access from patients without good health care insurance coverage, experts thought. One research expert stated, "Due to its relative ease of administration, selexipag has some potential to improve access to treatment and thereby reduce health disparities…. However, it appears that one of the major impediments to reducing health disparities is in diagnosing patients consistently, [so] improving access to treatment may not have significant impact on disparities."[272] One clinical expert noted, "For patients without insurance, the cost will be prohibitive. Even with insurance, copays may present a barrier to care."[270]

Valve and Structural Disorder Intervention

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

Unmet need: Significant mitral regurgitation (MR) occurs in an estimated 1.7% (about 4.1 million) of the U.S. adult population and about 9.3% of Americans aged 75 years or older.[78] More than 250,000 cases of significant MR are diagnosed each year in the United States, and each year, about 50,000 people undergo some type of surgery for the disease.[277] Although surgical intervention (i.e., valve repair or replacement) is the preferred treatment for severe MR, many patients are not candidates for these procedures because of a high surgical risk that stems from advanced age or extensive comorbidities.[278,279] Up to one-half of candidates with symptomatic, severe MR may not receive surgical intervention for this reason.[278] In light of this unmet need, investigators and manufacturers have developed less-invasive approaches to mitral valve repair. The MitraClip® Mitral Valve Repair System is a recently approved catheter-based approach to repairing the mitral valve that may offer a treatment option for patients at high risk for complications from surgery.[280]

Intervention: The MitraClip device is intended to simulate the functional effects achieved by the Alfieri edge-to-edge open surgical procedure used for treating MR.[279] 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.[281] The MitraClip device mimics this procedure by "clipping together" the mitral valve leaflets, rather than using sutures.[279,282]

To implant the MitraClip, a physician inserts a guide catheter into the femoral vein at the patient's groin and threads it up to the heart into the right atrium under fluoroscopic guidance in a cardiac catheterization lab.[283] To reach the mitral valve in the left atrium, the physician performs a transseptal puncture to create an opening in the septum, the wall that separates the right and left atrial chambers, with the needle-like dilator within the catheter.[283,284] Use of transseptal atrial puncture, a difficult procedure, has traditionally been limited to large interventional cardiac care programs staffed with electrophysiologists or interventional cardiologists who are well-experienced in the technique.[285]

As the procedure continues, the operator advances the catheter into the left atrium and through the mitral valve as the clip is expanded. Using Doppler ultrasound to assess the optimal clip placement, the physician grasps and fastens the edges of the valve leaflets together with the MitraClip.[283,284] Before releasing the implant from the clip delivery device for permanent placement, the physician confirms proper positioning with further ultrasound scans. If the device positioning is acceptable, the physician releases the clip from the delivery device and removes the catheter.[280,283]

The MitraClip device will most likely be used for patients with degenerative mitral valve disease with prolapse (backward collapse) originating mainly from the center of the valve, a fairly well-defined population that would not necessarily require additional types of cardiac intervention.[286,287]

Clinical trials: In March 2015, Sorajja and colleagues reported efficacy for 564 patients ineligible for surgery who underwent MitraClip implantation at 61 U.S. hospitals and were enrolled in the American College of Cardiology and Society of Thoracic Surgeons Transcatheter Valve Therapy registry. In this registry study, MitraClip valve repair was successful, defined as reduction in MR grade to moderate or lower, for 91.8% (518 of 564) of patients. Further, MR was reduced to mild or less in 63.7% of patients. Investigators noted that institutional experience with and case volume of MitraClip procedures had a bearing on procedural success but not on major adverse outcomes, complications, or device-related events. In-hospital mortality was 2.3%, and four of the

13 patient deaths were from heart-related causes. Procedural complications occurred in 7.8% of cases, and device-related events occurred in 2.7% of cases. At 30-day followup, 26 patients (5.8%) had died, 15 of them from heart-related causes. At 1 month, the stroke rate was 1.6%, and 8% of patients were hospitalized for HF.[288]

Also in March 2015, Schueler and colleagues observed persistent iatrogenic atrial septal defect (iASD) in 50% of 66 patients with symptomatic MR at prohibitive risk for open mitral valve surgery who underwent MitraClip implantation. Patients with or without iASD did not differ significantly in terms of baseline characteristics, New York Heart Association (NYHA) functional class, MR severity, or success rates for MitraClip implantation ($p>0.05$). Patients without iASD had longer procedural times (82.4±39.7 minutes vs. 68.9±45.5 minutes; $p=0.05$). Followup echocardiography showed that "only patients without iASD experienced a significant decrease" in measured systolic pulmonary artery pressure after MitraClip implantation. At followup, patients with iASD were more likely to present with greater functional limitation demonstrated by higher (above class II) NYHA functional class (57% vs. 30%; $p=0.04$) and higher levels of N-terminal pro-brain natriuretic peptide (BNP; 6,667.3±7,363.9 ng/dL vs. 4,835.9±6,681.7 ng/dL; $p=0.05$). Patients with iASD also showed smaller improvement in 6-minute walking distances (20.8±107.4 meters vs. 114.6±116.4 meters; $p=0.001$). Cox regression analysis found that persistence of iASD ($p=0.04$) was the only factor associated with change in 6-month mortality, which was 16.6% compared with 3.3% in patients without iASD ($p=0.05$).[289]

In April 2015, Rassaf and colleagues reported that MitraClip implantation was associated with improved renal function, as determined by degree of postprocedural MR reduction and preexisting kidney impairment. In a 66-patient observational study, effective reduction of MR by two to three grades acutely improved National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) class. Smaller MR reduction (1 grade or less) led to worsening renal function in patients with no or mild kidney dysfunction (KDOQI class 1 or 2) compared with renal function in patients with severe kidney dysfunction (KDOQI class 3 or 4). MR reduction was associated with improvement in Minnesota Living with Heart Failure Questionnaire scores and 6-minute walk test.[290]

In March 2015, Feldman and colleagues reported mortality and change in MR grade and NYHA class for "real world" patients with average risk (n=271) and high risk (n=628) of surgical complications who underwent MitraClip implantation for severe MR. Thirty-day mortality was 4.2% in high-risk patients and 1.5% in average-risk patients. Despite age and comorbidities including AF, coronary artery disease, and diabetes, 89% of all patients achieved MR reduction to grade 2+ or lower, and 90% were discharged home. At 1 year, mortality was 23% in the high-risk group and 10% in the average-risk group, and freedom from MR grade 2+ or more was 83% among surviving patients in both groups. The share of patients with NYHA functional class III or IV fell from 81% at baseline to 15% at 1 year in the high-risk group and from 51% to 9% in the average-risk group.[291]

In March 2015, Maini and colleagues reported cardiovascular outcomes, and change in MR grade and NYHA class for 42 patients at prohibitive surgical risk who underwent MitraClip implantation in a postmarket study. Investigators observed no procedural deaths, stroke, or vascular complications. At 1 month, 80.9% of patients had MR grade 1 to 2+. At baseline, 12.5% of patients had NYHA functional class I to II compared with 72.7% at 1 month ($p=0.0002$). At 1 month, two patients (4.7%) died, one due to respiratory failure and another due to stroke at 3 weeks. Left ventricular ejection fraction was unchanged at 1 month, but BNP levels dropped significantly, from 1,739 pg/mL at baseline to 377.84 pg/mL at 1 month ($p=0.02$).[292]

Manufacturer and regulatory status: The MitraClip is manufactured by the Abbott Vascular division of Abbott Laboratories (Abbott Park, IL). Abbott obtained the MitraClip technology

through its acquisition of Evalve, Inc. (Menlo Park, CA), in November 2009.[293] In October 2013, FDA approved the device for treating patients who have received a diagnosis of "significant symptomatic degenerative MR who are at prohibitive risk for mitral valve surgery."[294]

MitraClip's approval process took several years to complete. Originally, the device was anticipated to be reviewed by FDA in 2011. In May 2011, the manufacturer issued a voluntary device recall—because of issues with the delivery catheter's tip—in Europe, Australia, Singapore, and other countries where the device had been approved. Although the company resolved the issue and reintroduced the device in those countries, the recall prompted FDA to request additional information and analysis regarding the MitraClip, which the company provided in an amended premarket approval (PMA) application.[295]

In March 2013, the Circulatory System Devices Panel of FDA's Medical Devices Advisory Committee voted on three questions (safety, effectiveness, risk-benefit ratio) pertaining to the PMA application. The panel voted that MitraClip's benefits outweigh the risks for use in patients who meet the criteria specified in the proposed indication and that available data "show reasonable assurance" that MitraClip implantation would be safe when used for the proposed indication. However, the panel also voted that available trial data did not provide "reasonable assurance" that the MitraClip procedure would be effective for its proposed indication.[296]

Diffusion and costs: In Europe, according to a cost-effectiveness study published in October 2012, the MitraClip device's list price was about $26,200.[297] Hospitals reporting device costs to ECRI Institute's PriceGuide database reported an average price paid of $30,000 for the Mitral valve kit,[298] which concurs with prices reported from other sources.[299,300] Procedural costs to implant MitraClip might be somewhat higher than those of other interventions performed in a cardiac catheterization lab, such as percutaneous transluminal coronary angioplasty with stenting of the coronary arteries, because transseptal puncture is required to implant the MitraClip in the left heart. MitraClip therapy would be expected to substantially increase short-term treatment costs compared with medical management alone in patients who are ineligible for open mitral valve repair.

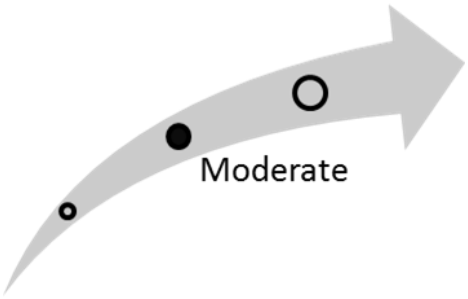
The device remains at an early stage of diffusion, although Medicare coverage for the procedure when conditions are met could broaden diffusion. Most large, private third-party payers initially considered the MitraClip procedure to be investigational and denied coverage. However, this could change as companies review and update their coverage policies. Aetna and Medica consider MitraClip implantation medically necessary when several conditions are met.[301,302] At this time, seven representative, private, third-party payers (i.e., Anthem, Blue Cross Blue Shield of Alabama, Blue Cross Blue Shield of Massachusetts, CIGNA, Humana, Regence, UnitedHealthcare) consider transcatheter mitral valve replacement investigational and deny coverage for the procedure.

In August 2014, the U.S. Centers for Medicare & Medicaid Services (CMS) announced that the agency will cover transcatheter mitral valve repair under its Coverage with Evidence Development program under several conditions.[303] These include independent preprocedure assessment of each patient by a cardiothoracic surgeon and a cardiologist, hospital care provided by a multidisciplinary heart team, infrastructure requirements, case volume requirements, and mandatory participation in a national registry.[303] As requested by Abbott, CMS approved the MitraClip System for a new technology add-on payment in fiscal year 2015. New technology add-on payments are limited to the lesser of 50% of the average cost of the device or 50% of the costs in excess of the Medicare Severity–Diagnosis Related Group (MS-DRG) payment for the case. The maximum add-on payment for the MitraClip procedure will be $15,000 per case.[67]

Clinical Pathway at Point of This Intervention

The preferred treatment for severe MR is open surgery for mitral valve repair or replacement.[278,279] ACC/AHA clinical guidelines recommend surgical mitral repair over mitral valve replacement in most patients with severe MR.[304] MitraClip implantation offers a new therapeutic option for patients ineligible for mitral valve surgery. The MitraClip procedure may potentially be positioned as a catheter-based (transcatheter) alternative to surgical valve repair.[278,279]

Figure 9. Overall high-impact potential: transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation



Overall, experts agreed this procedure addresses a considerable unmet need and has the potential to improve patient health. However, most experts opined that the procedure carries some risk and that more data concerning safety and long-term outcomes are needed for a more robust assessment. Experts' opinions differed somewhat about how much this intervention would disrupt health care delivery for this condition. Some experts believe the disruption would be limited because the infrastructure to perform the procedure is already in place at many health care facilities offering minimally invasive transcatheter valve procedures; other experts believe that the potential increase in the number of patients seeking treatment for functional MR has potential to cause a large disruption to health care delivery. The majority of experts thought the MitraClip would increase health care costs, but they wanted to see more long-term data to assess whether the device would reduce long-term costs of care for this patient population by reducing hospitalizations for HF as the disease progresses. 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 technology.[93,305-310] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for less-invasive interventions to treat MR is important, all of the experts agreed, citing the large number of patients with MR who are not candidates for surgical repair and the ineffectiveness of pharmacotherapy. One expert with a clinical perspective noted that "mitral regurgitation is a ubiquitous problem compounding issues such as cardiomyopathy (ischemic or nonischemic) with worsening shortness of breath."[309]

Experts generally agreed this intervention has potential to improve patient health outcomes, citing decreased mortality and morbidity in patients who are not good surgical candidates. One expert with a clinical perspective noted the generally positive patient outcomes, commenting that "These patients are often very ill, and even though the results may not be as good as valve replacement and up to 25% of patients may ultimately require valve replacement, many do not and

are markedly improved from a symptomatic standpoint."[310] However, some experts observed that additional randomized controlled trial data will not become available for several more years.

Experts also expressed concerns about device and procedure safety and believe that the numerous comorbidities seen in these patients would present risk and preclude some patients from achieving greatly improved outcomes. One expert representing a clinical perspective opined, "Early evidence suggests the device may be effective to treat MR but increased perioperative mortality and other device-related safety concerns need to be fully assessed."[306]

Acceptance and adoption: Most experts agreed that if clinical trial data continue to demonstrate benefits and safety, clinical acceptance of the MitraClip would follow. A clinical expert stated, "This technology is already entering physicians' minds earlier for their patients who are not candidates or at very high risk for [open] mitral valve replacement," however, "I don't see it gaining large acceptance until the [ongoing randomized] trials are completed."[309] Another clinical expert stated, "Surgeons and hospitals without highly trained interventionalists may be much slower to adopt this technology, but big centers are already embracing it, and it will trickle down."[310]

Experts generally agreed on the potential for wide patient acceptance of this intervention, citing the limited number of treatment options for this population and relatively less-invasive nature of the procedure compared with surgery. One clinical expert noted, "As we are already seeing with transcatheter aortic valve replacement, patients are extremely interested in considering less invasive options, even if our data show it to be inferior to proven surgical techniques."[309]

Health care delivery infrastructure and patient management: Experts offered varied perspectives about this intervention's potential impact on the health care system. Some experts commented that little disruption to health care delivery would occur, because the infrastructure is already in place, while other experts noted that an increase in case volume might cause a large disruption to health care delivery from patients who would otherwise not receive intervention. One clinical expert stated, "Smaller hospitals would need to have major resource expansion if they wanted to get into this field, which I wouldn't see happening for at least a long time."[309] Conversely, some experts attributed the potential for disruption to significant training requirements.

Most experts noted that the MitraClip procedure would represent a sizable change in patient management for patients ineligible for open mitral valve surgery. One clinical expert stated, "Ultimately when this or a related procedure is perfected, it may significantly change the number of surgical referrals and procedures."[310]

The device and its related procedure would be expensive and affect overall health care costs, the experts generally agreed. One clinical expert stated, "It will decrease length of stay as compared to surgery, but the numbers of patients having procedures will increase as patients not thought candidates for surgical procedures will undergo this one, and eventually less-severe disease will be treated this way."[310] Several experts cited the potential for long-term cost savings if the MitraClip procedure could ultimately reduce the number of hospitalizations for HF in this population, although data demonstrating this prospect are not yet available.

Health disparities: This device would have minimal impact on health care disparities, the experts all thought. However, several experts cited cost, reimbursement, availability and type of health insurance, and limited access to centers with established interventional cardiac programs to be potential factors that could affect, and possibly increase, health disparities. One expert with a clinical perspective noted, "Given the high technical expertise and infrastructure required to do this procedure, as well as needing surgical backup on-site, I think the same health disparities that exist for surgical mitral valve replacement will exist for this technology."[309]

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