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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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, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 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 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 750 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 195 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 18 topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; *and* (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Fifty-nine topics were being tracked in this priority area as of November 6, 2015.) We present 11 summaries on 12 topics that emerged as having potential for high impact on the basis of experts' comments (indicated below by an asterisk). The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. 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. Active compression-decompression device (ResQPump) for improved cardiopulmonary resuscitation	No high-impact potential at this time; archived November 2015 on basis of experts' comments
2. * Alirocumab (Praluent; PCSK9 inhibitor) for treatment of hypercholesterolemia	High
3. * Andexanet alfa for reversal of factor Xa inhibitors	Moderately high
4. Electrical stimulation of carotid baroreceptors (Barostim neo Legacy system) for treatment-resistant hypertension	No high-impact potential at this time; archived November 2015 on basis of experts' comments
5. * Evolocumab (Repatha; PCSK9 inhibitor) for treatment of hypercholesterolemia	High
6. * Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation	Lower end of the high-impact-potential range
7. * Idarucizumab (Praxbind) for reversal of dabigatran-induced anticoagulation	Lower end of the high-impact-potential range
8. * Ivabradine (Corlanor) for treatment of heart failure	Lower end of the high-impact-potential range
9. * Leadless pacemaker (Nanostim) for treatment of bradycardia	Lower end of the high-impact-potential range

Topic	High-Impact Potential
10. * Mobile unit for treatment of stroke	Lower end of the high-impact-potential range
11. Percutaneous left atrial appendage ligation (Lariat Suture Delivery Device) for prevention of atrial fibrillation–associated stroke	No high-impact potential at this time; reassigned topic to tracking status to monitor new developments
12. Percutaneous left atrial appendage occlusion device (Watchman) for prevention of atrial fibrillation–associated stroke	No high-impact potential at this time; reassigned topic to tracking status to monitor new developments
13. * Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation	Moderately high
14. Percutaneous left atrial appendage occlusion (Wavecrest) for prevention of atrial fibrillation–associated stroke	Manufacturer no longer seeking U.S. approval; archived November 2015
15. * Sacubitril/valsartan (Entresto) for treatment of heart failure	High
16. * Selexipag (Uptravi) for treatment of pulmonary artery hypertension	Moderately high
17. Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	FDA approved in October 2013; no longer meets horizon scanning criteria for tracking; archived October 2015
18. * Wireless monitoring system (CardioMEMS HF System) for management of heart failure	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 high-impact potential, pertain to devices that provide support for end-stage heart failure (HF) or address stroke prevention in patients with arrhythmias. Pharmaceuticals deemed as having high-impact potential include drugs to treat HF and hypercholesterolemia resistant to treatment with standard statin drugs and reversal agents targeting relatively new anticoagulants that have no antidote if serious bleeding occurs.

Prior Potential High Impact Topics Reassigned to Tracking Status

- **Percutaneous left atrial appendage ligation devices (Lariat Suture Delivery Device and Watchman Device™) for prevention of atrial fibrillation–associated stroke**: In the June 2015 AHRQ Potential High-Impact Interventions Report, experts rated these catheter-based devices at the lower end of the high-impact-potential range. The Lariat® device is in development, and is a potential competitor to the Watchman, which received U.S. Food and Drug Administration (FDA) marketing approval in March 2015 for reducing stroke risk in patients with atrial fibrillation. Both devices are intended to block blood clots that may form within the left atrial appendage (LAA) from entering systemic circulation and potentially blocking arteries that supply the brain. In 2009, FDA granted the Lariat 510(k) clearance for "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." However, the Lariat does not have FDA approval for percutaneous closure or ligation of the LAA. In July 2015, FDA issued a safety communication citing 45 serious adverse events including 6 deaths through June 2015 related to off-label use of the Lariat device for percutaneous occlusion of the LAA. FDA cautioned that the safety and effectiveness of this use of the Lariat device have not been established and advised physicians and patients to consider treatment options for which safety and effectiveness have been established for this indication (i.e., use of an FDA-

approved device). Additionally, in November 2015, the U.S. Centers for Medicare & Medicaid Services (CMS) issued a proposed decision memo that classifies percutaneous LAA occlusion as "not reasonable and necessary" at this time. The decision limits coverage to the Coverage with Evidence Development paradigm where only patients with contraindications to warfarin can receive it using an FDA-approved device and enrolling in a national registry that will monitor patient outcomes for 5 years. Also in November 2015, FDA issued a class 2 recall of Watchman catheter delivery systems; the recall addressed potential cross-threading of the catheter delivery system's hemostasis valve that might cause undesired blood leakage. Based on these developments, use of percutaneous LAA closure devices would be expected to be severely limited, thereby reducing the technology's high-impact potential. However, we will continue to monitor evidence development for these devices in the horizon scanning system for developments that may warrant obtaining new expert comments about impact potential.

Prior Potential High Impact Topics Archived

- **Percutaneous left atrial appendage occlusion (Wavecrest) for prevention of atrial fibrillation–associated stroke:** In the June 2015 Potential High-Impact Interventions Report, experts rated this potential competitor to the Watchman and Lariat suture LAA closure devices at the lower end of the high-impact-potential range. Although the technology is commercially available in Europe and other markets, the manufacturer is no longer pursuing U.S. regulatory approval. Therefore, the technology no longer meets criteria for tracking and was archived in the horizon scanning system in November 2015.
- **Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation:** The MitraClip® (Abbott Vascular division of Abbott Laboratories, Abbott Park, IL) was included in the June 2015 and earlier Potential High-Impact Interventions reports. FDA approved the MitraClip in October 2013; this intervention has been diffusing for more than 2 years and no longer meets criteria for tracking. We archived it in the horizon scanning system in October 2015. In the June 2015 Potential High-Impact Interventions Report (and earlier reports), experts were optimistic that procedure addresses a considerable unmet need and has the potential to improve health for patients who are not eligible for conventional mitral valve repair surgery. In March 2015, Sorajja and colleagues reported that MitraClip valve repair was successful, defined as reduction in mitral regurgitation (MR) grade to moderate or lower, for 91.8% (518 of 564) of patients enrolled in the American College of Cardiology and Society of Thoracic Surgeons Transcatheter Valve Therapy registry. Further, MR was reduced to mild or less in 63.7% of patients.

Eligible Topics Deemed Not High Impact

- **Active compression-decompression device (ResQPump) for improved cardiopulmonary resuscitation:** The ResQCPR® system is a two-part, combination device intended to improve outcomes of manual cardiopulmonary resuscitation (CPR). The ResQPump component is a handheld, multi-use device that actively re-expands (i.e., decompresses) the chest after each compression. The ResQPod component is a single-use impedance threshold device that limits air from passively entering the lungs as the chest wall recoils during CPR (i.e., decompression phase), therein lowering intrathoracic pressure when rescuers are not providing a breath and reportedly resulting in the heart pumping out more blood during the next compression. Experts commenting on this technology viewed

the ResQCPR as an incremental improvement to manual CPR and expressed concern that the supporting data came from a single trial that demonstrated modest benefit compared with conventional CPR. Experts noted that improving access to manual CPR for persons in cardiac arrest would likely have a larger overall health impact than addition of this device, for which use would be limited to CPR administered by trained paramedics equipped with the technology rather than any bystanders. Based on experts' comments, we archived this topic in November 2015 in the horizon scanning system.

- **Electrical stimulation of carotid baroreceptors (Barostim *neo* Legacy system) for treatment-resistant hypertension:** Baroreflex activation therapy is an emerging approach that uses an electronic device subcutaneously implanted in the chest to electrically stimulate the patient's carotid baroreceptors in the neck with the goal of reducing hypertension that is resistant to drug therapy. The Barostim *neo*® Legacy System is a replacement component for the now-obsolete Rheos™ Baroreflex Hypertension Therapy System. The *neo* Legacy device is intended to replace the Rheos implantable pulse generator upon battery depletion of the original component, connecting the *neo* Legacy to the existing Rheos electrode leads. In December 2014, FDA granted CVRx, Inc. (Minneapolis, MN), Humanitarian Device Exemption (HDE) approval for the Barostim *neo* Legacy System for use only in patients treated with the now-obsolete Rheos system during U.S. clinical trials and defined as responders to Rheos therapy. The HDE indication is limited to patients with resistant hypertension who had bilateral implantation of the now-discontinued Rheos carotid leads. Because it is not intended for further diffusion, we archived this topic in November 2015 in the Horizon Scanning System.

Topics Deemed High Impact

We present 12 interventions (2 proprotein convertase subtilisin/kexin type 9 [PCSK9] interventions are addressed together) that experts who commented thought have potential for high impact. The device interventions are intended to improve care and management of HF and acute stroke. The pharmaceutical interventions target hypercholesterolemia, HF, pulmonary artery hypertension (PAH), and reversal of newer anticoagulant drugs.

Atrial Fibrillation–Associated Stroke

A serious complication of atrial fibrillation (AF) is ischemic stroke, and patients with AF have a risk of stroke four to five times greater than that of 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 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 (e.g., warfarin) and coagulation 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, dabigatran, edoxaban, rivaroxaban) eliminate the need for routine monitoring and dietary restrictions. However, an unmet need has existed because no antidotes have been available for these newer anticoagulants in the event of uncontrolled bleeding.

Andexanet Alfa for Reversal of Factor Xa Inhibitors

- **Key Facts:** Coagulation factor Xa inhibitors (i.e., 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 with its inherent risk of bleeding. These patients have an urgent need for effective agents to reverse factor Xa inhibitor activity and restore normal hemostasis.

  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 is a highly specific decoy that rapidly reverses the activity of direct and indirect factor Xa inhibitors. Results from completed clinical trials demonstrated that, in healthy patients, intravenously infused andexanet alfa successfully reversed the activity of commonly prescribed factor Xa inhibitors apixaban, edoxaban, and rivaroxaban. An ongoing phase III trial is investigating andexanet alfa's effectiveness for reversing factor Xa inhibitor activity in patients experiencing acute major bleeds.

  In November 2015, Siegal and colleagues reported that andexanet alfa administration reduced anti–factor Xa activity by 92% to 94% compared with 18% to 21% in patients who received placebo. Further, thrombin generation was fully restored within 2–5 minutes in 96% to 100% of the treatment groups compared with 11% of the placebo groups. The findings were collected from the phase III ANNEXA™-A and ANNEXA-R trials that evaluated andexanet alfa's ability to reverse effects of the factor Xa inhibitors apixaban or rivaroxaban in healthy volunteers aged 50–75 years. Investigators reported no serious adverse or thrombotic events in either trial. 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 completing its rolling biologics license application submission to FDA December 18, 2015, under an accelerated approval pathway. As of December 2015, no pricing estimates were available. The drug is expected to be covered by third-party payers because it would be the first and only factor Xa reversal agent 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 moderated their 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

Idarucizumab for Reversal of Dabigatran-Induced Anticoagulation

- **Key Facts:** Idarucizumab is a fully humanized monoclonal antibody developed as a reversal agent for the oral anticoagulant dabigatran. Idarucizumab is administered intravenously at a recommended dose of 5 g. In October 2015, FDA granted accelerated approval for idarucizumab use to reverse dabigatran's anticoagulant effects during emergency surgery or uncontrolled bleeding events. The drug reportedly costs $3,500 for the recommended 5 g

dose and is available through specialty pharmacies. In August 2015, Pollack and colleagues reported that idarucizumab infusion achieved a median maximum reversal of 100% among 90 patients taking dabigatran who had serious bleeding or who required emergency surgery. The dilute thrombin time was normalized in 98% of bleeding patients who could be evaluated and in 93% of surgical patients who could be evaluated. In 51 patients with serious bleeding, idarucizumab restored hemostasis at a median of 11.4 hours. Among 39 patients who underwent a surgical procedure, the drug restored normal intraoperative hemostasis in 33 patients, mildly abnormal hemostasis in 2 patients, and moderately abnormal hemostasis in 1 patient.

- **Key Expert Comments:** Overall, experts agreed that idarucizumab has great potential to fill the large unmet need for a specific reversal agent to counteract dabigatran-induced bleeding events. However, several experts acknowledged the drug's overall impact would be moderated by the relative rarity of dabigatran-associated bleeding events and the emergence of other new oral anticoagulants that compete with dabigatran as a warfarin alternative. Acceptance of the drug is likely to be strong because it may provide a specific and rapid alternative to available nonspecific options for treating dabigatran-induced bleeding, experts thought. Although expensive, idarucizumab would have a moderate effect on health care costs and a small effect on health care disparities, the experts anticipated.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Bradycardia

Bradycardia is an abnormally slow heart rate, defined as a resting heart rate of less than 60 beats per minute. In most people, bradycardia is unlikely to cause symptoms unless heart rate drops below 50 beats per minute. It becomes clinically relevant when it impedes the supply of oxygenated blood to the body. Extremely low heart rate may cause cardiac arrest. According to the American Heart Association, mild bradycardia may be managed by adjusting dosage of various medications that can affect heart rate. Severe bradycardia may require implanting an electronic cardiac pacemaker. Although pacemaker use in most patients is uneventful, about 4% of patients encounter device-related complications, including about 3% who experience migration or other failure of the implanted electrode leads and about 1% who develop an implant-related infection, typically in the subcutaneous pocket housing the pacemaker. A new type of miniaturized, self-contained cardiac pacemaker that obviates the need for electrode leads or a subcutaneous pocket might alleviate potential problems sometimes associated with conventional pacemakers.

Leadless Pacemaker (Nanostim) for Treatment of Bradycardia

- **Key Facts:** The Nanostim™ Leadless Pacemaker is a self-contained, single-chamber cardiac pacemaker housed in a polished titanium cylinder about as large as an AAA battery. To implant the device, a physician inserts the delivery catheter at the femoral vein in the groin and advances it to the right ventricle in the heart. The operator secures the implant into the right ventricular wall using the implant's helical fixation coil, which doubles as the pacing electrode that delivers the pacing therapy. The Nanostim and a competing leadless pacemaker, the Micra Transcatheter Pacing System, are under evaluation in late-phase U.S. clinical trials. U.S. pricing is not yet established for the technology, but hospitals participating in clinical trials report paying about $9,000 each for the investigational devices. In September 2015, Reddy and colleagues reported preliminary outcomes from the LEADLESS II trial. Investigators successfully implanted the Nanostim device in 95.8% of patients. Overall, 29.8% of patients required device repositioning after initial implantation,

including 4.4% (22 patients) in whom operators had to reposition the pacemaker more than 2 times. Length of hospital stay was 1.1 days. In 300 patients for whom 6-month data were available, device-related serious adverse events occurred in 6.7% of patients. The most frequently occurring serious adverse events were device dislodgement with percutaneous retrieval (1.7%), cardiac perforation (1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (1.3%).

- **Key Expert Comments:** Most experts considered the ability to eliminate the use of electrode leads to be a moderately important unmet need. However, experts were divided in their opinions of whether the Nanostim device could adequately fill that need. Most experts anticipated moderate acceptance and diffusion, with higher acceptance from patients than from clinicians. Implantation of the Nanostim device would likely be performed by the same interventional teams that implant conventional cardiac pacemakers, experts thought, thus creating small disruptions to health care infrastructure and patient management. Further, experts did not expect the technology to have a substantial effect on changing health care disparities.
- **High Impact Potential:** Lower end of high-impact 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. About 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. Projections 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 HF treatment.

Freedom Driver System (Portable Driver) for Total Artificial Heart as Bridge to Heart Transplantation

- **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. As 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 generally come from small single-center reports. In July 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. In September 2015, FDA issued a class I recall because of potential device failure that may occur without warning and may lead to serious injury or death unless the patient is immediately switched to the backup driver. After FDA's recall notice, the manufacturer reported that 29 potentially affected units used by 12 patients had already been replaced as of August 14, 2015, after issuing its own voluntary recall August 6, 2015.

- **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

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 selectively inhibiting 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 was 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 physiologic markers of HF, and improved 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 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 December 2015, Corlanor reportedly retailed for about $380 to $415 for a 30-day supply, or about $4,560 to $4,980 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 unsure that ivabradine would significantly improve patient health outcomes. Multiple experts considered ivabradine to lack superiority to other available HF medications and were critical of pivotal trial data, which they judged to have design flaws. Overall, considering ivabradine's cost, lack of clear superiority, and approved indication as an adjunct to treatment, experts thought this intervention's potential was limited to some extent. Thus, we designated this to be in the lower end of the high-impact range.
- **High-Impact Potential:** Lower end of the high-impact-potential range

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

- **Key Facts:** A large proportion of donated hearts are not transplanted because they are not deemed acceptable. Finding a way to better preserve donated hearts after harvesting could address some of the unmet need for hearts to transplant. The Organ Care System™ (OCS) Heart is intended to better preserve donated hearts after harvesting by simulating the organ's natural environment and perfusing it with warm blood to maintain organ function (i.e., keep the heart beating). 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 and keep the heart beating. 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 and determining acceptability for transplantation. According to the manufacturer, the technology could expand the pool of donor organs acceptable for transplantation and allow more transplant candidates to receive a suitable donor heart. The OCS also is intended to extend the time window for safe organ transport. In April 2015, Dhital and colleagues reported the first use of the OCS-Heart 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. In November 2015, FDA cancelled a planned advisory committee meeting that was scheduled to discuss and make recommendations for the OCS Heart because the agency "has determined than an advisory committee meeting is no longer needed." An OCS-Heart decision by FDA is anticipated in early 2016. Cost information is not yet available; however the device manufacturer stated that the OCS Lung System—a similar device to preserve donor lungs that is also under development—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 make more donor hearts acceptable for transplantation after harvesting, although several noted the scarcity of published data documenting the technology's potential benefits. Experts anticipated that large heart-transplant programs would likely adopt the technology quickly if it receives approval 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, most experts did not expect the technology to substantially alter health care disparities in the heart transplantation setting.
- **High-Impact Potential:** Moderately high

Sacubitril/Valsartan (Entresto) for Treatment of Heart Failure

- **Key Facts:** Combination sacubitril/valsartan (Entresto™) is an oral angiotensin receptor neprilysin inhibitor primarily comprising two active antihypertensives, sacubitril and valsartan. The drug has a novel mechanism of action, with both active components inhibiting the renin-angiotensin-aldosterone system and enhancing endogenous natriuretic peptide activity. These functions purportedly enable the drug to relieve cardiovascular system strain, resulting in improvements in HF and other cardiovascular health outcomes.

  In July 2015, FDA approved sacubitril/valsartan "to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction." FDA had previously granted fast-track status and priority review.

  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. In a post-hoc analysis of PARADIGM-HF data presented in November 2015, Solomon and colleagues reported that the sacubitril/valsartan group had 44% fewer patients than the enalapril group who were readmitted for HF within 30 days of an index hospitalization for HF. Further, the sacubitril/valsartan group had 36% fewer patients than the enalapril group readmitted for any cause within 30 days of an index HF hospitalization.

  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 the combination therapy, has similar side effects.

  As of November 2015, the drug's reported retail cost was between $380 and $420 per month (about $4,560 to $5,040 per year) for 60 tablets at the recommended maintenance dose (97 mg sacubitril/103 mg valsartan tablets taken twice daily). A December 2015 cost-effectiveness analysis from the Institute for Clinical and Economic Review (ICER) calculated a $4,168 per year value benchmark for the drug, which is 9% lower than ICER's estimated wholesale drug acquisition cost of $4,560 per year. ICER recommended that "payers and purchasers should consider placing Entresto in the 'preferred brand' category, especially if discounts can be obtained" and that payers should consider developing performance-based agreements with manufacturers.
- **Key Expert Comments:** Please note that the experts provided comments before FDA approved the drug. Overall, experts commenting on this intervention agreed that HF is a

serious health issue and stated that sacubitril/valsartan has considerable potential to address HF and severe HF-related outcomes. Several experts favorably noted sacubitril/valsartan'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

Wireless Monitoring System (CardioMEMS HF System) for Management of Heart Failure

- **Key Facts:** The CardioMEMS™ HF System is an implantable device intended to identify early signs of worsening HF before overt symptoms develop, potentially allowing clinicians to modify treatment sooner and avoid additional HF-related hospitalizations. In May 2014, FDA approved the CardioMEMS device to wirelessly measure pulmonary artery pressure and monitor heart rate in patients with New York Heart Association (NYHA) Class III HF who have been hospitalized for HF in the previous year.

  In November 2015, Abraham and colleagues reported that patients receiving the CardioMEMS implanted device had 33% fewer HF-related hospitalizations over 18 months than patients with HF who received only standard care. In 13 additional months of open access study, HF-related hospitalizations in the former control group (which had the device implanted and used, but data were not reported to the physician to inform management) dropped by 48% compared with the control group's hospitalization rate during the initial randomized access period. The overall combined device-related or system-related complication rate was 0.02 events per patient-year in the entire followup period. No sensor failures occurred after an average of 31 months' followup.

  In December 2015, ICER issued a cost-effectiveness report that suggested the CardioMEMS device was priced too high to be cost-effective. ICER calculated a value-based price benchmark of $10,665 for the CardioMEMS device, which is 40% lower than its estimated full Medicare price of $17,750. Several private, third-party payers consider the technology investigational and deny coverage for it, despite FDA approval.
- **Key Expert Comments:** Experts cited a large unmet need for improving management of HF and preventing HF-related hospitalizations, especially as providers face increasing financial pressure to reduce repeat hospitalizations. Overall, experts thought the CardioMEMS device showed great potential for reducing HF-related hospitalizations. However, several experts cited the general lack of data demonstrating lower mortality over the long term. Experts believe that the device could help facilitate management of patients who have more difficulty traveling to HF clinics for regular monitoring, potentially reducing disparities for such patients. At the same time, the lack of insurance coverage could introduce disparities for HF patients who could benefit from, but cannot afford, the technology.
- **High-Impact Potential:** Moderately high

Hypercholesterolemia

Persistent hypercholesterolemia can have a genetic origin or occur because of resistance to standard statin medications. Two agents in a new class of drugs were recently approved to treat these patient populations. Familial hypercholesterolemia (FH), an inherited disorder, causes

accumulation of high levels of low-density lipoprotein cholesterol (LDL-C) due to a defect on chromosome 19 that impairs the low-density lipoprotein (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 (HeFH). In rare instances, the genetic defect is inherited from both parents, causing a genetic condition known as homozygous (HoFH), which is more severe than HeFH. According to the Familial Hypercholesterolemia Foundation, HeFH occurs in 1 of every 500 persons and HoFH occurs in 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 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.

PCSK9 Inhibitors (Alirocumab [Praluent], Evolocumab [Repatha]) for Treatment of Hypercholesterolemia

- **Key Facts:** Alirocumab (Praluent™) and evolocumab (Repatha™) are subcutaneously injected pharmacotherapies developed to treat hypercholesterolemia. In contrast to traditional statin-based therapy, these two monoclonal antibodies treat hypercholesterolemia by inhibiting PCSK9, an enzyme discovered to hinder LDL-C clearance. In clinical trials, treatment with PCSK9 inhibitor drugs has been reported to improve health outcomes by significantly decreasing LDL-C levels by up to 60%. In trials, PCSK9-inhibitor administration also reduced LDL-C levels in patients whose disease failed to adequately respond to statin therapy. Both alirocumab and evolocumab are designed for biweekly injections at various dosages, although alirocumab also has a monthly injection dosing option. FDA approved alirocumab and evolocumab in July 2015 and August 2015, respectively. The drugs' retail cost is more than $14,000 per patient per year. Since the drugs' approval, several private third-party payers have announced plans to cover one or both, generally limited to the FDA-approved patient populations and with conditions such as prior authorization and step-therapy requirements.
- **Key Expert Comments:** Please note experts provided comments before FDA approved the drugs in July and August 2015. 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 that 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:** 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 cases are diagnosed in the United States each year. Women are twice as likely as men to develop PAH. Increases in hospitalizations and deaths related to PAH, especially among women and older adults, are believed to reflect improved physician awareness and changes in diagnosis and reporting. 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 a new drug application to FDA supported by data from the GRIPHON study. FDA approved selexipag on December 22, 2015, for treating PAH in WHO Group I to delay disease progression and reduce the risk of hospitalization. Approval was based on the GRIPHON randomized controlled trial of patients with PAH WHO Functional Class II–III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%). GRIPHON enrolled 1,156 patients who took the drug for up to 4.2 years (median 1.4 years). Adverse reactions reported in the selexipag group compared with the placebo group (at least 3% or more over the course of the study) were headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia, anemia, decreased appetite, and rash. These adverse reactions occurred more often during the dose titration phase. Hyperthyroidism was observed in 1% (n=8) of patients taking selexipag and in none of the patients on placebo.
- **Key Expert Comments:** Please note that the following comments were received before FDA's approval of the drug in December 2015. 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:** Moderately high

Stroke

Stroke is an acute interruption of blood circulation in the brain that damages tissue. Stroke is one of the top five causes of death in the United States, and ischemic stroke (caused by a blood clot)

accounts for about 85% of all strokes. One drug, tissue plasminogen activator (tPA), is approved for dissolving blood clots and restoring blood flow in ischemic stroke. However, tPA's window of efficacy is narrow—within 3–4.5 hours of stroke symptom onset—and the great majority of stroke victims do not present to a hospital in time for tPA treatment. Only 2% to 7% of patients experiencing an ischemic stroke receive tPA, in large part because of the time lapse between symptom onset and presentation for treatment. Thus, an unmet need exits for improving stroke care by reducing the time to treatment for many patients.

Mobile Units for Treatment of Stroke

- **Key Facts:** Mobile stroke units (MSUs) are specially equipped and staffed ambulances intended to facilitate diagnosis and treatment of ischemic stroke in the field before the patient reaches a hospital. MSU equipment includes a portable computed tomography (CT) scanner, infusion lines for tPA and the drug, a mobile blood lab, and telemedicine equipment including broadband access to communicate with the neurologist at the hospital. Staffing includes a critical care nurse, CT technologist, and a vascular neurologist availability by telemedicine communication, in addition to the unit driver and emergency medical technician. MSUs are intended to allow thrombolytic therapy to be initiated early to dissolve blood clots blocking the arteries supplying the brain. As of December 2015, two such programs were operating in the United States at the Cleveland Clinic in Cleveland, OH, and Texas Medical Center at Houston, TX. In February 2015, Taqui and colleagues from Cleveland Clinic reported on comparative times to stroke treatment between MSU (n=23 patients) and traditional ambulances observed 3 months before MSU program initiation (n=34). MSUs arrived on the scene a median of 13 minutes after alarm (interquartile range 9–17). The median alarm-to-CT-scan completion time was 41 minutes (MSU) and 62 minutes (controls) ($p<0.0001$). Median alarm-to-thrombolysis times were 64 minutes (MSU) and 104 minutes (controls) ($p<0.008$). Thrombolysis with tPA was delivered to 26% of MSU patients and 14% of control patients. Investigators reported no early complications from thrombolysis in the MSU group. In July 2015, Cerejo and colleagues reported on median treatment times for MSU patients (n=155) in the Cleveland program and historical controls transferred to the Cleveland Clinic for intraarterial thrombolysis (n=5). After 164 days of service, the MSU had transported 155 patients, 5 of whom received tPA. The MSU showed shorter times than controls for several measures, including median door to initial CT scan, 12 versus 32 minutes; median CT scan to intraarterial thrombolysis, 82 versus 165 minutes; and door to MSU/primary stroke center departure, 37 versus 106 minutes. Reported costs for the initial retrofitting of an ambulance to convert it to an MSU and operate it for a year range from $600,000 to $1 million. One program operates 8 a.m. to 8 p.m.; the other operates 24 hours a day, 7 days a week.
- **Key Expert Comments:** Overall, experts thought that at this time, MSUs have greater theoretical rather than practical potential to meet the large unmet need for improved stroke treatment through faster care delivery. Several experts noted that economic and logistic barriers would likely limit MSU programs to larger metropolitan areas where most specialized stroke centers are already located, although rural patients could potentially experience the largest clinical benefit from rapid care delivery promised by MSUs. Clinical experts also called for further research to evaluate whether faster delivery of stroke thrombolysis corresponds to improved patient-centered outcomes, including lower mortality and stroke-related disability.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Atrial Fibrillation–Associated Stroke Interventions

Andexanet Alfa for Reversal of Factor Xa Inhibitors

Unmet need: Direct and indirect coagulation 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 nonvalvular atrial fibrillation (AF) and treating venous thromboembolism.[1,2] Oral factor Xa inhibitor use is widespread because drugs in this class are known to have high efficacy and require less monitoring than comparable vitamin K antagonist anticoagulants (primarily warfarin).[1] Although 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 restore normal hemostasis during emergencies.[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 it does not interfere with native factor Xa's prothrombinase complex activity. It 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 doses 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 November 2015, Siegal and colleagues reported findings from the phase III ANNEXA™-A and ANNEXA-R trials that evaluated andexanet alfa's ability to reverse effects of the factor Xa inhibitors apixaban or rivaroxaban in healthy volunteers aged 50–75 years.[7] In ANNEXA-A, andexanet alfa bolus administration reduced anti–factor Xa activity by 94% in 24 apixaban-treated subjects compared with a 21% reduction in 9 placebo-treated subjects ($p<0.0001$), and unbound apixaban concentration dropped by 9.3 ng per milliliter versus 1.9 ng per milliliter, respectively ($p<0.001$). Further, thrombin generation was fully restored within 2–5 minutes among 100% of the apixaban group compared with 11% of the placebo group ($p<0.001$).

In ANNEXA-R, andexanet alfa bolus administration reduced anti-factor Xa activity by 92% in 27 subjects compared with 18% in 14 subjects who received placebo, and unbound rivaroxaban concentration decreased by 23.4 ng per milliliter versus 4.2 ng per milliliter, respectively ($p<0.001$). Also, thrombin generation was fully restored within 2–5 minutes in 96% of the rivaroxaban group compared with 7% of the placebo group ($p<0.001$). Antifactor Xa activity persisted when andexanet alfa was administered as a bolus plus an infusion. A patient subgroup exhibited transient increases in levels of D-dimer and prothrombin fragments 1 and 2 that resolved within 24–72 hours. Investigators reported no serious adverse or thrombotic events in either trial.[7]

An ongoing phase III trial is investigating andexanet alfa's efficacy for reversing factor Xa inhibitor activity in patients presenting with acute major bleeds.[8] As of early December 2015, no data were available from that 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]

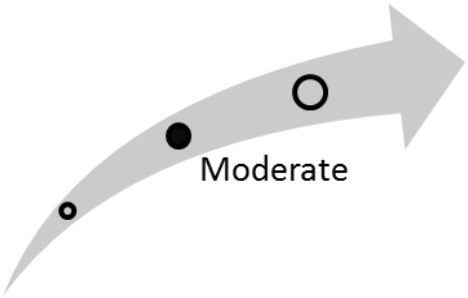
In November 2013, the U.S. Food and Drug Administration (FDA) granted breakthrough therapy status to andexanet alfa for reversing effects of factor Xa inhibitors in patients who experience a major bleeding episode or who require emergency surgery, with its risk of bleeding.[10] In December 2015, Portola announced completing submission of its rolling biologics license application to FDA under an accelerated approval pathway.[11]

Diffusion: As of December 2015, andexanet alfa was available only through clinical trials. Portola had 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 administering nonspecific procoagulants,[12,13] with a recent expert clinical panel (the working group on perioperative hemostasis) explicitly recommending either 30 to 50 U/kg of activated prothrombin complex concentrate (PCC), or 50 U/kg of nonactivated PCC for emergency indications.[12] 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 alfa 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 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.[14-19] 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, prescribing 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.[15,16,18,19]

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.[18,19]

Health disparities: Overall, experts anticipated that andexanet alfa would have minimal effects on health disparities. One clinical expert speculated that, compared with warfarin, factor Xa inhibitors' higher costs would limit their use by those with less financial means; subsequently, andexanet alfa might display similar stratification.[18]

Idarucizumab (Praxbind) for Reversal of Dabigatran-Induced Anticoagulation

Unmet need: Patients with venous thromboembolism or AF are usually prescribed long-term oral anticoagulants to prevent blood clot formation, which can cause stroke or lead to pulmonary embolism. Dabigatran is a relatively new alternative to warfarin that is reportedly easier to use than warfarin because it does not require periodic blood tests or have the same level of potential pharmacologic and dietary interactions as with warfarin. Like all anticoagulants, treatment with dabigatran carries a small risk of serious bleeding events. Since it became commercially available, no reversal agent for dabigatran has been available.[20] Limited data exist assessing the efficacy of frozen plasma and prothrombin complexes to stop bleeding.[21] Therefore, a need exists for an intervention that can rapidly counteract dabigatran's anticoagulation effect in the event of uncontrolled bleeding or the need for emergency surgical procedures.

Intervention: Dabigatran is a non–vitamin K antagonist oral anticoagulant used to reduce stroke risk in patients with AF and for treating systemic venous thromboembolism.[20] Dabigatran's mechanism of action is independent of vitamin K, so vitamin K cannot be used to reverse its anticoagulant effect.[21] Idarucizumab (Praxbind®) is a fully humanized monoclonal antibody fragment specific for dabigatran developed to reverse its anticoagulation effect. Idarucizumab purportedly inhibits dabigatran by binding to it in a 1:1 stoichiometric relation with an affinity of about 350 times higher than the affinity dabigatran has for thrombin.[20,21] Idarucizumab can bind free dabigatran as well as thrombin-bound dabigatran and inhibit the activity of both forms.[20] Idarucizumab is administered intravenously at a recommended dose of 5 g, supplied as two separate vials each containing 2.5 g/50 mL idarucizumab.[22]

Clinical trials: In August 2015, Pollack and colleagues reported interim results from 90 patients treated with idarucizumab who had serious bleeding (n=51) or required emergency surgery (n=39). More than 90% of patients were taking dabigatran for stroke prevention related to AF. Investigators removed from analysis 22 patients who were subsequently determined by central laboratory analysis to have dilute thrombin times within normal limits at enrollment (baseline) and 9 patients (all of whom had normal dilute thrombin times) subsequently determined to have normal baseline ecarin clotting times. (Ecarin is a metalloproteinase derived from viper venom that activates an intermediate step in the conversion of prothrombin to thrombin. Along with the dilute thrombin time, ecarin clotting time is used to assess dabigatran levels.) Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, idarucizumab infusion achieved a median maximum reversal of 100% (95% confidence interval [CI], 100 to 100). The dilute thrombin time was normalized in 98% of bleeding patients who could be evaluated and in 93% of surgical patients who could be evaluated. The ecarin clotting time was normalized in 89% of bleeding patients and 88% of surgical patients who could be evaluated. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of patients. Among 35 patients with serious bleeding who could be assessed, idarucizumab restored hemostasis at a median of 11.4 hours, as determined by local investigators. Among 36 patients who underwent a surgical procedure, investigators reported normal intraoperative hemostasis in 33 patients, mildly abnormal hemostasis in 2 patients, and moderately abnormal hemostasis in 1 patient.[20] Early (less than 72 hours after treatment) or late (72 or more hours after treatment) thrombotic events occurred in 5 patients in whom anticoagulation had not been resumed, as follows:[20]

- One patient had deep vein thrombosis and pulmonary embolism 2 days after treatment.
- One patient experienced deep vein thrombosis, pulmonary embolism, and left atrial thrombus 9 days after treatment.
- One patient had deep vein thrombosis 7 days after treatment.

- One patient had non–ST-segment elevation myocardial infarction 13 days after treatment.
- One patient experienced ischemic stroke 26 days after treatment.

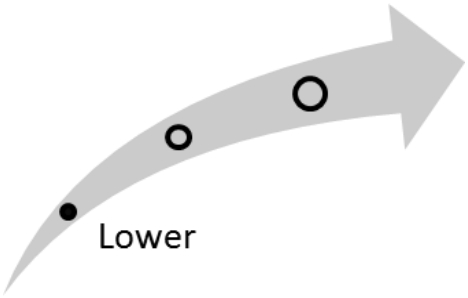
Manufacturer and regulatory status: Boehringer Ingelheim, GmbH (Ingelheim, Germany), manufactures idarucizumab. The company also manufactures dabigatran. In October 2015, FDA granted accelerated approval for idarucizumab use "when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding."[23,24] In November 2015, idarucizumab was approved for use in the European Union for a similar indication.[25]

Diffusion: Boehringer Ingelheim has not announced sales figures for idarucizumab since its U.S. product launch in October 2015. The drug reportedly costs $3,500 for the recommended 5 g dose and is available in the United States only through specialty pharmacies.[26]

Clinical Pathway at Point of This Intervention

Severe bleeding is sometimes an unavoidable complication of treating patients with anticoagulants such as dabigatran. Treatment options to stop bleeding in patients taking dabigatran include fresh frozen plasma or concentrated prothrombin complexes; however, few data exist that clearly establish the efficacy of these interventions to stop bleeding. Additionally, patients may undergo hemodialysis to remove dabigatran from the circulation.[21] Idarucizumab represents the first agent specifically reversing dabigatran and would be used in place of nonspecific reversal approaches.

Figure 2. Overall high-impact potential: idarucizumab (Praxbind) for reversal of dabigatran-induced anticoagulation



Overall, experts agreed that idarucizumab has great potential to fill the unmet need for a specific reversal agent to counteract dabigatran-induced bleeding events. Clinical and health systems experts acknowledged that although the incidence of dabigatran-related bleeding is relatively rare compared with the entire population treated with dabigatran, the clinical impact for patients affected by bleeding is potentially devastating. Acceptance of the drug is likely to be strong because it may provide a specific and rapid alternative to available nonspecific options for treating dabigatran-induced bleeding, experts thought. Although idarucizumab is expensive, experts anticipated that it would have only a moderate effect on health care costs and a small effect on changing health care disparities. Several experts noted that idarucizumab's potential importance would likely be affected by the increased use of factor Xa inhibitors (e.g., apixaban, rivaroxaban) that have emerged to challenge dabigatran as safer and easier-to-use alternatives to traditional warfarin therapy for long-term oral anticoagulation. 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, offered perspectives on this intervention.[27-32] Please note that the experts delivered comments on idarucizumab before FDA approved the drug in November 2015. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: All experts cited a large unmet need for a reversal agent specific to dabigatran. As noted by one health systems expert, the risk of dabigatran-related bleeding could be higher in general clinical practice than that observed in controlled clinical trials because use of newer anticoagulants such as dabigatran has increased greatly since their introduction.[27] A clinical expert noted that dabigatran has taken away market share from warfarin, but needed a reversal agent.[32] Idarucizumab has high potential to improve patient health and fulfill the unmet need for a dabigatran-specific reversal agent, all experts agreed. A clinical expert noted, "Most patients taking dabigatran do not have major bleeding complications and will never require the drug. However, you can't always predict who will need it, so in a way everyone benefits from the new drug."[32] Several experts noted that idarucizumab's potential importance and health impact would be moderated by the recent market entry of other new oral anticoagulants, such as factor Xa inhibitors (i.e., apixaban, edoxaban, rivaroxaban), that challenge dabigatran as safer and easier-to-use alternatives to traditional warfarin therapy for oral anticoagulation.

Acceptance and adoption: Clinicians and patients would be expected to welcome the availability of idarucizumab, all experts thought. One clinical expert stated, "Major bleeding while anticoagulated is a life-threatening condition…. Everyone fears bleeding in an anticoagulated patient, and everyone wants a reversal agent available."[32] Overall, experts anticipated that although idarucizumab was likely to be an expensive drug, it might have only a moderate impact on health care costs compared with the costs of nonspecific anticoagulant reversal therapy. A health systems expert noted, "the cost for severe bleeding adverse events and the cost to manage the bleeding events and their complications could be also very high."[27]

Health care delivery infrastructure and patient management: The use of idarucizumab is unlikely to cause much disruption to health care infrastructure, experts agreed. However, a clinical expert anticipated that "some pharmaceutical resources will need to be put into this drug, at least in the beginning, to purchase it and stock it. I suspect some supplies will have to be held in the intensive care unit setting as well as the emergency departments."[32] Experts thought idarucizumab would alter management of patients who experience dabigatran-associated bleeding. A clinical expert characterized the potential change as a "positive disruption [that] may simplify treatment/management of patients requiring urgent anticoagulation from dabigatran."[30]

Health disparities: Overall, experts did not expect the availability of idarucizumab to have a substantial effect on health care disparities, largely because it will be administered primarily in the emergency care setting. A clinical expert noted, "I suspect it will be expensive, but in a life-threatening situation, rarely does the expense or other health care disparity play a huge role."[32]

Bradycardia Intervention

Leadless Pacemaker (Nanostim) for Treatment of Bradycardia

Unmet need: In the past 20 years, use of permanent cardiac pacemakers has grown substantially. Between 1993 and 2009, 2.9 million patients in the United States received a pacemaker implant, with overall pacemaker use increasing by 56% during that period.[33] Although pacemaker use in most patients is uneventful, about 4% of patients encounter device-related complications, including about 3% who experience lead migration or other lead failure and about 1% who develop an implant-related infection, typically in the subcutaneous pocket housing the pacemaker.[34-38] Technology that could deliver necessary cardiac pacing while reducing or eliminating the risks of electrode lead failure and device-related infection associated with conventional single-chamber cardiac pacemakers could fill an unmet need.

Intervention: The Nanostim™ Leadless Pacemaker is a self-contained, single-chamber cardiac pacemaker housed in a seamless, polished titanium cylinder. The device is 42 mm long with a 5.99 mm diameter and weighs about 2 g. The Nanostim is reported to be about 10% the size of a conventional pacemaker, or about as large as an AAA battery.[39-42] To implant the device, an interventional cardiologist (typically an electrophysiologist) inserts the steerable delivery catheter at the femoral vein in the groin and advances it to the heart, entering the right ventricle across the tricuspid valve from the right atrium under fluoroscopic guidance.[43] The operator secures the implant into the bottom of the right ventricle by rotating the catheter a single turn, thus allowing the helical fixation coil to screw into the ventricular wall and releasing it from the delivery catheter.[41,43] The fixation coil doubles as the pacing electrode that delivers the pacing therapy.[44] A docking button on the end opposite the fixation coil allows the operator to recapture the implant using a catheter-based snare for periprocedural repositioning and (presumably) eventual removal upon battery depletion.[39,43] However, Neuzil and Reddy (2015)[45] noted that "although leadless pacemakers are reportedly retrievable acutely, the ability to remove a chronically implanted device remains untested in humans. As such, the strategy for device management (retrieval vs. abandonment) once the battery has been depleted remains unknown." Implantation typically takes about 1 hour to complete, with patients under conscious sedation and local anesthesia.[40] In clinical trials, patients were typically hospitalized overnight for observation after Nanostim implantation.[39,46] After implantation, the physician wirelessly programs the Nanostim device using a Merlin™ Patient Care System programmer,[39] which is also used to program many of the manufacturer's conventional cardiac pacemakers and implantable defibrillators.[41] According to the manufacturer and as demonstrated in clinical trials, the Nanostim's lithium battery has an estimated life of 9.8 years at 100% pacing, with a potential battery life of 15–21 years, depending on individual pacing requirements.[42]

Clinical trials: In September 2015, Reddy and colleagues reported preliminary outcomes for 526 patients and 6-month outcomes for 300 patients enrolled in the LEADLESS II trial.[44] Investigators successfully implanted the device in 95.8% (504 of 526) of patients. The intention-to-treat primary efficacy end point was met in 270 of the 300 patients in the primary cohort (90.0%; 95% CI, 86.0 to 93.2; p=0.007), and the primary safety end point was met in 280 of the 300 patients (93.3%; 95% CI, 89.9 to 95.9; p<0.001). Overall, 29.8% of patients required device repositioning after initial implantation, including 4.4% (22 patients) in whom operators had to reposition the pacemaker more than 2 times. Length of hospital stay from device implantation to discharge was 1.1±1.7 days (range, 0–33). In 300 patients for whom 6-month data were available, device-related serious adverse events occurred in 6.7% of the patients. The most frequently occurring serious adverse events were device dislodgement with percutaneous retrieval (1.7%), cardiac perforation

(1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (1.3%).[44]

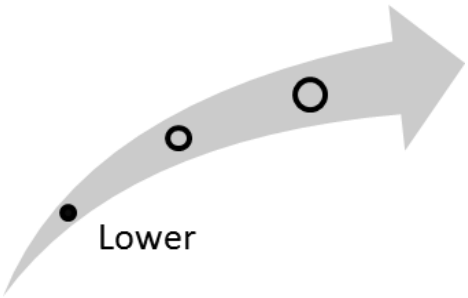
Manufacturer and regulatory status: St. Jude Medical, Inc. (St. Paul, MN), manufactures the Nanostim Leadless Pacemaker. The device is under evaluation in more than 650 patients at 56 sites in the United States, Australia, and Canada in the LEADLESS II study (NCT02030418) under an investigational device exemption from FDA.[42,44] The Nanostim pacemaker received CE mark for distribution in the European Union in October 2013.[47]

Diffusion and cost: In the United States, the Nanostim is available only through clinical trials. A competing leadless, single-chamber pacemaker, the Micra Transcatheter Pacing System from Medtronic, plc (Dublin, Ireland), is also under evaluation in late-phase clinical U.S. trials.[48] Neither St. Jude Medical nor Medtronic has announced estimated U.S. pricing for the Nanostim or Micra devices because neither has FDA approval. According to ECRI Institute's PriceGuide database, the average price paid for the Nanostim and Micra devices, as reported by member hospitals, is about $9,000 each.[49] Higgins and Rogers (2014)[43] noted that many U.S. centers participating in clinical trials of leadless pacemakers (Nanostim and Micra) were likely performing procedures at a financial loss because of uncertain reimbursement.

Clinical Pathway at Point of This Intervention

Bradycardia linked to problems with the heart's electrical pathways is typically corrected with implantation of an artificial cardiac pacemaker.[50-52] The Nanostim leadless pacemaker would be used instead of a conventional single-chamber cardiac pacemaker that requires implanting transvenous electrode leads. In clinical trials, the Nanostim has been evaluated in patients who require single-chamber pacing in the right ventricle.[39,44,53]

Figure 3. Overall high-impact potential: leadless pacemaker (Nanostim) for treatment of bradycardia



Most experts thought the ability to eliminate the use of electrode leads is a moderately important unmet need. However, experts were divided in their opinions of whether the Nanostim device could adequately fill that need. Generally, experts anticipated higher acceptance from patients than from clinicians. Implantation of the Nanostim device would likely be performed by the same interventional teams that implant conventional cardiac pacemakers, experts thought, thus creating only small disruptions to health care infrastructure and patient management. Further, experts did not expect the technology to have a substantial effect on changing health care disparities. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[54-60] Please note that experts provided comments on the Nanostim leadless

pacemaker. Our report on the Micra device was not yet available for comment. Two clinical experts reported potential conflicts of interest involving cardiovascular device manufacturers, including Medtronic, Biotronik, and Boston Scientific.[59,60] These potential conflicts are balanced by other experts who reported none. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Most experts saw the potential to remove the risk of electrode lead complications as a moderately important unmet need for patients who require single-chamber pacing. They thought the Nanostim device would fill this unmet need in that niche. A clinical expert stated it might be useful in patients who have upper vascular access issues (e.g., patients on dialysis).[60] This clinical expert said "I believe this is the technology of pacing's future, or at least a way station on the journey as pacing becomes less invasive."[60] However, other experts thought the technology has not been shown to be safe and effective or better than existing technology.

Overall, experts expected the Nanostim to have low potential for improving patient outcomes, largely because of its technical limitations compared to conventional cardiac pacemakers. These sentiments were exemplified by one clinical expert who stated, "It seems as though we would be trading one set of complications (lead failure or fracture, infection) for another set (procedure complications, embolization)."[55]

Acceptance and adoption: Experts were evenly divided on how widely this technology would be accepted. An expert who thought acceptance would be limited cited the steep learning curve for clinicians, the invasiveness of the device, and its relatively high rate of complications and noted the belief that Nanostim is not superior to available pacemakers. Other experts anticipated more moderate physician acceptance, with one clinical expert opining that cardiac interventionalists potentially have the most to gain. This clinical expert further surmised that "as the technology matures and especially as a comparable device for atrial sensing and pacing is developed, adoption will become much more widespread, leading to a major change in therapy delivery."[60]

Overall, experts anticipated greater patient acceptance of this technology than clinician adoption. "Patients would likely be thrilled to hear that they would not need a large subcutaneous generator in their chest," said one clinical expert.[55]

Health care delivery infrastructure and patient management: Most experts anticipated this technology would cause little disruption to health care infrastructure and patient management. However, a clinical expert saw this technology as potentially more disruptive because it will complicate decisions about which type of pacemaker a patient should receive. "[It] will also be more confusing in terms of determining who will pay for it," this clinical expert stated.[59] This clinical expert also expected patients to want the device and seek health care elsewhere if a practitioner does not recommend it.[59]

Health disparities: Generally, experts did not expect the Nanostim to have a large effect on health care disparities. However, one clinical expert was something of an outlier, stating, that disadvantaged patients might benefit from the technology "because sometimes these patients do not get pacemakers placed because of providers' fear of causing harm due to infection (poor hygiene) or lack of follow up, which would be less of an issue in a leadless system."[55] Most experts expected a small to moderate impact on health care costs and noted that more accurate cost projections would depend on actual pricing established if the Nanostim receives FDA approval.

Heart Failure Interventions

Freedom Driver System (Portable Driver) for Total Artificial Heart as Bridge to Heart Transplantation

Unmet need: Heart failure (HF) adversely affects quality of life and 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.[61] Projections show that HF prevalence will increase 46% from 2012 to 2030, affecting more than 8 million people aged 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.[61]

Ventricular-assist device implantation and cardiac transplantation are the only established surgical treatments for end-stage HF.[62] 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.[63,64] 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.[65]

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.[66,67] 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.[65] 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.[63]

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.[68]

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.[65]

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 rehospitalization 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.[69]

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."[70]

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.[71]

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.[72]

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."[70] In March 2010, SynCardia received a CE mark for the Freedom driver, allowing its use with the SynCardia TAH-t in Europe.[73] The TAH-t as a bridge to transplant had been approved by FDA in October 2004.[74] In September 2015, FDA issued a class I recall of the Freedom Driver because of potential device failure that may occur without warning and may lead to serious injury or death unless a patient is immediately switched to the backup driver.[75] After FDA's recall notice, the manufacturer reported that 29 potentially affected units used by 12 patients had already been replaced as of August 14, 2015, after issuing its own voluntary recall August 6, 2015.[76]

Diffusion and cost: In November 2015, the company reported that more than 485 SynCardia total artificial hearts had been implanted since January 2012, and that more than 235 patients had used the Freedom portable driver, which collectively has provided more than 160 patient years of support.[77]

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.[78] 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

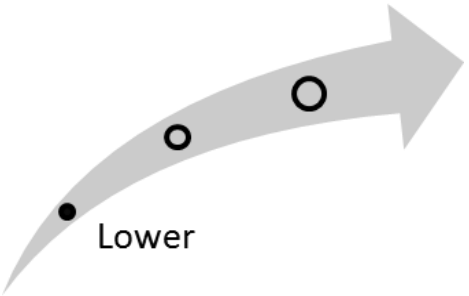
result in more of a cost shift than a significant cost reduction. Ambulatory patients would continue to need regular visits from specially trained nurses at home as well as followup office visits with specialist physicians to monitor device function. Furthermore, as with hospital-based pneumatic drivers, 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.[79] Staff training costs to meet the manufacturer's device-related certification requirements are about $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.[79] Annual per-patient maintenance costs for the TAH-t are estimated at $18,000.[80,81] 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.[62] The portable driver system is intended to complement TAH-t use.[65] 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 4. 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.[82-87] 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. They thought the Freedom driver would meet this unmet need, with one clinical expert calling it a "significant benefit."[86] However, they noted data on outcomes are lacking. Further, some thought the risk of driveline fractures limits the device's potential.

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 with concerns of increased risk to patients from possible device failures without access to immediate clinical support.

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."[86] However, an expert with a research background noted that other patients and their family caregivers might be too anxious about responding to alarms or emergencies to accept the device.

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. Some experts noted that although the location of care—and the resources that follow the patient—changes to a home setting,[82] that would not substantially alter actual patient management.[82]

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.

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."[86]

Ivabradine (Corlanor) for Treatment of Heart Failure

Unmet need: Standard of care for treating HF includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), digoxin, beta blockers, diuretics, and aldosterone antagonists.[88,89] These medications 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.[89,90]

Intervention: Ivabradine is a novel, antianginal, heart rate–lowering medication, originally developed for treating chronic stable angina pectoris.[91,92] Ivabradine directly lowers heart rate by selectively inhibiting the funny channel (I_f) pacemaker current and reducing the diastolic depolarization rate.[91,93] 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.[91,94] Ivabradine's heart rate–reducing activity is cardioprotective and relieves this systemic response cycle, potentially improving health outcomes.[95]

As a selective, highly specific binding agent, ivabradine is considered to be a "pure" heart rate–reducing medication.[91,94] 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.[91,92]

Ivabradine is administered orally for treating HF at a recommended dosage of 5 mg (up to 7.5 mg) taken twice daily.[96] 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).[97-99]

Clinical trials: Ivabradine's pivotal international clinical trial was SHIfT, which concluded in 2010.[100] 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 [HR], 0.76; 95% CI, 0.68 to 0.85; $p<0.0001$).[101,102] Additional subanalyses also indicated that ivabradine administration was associated with improved quality of life.[103] Ivabradine was well tolerated among patients, even when evaluating patients with severe comorbid conditions.[102,104]

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.[105-107]

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.[94,108] 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.[109,110] The applicability of this finding to patients with HF is unknown.

Manufacturer and regulatory status: Ivabradine was developed and originally manufactured by Servier (Suresnes, France).[108] Before FDA approval, ivabradine was available internationally in several branded and generic forms.[100]

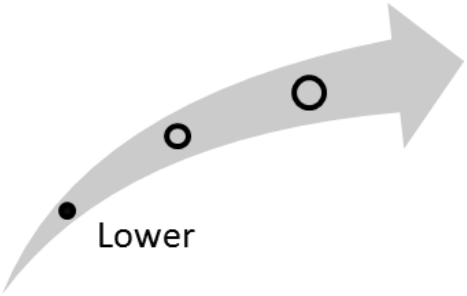
Amgen, Inc. (Thousand Oaks, CA), holds ivabradine's U.S. commercialization rights.[111] In April 2015, FDA approved ivabradine, branded as Corlanor®, for treating patients who have stable HF symptoms, a normal heartbeat with a resting heart rate of at least 70 beats per minute, and who are also taking optimized beta-blocker therapy.[112] This approval was based on results from the SHIfT study.[100,113]

Diffusion and cost: Amgen has not released any ivabradine sales data. As of December 2015, ivabradine reportedly cost $380 to $415 for a 30-day supply (60 tablets) at U.S retail pharmacies, or about $4,560 to $4,980 per year.[114] Ivabradine will likely be covered by many third-party payers; however, payers may require prior authorization or impose other restrictions on its use.

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.[88,89] Ivabradine is approved as an adjunct to optimal beta-blocker therapy for certain patients with HF.[112]

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 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.[115-120] 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 clinical 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.[116,117,120]

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 AF among patients with stable coronary artery disease without HF taking ivabradine].[116]

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 Warm Blood Perfusion System (Organ Care System) for Normothermic Heart Transplantation

Unmet need: Heart transplant surgeons at Stanford University published a study in February 2015 showing that a significant decrease in donor heart acceptance occurred from 44% in 1995 to 29% in 2006, and then subsequently increased to 32% in 2010.[121] Over this period, 82,053 hearts were donated. The researchers indicated that estimates show that more than 20,000 U.S. patients could benefit from heart transplant surgery each year, but only 1,949 patients received transplants in 2011, according to the study. According to the Organ Procurement and Transplantation Network (OPTN), the number of heart transplant candidates awaiting a suitable donor heart continues to grow. In 2012 in the United States, 3.5 hearts were donated for every 1,000 deaths.[122,123] In each year between 2010 and 2012, about 2,000 candidates underwent heart transplantation and about 400 patients died while waiting; another 100 patients became too ill to undergo transplantation and were removed from the list.[123] As of December 3, 2015, OPTN had registered 4,199 transplant candidates as waiting for a suitable donor heart;[124] but according to the Stanford researchers, many additional patients could benefit but are never listed. Other challenges to increasing heart transplantation rates include wide regional variation in donation rates; access to transplant centers, which tend to be concentrated near urban population centers; and acceptability of donated hearts.[123]

Static cold storage, also called cold ischemic storage, is the current standard of care for preserving donor hearts in transit to recipient patients.[125-127] Cold storage can adequately preserve donor hearts for about 4–6 hours.[126] However, the process of organ matching and obtaining consent from next of kin must be completed before heart transplantation can proceed.[128] Additionally, static cold storage can damage grafts and negatively affect heart transplantation outcomes.[126] New graft preservation methods that improve the condition of donated hearts and preserve them for longer before they can be transplanted could potentially help more patients undergo heart transplantation.

Intervention: The Organ Care System™ (OCS) is intended to address this need by extending the preservation period and improving the condition of donated hearts by simulating the organs' natural environment, keeping them beating during transit and perfusing them with warm blood to maintain function.[129] The OCS Heart is optimized for this purpose.[130] 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.[131] A portable console houses all the system components, including the Perfusion Module, the oxygen supply, interchangeable batteries, and a wireless monitor.[132,133] When physicians harvest the donor heart, they place it in the perfusion module and revive it to a beating state.[132] 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.[127,132] The wireless monitor allows clinicians to assess the organ's status and control system functions.[127,132]

According to the manufacturer, the OCS Heart may provide several advantages over cold ischemic storage. Keeping the donor heart beating and perfusing it with blood during transport may reduce cold ischemic injury to donor hearts.[130] 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.[125,130,133,134] These factors could also expand the pool of potential organ donors and increase use of available donor hearts,[125,131,133] which could improve health outcomes of heart transplant candidates.[125,135] Reducing the amount of expensive care before and after transplantation and shortening average post-transplant lengths of stay could reduce overall treatment costs in this population.[133,135]

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.[136]

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.[137]

In July 2014, Esmailian 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.[138]

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 vs. 28 days; p=0.80).[139]

Manufacturer and regulatory status: TransMedics, Inc. (Andover, MA), manufactures the OCS Heart. In November 2015, FDA cancelled a planned advisory committee meeting that had been scheduled to discuss, make recommendations, and vote on the company's premarket approval application for the OCS Heart on November 18, 2015. The FDA notice stated that the meeting was cancelled "because the FDA has determined than an advisory committee meeting is no longer needed."[140] An FDA decision is expected in early 2016. TransMedics has a CE mark allowing marketing of the OCS in the European Union for use in heart transplantation.[129]

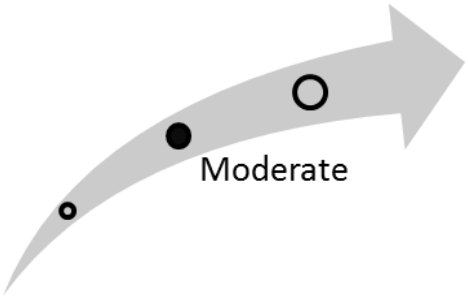
Diffusion and cost: The OCS Heart is expected to cost about $250,000 for the portable console plus about $45,000 for each single-use perfusion module.[141] Other associated costs would be expected to be similar to those for the OCS Lung, a closely related technology designed to preserve and transport 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 cost $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.[142] 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.[128]

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.[62] 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,[134,143] and in April 2015, Dhital and colleagues reported the first three cases of successful heart transplantation using donor hearts obtained after circulatory death.[137]

Figure 6. Overall high-impact potential: portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation



Although the intended patient population for this intervention is small at this time, experts noted the importance of finding alternatives to static cold storage, which has important limitations in the ability to assess hearts for acceptability, the ability to preserve them during transport, and in the amount of time they can be viable after harvesting. 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 could 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.[144-149] 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. Three clinical experts wanted to see more published data from larger trials before fully embracing the technology. A clinical expert stated that the device did not show increased efficacy of transplantation, but that the size of the donor pool might increase with use of the normothermic system.[149]

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, with large transplant centers more able to take it on than smaller transplant centers. Patient acceptance of the OCS Heart system would be high, the experts agreed.

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.

In terms of patient management, the experts also thought that use of the OCS Heart system would not cause much change to how patients are managed after undergoing heart transplantation, although it might shorten transplant wait times for some patients.

Health disparities: Experts generally did not expect use of the OCS Heart system to substantially alter health disparities. 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.

Sacubitril/Valsartan (Entresto) for Treatment of Heart Failure

Unmet need: Standard HF monotherapies and combination therapies attempt to reduce prominent symptoms and delay disease progression. Clinical practice guidelines recommend pharmacotherapies for HF including 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.[88,89] 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.[89,90] A significant unmet need exists for alternative, effective medications for treating HF.

Intervention: Combination sacubitril/valsartan (Entresto™) is a novel oral angiotensin receptor neprilysin inhibitor; its active components are sacubitril, a prodrug inhibitor of neprilysin, an enzyme that normally counteracts blood pressure-lowering atrial and brain natriuretic peptides, and valsartan, an approved angiotensin receptor blocker.[150,151] In a crystalline complex combination, sacubitril and valsartan are hypothesized to both inhibit the renin-angiotensin-aldosterone system, which normally regulates blood volume and systemic vascular resistance, and enhance endogenous natriuretic peptide activity. Purportedly, these actions result in reduced cardiovascular system strain, alleviating HF symptoms and other negative cardiovascular outcomes.[150]

Preliminary clinical results indicate that sacubitril/valsartan is superior to valsartan monotherapy for improving biomarkers of cardiac stress.[152,153] Additionally, in an animal model of HF, sacubitril/valsartan administration was associated with attenuated cardiac remodeling, potentially due to the drug's inhibition of cardiac fibrosis and hypertrophy.[154]

Based on completed studies, sacubitril/valsartan 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, sacubitril/valsartan's demonstrated ability to relieve cardiovascular strain also makes it a candidate drug for treating HF in patients with preserved ejection fraction. This added property potentially affords sacubitril/valsartan expanded indication over available HF medications.[155,156] According to product labeling, the drug is usually administered in conjunction with other HF therapies, in place of an ACE inhibitor or other ARB at the recommended maintenance dosage of 97 mg sacubitril/103 mg valsartan as an oral tablet, taken twice daily.[157]

Clinical trials: PARADIGM-HF (n=8,442) was a pivotal clinical trial designed to compare sacubitril/valsartan 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.[158]

Measured over 4 years, patients receiving daily sacubitril/valsartan demonstrated the following improved patient health outcomes relative to enalapril:[159,160]

- Fewer patients required intensification of HF medical treatment (520 vs. 604; HR, 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 sacubitril/valsartan showed superiority for reducing hospitalization within 30 days of starting treatment.[160]

Overall, sacubitril/valsartan 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 sacubitril/valsartan treatment-related adverse events.[159] Investigators also noted that sacubitril/valsartan treatment-related adverse events led to fewer study-participant discontinuations than did enalapril treatment (10.72% vs. 12.25%).[159,160] 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 sacubitril/valsartan trials, but ongoing trials may resolve any potential associations.[161]

In November 2015, Solomon and colleagues reported on 30-day rehospitalization rates from a post-hoc analysis of PARADIGM-HF data. The primary outcome was investigator-reported rehospitalizations within 30 days of discharge of an HF-related hospitalization. The sacubitril/valsartan group had 44% fewer patients than the enalapril group who were readmitted for HF within 30 days of an index HF hospitalization (unadjusted odds ratio [OR], 0.69; 95% CI, 0.54 to 0.89; random-effects OR, 0.66; 95% CI, 0.49 to 0.89). Similarly, the sacubitril/valsartan group had 36% fewer patients than the enalapril group who were readmitted for any cause within 30 days of an index HF hospitalization (OR, 0.73; 95% CI, 0.44 to 1.21).[162,163]

Manufacturer and regulatory status: Novartis International AG (Basel, Switzerland) developed sacubitril/valsartan.[158] In July 2015, FDA approved sacubitril/valsartan, branded as Entresto, after previously granting fast-track status and priority review.[164] The labeled indication is "to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA [New York Heart Association] Class II-IV) and reduced ejection fraction."[157] In November 2015, the European Commission granted Novartis approval for sacubitril/valsartan to treat symptomatic chronic HF in adults with reduced ejection fraction.[165]

Diffusion and cost: As of November 2015, the drug reportedly cost between $380 and $420 per month for 60 tablets at the recommended maintenance dose (97/103 mg tablets taken twice daily) at major U.S. retail pharmacies (i.e., about $4,560 to $5,040 annually).[157,166] 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.[167,168]

In December 2015, the Institute for Clinical and Economic Review (ICER) issued a final report analyzing the cost-effectiveness of two HF therapies: the CardioMEMS HF System and sacubitril/valsartan.[169] The ICER report proposed a value-based benchmark price of $4,168 per year for sacubitril/valsartan. The group defines its value-based price benchmarks as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per quality-adjusted life-year (QALY) gained, without exceeding the $904 million budgetary impact threshold for drugs. ICER estimated the wholesale acquisition cost for sacubitril/valsartan to be $4,560 per year, which is 9% higher than ICER's value benchmark. ICER panelists made three recommendations regarding use of sacubitril/valsartan, as follows:[169]

> (1) Provider groups and payers may wish to limit prescribing of Entresto to cardiologists or, at a minimum, require other clinicians to prescribe in consultation with a cardiologist, due to the potential for side effects at initiation, importance of selecting appropriate patients, and relatively large expense when compared to generic ACE inhibitors or ARBs.
> (2) Based on the combination of its clinical benefits, pricing aligned with patient benefit, and short-term affordability, payers and purchasers should consider placing Entresto in the 'preferred brand' category, especially if discounts can be obtained that bring the price in line with thresholds for health-system affordability.
> (3) Further research and real-world experience with Entresto are needed to help identify the most appropriate patients among those who have [NYHA] Class II-IV heart failure and reduced ejection fraction.

The ICER report also issued two additional recommendations that jointly apply to use of sacubitril/valsartan and the CardioMEMS HF System, as follows:[169]

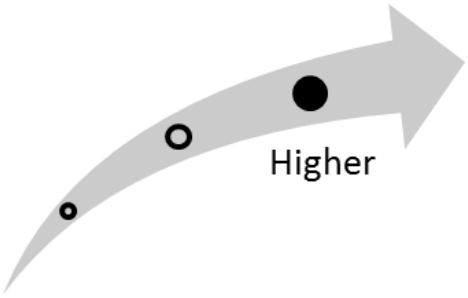
> (1) Manufacturers and payers should consider performance-based agreements (i.e., reduced costs or refunds) for both Entresto and CardioMEMS.
> (2) Clinicians and patients should work together to prevent and intensively manage health conditions that are a precursor to CHF [congestive heart failure], as this may improve patient outcomes including quality of life and reduce costs.

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.[88,89] Additionally, surgical interventions such as coronary artery bypass graft surgery, heart valve repair or replacement, implantable cardioverter-defibrillators, cardiac resynchronization therapy or biventricular pacing, heart pumps, and heart transplants can also be indicated.[88,170]

As an HF treatment, sacubitril/valsartan could be prescribed as a monotherapy or adjunct to standard HF medications because recent pharmacokinetic studies suggest that sacubitril/valsartan has limited interactions with drugs commonly prescribed for HF and comorbid conditions and does not interfere with the activities of these drugs.[171-173] Sacubitril/valsartan's FDA-approved labeling states that the drug "is usually administered in conjunction with other HF therapies, in place of an ACE inhibitor or other ARB" with a recommended maintenance dose of 97 mg sacubitril/103 mg valsartan as an oral tablet, taken twice daily.[157]

Figure 7. Overall high-impact potential: sacubitril/valsartan (Entresto) 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 sacubitril/valsartan 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 sacubitril/valsartan's potential acceptance and use. The majority of experts also favorably cited sacubitril/valsartan'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 sacubitril/valsartan.[174-179] Please note that the experts provided comments before FDA approved the

drug in July 2015. 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 are a prominent health issue that is inadequately controlled by available therapies. Concurrently, these experts also agreed that sacubitril/valsartan 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 sacubitril/valsartan would broadly diffuse 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.[174,175,177]

Health care delivery infrastructure and patient management: Most experts thought that, as an oral HF medication, sacubitril/valsartan would not significantly affect health care delivery infrastructure or patient management. However, one health systems expert noted that widespread use of sacubitril/valsartan might dramatically decrease emergency department visits and hospital admissions, shifting care from the inpatient to the outpatient setting.[178] One clinical expert anticipated that broad use of sacubitril/valsartan would require many patients to adjust treatment regimens, a process that could require several office visits per patient, consuming substantial management resources.[179]

Health disparities: Five of six experts thought that sacubitril/valsartan would have little to no impact on health disparities. In contrast, one clinical expert thought that sacubitril/valsartan's comparatively high anticipated cost could prevent uninsured or economically disadvantaged patients from accessing this intervention, subsequently increasing health disparities.[174]

Wireless Monitoring System (CardioMEMS HF System) for Management of Heart Failure

Unmet need: Patients in whom HF has been diagnosed are frequently readmitted to the hospital for worsening HF symptoms; readmission rates at 30 days and 6 months after discharge are about 24% and 50%, respectively.[180] Hospitalization of previously discharged patients with HF adds substantially to the cost of care for these patients, and strategies to reduce readmission rates are highly sought. In hospitalized patients, catheters placed temporarily in the heart to monitor left atrial pressure are the gold standard for tracking hemodynamics and worsening HF.[181] A need exists for technology that would allow physicians to monitor pulmonary artery pressure in ambulatory patients outside the hospital and give clinicians more timely access to changes in intracardiac pressure, potentially allowing them to quickly adjust medications and reduce HF-related hospitalizations.[180,182]

Intervention: The implantable CardioMEMS™ HF System potentially could identify early signs of worsening HF, allowing clinicians to modify treatment and possibly avoiding the development of overt symptoms that would require rehospitalization.[183] The CardioMEMS system has three components: a self-contained implantable pressure sensor/monitor with delivery catheter, an external electronics unit, and the CardioMEMS secure Web site.[184] A physician implants the paperclip-size sensor into the descending branch of the pulmonary artery using conventional catheter-based techniques. The sensor contains no battery and uses microelectromechanical systems (MEMS) technology to wirelessly measure arterial pressure, cardiac output, and heart rate.[184,185] To obtain a reading, a patient holds the external electronics module over the chest to wirelessly power the sensor and collect pulmonary artery pressure and other physiologic data. The handheld electronics unit then automatically transmits data to the password-protected CardioMEMS Web site for later clinician review. The CardioMEMS database software alerts a clinical user if a patient's pressure readings exceed their prescribed limits and if a pressure reading contains technical deficiencies.[184] Physicians can adjust HF medications based on changes in pulmonary artery pressure and other physiologic data.[183,186]

Clinical trials: In November 2015, Abraham and colleagues reported complete followup results from the CHAMPION randomized trial of the CardioMEMS HF System that enrolled 550 patients with symptomatic NYHA Class III HF who were hospitalized for HF within the past year. In the treatment group (n=270), physicians had access to daily uploaded pulmonary artery pressures to guide medical therapy.[187] In the control group (n=280), physicians did not have access to daily uploaded pressures but patients received all standard medical, device, and disease management strategies available. After the 18-month randomized access period, physicians of control group patients had access to daily uploaded pulmonary artery readings for an average of 13 months in the open access period, which included 347 patients from the former treatment group (n=177) and the former control group (n=170). During the randomized access period, HF-related hospitalizations were 33% lower in the treatment group than in the control group (HR, 0.67; 95% CI, 0.55 to 0.80; $p<0.0001$). During the open-access period, HF-related hospitalizations in the former control group dropped by 48% compared to the control group's hospitalization rate during the randomized access period (HR, 0.52; 95% CI, 0.40 to 0.69]; $p<0.0001$). Investigators observed 8 (1%) device-related or system-related complications and 7 (1%) procedure-related adverse events during the trial's first 6 months. The overall combined device-related or system-related complication rate was 0.02 events per patient-year in the entire followup period. No sensor failures occurred after an average of 31 months followup.[187]

Manufacturer and regulatory status: CardioMEMS, Inc. (Atlanta, GA), developed the technology. In May 2014, St. Jude Medical, Inc. (St. Paul, MN), acquired CardioMEMS. In May

2014, FDA approved the CardioMEMS HF System to wirelessly measure pulmonary artery pressure and monitor heart rate in patients with NYHA Class III HF who have been hospitalized for HF in the previous year.[188]

The device's FDA approval was a lengthy process that involved two FDA advisory panel meetings years apart. In October 2013, FDA's Circulatory Systems Devices advisory panel voted that the device was safe and that its benefits outweighed the risks of implantation. However, the panel also voted that the available data failed to provide "reasonable assurance" that the device was effective for the proposed indication.[189-191] Previously, in December 2011, another Circulatory Systems Devices advisory panel had voted to recommend against FDA approving the CardioMEMS HF System.[192] The panel had concluded that the device was safe but that the high level of medical attention paid to trial patients by company-employed nurses may have introduced bias in favor of device efficacy.[192]

Diffusion and cost: St. Jude Medical has announced about $57 million in CardioMEMS sales through the third quarter of 2015 and estimated $85 million to $90 million in CardioMEMS sales for the whole of 2015.[193,194] According to ECRI Institute's PriceGuide database, member hospitals reported paying between about $15,235 and $23,150 for the CardioMEMS sensor with catheter delivery system (as of December 2015).[195] Device implantation would significantly increase short-term treatment costs for HF compared with treatment costs for optimal medical therapy alone. However, if these devices give physicians more timely information about changes in patients' intracardiac pressure, they might be able to adjust patients' medications more quickly and avoid HF-related hospitalizations.[196]

In December 2015, ICER issued a cost-effectiveness report that suggested the CardioMEMS device was priced too high to be cost-effective.[169] ICER estimated a "full Medicare price" of $17,750 for the CardioMEMS device. To be cost-effective, the group developed a value-based price benchmark of $10,665 for the CardioMEMS device, which is 40% lower than its estimated full Medicare price. ICER noted, "Even though the Medicare price for CardioMEMS is near the price at which it would achieve a relatively low cost/QALY of $50,000, at the level of uptake that we have estimated (25% by the end of the fifth year), the annualized budgetary impact for CardioMEMS exceeds the $603 million threshold for devices by approximately $400 million per year." The ICER report continued, "when intervention costs and potential cost savings are evaluated on a population basis, and likely patterns of CardioMEMS uptake are considered, the annual costs of CardioMEMS exceed the potential budget impact threshold at which excessive cost burdens would be placed on the overall health care system."[169]

CMS has no national coverage determination for this technology, but did grant CardioMEMS a new technology add-on payment (NTAP) not to exceed $8,875 under the Acute Inpatient Prospective Payment System for Federal fiscal year 2015.[197] The NTAP amount is calculated for each eligible discharge that includes the technology, and NTAPs are made when the estimated cost of the case is greater than the payment that would otherwise be made to the hospital. The NTAP amount paid is up to 50% of the amount of the total covered costs that exceed the Medicare severity diagnosis-related group (DRG) payment or 50% of the cost of the new device. The NTAP limit is linked to the technology's price as reported by manufacturers to CMS. According to St. Jude Medical, CardioMEMS implantation would receive Medicare reimbursement under DRG 264 (other circulatory system O.R. procedures).[198] The average Medicare reimbursement for the procedure is estimated at about $18,000, although actual rates vary by geography.[198,199] CMS also established a transitional APC (ambulatory payment classification) pass-through payment status to provide incremental payment (in addition to the APC payment). The APC pass-through code for the CardioMEMS HF System was mapped to APC 0080 effective January 1, 2015, and the system was

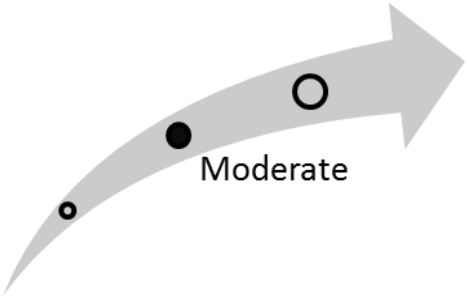
designated by a new C code, C2624 (implantable wireless pulmonary artery pressure sensor delivery catheter, including all system components).[200]

As of December 2015, several private third-party payers considered pulmonary artery pressure monitoring to be investigational and denied coverage for the procedure and technology. Payers with noncoverage policies include Aetna,[201] Anthem,[202] Blue Cross Blue Shield of Alabama,[203] Blue Cross Blue Shield of Massachusetts,[204] CIGNA,[205] and Regence.[206]

Clinical Pathway at Point of This Intervention

In hospitalized patients, catheters placed temporarily in the heart to monitor left atrial pressure are the gold standard for tracking hemodynamics and worsening HF.[207] Implantable pulmonary artery pressure monitors were developed to provide clinicians with similar information in ambulatory patients outside a clinical setting. Pulmonary artery pressure monitors are intended to complement conventional drug therapy for HF by helping physicians better manage the disease through more timely adjustments to medications, if needed. The technology would be unlikely to compete with or replace any existing treatments for HF.

Figure 8. Overall high-impact potential: wireless monitoring system (CardioMEMS HF System) for management of heart failure



Overall, experts thought the CardioMEMS device shows great potential for reducing HF-related hospitalizations. However, several experts cited the general lack of data demonstrating lower mortality over the long term. Experts believe the device could help facilitate management of patients who have more difficulty traveling to HF clinics for regular monitoring. At the same time, the lack of insurance coverage could introduce disparities for HF patients who could benefit from but not afford the technology. 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 intervention.[208-213] Experts provided comments before the study by Abraham and colleagues on complete follow up results of the CHAMPION trial was published. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: All experts recognized a large unmet need for improving management of patients with HF with new approaches to reduce HF-related hospitalizations and improve quality of life. A clinical expert also stated that hospitals face penalties for readmissions. The experts thought that because this technology can identify important changes before overt signs and symptoms of HF appear, it is important in meeting this need. Overall, experts concurred that the CardioMEMS device could have a moderate to large effect on improving patient health. But several

experts wanted to see additional studies of this technology and noted that most the available data evaluating the CardioMEMS' efficacy derive from a single randomized trial.

Acceptance and adoption: Experts generally expected moderate acceptance from clinicians, although several cited the lack of insurance coverage and lack of longer-term safety data as possibly dampening physician enthusiasm. One clinical expert stated that although studies have shown a definite improvement in reducing hospital readmissions, there has not been a substantial improvement in morbidity or mortality, probably because of "a) limited experience of providers with this device and b) the overall poor prognosis of patients with advanced [HF] who would have this device implanted."[212] Further, this clinical expert has seen "little adoption" of CardioMEMS at his two hospitals, both of which are university centers, with one having an advanced heart transplant/heart failure center.

Likewise, patient acceptance is likely to be moderate, most experts thought. They noted that although some patients would see a benefit, preventing hospital readmission, others might not, as one expert noted, because "it doesn't necessarily make them feel better, take fewer medications, or live longer."[208,212] Several experts cited the device's cost and lack of insurance coverage as potentially slowing acceptance and adoption, although the technology holds potential to reduce long-term costs by reducing HF-related hospitalizations.

Health care delivery infrastructure and patient management: Overall, experts anticipated the CardioMEMS device would create a moderate disruption to how patients are managed, with a somewhat smaller disruption to health care infrastructure. One clinical expert opined that CardioMEMS could allow more remotely delivered care, which would reduce patients' travel burden.[213] Consequently, the shift to remote care would change the type of resources that HF clinics need and require clinics to have or add telehealth capability, this clinical expert remarked.[213] Another clinical expert noted that patients will need to learn to "trust" the device, because it will provide clinicians with data they will use to inform changes in treatment before overt symptoms develop. "This may be difficult for some patients, but I wouldn't expect a large disruption here."[212]

Health disparities: The CardioMEMS device might have a small to moderate effect on health care disparities, the experts thought. Several experts opined that the device might reduce disparities for rural patients or others with more difficulty visiting HF clinics for followup visits. However, the device could actually increase disparities for many patients because many insurance plans do not cover the technology, several experts acknowledged.

Hypercholesterolemia Intervention

PCSK9 Inhibitors (Alirocumab [Praluent], Evolocumab [Repatha]) for Treatment of 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.[214-216] Additionally, some clinical indications, such as familial hypercholesterolemia (FH), are resistant to statins. In total, more than 6 million Americans (nearly 2% of the population) may have statin-resistant hypercholesterolemia.[217] For these patients, treatment alternatives, such as 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.[217]

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.[218] Hindering LDLR degradation is hypothesized to lower plasma low-density lipoprotein cholesterol (LDL-C) levels and improve health outcomes for patients with hypercholesterolemia indications.[219] 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.[219-221]

Alirocumab and evolocumab are both fully humanized monoclonal antibodies to PCSK9, developed as PCSK9 inhibitors for heritable and statin-resistant hypercholesterolemias.[221] Both are subcutaneously injected medications in preloaded syringe pens.[222,223] In FDA-approved labeling, alirocumab has a recommended starting dosage of 75 mg, administered once every 2 weeks; if response is inadequate, the dose may be increased to a maximum of 150 mg, every 2 weeks.[224] In FDA-approved labeling, evolocumab has a recommended dosage of 140 mg administered every 2 weeks or 420 mg administered once monthly (as 3 consecutive injections within 30 minutes) for primary hyperlipidemia with established clinical atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia (HeFH); the recommended evolocumab dosage for homozygous familial hypercholesterolemia (HoFH) is 420 mg administered once monthly.[225]

Clinical trials: In July 2015, Navarese and colleagues reported findings from a systematic review and meta-analysis of 24 phase II or III randomized, controlled trials that compared use of PCSK9 inhibitors with no PCSK9 inhibitors (placebo or ezetimibe) in 10,159 adults with hypercholesterolemia.[226] Trials included in the meta-analysis evaluated the PCSK9 inhibitors evolocumab, alirocumab, and bococizumab (in phase III development by Pfizer, Inc., New York, NY). PCSK9 inhibitor therapy demonstrated a mean reduction of 47.49% in LDL-C (95% CI, -69.64% to -25.35%; p<0.001). Further, PCSK9 inhibitor therapy reduced all-cause mortality (OR, 0.45; 95% CI, 0.23 to 0.86; p=0.015; heterogeneity p=0.63; I^2=0%) and cardiovascular mortality (OR, 0.50; 95% CI, 0.23 to 1.10; p=0.084; heterogeneity p=0.78; I^2=0%). Use of PCSK9 inhibitors significantly lowered the rate of myocardial infarction (OR, 0.49; 95% CI, 0.26 to 0.93; p=0.030; heterogeneity p=0.45; I^2=0%) and also lowered increases in serum creatine kinase levels (OR, 0.72; 95% CI, 0.54 to 0.96; p=0.026; heterogeneity p=0.65; I^2=0%). Use of PCSK9 inhibitors did not increase the incidence of serious adverse events.[226]

Alirocumab data collection continues in several ongoing phase III trials in the ODYSSEY study program, a series of short- and long-term studies enrolling patients with primary, heritable, and treatment-resistant hypercholesterolemias. Recently published trials comparing alirocumab to placebo or adding alirocumab to statins or other cholesterol-lowering agents (e.g., ezetimibe) have

reported that alirocumab lowered LDL-C levels about 40% to 60%.[227-231] 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.[232] 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).[233] 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.[222,232,234]

Additionally, ODYSSEY studies, including ODYSSEY Alternatives, Options I, and Options II, found that alirocumab was superior to statins and other standard therapies for lowering hypercholesterolemic patients' LDL-C levels.[231,235] 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 at reducing LDL-C (alirocumab, 50.6±1.4%; ezetimibe, 20.7±1.9%; difference, 29.8±2.3%; p<0.0001).[229] 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%).[229]

Evolocumab data collection continues in several ongoing phase III trials, including TAUSSIG, HAUSER, GLAGOV, OSLER, OSLER-2, EBBINGHAUS, and FOURIER. Evolocumab trials have evaluated treatment efficacy in patients with heritable hypercholesterolemia and across a series of large trials that enrolled patients with broad hypercholesterolemia indications. Recently published trials comparing evolocumab to placebo or adding evolocumab to statins or other cholesterol-lowering agents (e.g., ezetimibe) have reported that evolocumab offered additional lowering of LDL-C levels of about 30% to 60%.[236-239] In the phase II RUTHERFORD (n=147) and phase III RUTHERFORD-2 (n=331) studies, researchers found that within 12 weeks, biweekly or monthly evolocumab injections effectively lowered LDL-C levels in patients with heritable hypercholesterolemia.[237,240,241] 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.[239,242,243] 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).[243]

Overall, both PCSK9 inhibitors have been well tolerated; the most commonly observed adverse events across all studies are nasopharyngitis, injection-site reactions, and influenza.[237,244-246] Serious treatment-related adverse events were infrequent and, in most trials, occurred at rates similar to those observed for placebo or comparator drugs.[243,246] 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.[232,247,248]

Manufacturer and regulatory status: Regeneron Pharmaceuticals, Inc. (Tarrytown, NY), and Sanofi (Paris, France) jointly developed and manufacture alirocumab. In July 2015, FDA approved alirocumab, branded as Praluent™, as an adjunct to diet and maximally tolerated statin therapy for adults with HeFH or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.[224,249] The European Commission approved alirocumab in September 2015.[250]

Amgen, Inc. (Thousand Oaks, CA), developed and manufactures evolocumab. In August 2015, FDA approved evolocumab, branded as Repatha™, "as an adjunct to diet and:

- Maximally tolerated statin therapy for treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

- Other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C."

Diffusion: The drugs' high annual per-patient costs have generated spirited debate since they became commercially available. The annual wholesale acquisition costs in the United States are reportedly $14,600 for alirocumab and $14,100 for evolocumab.[251,252] In various European markets, evolocumab and alirocumab reportedly cost roughly 50% to 60% of the U.S. price.[253,254] As of December 2015, none of the manufacturers had announced detailed sales figures for either alirocumab or evolocumab. In a statement to investors about quarterly earnings, Sanofi reported €4 million ($4.4 million at December 15, 2015, exchange rates) in alirocumab sales for the third quarter 2015.[255] Some pharmaceutical industry analysts have reported that because of the high costs, physicians may hesitate to prescribe the drugs, as evidenced by 32% to 34% declines in new prescriptions written for evolocumab and alirocumab, respectively, in late November 2015 after previously steady increases since the drugs gained FDA approval in July and August 2015.[256] Pending safety and efficacy data are anticipated to result in expanded indications covering patients with primary statin-resistant hypercholesterolemia.[257]

Analysts previously predicted wide adoption of PCSK9 inhibitors based on preliminary cost estimates of $7,000 to $12,000 annually per patient, considerably lower than the drugs' actual U.S. wholesale costs.[257] In comparison, generic statins (e.g., atorvastatin) reportedly cost about $15 to $30 per month and brand-name statins (e.g., rosuvastatin [Crestor®]) reportedly cost about $150 to $225 per month at U.S. retail pharmacies.[258,259] Combination ezetimibe/atorvastatin (Liptruzet™) reportedly costs about $170 to $200 per month at U.S. retail pharmacies.[260] Thus, annual costs for these other drugs would be from $180 to $2,700.

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, pharmacy benefit manager (PBM) executives have stated plans to moderate PCSK9 inhibitor prices, with contrasting manufacturers' statements suggesting that pricing might be set by perceived treatment value and market tolerance.[261,262] Industry observers suggest that PCSK9-inhibitor cost-control measures could be similar to those employed for recently approved hepatitis C virus drugs; in those cases, PBMs established preferential formulary inclusions and omissions for competing drugs, based on manufacturer agreements to offer price discounts.[261] For more information on hepatitis C medication pricing, please refer to Chapter 9 of this report ("Infectious Disease Including HIV/AIDS"). In October 2015, PBM Express Scripts announced that it would include both alirocumab and evolocumab in its national preferred formulary.[263] In November 2015, CVS Health Corp. announced it had reached an exclusive deal with Amgen to provide evolocumab as the only PCSK9 inhibitor available through its PBM unit, although it has not disclosed details of the discount it negotiated with the pharmaceutical manufacturer.[256,264] According to the Boston Globe newspaper, Harvard Pilgrim Health Care reached a pay-for-performance agreement with Amgen to cover evolocumab in exchange for a discount, with the possibility of rebates if the drug does not meet certain performance targets.[265] ECRI Institute searches found that the private payers Aetna,[266] Anthem,[267] Blue Cross and Blue Shield of Alabama,[268,269] CIGNA,[270,271] HealthPartners,[272,273] Humana,[274] Medica,[275,276] and United Healthcare[277] all have reimbursement policies for alirocumab and evolocumab. The coverage criteria adhere to FDA-labeled indications and require prior authorization with additional requirements for coverage eligibility (e.g., documented diagnosis of HeFH or an existing cardiovascular disease, failure [defined as LDL-C >70 mg/dL] of two different treatment regimens).

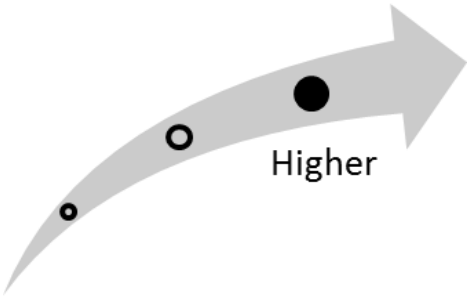
In November 2015, ICER published a cost-effectiveness model that projected PCSK9 inhibitors could cost the U.S. health care system $19 billion annually, if 25% of eligible patients were treated with the drugs at their list price, meaning that U.S. health care costs would increase by almost $100 billion over 5 years.[278] ICER also conducted a value-based benchmark analysis, concluding PCSK9 inhibitors should be priced at $2,177 per year, or at an 85% discount from the list price, to prove cost-effective and avoid excessive strain on the health care system.[278]

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, 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.[279] Surgical procedures including LDL apheresis and portacaval anastomosis (for HoFH) may also be indicated as late-line therapies for certain treatment-resistant cases.[279] Alirocumab and evolocumab are intended as alternative pharmacotherapies for these patients.

In 2013, FDA approved two other medications for high LDL-C levels, the adjunct drug lomitapide (Juxtapid®; Lojuxta®) and monotherapy mipomersen (Kynamro®), for treating heritable hypercholesterolemia.[280-282] Alirocumab and evolocumab are also alternate medications for patients with heritable hypercholesterolemia.

Figure 9. Overall high-impact potential: PCSK9 inhibitors (alirocumab [Praluent], evolocumab [Repatha]) for treatment of 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 desired long-term safety and efficacy data for both drugs. Experts did, however, note that some of these concerns may be adequately resolved by large ongoing studies. The majority of experts acknowledged PCSK9 inhibitors' significant potential economic impact, but considered potential cost-control 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 higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on alirocumab, and six experts, with similar backgrounds, offered perspectives on evolocumab.[283-294] Of these, three provided opinions for both interventions.[284,286,288,289,293,294] Please note that experts

provided comments before FDA approved the drugs in July and August 2015. 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.[292]

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 hesitate to adopt them when competing oral therapies are available.[289,290] 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 copayments are high.[283,287]

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 drugs' anticipated high cost, health disparities could be adversely affected if low-income individuals are unable to afford them.[285,291,294] 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.[285]

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.[295] 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.[295] 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.[296] An oral drug with a novel mechanism of action could provide these patients with an effective alternative to traditional medications.

Intervention: Administering 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' use. Additionally, prostacyclins can have adverse systemic effects (e.g., headache, flushing, diarrhea, jaw pain) in some patients.[296] 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.[296,297] In clinical trials, selexipag was administered as oral tablets at dosages between 200 and 1,600 mcg per day.[296,298]

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.[298] 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% (HR, 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.[298]

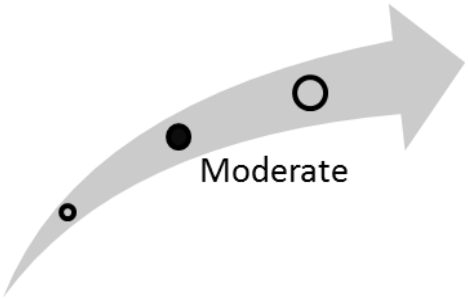
Manufacturer and regulatory status: Actelion Pharmaceuticals, Ltd. (Allschwil, Switzerland), has global development and commercialization rights for selexipag. Actelion acquired the rights from Nippon Shinyaku Co., Ltd., (Kyoto, Japan), which developed selexipag for treating PAH. In December 2014, Actelion submitted a new drug application to FDA for selexipag to treat PAH, supported by data from the GRIPHON study. FDA approved the drug December 18, 2015.[299] Actelion also submitted a marketing authorization application to the European Medicines Agency in December 2014 and submission of the registration dossier to other Health Authorities is ongoing with regulatory reviews under way in Australia, Canada, New Zealand, South Korea, Switzerland, and Taiwan.[297]

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. One recently approved oral PAH treatment, riociguat (Adempas®), reportedly costs up to $8,900 for 90 tablets (i.e., a typical 30-day supply) of each available dosage.[300] 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.[301] 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.[302]

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 surgery, including heart or heart-lung transplantation and atrial septostomy (in which a hole is created between the heart's top two chambers).[303] Selexipag would be another oral prostaglandin option in managing PAH.

Figure 10. 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 because of positive data for key outcomes, 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 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 moderate range 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.[304-310] 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. A clinical expert noted an unmet need in a subgroup of patients already on endothelin receptor antagonists and/or PDE-5 inhibitors but who need an additional oral drug, especially one with a unique mechanism of

action. This expert said, "This drug will fit in that niche."[305] Most experts expected selexipag to offer improved outcomes because of the endpoints reported in the GRIPHON study.

All experts cited the 40% decrease in morbidity and mortality reported in the GRIPHON study as a key differentiator encouraging selexipag use. One clinical expert said, "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!"[305]

Acceptance and adoption: Wide acceptance by physicians is likely because of selexipag's perceived improved efficacy and ease of use as an oral drug, 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 noted that long-term data still are not available.

Likewise, patients would welcome selexipag because they could avoid injectable forms of prostacyclin analogues, provided they can access the drug, the experts thought. Experts anticipated that although selexipag would be costly, cost would likely be comparable to other available PAH treatments. Thus, selexipag might have a moderate impact on treatment costs. One clinical expert thought that selexipag use could lead to fewer hospitalizations, lowering somewhat overall costs to the health care system.[304]

Health care delivery infrastructure and patient management: Experts expected that selexipag's use 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 would free up nursing resources now used to teach patients how to administer prostacyclins.[304]

Likewise, most experts did not expect the use of selexipag to substantially change the way PAH is managed in most patients. Experts noted as disruptors a need for prior authorization from third-party payers and a smaller number of patients needing labor-intensive inhaled or IV medications.[305,310] Further, 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."[306]

Health disparities: Experts thought that the availability of another oral prostacyclin drug could theoretically improve access to treatment compared with 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.

Stroke Intervention

Mobile Units for Treatment of Stroke

Unmet need: Stroke is a leading cause of death in the United States, and ischemic stroke (caused by a blood clot) accounts for about 85% of all strokes.[311,312] One drug, tissue plasminogen activator (tPA), has long been approved for clot thrombolysis to restore brain circulation in ischemic stroke. To be used safely and effectively, tPA must be administered within 3–4.5 hours of stroke symptom onset. However, only 2% to 7% of patients experiencing an ischemic stroke receive tPA, primarily because of the time lapse between symptom onset and hospital presentation.[313,314] Reducing the time from symptom onset to ischemic stroke intervention remains a substantial unmet need. Mobile stroke units (MSUs) are intended to enable faster treatment for stroke.

Intervention: The MSU concept is intended to enable an onboard team, in consultation with a stroke neurologist through telemedicine, to diagnose stroke and deliver prompt treatment at the scene where the patient is first encountered.[315] Not all MSUs are equipped to operate exactly the same way. As of December 2015, two MSU programs were operating in the United States. Other configurations may be developed as programs expand. Generally, MSUs are emergency response vehicles retrofitted with the equipment, medicine, and on-scene and remote personnel who communicate through telemedicine technology and have appropriate knowledge to recognize, distinguish, and treat different types of stroke before the patient reaches a hospital for further treatment. About 85% of strokes are ischemic, and MSUs focus on giving these patients tPA treatment within 3–4.5 hours of symptom onset, before they reach the hospital.[315]

MSU equipment to enable emergency treatment for stroke at the patient scene includes a portable computed tomography (CT) scanner, tPA with infusion lines, mobile blood lab, telemedicine equipment including broadband access, and other medical equipment commonly found in an ambulance.[315] Thus, tests using CT and bloodwork can be performed by the MSU before transport to the hospital. Remote clinicians use telemedicine technology to see and hear the patient, consult with first responders, and view test results. If appropriate, tPA treatment is initiated before transport, and infusion continues during the drive. Patients with confirmed strokes are transported to a stroke center while others may be transported to the closest emergency center. The receiving hospital must be notified before a patient experiencing a stroke arrives, to activate its stroke response team.[316]

MSU staff may include a paramedic, emergency medical services (EMS) driver, critical care nurse, CT technologist, and a vascular neurologist either in person or through telemedicine communication.[315] One MSU we identified includes a vascular neurologist onboard; however, this staffing scenario may not be cost-effective, and the program is intending to use only remote vascular neurologists in the future. One MSU program uses Google Glass (eyeglasses equipped with a computer and camera) worn by onboard personnel to transmit images (while their hands remain free) to remote clinicians.[317]

MSUs are integrated into a city's emergency dispatch and are sent in addition to EMS after the dispatcher determines that stroke-like symptoms are present.[315] If stroke is excluded as a possible cause, EMS may assume responsibility for care. One MSU program averages 1 tPA treatment per 10 MSU runs.[316] MSU teams may not always deliver tPA treatment to a stroke patient—it depends on the time from symptom onset (i.e., whether more than 4.5 hours) or on symptom presentation. If symptoms are too mild, the patient is too sick, or if the condition mimics hypoglycemia, seizure, migraine, or psychiatric problems, tPA may not be indicated.[316]

Although MSUs primarily target ischemic strokes, other stroke types may be treated. If the MSU team determines that the patient is experiencing a warfarin-related intracerebral hemorrhage, clinicians may administer a warfarin reversal drug.[318]

Clinical trials: In February 2015, Taqui and colleagues from Cleveland Clinic compared times to stroke treatment between MSUs (n=23 patients) and controls (i.e., traditional ambulances observed 3 months before MSU program initiation, n=34). MSUs arrived on the scene at a median of 13 minutes after alarm (interquartile range 9–17). The median alarm-to-CT-scan completion time was 41 minutes for MSUs and 62 minutes for controls ($p<0.0001$). Median alarm-to-thrombolysis times were 64 minutes for MSUs and 104 minutes for controls ($p<0.008$). Thrombolysis with tPA was delivered to 26% (6 of 23) of MSU patients and 14% (5 of 35) of control patients. Investigators reported no early complications from thrombolysis in the MSU group.[319]

In July 2015, Cerejo and colleagues reported on median treatment times for MSU patients (n=155) and historical controls transferred to the Cleveland Clinic for intraarterial thrombolysis (n=5), which included patients from previous research by Taqui and colleagues. After 164 days of service, the MSU had transported 155 patients, of whom 5 received intraarterial thrombolysis. MSUs showed shorter times than controls for several measures, including median door-to-initial CT scan, 12 versus 32 minutes; median CT-scan-to-intraarterial thrombolysis, 82 versus 165 minutes; and door to MSU/primary stroke center departure, 37 versus 106 minutes.[320]

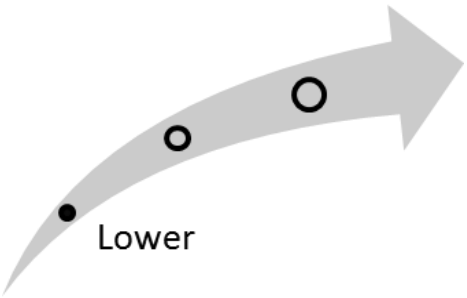
Program sponsors and regulatory status: As of December 2015, two MSU programs were operating in the United States. The first program started in May 2014 as a partnership between Memorial Hermann–Texas Medical Center (Houston), the University of Texas Health Science Center (Houston), and others. It operates 24 hours a day, 7 days a week within a limited area of Houston.[321] The second program was started in July 2014 at the Cleveland Clinic (Ohio) in partnership with MetroHealth Hospital (Cleveland, OH) and Cleveland Emergency Medical Services. It operates from 8 a.m. to 8 p.m. daily within a limited area of Cleveland.[322] The Cleveland Clinic may expand its program to Palm Beach County in Florida, where it has a comprehensive stroke center and satellite clinic.[323] The existing programs were modeled after the world's first MSU program, established at Charite University in Berlin, Germany, to serve rural populations.[315] A second program in Germany was established at the University Hospital of the Saarland (Homburg).[324]

Diffusion and costs: MSU programs have not yet diffused widely; as of December 2015, the Cleveland Clinic and Texas Medical Center at Houston were the only two MSUs known to exist in the United States. The estimated initial costs for retrofitting, equipping, and staffing an ambulance to become an MSU range from $600,000 to $1 million.[322,325] These costs include personnel and broadband coverage for telemedicine components. Equipment resupply, technology maintenance, and other costs are ongoing.[316] The Houston program estimated that its 5-year fixed and continuing costs are about $1.5 million based on 2–4 runs per day,[316] which corresponds to a per-patient cost of about $200 (4 MSU runs per day) to $400 (2 runs per day). Hospitals that have established MSU programs report having covered operational and capital costs largely through private donations. The Cleveland Clinic reportedly receives reimbursement from third-party payers for tPA administration in its MSU; however, the Memorial Hermann MSU reportedly does not.[326] It is unclear whether other services (e.g., blood test, CT scan) performed in the MSU are covered by third-party payers.

Clinical Pathway at Point of This Intervention

An MSU would be used in place of a conventional ambulance for patients with possible stroke for whom an emergency response team is summoned. MSUs would likely be affiliated with designated hospital stroke centers that use stroke-specific protocols, staff, and resources to improve door-to-needle times (i.e., from patient arrival at the hospital until the patient receives tPA).

Figure 11. Overall high-impact potential: mobile unit for treatment of stroke



Overall, based on current data, experts thought that MSUs' potential is more theoretical than actual at this time. Several experts noted that rural patients might have the greatest clinical improvement from MSU availability, but economic and logistic barriers would likely limit their use to larger metropolitan areas with good telemedicine connections and well-resourced hospitals and where most stroke care centers of excellence are concentrated. Clinical experts also called for additional research to evaluate whether the faster access to stroke thrombolysis offered by MSUs corresponds to lower stroke-related disability and higher survival. 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 technology.[327-332] One clinical expert reported a potential conflict of interest as a consultant on systems of care research for Medtronic Neurovascular. This expert's comments are balanced by comments from the other experts, who reported no potential conflicts of interest. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts generally acknowledged a large unmet need for improving treatment of ischemic stroke through efforts to expedite care. Further, most experts thought MSUs have theoretical potential to fill that unmet need, but that logistic and economic barriers could largely limit the practical application, thereby limiting their overall potential health benefit and ability to fill the large unmet need, the majority of experts concluded. Two clinical experts noted that the available studies did not report on whether faster times to treatment improved outcomes, such as stroke-related survival and disability.

Acceptance and adoption: Overall, experts anticipated moderate to good clinician acceptance and adoption, depending on the logistic and economic feasibility of MSU implementation in various geographical areas. They thought acceptance would be driven by a desire to get patients with stroke to treatment faster. From the patient perspective, experts acknowledged that patients generally don't electively choose their stroke care, but experts anticipated likely universal patient support for wider MSU availability if they were aware of it.

Health care delivery infrastructure and patient management: Experts were somewhat divided on the extent to which MSUs would disrupt health care infrastructure and patient management. The biggest effect of an MSU is to move technology from the hospital to the patient's location, they thought. One clinical expert stated a concern: "The lack of physicians at the bedside (if a telemedicine unit) as well as the pressure to treat rapidly may pose a barrier to explaining risks and benefits to family and patients [and] is something to consider."[331]

Health disparities: Several experts cited the MSU's theoretical potential to reduce disparities by expediting access to stroke treatment. Conversely, these experts also expressed concerns that the

introducing MSUs could actually increase disparities, albeit unintentionally. “This could make health disparities *worse*. Patients who have the least rapid access to acute stroke care are those in rural areas, which certainly will not get MSUs because of their low population density,” one clinical expert stated.[327]

References

1. Vanden Daelen S, Peetermans M, Vanassche T, et al. Monitoring and reversal strategies for new oral anticoagulants. Expert Rev Cardiovasc Ther. 2015 Jan;13(1):95-103. Also available: http://dx.doi.org/10.1586/14779072.2015.987126. PMID: 25431993.
2. Gomez-Outes A, Suarez-Gea ML, Lecumberri R, et al. Specific antidotes in development for reversal of novel anticoagulants: a review. Recent Pat Cardiovasc Drug Discov. 2014;9(1):2-10. PMID: 25494843.
3. Vilchez JA, Gallego P, Lip GY. Safety of new oral anticoagulant drugs: a perspective. Ther Adv Drug Saf. 2014 Feb;5(1):8-20. Also available: http://dx.doi.org/10.1177/2042098613507945. PMID: 25083259.
4. Andexanet alfa: FXa inhibitor antidote. [internet]. South San Francisco (CA): Portola Pharmaceuticals, Inc. [accessed 2015 Feb 20]. [3 p]. Available: http://www.portola.com/clinical-development/andexanet-alfa-prt4445-fxa-inhibitor-antidote/.
5. Crowther M, Lu G, Conley P, et al. Sustained reversal of apixaban anticoagulation with andexanet alfa using a bolus plus infusion regimen in a phase 2 placebo controlled trial. Eur Heart J. 2014 Sep 1;35(suppl 1):137. Also available: http://dx.doi.org/10.1093/eurheartj/ehu322.
6. Portola Pharmaceuticals announces phase 3 Annexa-A study of andexanet alfa and eliquis (apixaban) met primary and secondary endpoints with high statistical significance. [internet]. South San Francisco (CA): Portola Pharmaceuticals, Inc.; 2014 Oct 1 [accessed 2015 Feb 20]. [3 p]. Available: http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsroomArticle&ID=1972736.
7. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015 Nov 11:epub ahead of print. Also available: http://dx.doi.org/10.1056/NEJMoa1510991. PMID: 26559317.
8. Portola Pharmaceuticals. A study in patients with acute major bleeding to evaluate the ability of andexanet alfa to reverse the anticoagulation effect of direct and indirect oral anticoagulants. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Nov 12]. [5 p]. Available: https://clinicaltrials.gov/ct2/show/NCT02329327 NLM Identifier: NCT02329327.
9. Portola Pharmaceuticals announces commercial supply agreement for andexanet alfa with Lonza. [internet]. South San Francisco (CA): Portola Pharmaceuticals, Inc.; 2014 Oct 16 [accessed 2015 Feb 20]. [3 p]. Available: http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsroomArticle&ID=1978716.
10. Garrett AD. Factor Xa reversal agent designated breakthrough therapy. Drug Topics. 2014 Jan 10.
11. Portola Pharmaceuticals completes BLA submission to U.S. Food and Drug Administration for andexanet alfa. [internet]. South San Francisco (CA): Portola Pharmaceuticals, Inc.; 2015 Dec 18 [accessed 2015 Dec 22]. [2 p]. Available: http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsroomArticle&ID=2123971.
12. Pernod G, Albaladejo P, Godier A, et al. Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP) - March 2013. Arch Cardiovasc Dis. 2013 Jun-Jul;106(6-7):382-93. Also available: http://dx.doi.org/10.1016/j.acvd.2013.04.009. PMID: 23810130.
13. Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. Best Pract Res Clin Haematol. 2013 Jun;26(2):191-202. Also available: http://dx.doi.org/10.1016/j.beha.2013.07.001. PMID: 23953907.
14. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2083 - Andexanet alfa for reversal of factor Xa inhibitors. 2015 Apr 24 [review date].

15. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2083 - Andexanet alfa for reversal of factor Xa inhibitors. 2015 Apr 10 [review date].

16. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2083 - Andexanet alfa for reversal of factor Xa inhibitors. 2015 Apr 8 [review date].

17. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2083 - Andexanet alfa for reversal of factor Xa inhibitors. 2015 Apr 7 [review date].

18. Expert Commenter 278. (External, Clinical). Horizon Scanning Structured Comment Form. HS2083 - Andexanet alfa for reversal of factor Xa inhibitors. 2015 Apr 29 [review date].

19. Expert Commenter 1257. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS2083 - Andexanet alfa for reversal of factor Xa inhibitors. 2015 May 1 [review date].

20. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015 Aug 6;373(6):511-20. Also available: http://dx.doi.org/10.1056/NEJMoa1502000. PMID: 26095746.

21. Glund S, Stangier J, Schmohl M, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet. 2015 Aug 15;386(9994):680-90. Epub 2015 Jun 15. Also available: http://dx.doi.org/10.1016/S0140-6736(15)60732-2. PMID: 26088268.

22. Praxbind (idarucizumab) injection, for intravenous use prescribing information. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2015 Oct. 10 p. Also available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf.

23. FDA approves Praxbind (idarucizumab), specific reversal agent for Pradaxa (dabigatran etexilate). [internet]. Ingelheim (Germany): Boehringer Ingelheim GmbH; 2015 Oct 19 [accessed 2015 Oct 20]. [3 p]. Available: https://www.boehringer-ingelheim.com/news/news_releases/press_releases/2015/19_october_2015_dabigatranetexilate.html.

24. FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa. [internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2015 Oct 16 [accessed 2015 Oct 20]. [5 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm467300.htm.

25. Praxbind (idarucizumab) approved in European Union for the specific reversal of Pradaxa (dabigatran etexilate). [internet]. Ingleheim (Germany): Boehringer Ingelheim; 2015 Nov 26 [accessed 2015 Dec 02]. [4 p]. Available: https://www.boehringer-ingelheim.com/news/news_releases/press_releases/2015/26_november_2015_pradaxa.html.

26. Johnson SR. FDA approves drug to counter effect of blood thinner Pradaxa. [internet]. Chicago (IL): Modern Healthcare; 2015 Oct 16 [accessed 2015 Dec 02]. [7 p]. Available: http://www.modernhealthcare.com/article/20151016/NEWS/151019922.

27. Expert Commenter 1584. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS2135 - Idarucizumab for reversal of dabigatran-induced anticoagulation. 2015 Oct 12 [review date].

28. Expert Commenter 1649. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2135 - Idarucizumab for reversal of dabigatran-induced anticoagulation. 2015 Oct 2 [review date].

29. Expert Commenter 1473. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2135 - Idarucizumab for reversal of dabigatran-induced anticoagulation. 2015 Oct 7 [review date].

30. Expert Commenter 1026. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2135 - Idarucizumab for reversal of dabigatran-induced anticoagulation. 2015 Oct 21 [review date].

31. Expert Commenter 1573. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2135 - Idarucizumab for reversal of dabigatran-induced anticoagulation. 2015 Oct 2 [review date].

32. Expert Commenter 110. (External, Clinical). Horizon Scanning Structured Comment Form. HS2135 - Idarucizumab for reversal of dabigatran-induced anticoagulation. 2015 Sep 30 [review date].

33. Greenspon AJ, Patel JD, Lau E, et al. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. J Am Coll Cardiol. 2012 Oct 16;60(16):1540-5. Also available: http://dx.doi.org/10.1016/j.jacc.2012.07.017. PMID: 22999727.

34. Pakarinen S, Oikarinen L, Toivonen L. Short-term implantation-related complications of cardiac rhythm management device therapy: a retrospective single-centre 1-year survey. Europace. 2010 Jan;12(1):103-8. Also available: http://dx.doi.org/10.1093/europace/eup361. PMID: 19914920.

35. Borek PP, Wilkoff BL. Pacemaker and ICD leads: strategies for long-term management. J Interv Card Electrophysiol. 2008 Oct;23(1):59-72. Also available: http://dx.doi.org/10.1007/s10840-008-9249-7. PMID: 18392929.

36. Gul EE, Kayrak M. Chapter 16: Common pacemaker problems: lead and pocket complications. In: Das MK, editor. Modern pacemakers - present and future. Rijeka (Croatia): Intech; 2011 Feb 14. p. 22. Also available: http://www.intechopen.com/books/modern-pacemakers-present-and-future/common-pacemaker-problems-lead-and-pocket-complications.

37. Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. Circulation. 2007 Sep 18;116(12):1349-55. Also available: http://dx.doi.org/10.1161/CIRCULATIONAHA.106.678664. PMID: 17724263.

38. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Risk factors for lead complications in cardiac pacing: a population-based cohort study of 28,860 Danish patients. Heart Rhythm. 2011 Oct;8(10):1622-8. Also available: http://dx.doi.org/10.1016/j.hrthm.2011.04.014. PMID: 21699827.

39. Reddy VY, Knops RE, Sperzel J, et al. Permanent leadless cardiac pacing: results of the LEADLESS trial. Circulation. 2014 Apr 8;129(14):1466-71. Also available: http://dx.doi.org/10.1161/CIRCULATIONAHA.113.006987. PMID: 24664277.

40. Nanostim leadless pacemaker. [internet]. St. Paul (MN): St. Jude Medical, Inc.; 2014 Nov 11 [accessed 2015 Oct 09]. [2 p]. Available: https://professional-intl.sjm.com/products/crm/leadless-pacemakers/dual-and-single-chamber/nanostim#overview.

41. The Nanostim leadless pacemaker. St. Paul (MN): St. Jude Medical, Inc.; 2013. 6 p.

42. LEADLESS II trial results published in The New England Journal of Medicine confirm the positive benefits of the Nanostim leadless pacemaker. [internet]. St. Paul (MN): St. Jude Medical, Inc.; 2015 Aug 30 [accessed 2015 Oct 09]. [2 p]. Available: http://media.sjm.com/newsroom/news-releases/news-releases-details/2015/LEADLESS-II-Trial-Results-Published-in-The-New-England-Journal-of-Medicine-Confirm-the-Positive-Benefits-of-the-Nanostim-Leadless-Pacemaker/default.aspx.

43. Higgins SL, Rogers JD. Advances in pacing therapy: examining the potential impact of leadless pacing therapy. J Innov Cardiac Rhythm Manag. 2014 Nov. Also available: http://www.innovationsincrm.com/cardiac-rhythm-management/2014/november/655-potential-impact-of-leadless-pacing-therapy.

44. Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. N Engl J Med. 2015 Sep 17;373(12):1125-35. Also available: http://dx.doi.org/10.1056/NEJMoa1507192.

45. Neuzil P, Reddy VY. Leadless cardiac pacemakers: pacing paradigm change. Curr Cardiol Rep. 2015 Aug;17(8):68. Erratum in: Curr Cardiol Rep. 2015 Nov;17(11):97. Also available: http://dx.doi.org/10.1007/s11886-015-0619-3.

46. Health Policy Advisory Committee on Technology. Technology brief: leadless pacemaker. Brisbane (Australia): Department of Health, Queensland; 2015 Jul. 14 p. Also available: https://www.health.qld.gov.au/healthpact/docs/briefs/WP222.pdf.

47. St. Jude Medical announces start of European post-approval trial for Nanostim leadless pacemaker. [internet]. St. Paul (MN): St. Jude Medical, Inc.; 2014 Mar 18 [accessed 2015 Oct 09]. [2 p]. Available: http://media.sjm.com/newsroom/news-releases/news-releases-details/2014/St-Jude-Medical-Announces-Start-of-European-Post-Approval-Trial-for-Nanostim-Leadless-Pacemaker03182014/default.aspx.

48. Ritter P, Duray GZ, Steinwender C, et al. Early performance of a miniaturized leadless cardiac pacemaker: the Micra Transcatheter Pacing Study. Eur Heart J. 2015 Oct 1;36(37):2510-9. Also available: http://dx.doi.org/10.1093/eurheartj/ehv214. PMID: 26045305.

49. PriceGuide [database online]. Plymouth Meeting (PA): ECRI Institute [accessed 2015 Oct 08]. Leadless pacemakers. [1 p]. Available: http://www.ecri.org.

50. Mayo Clinic staff. Bradycardia. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2014 May 7 [accessed 2015 Oct 15]. [8 p]. Available: http://www.mayoclinic.org/diseases-conditions/bradycardia/basics/definition/con-20028373?p=1.

51. Causes and risk factors. [internet]. Marlborough (MA): Boston Scientific [accessed 2015 Oct 15]. [6 p]. Available: http://www.bostonscientific.com/en-US/health-conditions/bradycardia/Causes-and-Risk-Factors.html.

52. Bradycardia - slow heart rate. [internet]. Dallas (TX): American Heart Association (AHA) [accessed 2015 Oct 15]. [2 p]. Available: http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/Bradycardia-Slow-Heart-Rate_UCM_302016_Article.jsp#.Vh_v_GaFOUl.

53. Knops RE, Tjong FV, Neuzil P, et al. Chronic performance of a leadless cardiac pacemaker: 1-year follow-up of the LEADLESS trial. J Am Coll Cardiol. 2015 Apr 21;65(15):1497-504. Also available: http://dx.doi.org/10.1016/j.jacc.2015.02.022. PMID: 25881930.

54. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2074 - Leadless pacemaker (Nanostim) for treatment of bradycardia. 2015 Nov 12 [review date].

55. Expert Commenter 1561. (External, Clinical). Horizon Scanning Structured Comment Form. HS2074 - Leadless pacemaker (Nanostim) for treatment of bradycardia. 2015 Nov 9 [review date].

56. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2074 - Leadless pacemaker (Nanostim) for treatment of bradycardia. 2015 Nov 11 [review date].

57. Expert Commenter 1473. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2074 - Leadless pacemaker (Nanostim) for treatment of bradycardia. 2015 Nov 10 [review date].

58. Expert Commenter 1384. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2074 - Cabozantinib (Cometriq) for treatment of renal cell carcinoma. 2015 Nov 11 [review date].

59. Expert Commenter 1561. (External, Clinical). Horizon Scanning Structured Comment Form. HS2074 - Leadless pacemaker (Nanostim) for treatment of bradycardia. 2015 Nov 16 [review date].

60. Expert Commenter 769. (External, Clinical). Horizon Scanning Structured Comment Form. HS2074 - Leadless pacemaker (Nanostim) for treatment of bradycardia. 2015 Nov 10 [review date].

61. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. Circulation. 2015 Jan 27;131(4):e29-322. Also available: http://dx.doi.org/10.1161/CIR.0000000000000152. PMID: 25520374.

62. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239. PMID: 23747642.

63. SynCardia Systems. CardioWest total artificial heart (TAH): directions for use. Tucson (AZ): SynCardia Systems, Inc.; 28 p.

64. SynCardia Systems, Inc. SynCardia freedom driver system study. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Dec 13]. [3 p]. Available: http://www.clinicaltrials.gov/ct2/show/NCT00733447 NLM Identifier: NCT00733447.

65. Clinical trials: the Freedom driver system. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 09]. [3 p]. Available: http://www.syncardia.com/medical-professionals/clinical-trials.html.

66. Total artificial heart facts. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 09]. [2 p]. Available: http://www.syncardia.com/total-facts/total-artificial-heart-facts.html.

67. Reliability second to none. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 09]. [1 p]. Available: http://www.syncardia.com/Medical-Professionals/reliability-second-to-none.html.

68. University of Washington leads all SynCardia certified centers with 10 implants of the total artificial heart in 2012. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2012 Dec 06 [accessed 2012 Dec 13]. [3 p]. Available: http://www.syncardia.com/2012-Press-Releases/university-of-washington-leads-all-syncardia-certified-centers-with-10-implants-of-the-total-artificial-heart-in-2012.html.

69. Arabia F, Moriguchi J, Jocson R, et al. Freedom driver with the total artificial heart: a single center experience. Transplantation. 2014 Jul 28;(Abstract B1236):422.

70. FDA approves the Freedom portable driver that powers the SynCardia total artificial heart. [internet]. Tuscon (AZ): SynCardia Systems, Inc.; 2014 Jul 16 [accessed 2014 Dec 10]. [2 p]. Available: http://www.syncardia.com/2014-multimedia-releases/fda-approves-the-freedom-portable-driver-that-powers-the-syncardia-total-artificial-heart/itemid-1704.html.

71. Demondion P, Fournel L, Niculescu M, et al. The challenge of home discharge with a total artificial heart: the La Pitie Salpetriere experience. Eur J Cardiothorac Surg. 2013 Nov;44(5):843-8. Also available: http://dx.doi.org/10.1093/ejcts/ezt146. PMID: 23539421.

72. Shah KB, Volman RA, Harton SC, et al. Perforation of the pneumatic driveline in patients converted to a portable driver for the total artificial heart [abstract 125]. J Heart Lung Transplant. 2013 Apr;32(4 Suppl 1):S54.

73. Freedom driver system receives CE mark to power SynCardia's total artificial heart in Europe. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2010 Mar 04 [accessed 2010 Mar 04]. [1 p]. Available: http://www.syncardia.com/2010-Press-Release/freedom-driver-system-receives-ce-mark-to-power-syncardias-total-artificial-heart-in-europe.html.

74. 510(k) summary of safety and effectiveness data. CardioWest temporary total artificial heart. Rockville (MD): U.S. Food and Drug Administration (FDA); 2004 Oct 15. 28 p. Also available: http://www.fda.gov.

75. Freedom Driver System by SynCardia: Class I Recall - part may fail causing device to stop working. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Sep 18 [accessed 2015 Dec 14]. [3 p]. Available: http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm463318.htm.

76. SynCardia provides update regarding voluntary recall of potentially affected Freedom portable drivers. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2015 Sep 22 [accessed 2015 Dec 14]. [2 p]. Available: http://www.syncardia.com/2015-press-releases/syncardia-provides-update-regarding-voluntary-recall-of-potentially-affected-freedom-portable-drivers/itemid-1736.html.

77. The manufacturer of the SynCardia total artificial heart has hired investment bank Canaccord Genuity, Inc. to advise the BOD on strategic alternatives to maximize stakeholder equity. [internet]. Tucson (AZ): SynCardia Systems, Inc; 2015 Nov 4 [accessed 2015 Dec 03]. [2 p]. Available: http://www.syncardia.com/2015-press-releases/the-manufacturer-of-the-syncardia-total-artificial-heart-has-hired-investment-bank-canaccord-genuity-inc-to-advise-the-bod-on-strategic-alternatives-to-maximize-stakeholder-equity/itemid-1736.html.

78. PriceGuide [database online]. Plymouth Meeting (PA): ECRI Institute [accessed 2015 Apr 07]. PriceGuide [Total Artificial Heart]. [1 p]. Available: http://www.ecri.org.

79. PricePaid [database online]. Plymouth Meeting (PA): ECRI Institute [accessed 2013 Jul 25]. Total artificial heart - PricePoints. July 2010-July 2013. [1 p]. Available: http://www.ecri.org.

80. Ashton J. Man goes home with "total artificial heart". [internet]. New York (NY): CBS News; 2010 May 22 [accessed 2012 Dec 13]. [3 p]. Available: http://www.cbsnews.com/8301-18563_162-6507572.html.

81. Baier E. Man receives first artificial and portable heart in Minn. [internet]. Saint Paul (MN): Minnesota Public Radio; 2012 Apr 12 [accessed 2012 Dec 13]. [3 p]. Available: http://minnesota.publicradio.org/display/web/2012/04/12/michigan-man-receives-first-artificial-heart-in-minnesota/.

82. Expert Commenter 41. (External, Clinical). Horizon Scanning Structured Comment Form. HS334 - Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation. 2015 Apr 20 [review date].

83. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS334 - Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation. 2015 Apr 21 [review date].

84. Expert Commenter 399. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS334 - Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation. 2015 Apr 27 [review date].

85. Expert Commenter 334. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS334 - Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation. 2015 May 5 [review date].

86. Expert Commenter 1550. (External, Clinical). Horizon Scanning Structured Comment Form. HS334 - Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation. 2015 May 4 [review date].

87. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS334 - Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation. 2015 Apr 17 [review date].

88. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Oct 15;128(16):e240-327. Also available: http://dx.doi.org/10.1161/CIR.0b013e31829e8776. PMID: 23741058.

89. How is heart failure treated? [internet]. Bethesda (MD): National Heart, Lung, and Blood Institute, National Institutes of Health [accessed 2011 Mar 10]. [4 p]. Available: http://www.nhlbi.nih.gov/health/dci/Diseases/Hf/HF_Treatments.html.

90. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J. 2005 Jun;26(11):1115-40. PMID: 15901669.

91. Deedwania P. Selective and specific inhibition of If with ivabradine for the treatment of coronary artery disease or heart failure. Drugs. 2013 Sep;73(14):1569-86. Also available: http://dx.doi.org/10.1007/s40265-013-0117-0. PMID: 24065301.

92. Rognoni A, Bertolazzi M, Maccio S, et al. Ivabradine: cardiovascular effects. Recent Pat Cardiovasc Drug Discov. 2009 Jan;4(1):61-6. PMID: 19149708.

93. Rosa GM, Ferrero S, Ghione P, et al. An evaluation of the pharmacokinetics and pharmacodynamics of ivabradine for the treatment of heart failure. Expert Opin Drug Metab Toxicol. 2014 Feb;10(2):279-91. Also available: http://dx.doi.org/10.1517/17425255.2014.876005. PMID: 24377458.

94. Rushworth GF, Lambrakis P, Leslie SJ. Ivabradine: a new rate-limiting therapy for coronary artery disease and heart failure. Ther Adv Drug Saf. 2011 Feb;2(1):19-28. Also available: http://dx.doi.org/10.1177/2042098610393209. PMID: 25083199.

95. Su JB. Cardioprotective effects of the ?f current inhibition by ivabradine during cardiac dysfunction. Curr Pharm Biotechnol. 2014;14(14):1213-9. PMID: 24831809.

96. FDA approves Corlanor (ivabradine) to reduce the risk of hospitalization for worsening heart failure in patients with chronic heart failure. [internet]. Thousand Oaks (CA): Amgen; 2015 Apr 15 [accessed 2015 Apr 16]. [4 p]. Available: http://www.amgen.com/media/media_pr_detail.jsp?releaseID=2035505.

97. Hardman SMC. Ivabradine in heart failure: NICE guidance. Heart. 2014 Jan;100(2):93-5. Also available: http://dx.doi.org/10.1136/heartjnl-2012-303490. PMID: 23781111.

98. National Institute for Health and Clinical Excellence (NICE). Ivabradine for treating chronic heart failure. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Nov. 49 p. (Technology appraisal guidance; no.267).

99. European Medicines Agency recommends measures to reduce risk of heart problems with Corlentor/Procoralan (ivabradine). [internet]. London (UK): European Medicines Agency; 2014 Nov 21 [accessed 2015 Feb 18]. [4 p]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/11/WC500177591.pdf.

100. FDA grants Amgen priority review designation for ivabradine for the treatment of chronic heart failure. [internet]. Thousand Oaks (CA): Amgen Inc.; 2014 Aug 27 [accessed 2015 Feb 18]. [3 p]. Available: http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1961392.

101. Bohm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol. 2013 Jan;102(1):11-22. Also available: http://dx.doi.org/10.1007/s00392-012-0467-8. PMID: 22575988.

102. Komajda M, Tavazzi L, Swedberg K, et al. Clinical profiles and outcomes of patients with chronic heart failure and diabetes: Efficacy and safety of ivabradine. A shift study analysis. Eur J Heart Fail. 2014;16(Suppl 2):42.

103. Griffiths A, Paracha N, Branscombe N, et al. An analysis of eq-5d quality of life data for a cost-effectiveness analysis of ivabradine plus standard care versus standard care alone in chronic HF. Value Health. 2013;16(7):A533.

104. Tavazzi L, Swedberg K, Komajda M, et al. Clinical profiles and outcomes of patients with chronic heart failure and chronic obstructive pulmonary disease: Efficacy and safety of Ivabradine. A SHIFT study analysis. Eur Heart J. 2013;34(Suppl 1):652.

105. Glezer MG. LINCOR study: Ivabradine improves quality of life of post myocardial infarction (less than 12 months ago) patients with chronic heart failure. Eur J Heart Fail. 2014;16(Suppl 2):64.

106. Kozan O, Cavusoglu Y, Kucukoglu S, et al. Ivabradine adding on beta blocker based strategy provides better heart rate lowering than beta blocker alone based strategy in real life clinical practice: An analysis from REALITY HF study. Eur Heart J. 2014;35(Suppl 1):693.

107. Mareev V. Ivabradin in treatment of patients with ischemic heart failure, sinus rhythm and different LVEF in real clinical practice. Eur J Heart Fail. 2014;16(Suppl 2):160.

108. Les Laboratoires Servier. Summary of product characteristics. Brussels (Belgium): Les Laboratoires Servier; 39 p. Also available: http://www.servier.com/sites/default/files/SPC_Procoralan_012015_0.pdf.

109. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014 Sep 18;371(12):1091-9. Also available: http://dx.doi.org/10.1056/NEJMoa1406430. PMID: 25176136.

110. Zugck C, Martinka P, Stockl G. Ivabradine treatment in a chronic heart failure patient cohort: symptom reduction and improvement in quality of life in clinical practice. Adv Ther. 2014 Sep;31(9):961-74. Also available: http://dx.doi.org/10.1007/s12325-014-0147-3. PMID: 25160945.

111. Amgen statement on FDA fast track designation for investigational ivabradine for chronic heart failure. [internet]. Thousand Oaks (CA): Amgen Inc. [accessed 2015 Feb 18]. [2 p]. Available: http://www.amgen.com/media/fda_fast_track_ivabradine.html.

112. FDA approves Corlanor to treat heart failure. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Apr 15 [accessed 2015 May 27]. [5 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm442978.htm.

113. Institut de Recherches Internationales Servier. Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study [ISRCTN70429960]. In: ISRCTN Registry [database online]. London (UK): BioMed Central; 2014 Aug 13 [accessed 2015 Feb 18]. [10 p]. Available: http://www.isrctn.com/ISRCTN70429960.

114. Corlanor pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 03]. [10 p]. Available: http://www.goodrx.com/corlanor.

115. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS124 - Ivabradine (Corlanor) for treatment of heart failure. 2015 Apr 24 [review date].

116. Expert Commenter 167. (External, Clinical). Horizon Scanning Structured Comment Form. HS124 - Ivabradine (Corlanor) for treatment of heart failure. 2015 Apr 22 [review date].

117. Expert Commenter 1546. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS124 - Ivabradine (Corlanor) for treatment of heart failure. 2015 Apr 27 [review date].

118. Expert Commenter 1473. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS124 - Ivabradine (Corlanor) for treatment of heart failure. 2015 Apr 27 [review date].

119. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS124 - Ivabradine (Corlanor) for treatment of heart failure. 2015 Apr 30 [review date].

120. Expert Commenter 1241. (External, Clinical). Horizon Scanning Structured Comment Form. HS124 - Ivabradine (Corlanor) for treatment of heart failure. 2015 Apr 27 [review date].

121. Khush KK, Zaroff JG, Nguyen J, et al. National decline in donor heart utilization with regional variability: 1995-2010. Am J Transplant. 2015 Feb 10:1-8. Also available: http://onlinelibrary.wiley.com/enhanced/doi/10.1111/ajt.13055/.

122. U.S. Organ Procurement and Transplantation Network (OPTN). Organ Procurement and Transplantation Network home page. [internet]. Washington (D.C.): U.S. Organ Procurement and Transplantation Network (OPTN), U.S. Department of Health and Human Services (HHS); [accessed 2013 Sep 05]. [2 p]. Available: http://optn.transplant.hrsa.gov/.

123. Colvin-Adams M, Smithy JM, Heubner BM, et al. OPTN/SRTR 2012 annual data report: heart. Am J Transplant. 2014 Jan;14 Suppl 1:113-38. Also available: http://dx.doi.org/10.1111/ajt.12583. PMID: 24373170.

124. United Network for Organ Sharing (UNOS). Organ procurement and transplantation network: data. [internet]. Rockville (MD): Health Resources and Services Administration (HRSA) [accessed 2015 May 26]. [5 p]. Available: http://optn.transplant.hrsa.gov/converge/data/.

125. Frequently asked questions. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [2 p]. Available: http://www.transmedics.com/wt/page/faq.

126. Guibert EE, Petrenko AY, Balaban CL, et al. Organ preservation: current concepts and new strategies for the next decade. Transfus Med Hemother. 2011;38(2):125-42. Also available: http://dx.doi.org/10.1159/000327033. PMID: 21566713.

127. TransMedics. Randomized study of organ care system cardiac for preservation of donated hearts for eventual transplantation (PROCEEDII). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Jan 28]. [5 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT00855712 NLM Identifier: NCT00855712.

128. Stern DR. Heart preservation. In: Medscape Reference [internet]. New York (NY): WebMD LLC; 2014 Mar 21 [accessed 2015 Feb 03]. [8 p]. Available: http://emedicine.medscape.com/article/1012217-overview.

129. Corporate information. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [2 p]. Available: http://www.transmedics.com/wt/page/corporate.

130. OCS heart is designed to improve patient outcomes. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [1 p]. Available: http://www.transmedics.com/wt/page/ocsheart_improve_outcomes_med.

131. Organ care system. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [2 p]. Available: http://www.transmedics.com/wt/page/organ_care.

132. How it works. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [1 p]. Available: http://www.transmedics.com/wt/page/how_works.

133. Key advantages. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [1 p]. Available: http://www.transmedics.com/wt/page/advantages.

134. OCS heart is designed to increase transplant volume. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [1 p]. Available: http://www.transmedics.com/wt/page/ocsheart_increase_volume_med.

135. More heart transplants and better outcomes reduce cost of patient care. [internet]. Andover (MA): TransMedics, Inc. [accessed 2015 Jan 22]. [1 p]. Available: http://www.transmedics.com/wt/page/ocsheart_reduce_cost_med.

136. Ardehali A, Esmailian F, Deng M, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet. 2015 Jun 27;385(9987):2577-84. Epub 2015 Apr 14. Also available: http://dx.doi.org/10.1016/S0140-6736(15)60261-6. PMID: 25888086.

137. Dhital KK, Iyer A, Connellan M, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. Lancet. 2015 Jun 27;385(9987):2585-91. Epub 2015 Apr 14. Also available: http://dx.doi.org/10.1016/S0140-6736(15)60038-1. PMID: 25888085.

138. Concurrent oral sessions: heart. Transplantation. 2014 Jul 15;98 Suppl 1:51-60. Also available: http://dx.doi.org/10.1097/01.tp.0000452120.66974.92. PMID: 24978177.

139. Koerner MM, Ghodsizad A, Schulz U, et al. Normothermic ex vivo allograft blood perfusion in clinical heart transplantation. Heart Surg Forum. 2014 Jun;17(3):E141-5. Also available: http://dx.doi.org/10.1532/HSF98.2014332. PMID: 25002389.

140. November 18, 2015 meeting is CANCELLED and the November 19, 2015 is POSTPONED: Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee Meeting Announcement. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Nov 2 [accessed 2015 Dec 03]. [6 p]. Available: http://www.fda.gov/advisorycommittees/calendar/ucm465584.htm.

141. Helman S. Is this the next big leap for organ transplants? [internet]. Boston (MA): Boston Globe Media Partners LLC; 2014 Aug 10 [accessed 2015 Feb 11]. [13 p]. Available: http://www.bostonglobe.com/magazine/2014/08/09/this-next-big-leap-for-organ-transplants/5AGyD8UCgT7YCafkbtzkkM/story.html.

142. PricePaid [database online]. Plymouth Meeting (PA): ECRI Institute [accessed 2014 Aug 25]. PricePaid search summary: OCS lung. [1 p]. Available: http://www.ecri.org.

143. Beswick N. The TransMedics organ care system (OCS) heart technology was used to perform the world's first series of adult human heart transplants from donors after circulatory death (DCD donors) at St. Vincent's hospital in Sydney, Australia. [internet]. Andover (MA): TransMedics, Inc.; 2014 Oct 24 [accessed 2015 Jan 22]. [2 p]. Available: http://www.transmedics.com/wt/page/pr_1414117691.

144. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1366 - Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation. 2015 Mar 4 [review date].

145. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1366 - Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation. 2015 Mar 2 [review date].

146. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1366 - Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation. 2015 Mar 6 [review date].

147. Expert Commenter 399. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1366 - Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation. 2015 Mar 13 [review date].

148. Expert Commenter 167. (External, Clinical). Horizon Scanning Structured Comment Form. HS1366 - Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation. 2015 Mar 24 [review date].

149. Expert Commenter 110. (External, Clinical). Horizon Scanning Structured Comment Form. HS1366 - Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation. 2015 Mar 24 [review date].

150. Vardeny O, Tacheny T, Solomon SD. First-in-class angiotensin receptor neprilysin inhibitor in heart failure. Clin Pharmacol Ther. 2013 Oct;94(4):445-8. Also available: http://dx.doi.org/10.1038/clpt.2013.146. PMID: 23872864.

151. Voors AA, Dorhout B, Van Der Meer P. The potential role of valsartan + AHU377 (LCZ696) in the treatment of heart failure. Expert Opin Investig Drugs. 2013 Aug;22(8):1041-7. Also available: http://dx.doi.org/10.1517/13543784.2013.797963. PMID: 23663006.

152. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase II randomised controlled trial. J Card Fail. 2012 Nov;18(11):883. Also available: http://www.onlinejcf.com/article/S1071-9164(12)01283-3/fulltext.

153. Vardeny O, Skali H, Jhund P, et al. Influence of diabetes mellitus on cardiac structure and function and response to therapy with LCZ696 in heart failure with preserved ejection fraction [abstract 096]. J Card Fail. 2014 Aug;20(8 Suppl):S40. Also available: http://dx.doi.org/10.1016/j.cardfail.2014.06.114.

154. von Lueder TG, Wang BH, Kompa AR, et al. The angiotensin-receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. Circ Heart Fail. 2015 Jan;8(1):71-8. Also available: http://dx.doi.org/10.1161/CIRCHEARTFAILURE.114.001785. PMID: 25362207.

155. Novartis Pharmaceuticals. Efficacy and safety of LCZ696 compared to Valsartan, on morbidity and mortality in heart failure patients with preserved ejection fraction (PARAGON-HF). In: ClinicalTrials.gov [database online]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 Mar 06]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT01920711 NLM Identifier: NCT01920711.

156. Jessup M, Fox KA, Komajda M, et al. PARADIGM-HF--the experts' discussion. N Engl J Med. 2014 Sep 11;371(11):e15. Also available: http://dx.doi.org/10.1056/NEJMp1410203. PMID: 25184757.

157. Entresto (sacubitril and valsartan) tablets, for oral use prescribing info. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2015 Jul. 18 p. Also available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207620Orig1s000lbl.pdf.

158. PARADIGM-HF trial of Novartis' LCZ696 for chronic heart failure closes early based on strength of interim results. [internet]. Basel (Switzerland): Novartis International AG; 2014 Mar 31 [accessed 2015 Mar 06]. [4 p]. Available: http://www.novartis.com/newsroom/media-releases/en/2014/1772754.shtml.

159. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep 11;371(11):993-1004. Also available: http://dx.doi.org/10.1056/NEJMoa1409077. PMID: 25176015.

160. Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation. 2015 Jan 6;131(1):54-61. Also available: http://dx.doi.org/10.1161/CIRCULATIONAHA.114.013748. PMID: 25403646.

161. Vodovar N, Paquet C, Mebazaa A, et al. Neprilysin, cardiovascular, and Alzheimer's diseases: the therapeutic split? Eur Heart J. 2015 Apr 14;36(15):902-5. Epub 2015 Jan 29. Also available: http://dx.doi.org/10.1093/eurheartj/ehv015. PMID: 25636748.

162. Solomon SD, Packer M, Zile M, et al. Reduction in 30-day rehospitalization after discharge from a heart failure admission in patients receiving LCZ696 versus Enalapril: PARADIGM-HF. Circulation. 2015;132:A17955.

163. Novartis heart failure medicine Entresto substantially cuts 30-day hospital readmissions, new post-hoc analysis shows. [internet]. East Honover (NJ): Novartis Pharmaceuticals Corporation; 2015 Nov 10 [accessed 2015 Dec 03]. [9 p]. Available: http://www.prnewswire.com/news-releases/novartis-heart-failure-medicine-entresto-substantially-cuts-30-day-hospital-readmissions-new-post-hoc-analysis-shows-300176067.html.

164. FDA approves new drug to treat heart failure. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Jul 7 [accessed 2015 Nov 12]. [3 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453845.htm.

165. Novartis' heart failure medicine Entresto receives EU approval. [internet]. Basel (Switzerland): Novartis; 2015 Nov 24 [accessed 2015 Dec 03]. [6 p]. Available: https://www.novartis.com/news/media-releases/novartis-heart-failure-medicine-entrestotm-receives-eu-approval.

166. Entresto pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Nov 12]. [9 p]. Available: http://www.goodrx.com/entresto?form=tablet&dosage=97mg-103mg&quantity=60&label_override=Entresto.

167. Hopes build for new Novartis heart failure drug. [internet]. New York (NY): Thomson Reuters; 2014 Aug 5 [accessed 2015 Mar 06]. [4 p]. Available: http://www.reuters.com/article/2014/08/05/novartis-heart-idUSL6N0QB2D320140805.

168. Pollack A. New Novartis drug effective in treating heart failure. [internet]. New York (NY): The New York Times Company; 2014 Aug 30 [accessed 2014 Sep 02]. [7 p]. Available: http://www.nytimes.com/2014/08/31/business/new-novartis-drug-shows-striking-efficacy-in-treating-heart-failure.html?_r=0.

169. CardioMEMS HF system (St. Jude Medical, Inc.) and sacubitril/valsartan (Entresto, Novartis AG) for management of congestive heart failure: effectiveness, value, and value-based price benchmarks. Boston (MA): Institute for Clinical and Economic Review; 2015 Dec 1. 139 p. Also available: http://ctaf.org/sites/default/files/u148/CHF_Final_Report_120115.pdf.

170. Mayo Clinic staff. Heart failure: treatments and drugs. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2009 Dec 23 [accessed 2011 Feb 09]. [4 p]. Available: http://www.mayoclinic.com/health/heart-failure/DS00061/DSECTION=treatments-and-drugs.

171. Ayalasomayajula S, Jordaan P, Pal P, et al. Assessment of drug interaction potential between LCZ696 and warfarin. Hypertension. 2013 Sep;62(3):A448.

172. Ayalasomayajula S, Jordaan P, Pal P, et al. Assessment of pharmacokinetic drug interaction between LCZ696 and digoxin. Hypertension. 2013 Sep;62(3):A449.

173. Hsiao HL, Greeley M, Pal P, et al. Assessment of pharmacokinetic drug-drug interaction between LCZ696 and hydrochlorothiazide. Hypertension. 2013 Sep;62(3):A455.

174. Expert Commenter 1241. (External, Clinical). Horizon Scanning Structured Comment Form. HS1947 - Angiotensin receptor neprilysin inhibitor (LCZ696) for treatment of heart failure. 2015 Apr 27 [review date].

175. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1947 - Angiotensin receptor neprilysin inhibitor (LCZ696) for treatment of heart failure. 2015 Apr 9 [review date].

176. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1947 - Angiotensin receptor neprilysin inhibitor (LCZ696) for treatment of heart failure. 2015 Apr 8 [review date].

177. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1947 - Angiotensin receptor neprilysin inhibitor (LCZ696) for treatment of heart failure. 2015 Mar 30 [review date].

178. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1947 - Angiotensin receptor neprilysin inhibitor (LCZ696) for treatment of heart failure. 2015 Mar 25 [review date].

179. Expert Commenter 167. (External, Clinical). Horizon Scanning Structured Comment Form. HS1947 - Angiotensin receptor neprilysin inhibitor (LCZ696) for treatment of heart failure. 2015 Apr 22 [review date].

180. Abraham WT. The role of implantable hemodynamic monitors to manage heart failure. Heart Fail Clin. 2015 Apr 1;11(2):183-9. Also available: http://dx.doi.org/10.1016/j.hfc.2014.12.011.

181. Heart Failure Society of America, Lindenfeld J, Albert NM, et al. Managing patients with hypertension and heart failure: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010 Jun;16(6):e166-8.

182. Pamboukian SV. The future of implantable hemodynamic monitors. Future Cardiol. 2007 Nov;3(6):579-82. Also available: http://www.futuremedicine.com/doi/pdfplus/10.2217/14796678.3.6.579. PMID: 19804276.

183. CardioMEMS HF system: PA sensor and delivery system. [internet]. St Paul (MN): St. Jude Medical, Inc. [accessed 2014 Aug 15]. [2 p]. Available: http://professional.sjm.com/~/media/pro/therapies/cardiomems/documents/CMEMS-PA-Sensor-and-Delivery-System-Catalog-Page-FINAL-v2-US-2000054BEN.ashx.

184. CardioMEMS, Inc. FDA executive summary: P100045 CardioMEMS Champion HF monitoring system. Rockville (MD): U.S. Food and Drug Administration (FDA); 2011 Dec 8. 55 p. Also available: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM282098.pdf.

185. CardioMEMS completes CHAMPION clinical trial study. [internet]. Atlanta (GA): CardioMEMS, Inc.; 2010 Jun 1 [accessed 2010 Oct 01]. [3 p]. Available: http://media.sjm.com/files/doc_news/media_kit/HeartFailure/2010/StJudeMedical_CardioMEMS%20Completes%20CHAMPION%20Clinical%20Trial%20Study.pdf.

186. FDA executive summary: CardioMEMS champion HF monitoring system - P100045/A004. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2013 Oct. 52 p. Also available: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM370689.pdf.

187. Abraham WT, Stevenson LW, Bourge RC, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet. 2015 Nov 6:Epub ahead of print. Also available: http://dx.doi.org/10.1016/S0140-6736(15)00723-0.

188. St. Jude Medical and CardioMEMS announce FDA approval of the CardioMEMS heart failure management system. [internet]. St. Paul (MN): St. Jude Medical, Inc.; 2014 May 28 [accessed 2014 May 29]. [3 p]. Available: http://media.sjm.com/newsroom/news-releases/news-releases-details/2014/St-Jude-Medical-and-CardioMEMS-Announce-FDA-Approval-of-the-CardioMEMS-Heart-Failure-Management-System/default.aspx.

189. Husten L. CardioMEMS heart failure device gets mixed reception from FDA advisory panel. [internet]. New York (NY): Forbes.com LLC; 2013 Oct 09 [accessed 2013 Oct 21]. [5 p]. Available: http://www.forbes.com/sites/larryhusten/2013/10/09/cardiomems-heart-failure-device-gets-mixed-reception-from-fda-advisory-panel/.

190. O'Riordan M. CardioMEMS HF implant narrowly passes FDA advisory hurdle. [internet]. New York (NY): Medscape; 2013 Oct 10 [accessed 2013 Oct 22]. [2 p]. Available: http://www.medscape.com/viewarticle/812401_print.

191. Mechcatie E. Advisers support FDA approval of wireless HF monitoring device. [internet]. Rockville (MD): International Medical News Group, LLC; 2013 Oct 10 [accessed 2013 Oct 22]. [3 p]. Available: http://www.familypracticenews.com/index.php?id=2934&type=98&tx_ttnews%5btt_news%5d=218689&cHash=da03e20e36.

192. Morgan D. FDA panel votes against CardioMEMS device. [internet]. New York (NY): Reuters; 2011 Dec 08 [accessed 2012 Aug 16]. [1 p]. Available: http://www.reuters.com/article/2011/12/09/us-cardiomems-fda-idUSTRE7B801020111209.

193. St. Jude Medical reports third quarter 2015 results. [internet]. St. Paul (MN): St. Jude Medical, Inc.; 2015 Oct 21 [accessed 2015 Dec 04]. [11 p]. Available: http://investors.sjm.com/investors/financial-news/news-release-details/2015/St-Jude-Medical-Reports-Third-Quarter-2015-Results/default.aspx.

194. St. Jude Medical reports second quarter 2015 results. [internet]. St. Paul (MN): St. Jude Medical, Inc.; 2015 Jul 22 [accessed 2015 Dec 04]. [10 p]. Available: http://investors.sjm.com/investors/financial-news/news-release-details/2015/St-Jude-Medical-Reports-Second-Quarter-2015-Results/default.aspx.

195. PriceGuide [database online]. Plymouth Meeting (PA): ECRI Institute [accessed 2015 Dec 04]. St. Jude Medical Inc.: CardioMEMS. [1 p]. Available: http://www.ecri.org.

196. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011 Feb 19;377(9766):658-66. PMID: 21315441.

197. Centers for Medicare and Medicaid Services (CMS). Fiscal year (FY) 2015 inpatient prospective payment system (IPPS) and long term care hospital (LTCH) PPS changes. CMS manual system, Pub 100-04 Medicare claims processing transmittal 3138; change request 8900. Baltimore (MD): Centers for Medicare and Medicaid Services (CMS); 2014 Nov 26. 190 p. Also available: http://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R3138CP.pdf.

198. St. Jude Medical, Inc. CardioMEMS HF system: MS-DRG new technology add-on payment (NTAP). St. Paul (MN): St. Jude Medical, Inc.; 2014. 4 p.

199. Miller R. Medicare add-on payments granted for cardiac, neuro devices. In: Pharma & MedTech Business Intelligence [internet]. New York (NY): Informa Business Information, Inc.; 2014 Aug 5 [accessed 2015 Apr 22]. [3 p]. Available: https://www.pharmamedtechbi.com/publications/the-gray-sheet/40/32/cms-offers-addon-payments-for-emcardiomemsem-emmitraclipem-responsive-neurostimulator.

200. CardioMEMS HF system reimbursement guide. St. Paul (MN): St. Jude Medical Inc.; 2015 Jan 1. 12 p. Also available: http://professional.sjm.com/professional/resources/reimbursement/crm-ep/cardiomems.

201. Aetna, Inc. Clinical policy bulletin: cardiovascular monitoring equipment for home use: pulse, blood pressure, telemonitors, and pacemaker monitors. Number: 0548. [internet]. Hartford (CT): Aetna, Inc.; 2015 Oct 23 [accessed 2015 Nov 10]. [47 p]. Available: http://www.aetna.com/cpb/medical/data/500_599/0548.html.

202. Anthem Insurance Companies. Outpatient cardiac hemodynamic monitoring using a wireless sensor for heart failure management. Policy #MED.00115. [internet]. North Haven (CT): Anthem Insurance Companies, Inc.; 2015 Jul 7 [accessed 2015 Nov 10]. [4 p]. Available: https://www.anthem.com/ca/medicalpolicies/policies/mp_pw_c178379.htm.

203. Blue Cross and Blue Shield of Alabama. Cardiac hemodynamic monitoring for the management of heart failure in the outpatient setting. Policy #: 441. East Birmingham (AL): Blue Cross and Blue Shield of Alabama; 2015 Jul. 17 p. Also available: https://www.bcbsal.org/providers/policies/final/441.pdf.

204. Blue Cross and Blue Shield of Massachusetts. Cardiac hemodynamic monitoring for the management of heart failure in the outpatient setting. Policy 287. [internet]. Rockland (MA): Blue Cross and Blue Shield of Massachusetts; 2015 Aug [accessed 2015 Nov 10]. [6 p]. Available: http://www.bluecrossma.com/common/en_US/medical_policies/287%20Cardiac%20Hemodynamic%20Monitoring%20for%20the%20Management%20of%20Heart%20Failure%20in%20the%20Outpatient%20Setting%20prn.pdf.

205. CIGNA Corporation. Omnibus codes. Coverage policy number: 0504. Bloomfield (CT): CIGNA Corporation; 2015 Oct 15. 115 p. Also available: https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0504_coveragepositioncriteria_omnibus_codes.pdf.

206. Regence Group. Cardiac hemodynamic monitoring for the management of heart failure in the outpatient setting. Policy no. 33. [internet]. Portland (OR): Regence Group; 2015 Jun 1 [accessed 2015 Apr 22]. [12 p]. Available: http://blue.regence.com/trgmedpol/medicine/med33.pdf.

207. Heart Failure Society of America, Lindenfeld J, Albert NM, et al. Evaluation and therapy for heart failure in the setting of ischemic heart disease: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail. 2010 Jun;16(6):e157-65.

208. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1468 - Wireless monitoring system (CardioMEMS HF System) for management of heart failure. 2015 Jul 21 [review date].

209. Expert Commenter 1473. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1468 - Wireless monitoring system (CardioMEMS HF System) for management of heart failure. 2015 Aug 4 [review date].

210. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1468 - Wireless monitoring system (CardioMEMS HF System) for management of heart failure. 2015 Jul 20 [review date].

211. Expert Commenter 1468. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1468 - Wireless monitoring system (CardioMEMS HF System) for management of heart failure. 2015 Jul 24 [review date].

212. Expert Commenter 1561. (External, Clinical). Horizon Scanning Structured Comment Form. HS1468 - Wireless monitoring system (CardioMEMS HF System) for management of heart failure. 2015 Aug 24 [review date].

213. Expert Commenter 167. (External, Clinical). Horizon Scanning Structured Comment Form. HS1468 - Wireless monitoring system (CardioMEMS HF System) for management of heart failure. 2015 Aug 24 [review date].

214. Guyton JR, Bays HE, Grundy SM, et al. An assessment by the Statin Intolerance Panel: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S72-81. Also available: http://dx.doi.org/10.1016/j.jacl.2014.03.002. PMID: 24793444.

215. Reiner Z. Resistance and intolerance to statins. Nutr Metab Cardiovasc Dis. 2014 Oct 1;24(10):1057-66. Also available: http://dx.doi.org/10.1016/j.numecd.2014.05.009. PMID: 24996502.

216. Bangalore S, Fayyad R, Laskey R, et al. Lipid lowering in patients with treatment-resistant hypertension: an analysis from the Treating to New Targets (TNT) trial. Eur Heart J. 2014 Jul 14;35(27):1801-8. Epub 2013 Aug 29. PMID: 23990605.

217. Alonso R, Mata P, Zambon D, et al. Early diagnosis and treatment of familial hypercholesterolemia: Improving patient outcomes. Expert Rev Cardiovasc Ther. 2013 Mar;11(3):327-42. PMID: 23469913.

218. Vogel RA. PCSK9 inhibition: the next statin? J Am Coll Cardiol. 2012 Jun 19;59(25):2354-5. Also available: http://dx.doi.org/10.1016/j.jacc.2012.03.011. PMID: 22465426.

219. Abifadel M, Elbitar S, El Khoury P, et al. Living the PCSK9 adventure: from the identification of a new gene in familial hypercholesterolemia towards a potential new class of anticholesterol drugs. Curr Atheroscler Rep. 2014 Sep;16(9):439. Also available: http://dx.doi.org/10.1007/s11883-014-0439-8.

220. Edelberg J. Lowering LDL-C with alirocumab, an investigational PCSK9 inhibitor. Clin Lipidol. 2014 Dec 1;9(6):603-6. Also available: http://dx.doi.org/10.2217/clp.14.55.

221. Salam AM. The therapeutic potential of PCSK9 inhibition in primary dyslipidemia, the example from SAR236553/REGN727. Expert Opin Investig Drugs. 2012 Oct;21(10):1585-8. Also available: http://dx.doi.org/10.1517/13543784.2012.707193.

222. Robinson JG, Farnier M, Krempf M, et al. Long-term safety, tolerability and efficacy of alirocumab versus placebo in 2,341 high cardiovascular risk patients: ODYSSEY LONG TERM [abstract]. Circulation. 2014;130:2120.

223. Cicero AF, Tartagni E, Ertek S. Efficacy and safety profile of evolocumab (AMG145), an injectable inhibitor of the proprotein convertase subtilisin/kexin type 9: the available clinical evidence. Expert Opin Biol Ther. 2014 Jun;14(6):863-8. Also available: http://dx.doi.org/10.1517/14712598.2014.902929.

224. Sanovi-Aventis U.S. LLC. Praluent (alirocumab) injection, for subcutaneous use prescribing information. Bridgewater (NJ): Sanovi-Aventis U.S. LLC; 2015 Oct. 4 p p. Also available: http://products.sanofi.us/praluent/praluent.pdf.

225. Amgen, Inc. Repatha (evolocumab) injection, for subcutaneous use prescribing information. Thousand Oaks (CA): Amgen, Inc.; 2015 Sep. 34 p. Also available: http://pi.amgen.com/united_states/repatha/repatha_pi_hcp_english.pdf.

226. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med. 2015 Jul 7;163(1):40-51. Also available: http://dx.doi.org/10.7326/M14-2957. PMID: 25915661.

227. Stroes E, Guyton R, Farnier M, et al. Efficacy and safety of alirocumab 150 mg and 300 mg every 4 weeks in patients with poorly controlled hypercholesterolemia: the ODYSSEY CHOICE I and CHOICE II studies. In: American College of Cardiology ACC 2015 Scientific Sessions; March 14-16, 2015; San Diego, California. 2015 Mar. Also available: http://www.ccmdweb.org/dsl/newslide.aspx?Slideid=3694.

228. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1489-99. Also available: http://dx.doi.org/10.1056/NEJMoa1501031.

229. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015 May 15;36(19):1186-94. Also available: http://dx.doi.org/10.1093/eurheartj/ehv028. PMID: 25687353.

230. Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. Future Cardiol. 2015 Jan;11(1):27-37. Also available: http://dx.doi.org/10.2217/fca.14.82. PMID: 25606700.

231. Bays H, Farnier M, Gaudet D, et al. Clinical science special reports: results of ODYSSEY: efficacy and safety of combining alirocumab with atorvastatin or rosuvastatin versus statin intensification or adding ezetimibe in high cardiovascular risk patients: ODYSSEY options I and II [abstract]. Circulation. 2014;130:2118.

232. Ginsberg HN, Rader DJ, Raal FJ, et al. ODYSSEY HIGH FH: efficacy and safety of alirocumab in patients with severe heterozygous familial hypercholesterolemia [abstract]. Circulation. 2014;130:2119.

233. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with suboptimally controlled hypercholesterolemia on maximally tolerated doses of statins: the ODYSSEY COMBO I study [abstract]. Circulation. 2014;130:2119.

234. Kastelein JP, Ginsberg HN, Langslet G, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolaemia not adequately controlled with current lipid-lowering therapy: results of ODYSSEY FH I and FH II studies. In: European Society of Cardiology (ESC) Congress 2014; 2014 Aug 30 - Sep 3; Barcelona (Spain). Also available: http://www.escardio.org/congresses/esc-2014/congress-reports/Pages/707-3-Hotline3-ODYSSEY-COMBO-FH.aspx#presenter2.

235. Moriarty PM, Thompson PD, Cannon CP, et al. ODYSSEY alternative: efficacy and safety of the proprotein convertase subtilisin/kexin type 9 monoclonal antibody, alirocumab, versus ezetimibe, in patients with statin intolerance as defined by a placebo run-in and statin rechallenge arm. Circulation. 2014;130:2108.

236. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):341-50. Also available: http://dx.doi.org/10.1016/S0140-6736(14)61374-X. PMID: 25282520.

237. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): A randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):331-40. Also available: http://dx.doi.org/10.1016/S0140-6736(14)61399-4. PMID: 25282519.

238. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1500-9. Also available: http://dx.doi.org/10.1056/NEJMoa1500858.

239. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014 May 8;370(19):1809-19. Also available: http://dx.doi.org/10.1056/NEJMoa1316222. PMID: 24678979.

240. Harada-Shiba M, Kishimoto I, Makino H, et al. Efficacy of evolocumab (AMG 145) in patients with PCSK9 gain-of-function mutations. Atherosclerosis. 2014;235(2):e11.

241. Bruckert E, Blaha V, Stein EA, et al. Trial assessing long-term use of PCSK9 inhibition in patients with genetic LDL disorders (TAUSSIG): efficacy and safety in patients with homozygous familial hypercholesterolemia receiving lipid apheresis. Circulation. 2014;130(suppl 2):A17016.

242. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2531-40. Also available: http://dx.doi.org/10.1016/j.jacc.2014.03.018.

243. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1500-9. Also available: http://dx.doi.org/10.1056/NEJMoa1500858. PMID: 25773607.

244. Cannon CP, Farnier M, Luscher TF. Efficacy and safety of alirocumab: results from the ODYSSEY COMBO II study and results of ODYSSEY FH I and FH II studies. In: European Society of Cardiology (ESC) Congress 2014; 2014 Aug 30 - Sep 3; Barcelona (Spain). Also available: http://www.escardio.org/congresses/esc-2014/congress-reports/Pages/707-3-Hotline3-ODYSSEY-COMBO-FH.aspx#.VPcx_S90zop.

245. Hopkins PN, Swergold GD, Mellis S, et al. A randomized placebo-phase clinical trial with the monoclonal antibody alirocumab demonstrates reductions in low-density lipoprotein cholesterol in patients with proprotein convertase subtilisin/kexin type 9 gain-of-function mutations [abstract]. Circulation. 2013;128:A17156. Also available: http://circ.ahajournals.org/cgi/content/meeting_abstract/128/22_MeetingAbstracts/A17156?sid=5bfb59cd-f297-4efd-a0b9-e0616db49d0d.

246. Koren MJ, Giugliano RP, Raal FJ, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the open-label study of long-term evaluation against LDL-C (OSLER) randomized trial. Circulation. 2014 Jan 14;129(2):234-43. Also available: http://dx.doi.org/10.1161/CIRCULATIONAHA.113.007012. PMID: 24255061.

247. Amgen. Evaluating PCSK9 binding antibody influence on cognitive health in high cardiovascular risk subjects (EBBINGHAUS). [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [updated 2014 Apr 03] [accessed 2015 Mar 05]. [4 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT02207634 NLM Identifier: NCT02207634.

248. Carroll J. UPDATED: Regeneron, Sanofi and Amgen shares suffer on FDA's frets about PCSK9 class. [internet]. FierceBiotech; 2014 Mar 7 [accessed 2015 Mar 04]. [4 p]. Available: http://www.fiercebiotech.com/story/regeneron-sanofi-and-amgen-shares-suffer-fdas-frets-about-pcsk9-drug/2014-03-07.

249. Regeneron and Sanofi announce FDA approval of Praluent (alirocumab) injection, the first PCSK9 inhibitor in the U.S., for the treatment of high LDL cholesterol in adult patients. [internet]. New York (NY): PR Newswire; 2015 Jul 24 [accessed 2015 Jul 30]. [8 p]. Available: http://www.prnewswire.com/news-releases/regeneron-and-sanofi-announce-fda-approval-of-praluent-alirocumab-injection-the-first-pcsk9-inhibitor-in-the-us-for-the-treatment-of-high-ldl-cholesterol-in-adult-patients-300118572.html.

250. Markham A. Evolocumab: first global approval. Drugs. 2015 Sep;75(13):1567-73. Also available: http://dx.doi.org/10.1007/s40265-015-0460-4. PMID: 26323342.

251. Herman B. Insurers begin to review coverage of costly cholesterol drugs. Mod Healthc. 2015 Aug 28; Also available: http://www.modernhealthcare.com/article/20150828/NEWS/150829865.

252. Repatha pricing info. [database online]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 08]. [10 p]. Available: http://www.goodrx.com/repatha.

253. Barber J. Amgen prices PCSK9 inhibitor Repatha in Europe at steep discount to US. In: FirstWord Pharma [internet]. New York (NY): Doctor's Guide Publishing Limited; 2015 Sep 1 [accessed 2015 Nov 11]. [2 p]. Available: http://www.firstwordpharma.com/node/1311471?tsid=33#axzz3r3FNG1ts.

254. McKee S. Amgen prices Repatha in Europe at huge discount to US tag. [internet]. London (UK): PharmaTimes Media Limited; 2015 Sep 2 [accessed 2015 Nov 10]. [2 p]. Available: http://www.pharmatimes.com/Article/15-09-02/Amgen_prices_Repatha_in_Europe_at_huge_discount_to_US_tag.aspx.

255. Q3 2015 results [slide show]. [internet]. Paris (France): Sanofi; 2015 Oct 29. 36 p.

256. Ishmael H. Amgen and Regeneron face declining PCSK-9 prescription volumes. [internet]. St. Louis (MO): Bidness Etc; 2015 Dec 7 [accessed 2015 Dec 08]. [6 p]. Available: http://www.bidnessetc.com/58768-amgen-and-regeneron-face-declining-pcsk9-prescription-volumes/.

257. Shrank W, Lotvin A, Singh S, et al. In the debate about cost and efficacy, PCSK9 inhibitors may be the biggest challenge yet. [internet]. Bethesda (MD): Health Affairs; 2015 Feb 17 [accessed 2015 Mar 04]. [6 p]. Available: http://healthaffairs.org/blog/2015/02/17/in-the-debate-about-cost-and-efficacy-pcsk9-inhibitors-may-be-the-biggest-challenge-yet/.

258. Crestor pricing info. [database online]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 08]. [11 p]. Available: http://www.goodrx.com/crestor.

259. Lipitor pricing info. [database online]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 08]. [11 p]. Available: http://www.goodrx.com/lipitor.

260. Liptruzet pricing info. [database online]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Dec 08]. [10 p]. Available: http://www.goodrx.com/liptruzet.

261. Langreth R, Armstrong D. Sanofi and Regeneron gain an edge in cholesterol drug race. [internet]. New York (NY): Bloomberg; 2014 Jan 26 [accessed 2015 Mar 04]. [10 p]. Available: http://www.bloomberg.com/news/articles/2015-01-26/sanofi-and-regeneron-gain-edge-on-amgen-in-cholesterol-drug-race.

262. Staton T. Payers fret about the next drug doomsday: pricey PCSK9 cholesterol meds. [internet]. FiercePharmaMarketing; 2014 May 7 [accessed 2015 Mar 04]. [4 p]. Available: http://www.fiercepharmamarketing.com/story/payers-already-fretting-about-next-pharm-apocalypse-pricey-pcsk9-cholestero/2014-05-07.

263. Both PCSK9 inhibitors included on National Preferred Formulary. [internet]. St. Louis (MO): Express Scripts Holding Company; 2015 Oct 6 [accessed 2015 Dec 09]. [3 p]. Available: http://lab.express-scripts.com/insights/drug-options/both-pcsk9-inhibitors-included-on-national-preferred-formulary#sthash.T2EmtrqC.3PwHN0cA.dpuf.

264. CVS Health announces formulary and therapy strategy for PCSK9 inhibitors . [internet]. Woonsocket (RI): CVS Health; 2015 Nov 23 [accessed 2015 Dec 09]. [4 p]. Available: http://www.cvshealth.com/content/cvs-health-announces-formulary-and-therapy-strategy-pcsk9-inhibitors.

265. Weisman R. Harvard Pilgrim strikes 'pay-for-performance' deal for cholesterol drug. [internet]. Boston (MA): Boston Globe; 2015 Nov 8 [accessed 2015 Nov 10]. [8 p]. Available: https://www.bostonglobe.com/business/2015/11/08/harvard-pilgrim-strikes-pay-for-performance-deal-for-cholesterol-drug/iGIV7rBie4K20HNbKORsPJ/story.html.

266. Specialty pharmacy clinical policy bulletins. Aetna non-Medicare prescription drug plan. Subject: PCSK9 inhibitors. [internet]. Hartford (CT): Aetna, Inc.; 2015 Dec 1 [accessed 2015 Dec 09]. [4 p]. Available: http://www.aetna.com/products/rxnonmedicare/data/2015/MISC/PCSK9_Inhibitors.html.

267. Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors. Policy #: DRUG.00078. [internet]. North Haven (CT): Anthem Insurance Companies, Inc.; 2015 Sep 21 [accessed 2015 Dec 09]. [10 p]. Available: https://www.anthem.com/medicalpolicies/policies/mp_pw_c182635.htm.

268. Drug coverage guidelines: Praluent. [internet]. East Birmingham (AL): BlueCross BlueShield of Alabama [accessed 2015 Dec 09]. [3 p]. Available: https://www.bcbsal.org/web/pharmacy/guidelines.html?p_p_id=prescriptiondrugguidlines_WAR_mbr_prescriptiondrugguidelines&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=2&p_p_col_count=3.

269. BlueCross BlueShield of Alabama. Drug coverage guidelines: Repatha. [internet]. East Birmingham (AL): BlueCross BlueShield of Alabama [accessed 2015 Dec 09]. [3 p]. Available: https://www.bcbsal.org/web/pharmacy/guidelines.html?p_p_id=prescriptiondrugguidlines_WAR_mbr_prescriptiondrugguidelines&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=2&p_p_col_count=3.

270. Cigna Corporation. Praluent (alirocumab) prior authorization form. Bloomfield (CT): Cigna Corporation; 2 p. Also available: https://cignaforhcp.cigna.com/public/content/pdf/resourceLibrary/prescription/Praluent.pdf.

271. Cigna Corporation. Repatha (evolocumab) prior authorization form. Bloomfield (CT): Cigna Corporation; 3 p. Also available: https://cignaforhcp.cigna.com/public/content/pdf/resourceLibrary/prescription/Repatha.pdf.

272. Search the PreferredRx formulary - Praluent pen 75 mg/ml subcutaneous pen injector. [internet]. Minneapolis (MN): HealthPartners [accessed 2015 Dec 09]. [1 p]. Available: https://www.healthpartners.com/public/pharmacy/formularies/preferredrx/.

273. Search the PreferredRx formulary - Repatha sureclick 140 mg/ml subcutaneous pen injector. [internet]. Minneapolis (MN): HealthPartners [accessed 2015 Dec 09]. [1 p]. Available: https://www.healthpartners.com/public/pharmacy/formularies/preferredrx/.

274. Humana, Inc. Praluent (alirocumab). Louisville (KY): Humana, Inc.; 2015 Sep 16. 6 p. Also available: http://www.humana.com.

275. Medica. Medica utilization management policy: alirocumab (Praluent). Minnetonka (MN): Medica; 2015 Aug 18. 2 p. Also available: https://www.medica.com/.

276. Medica. Medica 2015 comprehensive preferred drug list (PDL) with HSA preventive maintenance benefit. Minnetonka (MN): Medica; 2015. 175 p. Also available: https://www.medica.com/.

277. United HealthCare Services, Inc. UnitedHealthcare Pharmacy clinical pharmacy programs: prior authorization/medical necessity - Repatha (evolocumab). 2015 P 2063-2. Edina (MN): United HealthCare Services, Inc.; 2015 Sep 23. 8 p. Also available: https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Ox_MPUB_Future_Pharmacy/Med_Nec_Repatha.PDF.

278. Institute for Clinical and Economic Review (ICER). PCSK9 inhibitors for treatment of high cholesterol: effectiveness, value, and value-based price benchmarks final report. Boston (MA): New England Comparative Effectiveness Public Advisory Council (CEPAC), Institute for Clinical and Economic Review (ICER); 2015 Nov 24. 139 p. Also available: http://cepac.icer-review.org/wp-content/uploads/2015/04/Final-Report-for-Posting-11-24-15.pdf.

279. National Human Genome Research Institute. Learning about familial hypercholesterolemia. [internet]. Bethesda (MD): National Human Genome Research Institute, National Institutes of Health (NIH); 2011 Mar 23 [accessed 2011 Jul 12]. [3 p]. Available: http://www.genome.gov/25520184#al-4.

280. FDA approves new orphan drug Kynamro to treat inherited cholesterol disorder. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2013 Jan 29 [accessed 2013 Feb 22]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm337195.htm.

281. FDA approves Aegerion Pharmaceuticals' Juxtapid (lomitapide) capsules for homozygous familial hypercholesterolemia (HoFH). [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2012 Dec 24 [accessed 2013 Jun 05]. [4 p]. Available: http://ir.aegerion.com/releasedetail.cfm?ReleaseID=728650.

282. Aegerion Pharmaceuticals receives European approval for Lojuxta (lomitapide) to treat homozygous familial hypercholesterolemia (HoFH). [internet]. Cambridge (MA): Aegerion Pharmaceuticals, Inc.; 2013 Aug 1 [accessed 2013 Nov 27]. [2 p]. Available: http://ir.aegerion.com/releasedetail.cfm?ReleaseID=782124.

283. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1593 - Alirocumab (Praluent) for treatment of hypercholesterolemia resistant to statins. 2015 Mar 25 [review date].

284. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1593 - Alirocumab (Praluent) for treatment of hypercholesterolemia resistant to statins. 2015 Apr 6 [review date].

285. Expert Commenter 656. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1593 - Alirocumab (Praluent) for treatment of hypercholesterolemia resistant to statins. 2015 Mar 26 [review date].

286. Expert Commenter 663. (External, Clinical). Horizon Scanning Structured Comment Form. HS1593 - Alirocumab (Praluent) for treatment of hypercholesterolemia resistant to statins. 2015 Apr 13 [review date].

287. Expert Commenter 993. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1593 - Alirocumab (Praluent) for treatment of hypercholesterolemia resistant to statins. 2015 Mar 30 [review date].

288. Expert Commenter 1241. (External, Clinical). Horizon Scanning Structured Comment Form. HS1593 - Alirocumab (Praluent) for treatment of hypercholesterolemia resistant to statins. 2015 Apr 17 [review date].

289. Expert Commenter 410. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1815 - Evolocumab (Repatha) for treatment of hypercholesterolemia. 2015 Apr 9 [review date].

290. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1815 - Evolocumab (Repatha) for treatment of hypercholesterolemia. 2015 Apr 27 [review date].

291. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1815 - Evolocumab (Repatha) for treatment of hypercholesterolemia. 2015 Apr 16 [review date].

292. Expert Commenter 420. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1815 - Evolocumab (Repatha) for treatment of hypercholesterolemia. 2015 Apr 8 [review date].

293. Expert Commenter 663. (External, Clinical). Horizon Scanning Structured Comment Form. HS1815 - Evolocumab (Repatha) for treatment of hypercholesterolemia. 2015 Apr 13 [review date].

294. Expert Commenter 1241. (External, Clinical). Horizon Scanning Structured Comment Form. HS1815 - Evolocumab (Repatha) for treatment of hypercholesterolemia. 2015 Apr 17 [review date].

295. Pulmonary arterial hypertension. In: Genetics Home Reference [internet]. Bethesda (MD): National Library of Medicine (U.S.); 2011 Sep 12 [accessed 2011 Sep 20]. [4 p]. Available: http://ghr.nlm.nih.gov/condition/pulmonary-arterial-hypertension.

296. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eu Respir J. 2012 Oct;40(4):874-80. Also available: http://dx.doi.org/10.1183/09031936.00137511. PMID: 22362844.

297. Actelion submits US FDA New Drug Application for selexipag (Uptravi) in patients with pulmonary arterial hypertension. [internet]. Allschwil (Switzerland): Actelion Pharmaceuticals Ltd; 2014 Dec 23 [accessed 2015 Mar 02]. [3 p]. Available: http://www1.actelion.com/en/our-company/news-and-events.page?newsId=1883059.

298. McLaughlin VV, Channick R, Chin K, et al. Effect of selexipag on morbidity/mortality in pulmonary arterial hypertension: results of the GRIPHON study. In: American College of Cardiology (ACC) ACC.15; 2015 Mar 14-16; San Diego (CA). 2015. p. 2. Also available: http://www.abstractsonline.com/pp8/#!/3658/presentation/29719.

299. Actelion receives US FDA approval of Uptravi (selexipag) for the treatment of pulmonary arterial hypertension. [internet]. Allschwil (Switzerlandd): Actelion; 2015 Dec 22 [accessed 2015 Dec 22]. [4 p]. Available: http://www1.actelion.com/en/our-company/news-and-events.page?newsId=1975263.

300. Adempas pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Feb 06]. [8 p]. Available: http://www.goodrx.com/adempas.

301. Orenitram pricing information. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2014 Mar 10]. [5 p]. Available: http://www.goodrx.com/orenitram.

302. Prostacyclin. [internet]. San Francisco (CA): PHCentral [accessed 2011 Sep 20]. [2 p]. Available: http://www.phcentral.org/medical/treatments/prostacyclin.

303. What are the symptoms of pulmonary arterial hypertension? [internet]. Washington (DC): American Lung Association [accessed 2011 Sep 20]. [2 p]. Available: http://www.lungusa.org/lung-disease/pulmonary-arterial-hypertension/symptoms-diagnosis.html.

304. Expert Commenter 1241. (External, Clinical). Horizon Scanning Structured Comment Form. HS1016 - Selexipag (Uptravi) for treatment of pulmonary artery hypertension. 2015 May 6 [review date].

305. Expert Commenter 1399. (External, Clinical). Horizon Scanning Structured Comment Form. HS1016 - Selexipag (Uptravi) for treatment of pulmonary artery hypertension. 2015 May 6 [review date].

306. Expert Commenter 1384. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS1016 - Selexipag (Uptravi) for treatment of pulmonary artery hypertension. 2015 Apr 8 [review date].

307. Expert Commenter 424. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1016 - Selexipag (Uptravi) for treatment of pulmonary artery hypertension. 2015 Apr 1 [review date].

308. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS1016 - Selexipag (Uptravi) for treatment of pulmonary artery hypertension. 2015 Apr 20 [review date].

309. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS1016 - Selexipag (Uptravi) for treatment of pulmonary artery hypertension. 2015 Apr 2 [review date].

310. Expert Commenter 695. (External, Clinical). Horizon Scanning Structured Comment Form. HS1016 - Selexipag (Uptravi) for treatment of pulmonary artery hypertension. 2015 Apr 29 [review date].

311. Centers for Disease Control and Prevention (CDC). Types of stroke. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2013 Dec 06 [accessed 2014 Sep 23]. [3 p]. Available: http://www.cdc.gov/stroke/types_of_stroke.htm.

312. Mayo Clinic staff. Stroke. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2015 May 15 [accessed 2015 May 22]. [13 p]. Available: http://www.mayoclinic.org/diseases-conditions/stroke/home/ovc-20117264.

313. Lahr MM, Luijckx GJ, Vroomen PC, et al. The chain of care enabling tPA treatment in acute ischemic stroke: a comprehensive review of organisational models. J Neurol. 2013 Apr;260(4):960-8. Also available: http://dx.doi.org/10.1007/s00415-012-6647-7. PMID: 22915092.

314. Amaro S, Canovas D, Castellanos M, et al. The URICO-ICTUS study, a phase 3 study of combined treatment with uric acid and rtPA administered intravenously in acute ischaemic stroke patients within the first 4.5 h of onset of symptoms. Int J Stroke. 2010 Aug;5(4):325-8. Also available: http://dx.doi.org/10.1111/j.1747-4949.2010.00448.x. PMID: 20636718.

315. Mobile stroke unit. [internet]. Cleveland (OH): Cleveland Clinic [accessed 2015 May 12]. [2 p]. Available: http://my.clevelandclinic.org/services/neurological_institute/cerebrovascular-center/treatment-services/mobile-stroke-unit.

316. Grotta JC. Delivering acute stroke therapy in the pre-hospital environment in Houston, Texas, U.S.A. Houston (TX): Memorial Hermann Hospital; 2015. 40 p. Also available: http://c.ymcdn.com/sites/www.texasneurologist.org/resource/resmgr/Winter_2015_Presentations/Grotta.TNS.pdf.

317. Hines L. Memorial Hermann tries Google Glass to speed stroke treatment. [internet]. Houston (TX): Houston Chronicle, Hearst Newspapers, LLC; 2014 Nov 4 [accessed 2015 Aug 13]. [6 p]. Available: http://www.houstonchronicle.com/local/prognosis/article/Memorial-Hermann-unit-uses-Google-Glass-to-speed-5868724.php.

318. Gomes JA, Ahrens CL, Hussain MS, et al. Prehospital reversal of warfarin-related coagulopathy in intracerebral hemorrhage in a mobile stroke treatment unit. Stroke. 2015 May;46(5):e118-20. Also available: http://dx.doi.org/10.1161/STROKEAHA.115.008483. PMID: 25873600.

319. Taqui A, Cerejo R, Itrat A, et al. Reduction in time to imaging and intravenous thrombolysis by in-field evaluation and treatment in a mobile stroke treatment unit [abstract]. Stroke. 2015;46:A54.

320. Cerejo R, John S, Buletko AB, et al. A mobile stroke treatment unit for field triage of patients for intraarterial revascularization therapy. J Neuroimaging. 2015 Nov;25(6):940-5. Epub 2015 Jul 14. Also available: http://dx.doi.org/10.1111/jon.12276. PMID: 26179631.

321. Bartley R. CloudVisit takes telemedicine platform mobile. [internet]. New York (NY): FierceMarkets; 2015 Mar 10 [accessed 2015 Aug 13]. [3 p]. Available: http://www.fiercemobileit.com/story/cloudvisit-takes-telemedicine-platform-mobile/2015-03-10.

322. Brain and Spine Team. Mobile stroke units bring you quicker, lifesaving treatment. [internet]. Cleveland (OH): Cleveland Clinic; 2014 Oct 29 [accessed 2015 May 12]. [3 p]. Available: http://health.clevelandclinic.org/2014/10/mobile-stroke-units-bring-you-quicker-lifesaving-treatment/.

323. Rogers D. County could get mobile stroke unit; Cleveland Clinic ambulance scans brain, gives clot-busters, gets patients to best hospital for condition. [internet]. Palm Beach (FL): Palm Beach Daily News; 2014 Dec 6 [accessed 2015 Aug 12]. [2 p]. Available: http://www.palmbeachdailynews.com/news/news/local/mobile-stroke-unit-could-save-lives-in-county/njMXD/.

324. Walter S, Kostopoulos P, Ragoschke-Schumm A, et al. 'Mobile stroke unit' for stroke treatment at the emergency site. J Neurol Sci. 2013 Oct 15;333(Suppl 1):e190. Also available: http://dx.doi.org/10.1016/j.jns.2013.07.769.

325. Zage J. Mobile stroke units get their first US test drive. [internet]. Skokie (IL): Sg2; 2014 Nov 7 [accessed 2015 May 12]. [5 p]. Available: https://www.sg2.com/health-care-intelligence-blog/2014/11/mobile-stroke-units-get-first-us-test-drive/.

326. Fellows J. Keeping up with stroke advances: despite strides in neuroscience service line and stroke care, leading organizations are finding there still are improvements that can be made. [internet]. Danvers (MA): HealthLeaders Media; 2015 Apr 1 [accessed 2015 Aug 18]. [5 p]. Available: http://www.healthleadersmagazine-digital.com/healthleadersmagazine/april_2015#pg48.

327. Expert Commenter 234. (External, Clinical). Horizon Scanning Structured Comment Form. HS2288 - Mobile unit for treatment of stroke. 2015 Oct 12 [review date].

328. Expert Commenter 1219. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2288 - Mobile unit for treatment of stroke. 2015 Oct 2 [review date].

329. Expert Commenter 1473. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2288 - Mobile unit for treatment of stroke. 2015 Oct 9 [review date].

330. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2288 - Mobile unit for treatment of stroke. 2015 Oct 5 [review date].

331. Expert Commenter 1493. (External, Clinical). Horizon Scanning Structured Comment Form. HS2288 - Mobile unit for treatment of stroke. 2015 Oct 1 [review date].

332. Expert Commenter 1547. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2288 - Mobile unit for treatment of stroke. 2015 Oct 2 [review date].