2.2 Existing Solutions

INTRODUCTION

The team is about to take its second-generation prototype into the animal lab for testing. The pressure is on because the initial seed round of $200,000 is almost gone. Then, the bad news arrives: another group has just presented an abstract at the European College meetings describing the first eight patients treated with an approach that will most likely render this technology obsolete. The team now recalls one of their early clinical advisors mentioning another technology under development in Germany. If only they had tracked down this lead at the time, they might have saved money, time – and maybe the company.

The goal of any solution is to improve outcomes for patients with a particular disease or disorder. The analysis of existing solutions involves detailed research to understand what established *and* emerging products and services are available for diagnosing, treating, and managing a condition, how and when they are used, how and why they work, their effectiveness, their costs, and the overall value they deliver. Through the process of investigating existing solutions and creating a comprehensive profile of how a condition is typically addressed, areas for improvement and new opportunities may become apparent. This analysis also helps provide innovators with an understanding of the clinical, patient-related, and economic requirements that any new solution must meet to be considered equivalent or superior to existing alternatives. It further establishes a baseline of knowledge against which the uniqueness and other merits of new solutions can eventually be evaluated.

See ebiodesign.org for featured videos on researching existing solutions.

OBJECTIVES

- Appreciate the importance of understanding the full range of existing and emerging solutions for diagnosing, treating, and managing a given disease state.
- Know how to effectively search for and summarize information about existing solutions into a useful format.
- Understand how to perform a gap analysis that can lead to the identification of opportunities to create value within the landscape of existing solutions.

EXISTING SOLUTION FUNDAMENTALS

Existing solutions can only be evaluated after gaining a working knowledge of the disease state (see chapter 2.1). As with disease state analysis, initial research of existing solutions is performed broadly at first, and then again in much greater detail as part of validating or screening promising **needs**.

The primary goal of researching existing solutions is to learn what alternatives are already available for diagnosing, treating, and managing a disease, as well as to identify where the most compelling opportunities to address unmet needs may exist. Solution research also provides a platform for better understanding patient, provider, and system-related requirements that will ultimately become a vital component of the **need specification** (as described in 2.5 Needs Selection).

Types of solutions to consider

Innovators are encouraged to perform a comprehensive search of existing solutions, being careful not to overlook any relevant diagnostics, interventional or surgical therapies, or management tools and services. For example, a team of innovators may have a primary interest in developing device-related therapies, but their research should include all diagnostics, treatment alternatives that extend beyond devices (e.g., drugs, surgery), and products and services related to managing a patient's condition (e.g., rehabilitation, monitoring). Table 2.2.1 outlines the full range of solutions to assess.

Other solution considerations

In addition to being exhaustive about the types of existing solutions associated with a given disease state, innovators should carefully evaluate the type of provider that delivers each one. The mapping of different solutions to their practitioners will be a useful input to **stakeholder** analysis (see 2.3 Stakeholder Analysis). It also provides a construct to think about the capabilities of each provider type. For instance, colonoscopy requires dexterity and finesse on the part of the physician to avoid patient discomfort. Gastroenterologists who routinely perform this procedure are more likely to have the skills required for other delicate or sensitive procedures using this approach, while other types of physicians working in the space might be less suited to deliver new solutions of this nature.

The skills or requirements that each solution places on patients should also be taken into account. For example, orthopedic surgical procedures are usually associated with rehabilitation in order to optimize the surgical result. Clearly, compliance varies among different patient populations based on age, functional status, and even economic background. These issues are often tied to the likelihood of procedural success or follow-up complications. More generally, the degree of compliance with existing solutions (be it rehabilitation, medication, diet, exercise, or other lifestyle factors) is a fertile area to survey in assessing the needs landscape. A great deal of the current excitement surrounding the mobile health (**mHealth**) "revolution" is based on the expectation that compliance gaps can be narrowed, in

Table 2.2.1 Be careful not to overlook any solution types when researching existing solutions.

Type of solution	Description
Diagnostics	Determination of whether (and to what extent) patients are affected by a given condition.
Behavioral and lifestyle treatments	Patient-driven solutions such as modifying one's diet and exercise.
Pharmacologic or biologic treatments	Chemical or biologic agents; usually injected or orally delivered.
Percutaneous treatments	Therapies administered via a catheter.
Minimally invasive treatments	Procedures performed using small incisions (e.g., laparoscopic procedures to access the abdomen or a joint; pacemaker placement).
Open surgery	Procedures that require the surgeon to cut larger areas of skin and tissues to gain direct access to the structures or organs involved.
Services	Human-centered interventions such as physical therapy and respiratory therapy.
Disease management	Products or services to monitor a patient's condition and guide therapy.

Table 2.2.2 Several different types of gaps can exist in the landscape of existing solutions, each leading to different types of opportunities.

Solution gaps	Description
Gap between the desired outcomes and the outcomes achieved by existing solutions	As existing solutions are researched and evaluated, think about ways in which they fail to meet the desired outcomes defined in the preliminary need criteria and what may be the cause of their shortcomings. For instance, gaps may be caused by applying an inappropriate solution to a clinical need. Or, they may stem from solutions that embody the correct approach, but need further development or specific refinements to achieve improved results.
Gap between what specific subsegments of patients need and what is offered by existing/emerging solutions	Diseases and disorders often have different manifestations depending on the stage or severity of the condition. Particular subgroups, such as the elderly or patients with certain comorbidities (e.g., diabetes) may also respond differently to differing solution. Accordingly, gaps may exist for specific patient subtypes and/or stages of a disease.
Gap between the outcomes/effectiveness that existing or emerging solutions deliver and their cost	Value gaps take into account the cost of a solution relative to its effectiveness. In an increasingly cost-sensitive environment, where facility administrators and purchasing managers are playing a more dominant role in adoption decisions for new medical technologies, value gaps must be addressed by driving up effectiveness, bringing down costs, or ideally accomplishing both.

part, by new technologies and services. Accordingly, innovators should think about how the various solutions in the disease area of interest are likely to align with the interests, motivations, and capabilities of patients.

Finding gaps to identify opportunities

The desired outcome of this analysis is to find a gap (or gaps) in the landscape of existing solutions that represents an opportunity to address the stated need. There are at least three types of gaps to consider, as shown in Table 2.2.2.

When performing a gap analysis, it is important to think about how the solution landscape will look several years in the future, not just how it appears today. Solutions represent a moving target, so the analysis of existing and emerging solutions needs to be referenced to the time frame of the team's entry into the market. If the group anticipates a long development cycle (some devices can take 10 years or more to get into patient care), there is a much bigger time frame for other technologies to enter the market and eliminate or substantially change the opportunity. Without considering this temporal aspect to the improvement of existing solutions and the development of new ones, innovators may focus only on the current opportunity gap, not realizing that it is already diminishing or even on the path to closing altogether.

Just as looking forward is important, a great deal can be learned from looking backward. If there appears to be a major gap in the solution landscape, an innovator would be well served to do some research on prior diagnostics, therapies, and management tools that sought to address that gap but failed. Studying the unsuccessful experiments of other innovators can highlight important pitfalls, risks to be avoided, and fundamental learnings that can be leveraged to accelerate efforts moving forward. The example below, focused on another company from The Foundry, called Emphasys Medical, illustrates this approach.

FROM THE FIELD THE FOUNDRY AND EMPHASYS MEDICAL

Understanding existing solutions as part of the needs screening process

Medical device incubator The Foundry has learned that, early in the innovation process, a thorough examination of all available options for diagnosing, treating, and managing a disease can spark ideas that others may have missed.

In the late 1990s, managing partners Hanson Gifford and Mark Deem were interested in pursuing opportunities related to the treatment of emphysema (see Figure 2.2.1). As part of their early research, they performed a detailed assessment of established and emerging solution alternatives in the space. At the time, Gifford pointed out, "The only real treatment for emphysema was lung volume reduction surgery (LVRS)."[1] LVRS is a highly invasive procedure in which the surgeon opens a patient's chest and removes roughly 30 percent of the diseased tissue in order to increase the flow of oxygen to the remainder of the lungs. The operation is difficult to perform and extremely painful for the patient. Moreover, the associated mortality rate ranges from 6 to 10 percent, among the highest for any elective procedure.[2] "We spent a lot of time trying to understand how we might be able to do the surgery better. We did extensive literature research, talked with many surgeons and pulmonologists, and really explored the disease state, including its natural history, the cellular degradation of the lungs, and so on," explained Gifford. Besides disease state analysis, they also proactively and exhaustively researched existing and emerging solutions by cold-calling inventors, companies, and experts working in the field and networking with other entrepreneurs. Through this process, they realized that emerging technologies were predominantly focused on incrementally improving LVRS and almost no research was being done to look for an alternative, non-surgical procedure.

FIGURE 2.2.1
Mark Deem and Hanson Gifford of The Foundry (courtesy of Stanford Biodesign).

Recognizing that there was a huge gap in the solution landscape for emphysema (and driven by a desire to develop a less painful and invasive option for patients), Gifford and Deem decided to refocus their solution research on non-surgical alternatives. "One of our major breakthroughs came when we decided that no matter what kind of a device we came up with, what we really needed to do was make this a non-surgical procedure," recalled Gifford. "Everybody was looking at surgery, which became just this little corner of the solution landscape for us," added Deem. "There was this huge area outside of surgery where nobody was working that was full of potential opportunities."

The absence of other innovators or companies pursuing non-surgical treatments for emphysema left the field wide open, but it also created a host of difficult challenges that they would potentially face in pioneering a new procedure and/or device. Their research had shown that pulmonologists (physicians specializing in the lungs) saw emphysema patients on a regular basis, but it was surgeons who performed LVRS. In order for a solution to be non-surgical, pulmonologists would have to be able to deliver treatment. At the time, "Pulmonologists didn't really perform therapeutic procedures," said Deem. "In some ways, we would have to develop a new field of medicine, or at least expand a traditional specialty to make a non-surgical treatment for

emphysema possible." To evaluate the feasibility of such a shift, they invested significant effort in examining the current referral patterns among doctors, how equipment was procured and funded in hospitals, and whether pulmonologists had the right skills, resources, and physical space to perform therapeutic procedures.

They also evaluated economics in the solution area. "We took a fairly broad brush toward the financials at that point," said Gifford. "We looked at the overall cost to the doctor, the hospital, and the healthcare system for comparable procedures because – right or wrong – if these entities are already used to paying 'X' dollars for the treatment of a disease, you're more likely to be able to get that same amount." He added, "LVRS cost in the range of $20,000 to $30,000. If we could come up with a therapeutic procedure that only costs a few thousand dollars, then there would be room for a reasonably well-priced device."

Despite the many challenges in the field, Gifford and Deem saw the potential for a breakthrough product. More than 3.7 million patients have been diagnosed with emphysema in the United States alone.[3] While a relatively small number of LVRS procedures are performed each year, the market for a less invasive treatment alternative would be significant, particularly given the mortality rates associated with the current LVRS procedure and the pain and suffering to patients associated with both the surgery and the disease. According to Deem, "The standard line that physicians would hear from emphysema patients was, 'Cure me or kill me. I don't care which one, but I can't stand being perpetually short of breath.' "

Ultimately, The Foundry decided to move forward with this project, collaborating with John McCutcheon and Tony Fields to found Emphasys Medical in 2000. Emphasys developed a minimally invasive procedure utilizing removable valves that could be inserted into a patient in as little as 20 minutes.

The valves could control air flow in and out of the diseased portions of the lungs to help healthier portions function normally. The **concept** was to collapse the diseased portions of the lungs without having to remove the tissue surgically. More about Emphasys Medical can be found in chapters 5.3 Clinical Strategy and 5.4 Regulatory Strategy.

Approach to existing solution analysis

A complete analysis of existing solutions should include information in the core areas outlined below:

- **Overview of solution options:** Provide a high-level description of relevant solutions in the field, including a summary of each alternative, how it is typically used in practice, and the skills required by the **user**. This provides a foundation for both gap analysis and the refinement of needs criteria.
- **Clinical solution profile:** Describe the clinical rationale for why and when each solution is used. In particular, outline the clinical **mechanism of action**, clinical evidence on safety and effectiveness, indications, and patient segments. This information can be useful for performing gap analysis and refining needs criteria.
- **Economic solution profile:** Outline the cost associated with each solution, including both direct and ancillary costs and who or what entity is incurring them. Begin to understand the **value** of available treatment options by exploring costs relative to their effectiveness. This information is useful in performing a more in-depth market analysis of the solution landscape (see 2.4 Market Analysis).
- **Utilization solution profile:** Describe how each solution is used in clinical practice, by whom, and where. Utilization is another important component of the market analysis.
- **Emerging solution profile:** Capture new products and procedures for the diagnosis, treatment, and management of a condition likely to affect the solution landscape within the next 3 to 10 years. Diligent research of possible emerging technologies

helps prepare the gap analysis, refine the needs criteria, and provide support for the technical and clinical feasibility of potentially new solutions.

- **Summary of the solution landscape:** Develop a cohesive assessment of potential opportunities within the current and emerging solution environment, focusing on the gap between these alternatives and the defined need criteria.

The remainder of this chapter examines each of the areas above, using atrial fibrillation (AF) as an example. In this case, detailed analysis is provided for one existing therapy (pulmonary vein isolation) and one emerging therapy (left atrial appendage occlusion). To better understand the example, refer back to the information given in 2.1 Disease State Fundamentals as it provides an overview of AF, which is relevant to understanding existing solutions. The focus on only two example treatments in this chapter is for the purpose of illustration. In reality, innovators must examine all available solution and solution types within their area of interest.

As with disease state analysis, the appropriate level of detail for assessing existing solutions varies significantly based on the number of alternatives that exist within a particular field, as well as the number of different needs being evaluated. Innovators should remember to take an iterative approach, exploring each solution in progressively more depth, as their direction becomes increasingly clear. They should also revisit this analysis as additional information is gathered via other steps of the biodesign innovation process (such as 4.3 Reimbursement Basics). The example below has been prepared at a relatively high level as a simplified illustration of the approach.

Overview of existing solutions

The first step in performing this analysis is to investigate and summarize the current solutions for the disease. Developing an overview of the solution landscape may be best accomplished by categorizing the options based on common or shared features (see the Working Example "Overview of Existing Solutions for Atrial Fibrillation" for a sample). These common features are usually unique to the particular clinical need area, but may include patient populations, technology platform, or even mechanism of action. Remember not to limit this analysis to any specific solution type, but to include everything from diagnostics and lifestyle modification to open surgical therapies and disease management tools. For each one, explain the objective(s) of the solution, how it is typically applied in practice (e.g., does the solution have progressive steps?), the person delivering the solution, and the skills required by the user. Organize the information in such a way that it provides a complete sense of the solution alternatives that are currently used in practice. It is also important to elaborate on the relative strengths and weaknesses of each approach.

Working Example
Overview of existing solutions for atrial fibrillation

Atrial fibrillation is a disease in which an irregular, typically rapid, and chaotic heart rhythm replaces sinus rhythm (normal heart rhythm) leading to a variety of symptoms as well as blood clot formation that can result in a stroke. Available treatments for AF typically seek to accomplish one of three different objectives: (1) the restoration and maintenance of normal sinus rhythm; (2) the control of the ventricular rate; or (3) the reduction of the risk of forming and dislodging a clot, or thromboembolic risk (to be explained in more detail below). Therefore, it is natural to classify the different treatments into one of these three categories according to their objective. Within each category, a variety of pharmacological, surgical, and device therapies are utilized. Depending on the type of atrial fibrillation (paroxysmal, persistent, or permanent) and symptoms, an appropriate therapy can be selected. Typically, a pharmacological approach is used first for treating AF, along with lifestyle changes such as limiting the intake of alcohol and caffeine. When medications do not work, are not tolerated, or lose their effectiveness over time, surgical and/or device therapy may be required.[4]

Restoration and maintenance of sinus rhythm

One treatment strategy for patients with AF, termed rhythm control, is to reestablish and maintain normal sinus rhythm since this can improve symptoms, correct atrial function and structure, reduce the risk of blood clot formation (thereby reducing stroke risk), and potentially reduce the need for long-term treatment with anticoagulants. Regardless of whether underlying heart disease is present in a patient, restoring sinus rhythm is associated with improved oxygen utilization, lifestyle improvements, and increased exercise capacity.[5]

The primary advantages of rhythm control treatments are improved cardiac function and reduced symptoms in some patients. While a rhythm control strategy can help reduce the frequency of AF, it may not eliminate it all together. As a result, most patients using rhythm control treatments are still required to take anticoagulants on a long-term basis to reduce their risk of blood clots and strokes.

Cardioversion and pharmacologic rhythm maintenance

The most common way to return the heart to sinus rhythm is through direct current cardioversion – the restoration of the heartbeat to normal function by electrical countershock. Another approach is chemical cardioversion, which involves the use of antiarrhythmic drugs to convert the heart rhythm to normal.

Regardless of whether an electrical or pharmacological approach to cardioversion is used, patients are generally also required to take anticoagulants for some period after the cardioversion to prevent blood clots from forming while the atria recover from the stunning of the cardioversion procedure. Some patients are also required to take such medication before the cardioversion to reduce the risk of stroke due to the cardioversion itself. This is separate from the need for long-term treatment with anticoagulants due to the possibility of AF recurrence.

The relatively high rate of AF recurrence using a cardioversion and antiarrhythmic medication strategy for rhythm control is one of the key disadvantages of this treatment approach. After successfully being returned to a normal sinus rhythm, only 20–30 percent of patients remain in sinus rhythm after one year. Although this percentage can be increased to 40–80 percent through the sustained use of antiarrhythmic drugs,[6] medications that affect the electrical properties of cells in the heart to help prevent the occurrence of AF, the overall risk of recurrence remains significant. Antiarrhythmic medications also have serious potential side effects, including the development of new, abnormal heart rhythms.[7]

Catheter-based pulmonary vein isolation

Catheter ablation is a minimally invasive procedure used to terminate AF by eliminating and/or "disconnecting" the pathways supporting the initiation and maintenance of AF. Catheters introduced into the heart direct energy to destroy tissue in specific areas (mostly located in or around the pulmonary veins) that are the source of AF, and to prevent it from initiating or conducting any type of electrical impulse to the rest of the heart, thereby allowing normal sinus rhythm to continue. While there are several variations of catheter ablation procedures currently in use to address AF, they all seek to either electrically isolate or eliminate the pulmonary vein triggers of AF and/or eliminate any other areas in the left or right atrium capable of initiating or maintaining AF. For the sake of simplicity, all of these varied procedures will be categorized together under the term "pulmonary vein isolation" in this example.

Cox–Maze surgery

The primary surgical approach to restoring sinus rhythm in patients with AF is the Cox–Maze procedure, during which a series of precise incisions in the right and left atria are made to interrupt the conduction of abnormal electrical impulses and to direct normal sinus impulses to the atrioventricular (AV) node, as in normal heart function.[8] Because this procedure is very invasive and complex, it is usually offered only to patients with a high risk of stroke and who are already undergoing another form of cardiac surgery.

Implantable atrial defibrillators

Another method of restoring sinus rhythm is through an implantable atrial defibrillator. This device delivers small electrical shocks via leads placed in the heart to convert abnormal rhythms to sinus rhythm. Patients can turn them on and off to treat AF when episodes occur, or they

can be set to operate automatically. The device is inserted by a cardiologist in a cardiac catheterization laboratory using X-ray guidance. The primary limitations of atrial defibrillators are their relatively large size and, more importantly, the fact that the shocks they deliver can be quite painful. As such, they are not currently used to treat AF on a widespread basis.

Ventricular rate control

In patients who receive ventricular rate control treatments, no attempt is made to cure or eliminate AF. Rather, these treatment alternatives are focused on slowing the conduction of electrical impulses through the AV node, the part of the heart's conduction system through which all impulses from the atria typically need to pass before activating the ventricles. By controlling the rate at this junction point, the ventricular heart rate can be brought back into the normal range and thereby potentially mitigate symptoms due to the rapid pumping of the heart.[9] Because AF continues, anticoagulants are recommended to prevent blood clot formation and strokes, typically on an indefinite basis. Another disadvantage associated with these treatment options is the fact that it can be difficult to adequately control the heart rate and relieve the symptoms on a long-term basis.[10]

Pharmacological rate control

Rate therapy using various medications leverages the gatekeeper properties of the AV node to reduce the ventricular rate to 60 to 90 beats per minute during AF. Such a change does not eliminate the irregular heartbeat but, by slowing the heart rate, reduces the workload of the heart and potentially the symptoms that a patient may be experiencing.

Catheter ablation of the AV node

Catheter ablation of the AV node is typically reserved as a last resort for patients who have failed other treatment options.[11] This procedure, in which a catheter is inserted into the heart and energy is delivered to destroy the AV node, thereby disconnecting the electrical pathway between the atria and the ventricles. Without an atrial source to drive the contraction of the ventricles, which are responsible for pumping blood to the lungs and body, a permanent pacemaker needs to be implanted at the time of the procedure to restore and sustain regular ventricular contractions. The pacemaker is a device that sends electrical pulses to the heart muscle, causing it to contract at a regular rate. Even though the atria continue to fibrillate, the symptoms of AF are reduced in many patients.

Reduction of thromboembolic risk

Preventive treatment to reduce the risk of blood clots and strokes (thromboembolic risk) in patients with AF is an important consideration in any AF treatment regime. Anticoagulant or antiplatelet therapy medications are commonly used on both a short-term (e.g., before and after electrical cardioversion) and long-term (e.g., in conjunction with ventricular rate control treatments) basis. While anticoagulant and antiplatelet therapies carry a bleeding risk, their use is warranted in patients where the risk of thromboembolic events is greater than the risk of bleeding complications. Key risk factors for stroke in AF patients include previous history of ischemic attack or stroke, hypertension, age, diabetes, rheumatic, structural, or other heart disease, and ventricular dysfunction.[12]

Pharmacological therapy

For many years, the most common drugs used to treat the risk of thromboembolic events were aspirin and warfarin. Aspirin is an over-the-counter medication that is an antiplatelet therapy; platelets are blood constituents that play an important role in the clotting cascade. By affecting the adherence of circulating platelets to one another, aspirin can reduce the likelihood of clot formation. However, aspirin is usually only effective in AF patients who are young and who do not have any significant structural heart disease. Warfarin (Coumadin) is an anticoagulant used to prevent blood clots, strokes, and heart attacks. Warfarin is a vitamin K antagonist which reduces the rate at which several blood clotting factors are produced. The metabolism and activity of warfarin can be affected by various other medications, foods, and physiologic states. As such, the dosage of warfarin needs to be monitored closely and usually necessitates frequent blood tests to check the degree to which it is anticoagulating a patient's blood. Over-anticoagulation with warfarin can lead to a significantly higher bleeding risk for a patient.

The development of direct thrombin inhibitors (DTIs) for prevention of thromboembolic risk has been a major medical advancement. For years, numerous companies sought to develop a therapy to reduce the risk of thromboembolism without the elevated risk of bleeding. The direct thrombin inhibitors are a class of anticoagulants that includes vitamin K antagonists and Factor Xa inhibitors. These medications were initially developed for the prevention of deep vein thrombosis. However, their safety profile made them ideally suited for use in patients with atrial fibrillation not due to valvular heart disease. Dabigatran (Pradaxa®), the commercially available DTI, received US Food and Drug Administration (FDA) approval in October 2010[13] for prevention of stroke and systemic embolism in patients with non-valvular AF. The American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recently gave dabigatran a Class I indication recommendation[14] for use as an alternative pharmacologic agent to warfarin based on the results of two large studies. The PETRO study evaluated 502 patients with non-valvular atrial fibrillation and increased risk of thromboembolism. Study results demonstrated non-inferiority to warfarin.[15] The RE-LY study then evaluated two different does of dabigatran in 18,113 patients compared to warfarin and demonstrated non-inferiority and superiority to warfarin depending on the dose.[16] The second DTI rivaroxaban (Xarelto®) was approved by the FDA for prevention of stroke in patients with non-valvular AF in November 2011.[17] This was the result of the ROCKET AF study which evaluated 14,264 patient with non-valvular AF and increased risk of stroke. The results demonstrated non-inferiority to warfarin therapy, but a statistically significant reduction in intracranial bleeding without a mortality benefit.[18] This second DTI offers the advantage of being a once-a-day medication compared to dabigatran which must be taken twice a day. Both of these therapies have been widely adopted because they do not require regular monitoring of blood thinning effects as warfarin does.

Clinical solution profile

With the universe of existing solutions defined, the next step is to assess the clinical rationale for why and when each one is used. This includes researching the following areas:

- **Mechanism of action:** Review what has been learned about the disease in terms of the steps or sequence of events that occurs – also called its mechanism(s) of action. Then, identify which disease mechanisms are targeted by a given solution option and how each one seeks to affect the disease.
- **Indications:** Identify the patient populations for which each solution is indicated or contraindicated. For drugs and devices, consider the specific indications approved by the FDA or other regulatory bodies outside the US. For any type of invasive procedure, determine whether there are specific patient segments for which the solution is recommended and understand why.
- **Efficacy:** Define the benefits for each solution. Ideally, these should be measurable benefits (e.g., reduction in mortality), which are best demonstrated by **clinical trials** for relevant solution types.
- **Safety:** Describe the risks of each solution, including precautions and adverse reactions.

Working Example
Clinical solution profile for pulmonary vein isolation

Pulmonary vein isolation seeks to prevent abnormal electrical impulses that initiate and maintain AF from reaching the atria. The procedure is focused on destroying, or ablating, the abnormal "triggers" that originate in and around the pulmonary veins, or creating lesions to effectively isolate them such that they can no longer electrically communicate with the rest of the heart.

The procedure is performed using conscious sedation (intravenous medications for pain and anesthesia) or general anesthesia, depending on the complexity and length of the planned procedure. Patients also receive an injection of local anesthetic to the groin where catheters are inserted (there is usually minimal patient discomfort). The procedure is performed by a cardiac electrophysiologist and can take between three to six hours, depending on the number of areas treated (although estimates range from as few as two to as many as 10 hours). Careful monitoring and a series of tests are completed following the procedure. If there are no complications, patients can be discharged from the hospital after approximately 24 hours. Patients generally resume their normal activities after two or three days.

Mechanism of action

During the pulmonary vein isolation procedure, multiple catheters are advanced through the blood vessels and positioned in various locations of the heart chambers. The catheters are used to electrically stimulate the heart and intentionally trigger AF, after which the catheters record and/or map the heart's electrical activity in and around the pulmonary veins and atria. Using this data, the tissue responsible for the abnormal electrical impulses causing AF can usually be identified. A different type of catheter then can be used to apply energy to destroy, or ablate, this tissue. Radiofrequency energy can be used to heat the tissue to create the lesions, or cryothermy can be used to create the lesions through freezing. Ultrasound and laser techniques are also under development.

Ablation lesions are placed at the interface between the atrial tissue and pulmonary veins to effectively create continuous encircling lesions which electrically isolate the pulmonary veins so that any abnormal impulses originating in them cannot reach the rest of the heart and initiate AF (see Figure 2.2.2). Ablating too deep in the pulmonary veins can cause narrowing, which will cause long-term complications for the patient. The lesions heal within four to eight weeks, forming scars around the pulmonary veins. The use of this technique can "cure" AF in many patients.

Indications

Technologies used by physicians to treat atrial fibrillation using pulmonary vein isolation can be separated into diagnostic mapping systems and therapeutic ablation systems, including radiofrequency ablation products and cryoballoon catheter ablation devices.[19] In the US, the FDA has approved both technologies for clinical use in patients with paroxysmal atrial fibrillation. The same technologies are also used to perform the procedure in patients with persistent or permanent atrial fibrillation, although these indications are not FDA-approved and so technically are considered "**off-label**."[20,21] Guidelines released by the American College of Cardiology, the American Heart Association, and the European Cardiology Society in 2012 specified that the procedure has a Class I indication recommendation for patients with paroxysmal atrial fibrillation who are symptomatic and refractory to medications. It also has a 2A indication recommendation (slightly lower but still recommended indication)[22] for patients with paroxysmal atrial fibrillation who are symptomatic with limited or no drug therapy. Lastly, it has a 2A indication for patients with persistent atrial fibrillation who are symptomatic. It is not indicated for patients with permanent atrial fibrillation or that will soon be identified as long-standing persistent atrial fibrillation.[23]

Based on the approach, pulmonary vein isolation is most successful for patients with AF originating in the

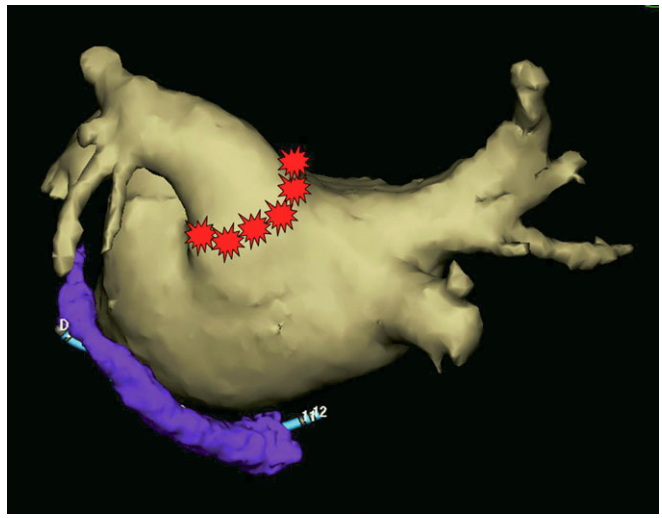

FIGURE 2.2.2
A three-dimensional image of the left atrium and pulmonary veins prior to pulmonary vein isolation (obtained using NavX™ navigation and visualization technology by St. Jude Medical). The star-shaped marks indicate the targeted region for pulmonary vein isolation; the structure beneath the left atrium illustrates the position of the coronary sinus, which wraps around the atria (courtesy of Amin Al-Ahmad and Paul Wang, Stanford University).

pulmonary vein(s), although continued variations in the procedure have additionally incorporated the identification and ablation of non-pulmonary vein triggers, such as those in the atria. However, since it is nearly impossible for clinicians to determine the origin of the arrhythmia without intracardiac mapping, which is too invasive and resource intensive to use on all patients as a screening tool to determine whether they need subsequent pulmonary vein ablation, clinicians typically need to rely on the clinical pattern and patient profile to determine whether a patient will be a good candidate for the procedure.

Efficacy

While there have been numerous non-controlled studies demonstrating the efficacy of varied types of pulmonary vein isolation in patients primarily with paroxysmal AF, there are several **randomized controlled trials** comparing pulmonary vein isolation with **standard treatments**. While each of the studies has limitations, they all report differences in favor of an ablation strategy in terms of relevant outcomes.

Wazni et al. (2005) conducted a small, randomized, unblinded trial that compared the procedure with a rhythm-control strategy. In this study, the magnitude of benefit in reducing AF recurrence was large at one year (13 percent recurrence in pulmonary vein isolation versus 63 percent recurrence in the medical group). There was also an improvement in quality that was considered clinically significant.[24]

Pappone et al. (2006) conducted a larger randomized trial to compare pulmonary vein isolation with antiarrhythmic drug therapy in patients with paroxysmal AF. This study concluded that pulmonary vein isolation is more successful than drug therapy with few complications. 86 percent of patients receiving pulmonary vein isolation were free from recurrent atrial tachyarrythmias versus 22 percent of patients receiving antiarrhythmic drug therapy.[25]

Wilber et al. (2010) conducted a multi-center controlled, 2:1 randomized trial to investigate the effectiveness of the Thermacool system (Biosense Webster). This study evaluated 167 patients and demonstrated that 66 percent of those treated with the catheter technique versus 16 percent treated with anti-arrhythmic drugs were free from atrial fibrillation at the nine-month primary endpoint.[26] This study led to the approval of the first combined diagnostic mapping and therapeutic ablation system for atrial fibrillation.

Table 2.2.3 Common complication rates for pulmonary vein isolation (from Atul Verma and Andrea Natale, "Why Atrial Fibrillation Should be Considered for First Line Therapy," *Circulation*.

Complication	Rate of occurrence
Transient ischemic stroke	0.4 percent
Permanent stroke	0.1 percent
Severe PV stenosis (greater than 70 percent, symptomatic)	0.3 percent
Moderate PV stenosis (40–70 percent, asymptomatic)	1.3 percent
Tamponade/perforation	0.5 percent
Severe vascular access complication	0.3 percent

Overall, these studies built the foundation for the first approved system for treatment of atrial fibrillation using pulmonary vein isolation. As a result, several ongoing studies are now broadening the experience with pulmonary vein isolation in an effort to gain approval for additional systems for treatment. Ultimately, long-term survival data will be important to demonstrate the value of such technologies in the scheme of therapies for AF.

Safety

While pulmonary vein isolation is generally considered safe when performed by experienced doctors, there are serious risks to consider, especially in patients in whom the likelihood of success may be low due to various factors such as structural heart disease. Complications from the procedure include those shown in Table 2.2.3 (based on pooled data from six studies involving more than 1,000 patients).

The procedure also can result in valvular injury, esophageal injury, and proarrhythmia. Complications appear to be declining with modifications to the procedure, new technology, and greater clinician experience. Advocates for the procedure assert that it is safe and may reduce **morbidity** and mortality associated with medical therapy.[27] Critics acknowledge that the short-term safety of newer ablation procedures has improved, but maintain that serious life-threatening complications do exist and that long-term safety is relatively unknown.[28]

Economic solution profile

For each existing solution, it is important to understand the financial impact at the individual level, as well as at the level of the healthcare system. The innovator should seek to identify the costs of providing the solution (diagnosis, drug cost, procedure, hospital stay, rehabilitation, ongoing management, etc.), as well as potential cost savings for using one particular solution versus another. This information will be considered in combination with the efficacy or effectiveness of the solutions later in the chapter.

Remember to determine the total cost of a solution across the entire **episode of care**. A long-term treatment, such as medical therapy, should be evaluated for its long-term beneficial potential for the estimated remaining lifetime of a patient versus the benefits of one-time surgical or device therapy. It is also important to take into account how cost-effective each solution is perceived to be by the various stakeholders in the healthcare system. **Reimbursement** is another critical consideration; however, it will be evaluated in more detail later in the biodesign innovation process (see 4.3 Reimbursement Basics).

Working Example

Economic solution profile for pulmonary vein isolation

The cost of pulmonary vein isolation procedures varies and limited data is available. However, in a Canadian study designed to compare the cost of medical therapy to catheter ablation in patients with paroxysmal AF, the cost of the procedure was found to range from $16,278 to $21,294, with a median estimate of $18,151. Follow-up costs ranged from $1,597 to $2,132 per year.[29]

In another study, Verma and Natale found that the initially high cost associated with pulmonary vein isolation would offset the ongoing costs of antiarrhythmic medication in year three, assuming a 72 percent ablation cure rate after 1.5 procedures. After four years, ablation becomes more cost-effective than treatment with antiarrhythmic medication.[30]

Additional studies have attempted to evaluate the economics of catheter ablation with an eye to selecting the best patient candidates for the procedure. One European study compared the costs of medical therapy for atrial fibrillation, with its accompanying need for long-term management and monitoring, with the costs of ablation. The authors concluded that catheter ablation was a cost-effective procedure primarily in patients with paroxysmal atrial fibrillation who are refractory to antiarrhythmic medications, especially if the success of the procedure and accompanying benefit in **quality of life** persist for more than five years, and the complication rate is low. (The authors noted that the lower complication rates experienced in high-volume centers would further increase the cost-effectiveness of the procedure.) However, for patients whose quality of life is not significantly affected by atrial fibrillation, or those whose poor quality of life is attributable to other health conditions besides atrial fibrillation, catheter ablation was unlikely to be cost effective.[31]

As noted earlier, the lack of long-term outcome data on quality of life and potential reduction of adverse outcomes (e.g., stroke reduction) hampers definitive statements about cost-effectiveness. A recent systematic review and meta-analysis sought to address this issue by reviewing studies that described outcomes at three years post-treatment and beyond, with a mean follow-up of more than 24 months after the index procedure. Data extracted from 19 studies found 53.1 percent of patients undergoing a single ablation procedure were free of atrial arrhythmia at long-term follow up and that, with multiple procedures (the average number per patient was 1.51), the long-term success rate was 79.8 percent.[32] Recognizing the importance of the long-term results to patient decision-making, as well as the determination of cost-effectiveness, the authors concluded, "The data presented in the current study suggest that long-term freedom of atrial arrhythmia can be achieved in the majority of AF cases, taking into account the need for multiple procedures in a significant proportion of patients."[33]

Utilization solution profile

Next, an innovator should seek to provide an overview of how each solution is currently used in clinical practice. This may include when (and why) certain solutions are used and the frequency of procedures. Physician organizations disseminate best practices for treatment regimens via guideline documents, which may be helpful. However, keep in mind that physicians may deviate from or modify these guidelines (as well as FDA regulations) in certain medically appropriate circumstances. Physicians are legally obliged to provide standard of care to their patients. As medical practice evolves, it sometimes outpaces regulatory approvals. This is particularly relevant in the area of pulmonary vein isolation devices since tens of thousands of procedures are performed annually using existing ablation devices on an off-label basis. This type of usage highlights the importance of gaining insight into how diagnostics, drugs, surgical procedures, devices, and other services are used by the majority of physicians in everyday practice, not just what usage they are cleared for in the market.

Working Example

Utilization profile for pulmonary vein isolation

Without access to costly analyst reports, getting detailed information about the number of catheter ablation procedures performed each year can be challenging. In 2011, approximately 50,000 AF ablations were performed in the US, with another 60,000 performed in Europe.[34] The vast majority of these AF ablations were pulmonary vein isolation. Use of the AF ablation is growing at a rate of roughly 15 percent per year.[35]

Traditionally, pulmonary vein isolation had been used as a therapy after a patient has failed at least one (if not two or more) antiarrhythmic drugs or had an intolerance or contraindication to antiarrhythmic therapy. As a result, the Centers for Medicare and Medicaid Services (CMS), as well as many private insurance plans, covered pulmonary vein isolation as a second-line therapy for specific patient groups. However, with changes in the guidelines in 2012, first line therapy is now broadly covered. (See 2.3 Stakeholder Analysis for more information about the role of public and private insurance companies – or **payers** – in the **medtech** field.)

Emerging solution profile

Clinical solutions change over time as companies develop new products and physicians (and other care providers) develop new techniques. For some disease states, new solutions are introduced at a rapid rate and have the potential to dramatically change the landscape. Researching emerging solutions provides innovators with a working understanding of new diagnostics, treatments, and management tools potentially on the horizon, the areas they are targeting, and their timeline for their development and/or entry into the market. Although available information may be limited, try to cover as many of the topics outlined under the clinical solution profiles section as possible.

When investigating emerging solutions, look for leads by talking with experts in the field who might be aware of what technologies are under development. Clinicians may be aware of new products and services being tested in clinical trials, and investors may have information about new products and companies seeking funding. In terms of useful secondary research, innovators can learn a great deal by looking carefully at the abstracts of the relevant clinical meetings as soon as they are published to get late-breaking information about new technologies. Clinical trial databases are another source of information about products under development. For each emerging solution, seek to understand which mechanism or symptom of the disease it addresses and how it works. Evaluate the hypothesized efficacy and safety of the solution, as well as its anticipated time to market.

Working Example

Emerging solution profile for left atrial appendage occluder

As much as 90 percent of the embolisms, or clots that dislodge, associated with AF originate from the left atrial appendage (LAA), a small pouch-like sac attached to the left atrium.[36] Traditionally, chronic anticoagulation therapy has been used to manage this risk; however, these drugs can present safety and tolerability problems, particularly in patients older than 75 years of age (the group accounting for approximately half of AF-related stroke patients). Unfortunately, antiplatelet medications, such as aspirin, are less effective compared to drugs such as warfarin. Long-term warfarin therapy has additional downsides in that it requires costly and inconvenient patient monitoring, can have unpredictable drug and dietary interactions, and can be difficult to administer due to the frequent dosage adjustments needed to keep the risks of clotting and bleeding events appropriately balanced.

Since most clots in AF form in the LAA, one option for preventing clot formation would be to occlude or eliminate the LAA through surgical means. However, the Left Atrial Appendage Occlusion Study (LAAOS), which evaluated LAA occlusion performed at the time of coronary artery bypass grafting, showed that complete occlusion was achieved in only 45 percent of cases using sutures and in 72 percent of cases using a stapler.[37]

These observations laid the foundation for the development of device-based approaches to address the shortcomings of surgery and traditional drug therapy by controlling embolisms that come from thrombus in the LAA to reduce the risk of stroke. These devices work by mechanically preventing communication between the appendage and left atrium, thereby isolating or occluding the LAA from blood flow that would prevent harmful-sized emboli that may form in this location from exiting into the blood stream and traveling to the brain, resulting in a stroke.[38] The LAA occluders typically have a nitinol wire cage with a material coating that promotes endothelialization on the atrial side such that approximately four months following implantation, the device becomes part of the atrial wall. These devices have been designed to be placed surgically during open heart surgery, through minimally invasive approaches, or percutaneously.[39]

Appriva Medical (later acquired by ev3, Inc.) was the first company to develop a device to be placed percutaneously. The device received CE mark approval in Europe for its nitinol-based PLAATO™ (Percutaneous Left Atrial Appendage Transcatheter Occlusion) system in 2002 (see 4.2 Regulatory Basics for more information about CE marking and other forms of regulatory clearance).[40] Ultimately, the device was not commercialized in the US.

However, the WATCHMAN™ device (by Atritech, later acquired by Boston Scientific) is actively being targeted to the US market. In 2009, an FDA review panel initially voted 7:5 to recommend approval of the device, yet the agency opted to not grant its approval in 2010, citing concerns over safety from procedural complications in the initial 800-patient PROTECT AF study, as well as other issue with the conduct of the trial.[41] The initial study showed significantly lower hemorrhagic stroke in the device compared to treatment with warfarin. However, more safety events occurred in the device group.[42] The follow up PREVAIL study demonstrated non-inferiority comparing the device to warfarin for prevention of ischemic stroke and systemic embolization,[43] as well as a lower rate of procedural complications. Based on these results, a panel of FDA advisors voted 13:1 to recommend approval for WATCHMAN.[44] The FDA still registered additional data, and a third panel meeting was convened a lyear later. As of November 2014, a final decision from the FDA was still pending.

Lastly, the Amplatzer device (by AGA Medical, later acquired by St. Jude Medical), which was originally designed for the closure of atrial septal defects, has also been used to close the appendage but has not received regulatory approval for this indication in the US.

Solution landscape

Once a comprehensive set of data has been gathered, innovators should synthesize all of the findings into a comprehensive framework that summarizes the solution landscape. Such a summary should include an overview of what is known about a disease's mechanisms of action, which mechanisms are targeted by what solutions, and which are not currently targeted.

After creating an overarching summary, innovators should assess the more granular information they have gathered in a variety of different ways in an effort to better understand where potential solution gaps exist. Experiment with several of these approaches, choosing the ones that seem most likely to highlight opportunities in the solution landscape.

Causes versus consequence Certain solutions attack the cause of the disease while others ameliorate symptoms. In the case of atrial fibrillation, rhythm control works to target the disease mechanism and rate control targets the improvement of symptoms associated with rapid ventricular rates. It might be helpful to draw a tree diagram, with the causes shown nearer to the trunk and symptoms branching out from them. Place each solution above the location in the diagram that it targets to understand the hierarchy and where new solutions might supersede existing alternatives.

Mechanism of action frequency tally Typically, a number of solutions may target a single mechanism of action. Based on the clinical need area, more than one mechanisms may be targets. Count the treatments in each area to see which spaces are more crowded than others. In AF, for example, it would be instructive to count the number of therapies directed at treatment of primary arrhythmia versus the control of ventricular rate.

Patient segment frequency plot Different solutions are indicated and utilized for different patient populations. Plotting how many options are available to each segment may uncover underserved populations. In AF, for example, elderly patients tend to have better outcomes with a rate control strategy as opposed to a rhythm control strategy; this is not same for younger patients.[45]

Risk versus benefit Summarize the risks and benefits of each solution. In doing so, think about the inherent trade-offs associated with each one and where opportunities exist for lowering risks while improving a wide range of benefits.

Cost versus effectiveness Cost-effectiveness analysis puts a slightly different twist on risk–benefit analysis by specifically describing the trade-offs between the cost of the various solutions and their clinical efficacy and/or the outcomes they deliver. Performing this analysis for existing (and emerging) solutions is the first step in initiating a market analysis for the needs under consideration and estimating their potential value to the stakeholders they affect (see 2.4 Market Analysis for a more detailed exploration of this topic). The classic way of presenting this analysis is to create a grid with effectiveness on one axis and cost on the other and then place solutions within that construct, based on what is known about their performance and price. By viewing the solution landscape in this way, innovators can potentially identify gaps that may be associated with an opportunity to create value by developing a solution with a better combination of cost and effectiveness.

Once a variety of analyses have been performed, innovators may find it useful to summarize their key takeaways in an overall gap analysis of available solutions.

Working Example

Summary of the solution landscape for atrial fibrillation

AF is the most common sustained cardiac arrhythmia, affecting millions of people in the US each year, yet there is not a clearly defined and agreed-upon strategy for the treatment of the disease.[46] Treatments to address the three categories of sinus rhythm maintenance, rate control, and thromboembolic risk are often administered according to the general guidelines that exist in the field. Typically, clinicians seek to achieve rhythm control through the use of cardioversion and antiarrhythmic drugs. If that approach fails, the next step is to try ventricular rate control therapy or AV node ablation with the insertion of a pacemaker. Throughout the treatment process, thromboembolic risk is treated on an as-needed basis, typically with anticoagulants. A visual representation of these treatment options is presented in Figure 2.2.3. (Without delving into all of

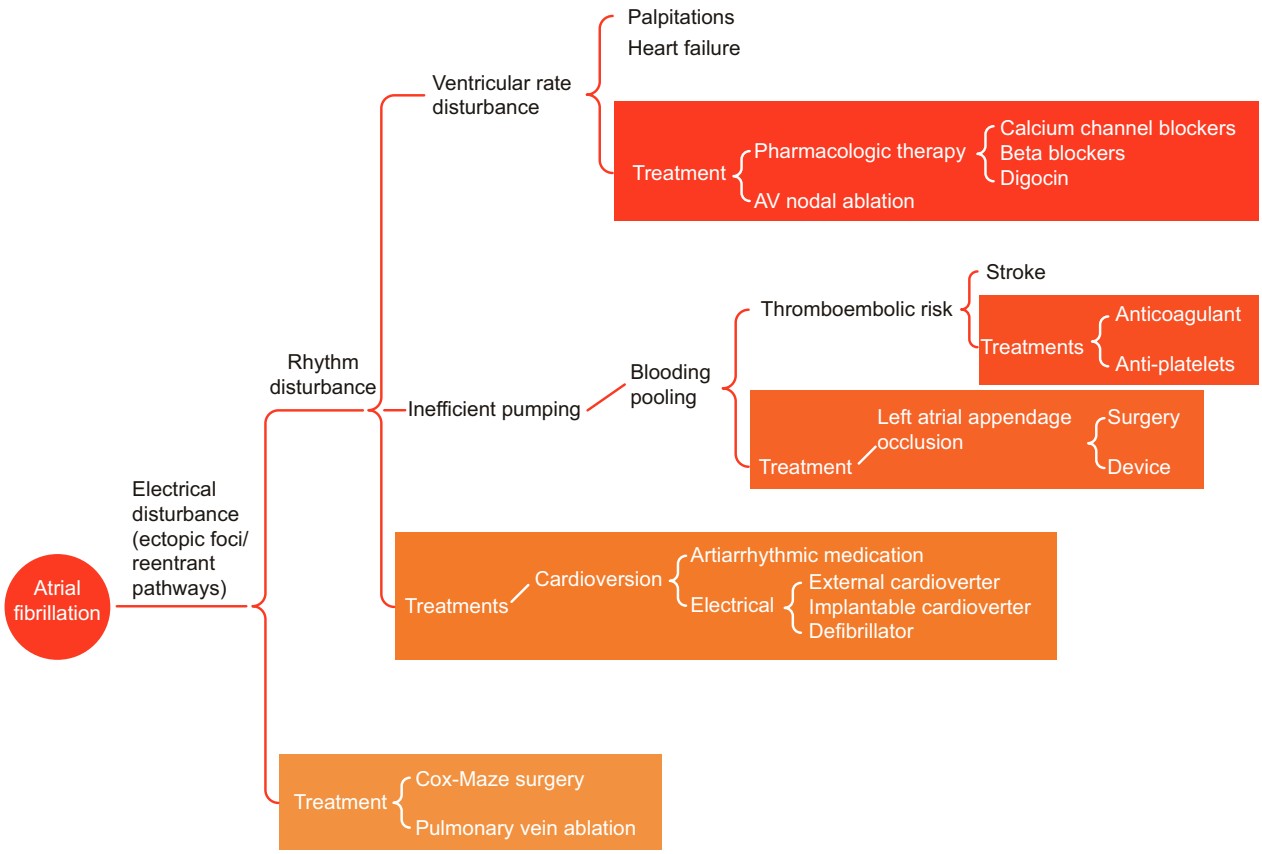

FIGURE 2.2.3
A high-level summary of select AF treatment options.

the solutions considered throughout this chapter, innovators can consider the debate regarding rhythm and rate control as an example of how to compare solution options.)

Until recently, there was little evidence that supported the traditional, somewhat sequential approach that favored rhythm control over rate control as a first-line therapy. In the AFFIRM trial, which included 4,060 patients, researchers compared the effects of long-term rhythm management and rate management treatment strategies to determine whether one approach offered significant advantages over the other in terms of benefits and risks to patients. Over a mean follow-up time of 3.5 years, the results of the study showed that there were no clear advantages to rhythm versus rate control. In fact, there was a trend toward increased mortality in the rhythm control group. The patients in the rhythm control group were also significantly more likely to be hospitalized and have adverse drug effects than those in the rate control group.[47] The conclusion of the researchers was that rate control therapy should be considered a primary approach to the treatment of AF and that rhythm control should be abandoned early if it is not fully satisfactory.[48] However, this study focused on an older patient population so the generalizability of the study needs to be approached cautiously. As well, this trial did not include catheter ablation strategies for achieving rhythm control.

This information highlights the fact that while the study is an important first step in starting to evaluate one type of treatment option against another in the management of AF, more research is needed before conclusive guidelines that address all patient variations and the use of newer therapies are in place.

At a high level, the benefits and risks of the primary treatment alternatives for AF are summarized in online

Appendix 2.2.1. A gap analysis is provided in online Appendix 2.2.2. As can be seen, despite the significance and consequences of AF, many areas remain open for further research and development. Some examples include higher efficacy ablation procedures, improved medications for rhythm or rate control, better devices for the treatment of the thromboembolic complications of AF, and safer and less invasive surgical procedures. By understanding the entire treatment landscape, gaps and inadequacies in current treatment methods can be used to help identify where promising clinical needs may exist that require innovative solutions.

Online Resources

Visit www.ebiodesign.org/2.2 for more content, including:

Activities and links for "Getting Started"

- Develop an overview of solution options
- Evaluate clinical solution profiles
- Analyze economic solution profiles
- Explore utilization solution profiles
- Investigate emerging solution profiles
- Summarize the solution landscape

Videos on existing solutions

Sample appendices that demonstrate

- A summary of risks and benefits for atrial fibrillation
- A gap analysis matrix for atrial fibrillation

CREDITS

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NOTES

1 All quotations are from interviews conducted by the authors, unless otherwise cited. Reprinted with permission.

2 "Lung Volume Reduction Surgery," Thoracic Surgery Division, University of Maryland Medical Center, http://umm.edu/programs/thoracic/services/lvr (October 16, 2013).

3 "Understanding Emphysema?," American Lung Association, http://www.lung.org/lung-disease/emphysema/understanding-emphysema.html (October 16, 2013).

4 "What is Atrial Fibrillation?," Cleveland Clinic: Heart and Vascular Institute, http://my.clevelandclinic.org/heart/atrial_fibrillation/afib.aspx (October 16, 2013).

5 Nicholas S. Peters, Richard J Schilling, Prapa Kanagaratnam, and Vias Markides, "Atrial Fibrillation: Strategies to Control, Combat, and Cure," *The Lancet*, 2002, p. 596.

6 Leonard Ganz, "Patient Information: Atrial Fibrillation (Beyond the Basics)," Up-to-Date, http://www.uptodate.com/contents/atrial-fibrillation-beyond-the-basics (October 16, 2013).

7 Ibid.

8 "What is Atrial Fibrillation?," Cleveland Clinic: Heart and Vascular Institute, http://my.clevelandclinic.org/heart/atrial_fibrillation/afib.aspx (October 16, 2013).

9 Ganz, op. cit.

10 Ibid.

11 Peters, Schilling, Kanagaratnam, Markides, loc. cit.

12 Ibid., p. 600.

13 "FDA Approves Pradaxa to Prevent Stroke in People with Atrial Fibrillation," U.S. Food and Drug Administration, October 19, 2010, http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm230241.htm (March 27, 2014).

14 A Class I indication recommendation means that there is evidence and/or general agreement that the treatment should be utilized as indicated. As the consensus to use the treatment increases, its class of indication is improved. Class I is the highest recommendation.

15 M. D. Ezekowitz, P. A. Reilly, G. Nehmiz, T. A. Simmers, R. Nagarakanti, K. Parcham-Azad, K. E. Pedersen, D. A. Lionetti, J. Stangier, and L. Wallentin, "Dabigatran with or without Concomitant Aspirin Compared with Warfarin Alone in Patients with Nonvalvular Atrial Fibrillation (PETRO Study)," *American Journal of Cardiology*, November 1, 2007, http://www.ncbi.nlm.nih.gov/pubmed/17950801 (March 27, 2014).

16 Connolly et al., "Dabigatran versus Warfarin in Patients with Atrial Fibrillation," *New England Journal of Medicine*, September 17, 2009, http://www.nejm.org/doi/full/10.1056/NEJMoa0905561 (March 27, 2014).

17 "FDA Approves Xarelto to Prevent Stroke in People with Common Type of Abnormal Heart Rhythm," U.S. Food and

Drug Administration, November 4, 2011, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm278646.htm (March 27, 2014).

18 Patel et al., "Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation," *New England Journal of Medicine*, September 8, 2011, http://www.nejm.org/doi/full/10.1056/NEJMoa1009638 (March 27, 2014).

19 Jeffrey Mandell, Frank Amico, Sameer Parekh et al., "Early Experience with the Cryoablation Balloon Procedure for the Treatment of Atrial Fibrillation by an Experienced Radiofrequency Catheter Ablation Center," *Journal of Invasive Cardiology*, June 2013, http://www.ncbi.nlm.nih.gov/pubmed/23735354 (April 10, 2014).

20 Oussama Wazni, Bruce Wilkoff, and Walid Saba, "Catheter Ablation for Atrial Fibrillation," *New England Journal of Medicine*, December 15, 2011, http://www.nejm.org/doi/pdf/10.1056/NEJMct1109977 (April 10, 2014).

21 If a device is used in a way that deviates from the indication on the FDA-approved label, it is called "off-label" usage. While physicians may elect to engage in off-label use, the manufacturer of the device is not allowed to promote any methods of use other than those cleared by the FDA.

22 A Class 2A indication means that the weight of evidence/opinion is in favor of the treatment's usefulness/efficacy as indicated.

23 Calkins et al., "2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation," EP Europace, March 27, 2012, http://europace.oxfordjournals.org/content/early/2012/02/29/europace.eus027 (March 27, 2014).

24 Wazni et al., "Radiofrequency Ablation versus Antiarrhythmic Drugs as First-Line Treatment of Symptomatic Atrial Fibrillation," *JAMA*, 2005, pp. 634–40.

25 Pappone et al., "A Randomized Trial of Circumferential Pulmonary Vein Ablation versus Drug Therapy in Paroxysmal Atrial Fibrillation," *Journal of the American College of Cardiology*, 2006, pp. 2340–7.

26 Wilber et al., "Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients with Paroxysmal Atrial Fibrillation," *Journal of the American Medical Association*, January 27, 2010, http://jama.jamanetwork.com/article.aspx?articleid=185277 (March 27, 2014).

27 Ibid., p. 1219.

28 Benzy J. Pandanilam and Eric N. Prystowsky, "Should Ablation Be First-Line Therapy and for Whom: The Antagonist Position," *Circulation*, August 23, 2005, p. 1227.

29 Khaykin et al., "Cost Comparison of Catheter Ablation and Medical Therapy in Atrial Fibrillation," *Journal of Cardiovascular Electrophysiology*, September 2007, p. 909.

30 Atul Verma and Andrea Natale, "Why Atrial Fibrillation Ablation Should Be Considered First-Line Therapy for Some Patients," *Circulation*, http://circ.ahajournals.org/content/112/8/1214.full (March 27, 2014).

31 Josef Kautzner, Veronika Bulkova, and Gerhard Hindricks, "Atrial Fibrillation Ablation: A Cost or an Investment?," *Europace*, European Society of Cardiology, 2011, http://europace.oxfordjournals.org/content/13/suppl_2/ii39.full.pdf+html (April 10, 2014).

32 Anand N. Ganesan, Nicholas J. Shipp, Anthony G. Brooks et al., "Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation: A Systematic Review and Meta-Analysis," *Journal of the American Heart Association*, March 18, 2013, http://jaha.ahajournals.org/content/2/2/e004549.full.pdf (April 10, 2014).

33 Ibid.

34 Andrew D'Silva and Matthew Wright, "Advances in Imaging for Atrial Fibrillation Ablation," *Radiology and Research Practice*, 2011, http://www.hindawi.com/journals/rrp/2011/714864/ (March 27, 2014).

35 Patrick P. Kneeland and Margaret C. Fang, "Trends in Catheter Ablation for Atrial Fibrillation in the United States," *Journal of Hospital Medicine*, September 2009, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2919218/ (March 27, 2014).

36 B. Meier, I. Palacios, S. Windecker, M. Rotter, Q. L. Cao, D. Keane, C. E. Ruiz, and Z.M. Hijazi, "Transcatheter Left Atrial Appendage Occlusion with Amplatzer Devices to Obviate Anticoagulation in Patients with Atrial Fibrillation," *Catheter and Cardiovasc Intervention*, vol. 60, no. 3, 2003, pp. 417–22.

37 Jeff S. Healey, Eugene Crystal, Andre Lamy, Kevin Teoh, Lloyd Semelhago, Stefan H. Hohnloser, Irene Cybulsky, Labib Abouzahr, Corey Sawchuck, Sandra Carroll, Carlos Morillo, Peter Kleine, Victor Chu, Eva Lonn, and Stuart J. Connolly, "Left Atrial Appendage Occlusion Study (LAAOS): Results of a Randomized Controlled Pilot Study of Left Atrial Appendage Occlusion During Coronary Bypass Surgery in Patients at Risk for Stroke," MedScape, September 9, 2005.

38 Ibid.

39 A procedures that is performed by entering the left atrium via the right atrium across the septum, which is the wall that separates them.

40 "APS: Appriva Medical Receives Approval to Commercialize PLAATO," ANP Pers Support, http://www.perssupport.anp.nl/Home/Persberichten/Actueel?itemId=40776&show=true (October 17, 2006).

41 David Pittman, "Watchman Afib Device Wins FDA Panel Nod," *MedPage Today*, December 11, 2003, http://www.medpagetoday.com/Cardiology/Strokes/43380 (March 27, 2014).

42 David R. Holmes and Robert S. Schwartz, "Controversies in Cardiovascular Medicine," *Circulation*, https://circ.ahajournals.org/content/120/19/1919.full (March 27, 2014).

43 "Final Results of Randomized Trial of Left Atrial Appendage Closure versus Warfarin for Stroke/ Thromboembolic

Prevention in Patients with Non-Valvular Atrial Fibrillation (PREVAIL)," American Heart Association and American Stroke Association, http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_449994.pdf (March 27, 2014).

44 Pittman, op. cit.

45 Philip A. Wolf, Emelia J. Benhamin, Albert J. Belanger et al., "Secular Trends in the Prevalence of Atrial Fibrillation: The Framingham Study," *American Heart Journal*, vol. 131, 1996, pp. 790–5. Cited by Craig T. January, Samuel Wann, Joseph S. Alpert et al., in the "2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation," *Journal of the American College of Cardiology*, 2014, accepted manuscript. http://content.onlinejacc.org/article.aspx?articleid = 1854231 (April 10, 2014).

46 The AFFIRM Writing Group, "A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation," *New England Journal of Medicine*, December 5, 2002, pp. 1825–33.

47 Ibid.

48 Ibid.