2.1 Disease State Fundamentals

INTRODUCTION

In the excitement of having identified one or more compelling needs, innovators' instincts may compel them to quickly jump ahead and begin inventing. However, establishing a detailed knowledge of the relevant disease state, with a particular focus on its mechanism of action, is fundamental to validating any need and understanding how it can best be addressed. Disciplined disease state research is an essential part of the biodesign innovation process and an invaluable activity for clinician and non-clinician innovators alike.

OBJECTIVES

- Understand the importance and role of disease state analysis.
- Know what factors to investigate as part of this research.
- Appreciate how to effectively search for and summarize this information to aid the needs screening process.

Understanding disease state fundamentals involves researching the epidemiology, anatomy and physiology, pathophysiology, symptoms, outcomes, and economic impact of a disease. This information is pertinent to the process of finding a clinical need or in validating a need that has already been established. The process also provides innovators with a critical level of knowledge about a condition so they can be credible when speaking to external healthcare stakeholders, such as physicians or other experts in the field.

See ebiodesign.org for featured videos on disease state fundamentals.

DISEASE STATE FUNDAMENTALS

Performing disease state research is iterative. It begins at the highest level when choosing a strategic focus (chapter 1.1), preparing for observation (chapter 1.2), and creating **need statements** (chapter 1.3). It becomes even more important once need statements have been created. Disease state research serves a critical role in forming the basis for screening multiple **needs** against one another later in the biodesign innovation process (2.5 Needs Selection). Additionally, innovators often underappreciate that a team's understanding of the disease anatomy, physiology, **pathophysiology**, and **mechanism of action** provides the foundation for **concept** generation during the Invent phase of the biodesign innovation process.

Disease state research is first performed using general scientific resources such as medical textbooks or medical information websites, then transitions over time into a more comprehensive, in-depth review of historical and current medical literature. This approach allows the innovator to begin by developing a general understanding of a disease and then become increasingly

knowledgeable about aspects of the condition that are most relevant to the need. Obtaining an understanding of a condition's mechanism of action – or the science behind how the disease works from a biologic or physiologic perspective – is especially important. Some disease states are well understood and, therefore, needs in the field are more readily approachable. Disease states in which the mechanism of action is unclear may pose a significant challenge, and needs in these areas may not be selected for projects for just this reason.

Because disease state research can be tedious, innovators may be tempted to skip this step. Those with a medical background may figure that they already know enough to understand the disease state associated with a need. In contrast, innovators from business or engineering backgrounds may have a tendency to shortcut the research in their enthusiasm to evaluate the market or other factors that will help determine if an opportunity is promising. However, underinvesting in this process is almost always shortsighted. Disease research not only provides a foundation for understanding the underlying disease state, but lends valuable knowledge that aids in the investigation of existing treatments, the current market, and important **stakeholders**. It also helps with ideation – without a sufficient disease state knowledge, brainstorming can stall within the first few minutes of a session. Later in the biodesign innovation process, this information can be used again to assess the clinical, technical, and commercial feasibility of any solution concept that will eventually be developed.

The following example, which references one of the great **medtech** success stories of the 1990s, illustrates that even the most experienced innovators and companies, regardless of their prior experiences and training, can realize significant value from disease state research and should regard the analysis as indispensable.

FROM THE FIELD JOHNSON & JOHNSON

Understanding disease state fundamentals as part of the needs screening process

Johnson & Johnson (J&J), through its subsidiary Cordis, was an early pioneer in the market for bare metal stents, small mesh-like tubular scaffolds which can be used to open narrowed heart arteries. The company dominated the treatment space after the introduction of its Palmaz-Schatz® coronary stent in 1994. J&J held a firm leadership position until 1997 when competition from other medical device manufacturers began to intensify, particularly with the launch of Guidant's Multi-Link® bare metal stent. Seeking a way to regain the company's leadership position while further reducing the need for repeat procedures in patients with coronary artery disease, Bob Croce, J&J's group chairman of Cordis Corporation at the time, went back to the drawing board with his team to reexamine disease state fundamentals as part of the need screening process.

Coronary artery disease occurs when plaque, a mixture of cholesterol and other substances, accumulates over time within the arterial wall, through a process called atherosclerosis (see Figure 2.1.1). This causes a reduction in the available area for blood flow.

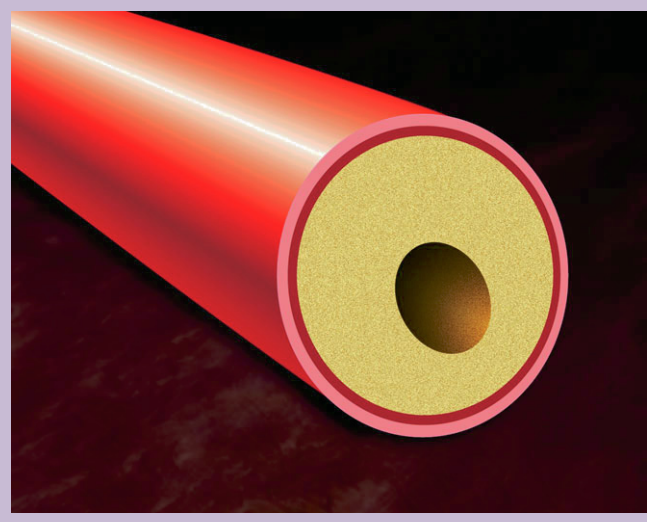


FIGURE 2.1.1
A blood vessel narrowed by atherosclerosis (developed by Yasuhiro Honda; reprinted with permission).

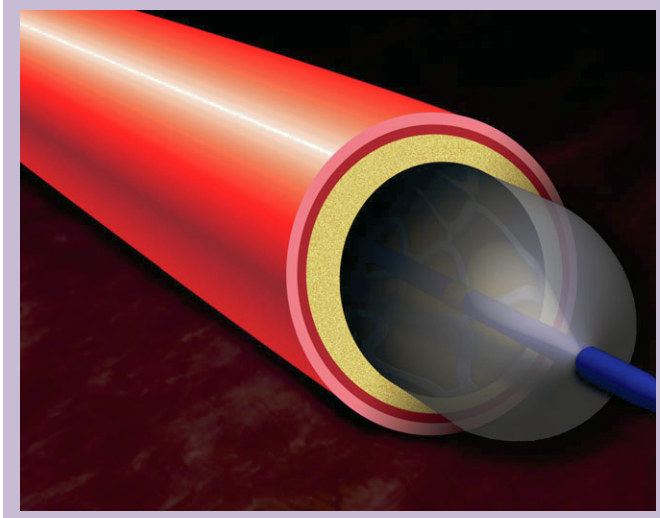
The restriction of blood flow to the heart can result in angina (chest pain) or lead to a myocardial infarction (heart attack), depending on the severity of the narrowing. Nearly 7 million people suffer from angina,[1] and 1.2 million people experience new or recurrent heart attacks each year in the United States (the company's primary market at the time).[2] Approximately 40 percent of these heart attacks are fatal,[3] making cardiovascular disease the leading cause of death in the US. The treatment of coronary artery disease is a major contributor to the roughly $15 billion market for cardiology devices.[4]

Angioplasty, an interventional procedure in which a physician inserts a balloon-tipped catheter into a narrowed artery to increase blood flow, revolutionized the treatment of coronary artery disease in 1977 by providing a less invasive, lower-risk alternative to coronary artery bypass surgery.[5] However, there was often a recoiling effect of the arterial wall, which meant that the artery remained only partially open after the balloon catheter was removed. In addition, there was scarring within the artery as a response to the injury from the balloon – called restenosis – that occurred in 30–40 percent of patients within 6 months of the angioplasty as the body sought to heal the artery.[6] For these reasons, many patients required repeat angioplasty procedures or bypass surgery, resulting in increased risk for the patient and added cost for the healthcare system.

Bare metal stents were incorporated into the balloon angioplasty procedure to address these issues. When the balloon was inflated at the site of the blockage, a stent – a small mesh-like tubular scaffold – was expanded and locked into the wall of the artery (see Figure 2.1.2).

The stent physically held the artery open and prevented it from recoiling once the balloon was extracted. As a result, the number of repeat procedures declined and patient restenosis rates dropped to approximately 20–25 percent. While bare metal stents were widely considered to be a major breakthrough, "The statistics weren't that great," said Croce.[7] "The stents corrected one problem, the retracting of the arterial wall, and they improved outcomes compared to using the balloon alone. Unfortunately, they also caused the re-narrowing of the arteries through neointimal growth." Neointimal growth was the formation of scar tissue within the stent as a result of the trauma involved with the insertion of the stent and the body's reaction to it. Thus, through a different mechanism, the arteries could still eventually become narrowed.

(a)



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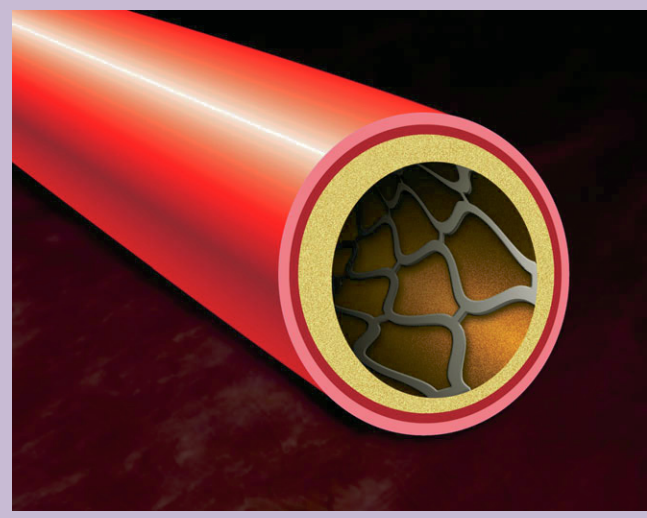

FIGURE 2.1.2
A balloon is used to deploy a stent within the arterial wall (developed by Yasuhiro Honda; reprinted with permission).

To better understand the **need criteria** that any new solution would have to satisfy, Croce and his team spent significant time revisiting the physiology of the coronary arteries and the pathophysiology associated with neointimal growth. One of the most significant insights from this research was that the original disease state had shifted. The need was not just to address atherosclerosis, the build-up of plaque in the vessel wall, but ultimately, the new disease state of restenosis caused by neointimal growth. The fundamentals of the disease state were generally known, so "It wasn't like the cycle of neointimal growth in the arteries was a brand new discovery," recalled Croce. However, "Many smart people in the area had not been trained in neointimal growth for a long time and in some cases they never did understand it since it wasn't important to them in their practice," he continued. By conducting a thorough study of the disease state, Croce and team increased their understanding, as well as their confidence that no opportunities would be overlooked. "No matter how experienced you are, you can't go into this process assuming that you know everything. It's essential to stay open-minded and force yourself to analyze all the different aspects of the disease," he said.

An in-depth understanding of the pathophysiology of the disease was particularly important in this situation because of the solution that was eventually chosen – a combination of drug and device – which eventually became the drug-eluting stent. Only through revisiting the underlying need and studying neointimal growth, a fundamental aspect of the disease state, did the team determine that certain drugs could be used to prevent the problem linked to stent placement. However, the marriage of medical device developers with pharmaceutical scientists was not an easy one. Medical device companies had a **bias** toward engineering a better stent that would not scar the arteries, while pharmaceutical companies were predisposed toward small molecule and biotech solutions, and did not necessarily want or know how to consider device development. "Before drug-eluting stents, there were no major drug-device combination products. So, there was a lot of hesitation on all sides of this project," remembered Croce. In addition, physicians were skeptical that such a novel concept could produce results. Nonetheless, the science behind the disease provided a uniting factor around which all parties could converge and, therefore, served as a critical building block for the effort.

After years of development, J&J's drug-eluting stent moved into **clinical trials**. In its first-in-human studies, the Cypher stent demonstrated in-stent restenosis rates of 0–3 percent and in-segment or vessel restenosis rates of up to only 9 percent, compared to 33 percent in the baremetal stent arm.[8] When Cypher received **FDA** approval in April 2003, J&J decisively regained its leadership position in the treatment of coronary artery disease.

As this case illustrates, understanding a disease state can be a dynamic exercise. In some scenarios, new physiological issues can arise in response to an existing, widely adopted treatment. As a result, innovators must be certain they stay abreast of new developments over time.

An approach to disease state analysis

Disease state research is best approached in a systematic manner, particularly if the need is related to a single, specific disease area. Six key areas, outlined in Table 2.1.1, should be addressed to ensure a thorough understanding of a disease state.

For needs that cross more than one disease area, the innovator should establish a clear understanding of each interrelated condition. Realistically, it may be necessary to take a somewhat broader perspective, paying close attention to those aspects of the various disease areas that are most directly related to the need. In these cases, the anatomy, physiology, and even pathophysiology that are studied may not be for a specific organ or system, but instead for a fundamental biologic process that is shared across the multiple disease areas.

Throughout the remainder of this chapter, atrial fibrillation (AF), a disease in which the heart has an abnormal

Table 2.1.1 Six key areas of disease state analysis.

Focus area	Description
Epidemiology	Describes the causes, distribution, and control of disease in the population.[9]
Anatomy and physiology	Describes the normal anatomy and/or function of the organ system, which may include various organs or areas of the body affected by the need.
Pathophysiology	Describes the disturbance of normal anatomy and physiology caused by a disease or other underlying physical, mechanical, electrical, or biochemical abnormality.
Clinical presentation	Profiles the patient state and clinical status associated with a disease. These include the symptoms (what the patient feels and experiences) and signs of the disease (what one might find on a clinical exam or with lab testing).
Clinical outcomes	Profiles the most common outcomes experienced by patients as a result of having the disease.
Economic impact	Outlines the cost of the disease to the healthcare system.

rhythm, is used as an example to illustrate the types of disease state analysis innovators should perform. Importantly, the evaluation of disease state fundamentals is distinct from understanding the existing solutions used to address the disease. An in-depth review of existing solutions is covered in a separate chapter (see 2.2 Existing Solutions). However, the analysis of available diagnostics, therapies, and management tools may lead to a refined understanding of disease state fundamentals and vice versa.

Epidemiology

Review of disease **epidemiology** is one of the most efficient ways to gain an understanding of the breadth and impact of a particular disease state. This data is extremely helpful when trying to make early decisions in the needs selection process. It also serves as essential inputs to performing market analysis (see chapter 2.4). Understanding the extent and severity of a disease also can be useful in refining a need statement and selecting which needs to take forward.

Effective epidemiology evaluation must be detailed and specific. Innovators should seek data for the disease as a whole, as well as the most relevant patient subsegments. Additionally, they should try to find information about disease dynamics, such as its growth rate, to illustrate how the disease will impact society in the future.

A thorough assessment of epidemiology addresses the *incidence* of a disease, which is the rate at which it occurs (i.e., number of new cases diagnosed per year). It will also include *prevalence* data, or a measurement of all people afflicted with the disease at a given point in time.

For the AF example, innovators should start by capturing incidence and prevalence data for the overall disease state and its most meaningful subgroups (e.g., paroxysmal AF). They should also understand how incidence and prevalence rates are changing.

Working Example
Epidemiology of atrial fibrillation

Estimates of the diagnosed incidence and prevalence of AF in the US vary widely in medical literature. These inconsistencies are attributable to differences in study design, covered time period, birth cohort, and temporal effects, as well as improvements in AF diagnosis.[10] The objective of a study published in 2012 was to estimate and project the incidence and prevalence of diagnosed AF among adults in the US from 2010 through 2030. Researchers used data from a large health insurance claims database for the years 2001 to 2008 to represent

a geographically diverse 5 percent of the target population. The trend and growth rate in AF incidence and prevalence was then projected by a dynamic age-period cohort simulation progression model that included all diagnosed AF cases in future prevalence projections regardless of follow-up treatment, as well as those cases expected to be chronic in nature.[11] The model showed that AF incidence was 1.2 million cases in 2010 and expected to double to 2.6 million cases in 2030. Prevalence, in turn, was forecast to increase from 5.2 million in 2010 to 12.1 million cases in 2030.[12]

This dramatic increase in prevalence is due, in part, to the aging of the general population. Additionally, improvements in medical care are leading to increased longevity in patients with coronary artery disease, hypertension, and heart failure, which are all chronic cardiac conditions that increase an individual's risk for AF.[13]

Anatomy and physiology

Obtaining a basic working knowledge of the normal anatomy and physiology of the organ, system, or structure of the body that is affected by a need is important because it establishes a baseline against which abnormalities are understood. While some diseases affect a specific organ or system, other disease states affect multiple organs or systems within the body. Through research of the normal anatomy and physiology, innovators should quickly be able to determine whether narrowing their focus to one organ or area is appropriate. This research also provides innovators with an understanding of important vocabulary and context as they delve into further research.

The disease will be much easier to comprehend if the anatomy of the affected organ or organ system is clearly understood and can be visualized. For example, an innovator with an engineering mindset will likely be assisted in understanding the disease by knowing the position, size, and proximity of the affected organ or system in relation to other systems. In addition, both gross and cellular anatomy must be evaluated. Gross anatomy refers to the study of the anatomy at a macroscopic level (through dissection, endoscopy, X-ray, etc.). Cellular anatomy, also called histology, refers to the study of the body using a microscope. It is often most effective to start with gross anatomy, as this is generally easier for most innovators to grasp. Then, with knowledge of the gross anatomy serving as context, innovators can more effectively tackle cellular anatomy.

Physiology, or the way in which biologic tissues function, is often better understood after innovators establish a working knowledge of the normal anatomy. As with anatomy, physiology should be investigated at both the gross and cellular levels. Once innovators learn about normal patterns of function within an affected area, they have a basis for understanding how the disease functions (as described in the next section). Biologic and physiologic processes can be evaluated in terms of their mechanical, electrical, and chemical mechanisms. Later in the biodesign innovation process, this information can serve as a basis for brainstorming new concepts that act on these mechanisms of action.

Using the AF example, innovators would begin by determining that AF is a disease of the electrical system of the heart, which is part of the cardiovascular system. As the heart is the primarily affected organ, they could then focus on investigating the basic gross anatomy of the heart and its normal function. Understanding the heart's size, location, and position in relation to other structures quickly establishes a baseline context for exploring more complex concepts and interactions, such as how the electrical system of the heart establishes a rhythm that affects the organ's ability to mechanically contract. While the appropriate level of detail to capture varies significantly with each specific need and its associated disease state, the Working Example below is representative of the detail that is appropriate for a *preliminary* disease state assessment.

Working Example
Normal anatomy and physiology of the heart

The pumping action of the heart depends on precise electrical coordination between the upper loading chambers (atria) and lower pumping chambers (ventricles) as shown in Figure 2.1.3.

The contraction of the atria and ventricles is regulated by electrical signals. During normal sinus rhythm[14] the sinoatrial (SA) node (often referred to as the "pacemaker"), which is located in the high right atrium, releases an electrical discharge that causes the atria to contract. The electrical signal then propagates through the atria to the atrioventricular (AV) node, which is located between the atria and the ventricles to help regulate the conduction of electrical activity to the ventricles. Electrical signals are conducted from the AV node through Purkinje fibers[15] into the ventricles, causing the ventricles to contract.

The rate of the electrical impulses discharged by the SA node determines the heart rate. At rest, the frequency of discharges is low, and the heart typically beats at a rate of 60 to 80 beats per minute. During periods of exercise or excitement, an increase in the heart rate is mediated by the input of the central nervous system onto the SA node, which subsequently discharges more rapidly.

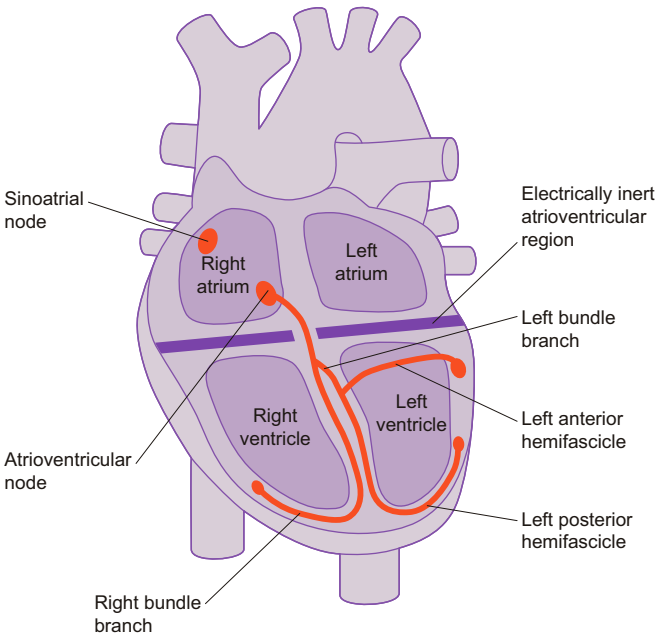

FIGURE 2.1.3
The heart's electrical system is one aspect of normal anatomy and physiology that an innovator must understand when initiating an investigation of AF (reproduced from Steve Meek and Francis Morris, "ABC of Clinical Electrocardiography: Introduction," *British Medical Journal*, 324, 415–18, 2002; reprinted with permission from BMJ Publishing Group Ltd.).

The heart's mechanical and electrical coupling is the result of the organ's fundamental cardiac cellular physiology. While the heart is composed primarily of connective tissue, cardiac muscle tissue is responsible for the electromechanical coupling of electrical signals and mechanical pumping. Muscle contraction is essentially the result of changes in the voltage of a cell due to the movement of charged ions across the cell's surface. This initial voltage change is the result of ions flowing from cell to cell, and is usually initiated by pacemaker cells, such as the cells of the SA node, which intrinsically cycle through voltage changes. This voltage change then triggers the movement of other ions within the cardiac muscle cell to cause changes in mechanical structures that result in contraction. The majority of cardiac muscle contracts due to depolarization, which is a change in voltage caused by the influx of sodium ions and the outflux of potassium ions.

This flow of ions results in changes in the heart's baseline voltage, which causes both the influx of calcium ions and the release of internal calcium stores. Calcium, in turn, results in the interaction of various cellular components, bringing about a contraction in the mechanical filaments of the muscle cell (see Figure 2.1.4).

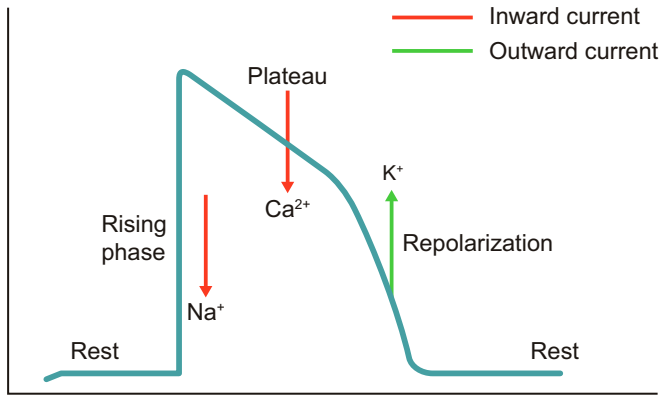

FIGURE 2.1.4
Depolarization is the result of the inward flux of sodium and the outward flux of potassium ions. Changes in the baseline voltage due to depolarization results in the inward flow and intracellular release of calcium and muscle contraction.

This process propagates throughout the heart from cell to cell, such that the result of all the cellular filaments contracting is the temporally and spatially coordinated contraction of the heart muscle. Once contraction is complete, various cellular components are activated to reset the filament structure and ionic balance so that the process can begin again.

Pathophysiology

Once an understanding of anatomy and physiology of the relevant organ in a healthy individual is established, then innovators can examine how the disease disturbs the normal structure and function. It is critically important to take into account the fact that most diseases are not homogeneous. Stated another way by some medical educators, "diseases don't read textbooks," which underscores the point that the description of a disease in a book or other reference only represents one example of its presentation. Different subtypes of a disease often exist and the heterogeneous nature of patient populations can result in a broad range of effects for any given disease state.

When investigating pathophysiology, the first step is to better understand how the disease works from a biologic and physiologic perspective and then how this affects the normal function of the organ or system. The second step is to identify the risk factors and causal associations (e.g., genetics, age, associated diseases, lifestyle) that characterize the disease. Finally, innovators can seek to understand the disease progression. Disease progression examines the rate (e.g., days, weeks, or years) at which the disease leads to abnormal function. This includes the peak age of the effect and the types of changes that occur at each stage of the disease.

In the AF example, innovators would explore how the heart might be structurally altered, leading to abnormal function, and whether or not the condition can cause structural changes in the organ. They should also look at the common causes of AF, its primary risk factors, and how AF progresses. Time should be spent understanding the different types of AF and the unique characteristics of each variation of the disease. This might include looking at which type of AF is most common among different groups of patients, whether all AF patients progress in the same way (or if progression is more directly affected by other factors such as coexisting conditions), and how likely patients are to progress from one type of AF to another.

Working Example
Pathophysiology of atrial fibrillation

Disease function

In a normally functioning heart, the rates of contraction for the atria and ventricles are typically equal and result in a regular heartbeat. However, during AF, ventricular and atrial contractions become irregular and unsynchronized. Instead of electrical discharges being regularly generated solely by the SA node, rapid and irregular discharges come from other areas in the atria. Since these other areas are discharging so fast, the SA node's slower, more regular rate is suppressed. There are several "trigger points" for this electrical activity, which create a pattern of rapid, chaotic electrical activity that is characteristic of AF. The majority of these focal sources (approximately 94 percent) are located in areas around the four pulmonary veins, which are connected to the left atrium. Other less common areas include the superior vena cava, right and left atrium, and the coronary sinus.[16] Though not fully understood, causal factors (see below) may result in inflammation and injury to the heart, causing alterations in cell structure and predisposing it to abnormal electrical discharges that can initiate and maintain AF.

As a result of these irregular discharges, the atria contract between 300 and 600 times per minute.[17]

However, the atria do not actually contract as a whole – the rapid contractions of parts of the atria may be better thought of as a quiver, or fibrillation, rather than regular beating. This results in improper filling and ejection of blood, as well as a decreased efficiency of the heart's pumping process. Since all electrical activity from the atria can typically only get to the ventricle via the AV node, the AV node is able to filter many of the irregular electrical discharges associated with AF, preventing the rapid rate of the atrial beat from being conducted into the ventricles. However, not all of the signals are blocked and AF is often accompanied by irregular ventricular beating, at 50 to 150 per minute.[18]

Causal factors

The most common causes of AF are advanced age, abnormalities in the heart's structure, uncontrolled hypertension (e.g., high blood pressure), thyroid disease (e.g., an overactive thyroid or other metabolic imbalance), and acute exposure to heart stimulants (e.g., alcohol).

Disease progression

According to the American Heart Association, AF can be classified into three clinical subtypes: paroxysmal, persistent, and permanent. In the case of AF, the subtypes parallel disease progression with one subtype transitioning to the next over several years in a large majority of patients. These subtypes are defined by the ease with which episodes of AF terminate. Paroxysmal AF refers to recurrent or lone[19] episodes that spontaneously self-terminate after a relatively short period of time. Persistent AF requires pharmacological or electrical cardioversion[20] (e.g., giving medicines or an electric shock) to restore regular sinus rhythm. In patients with permanent AF, regular sinus rhythm cannot be restored and the irregular heartbeat becomes the accepted rhythm.[21] These subtypes stand in stark contrast to AF associated with reversible causes (e.g., thyrotoxicosis,[22] electrolyte abnormalities) and the occurrence of AF secondary to acute myocardial infarction, cardiac surgery, or acute pulmonary disease. These conditions are considered separately since the AF is unlikely to recur once the precipitating condition has been treated.

Clinical presentation

Research of clinical presentation focuses on the impact of the disease on the patient. It emphasizes the symptoms (what patients say they experience) and the signs (what the astute healthcare provider identifies or observes during the patient examination) of a disorder or disease. Gaining an understanding of clinical presentation is important because it is often the target for improved care and the development of new therapies that address identified needs. When evaluating clinical presentation, describe what patients complain about when they see a clinician and how they feel. Note that patients with the same disease may present differently based on a number of factors, such as age, gender, ethnicity, and coexisting conditions. Since every individual is different, each is likely to experience symptoms slightly differently. Ultimately, clinical presentation may manifest itself in the signs/symptoms that result from the primary effect of the disease or from the long-term consequences of having and managing the disease over time.

When researching AF, innovators would seek to understand the most common symptoms for patients with the disease, how they feel with AF, and the signs most commonly observed by physicians in patients with the disease. They should also consider whether all AF patients are affected by the same symptoms and what factors have the greatest impact on symptoms presented (e.g., age, coexisting conditions). For example, young patients are much more likely to report symptoms of palpitations with AF than older ones. This may directly impact the goal of therapy for different age groups.

One strategy that may be helpful in evaluating clinical presentation is to take the perspective of the healthcare delivery system (e.g., insurance company or hospital). From a provider's perspective, what symptoms or comorbidities bring patients in for clinical care? From an insurance company's perspective, what types of bills are submitted from the providers who first see a patient with the disease and what is the frequency of care?

Working Example
Clinical presentation of atrial fibrillation

While some patients do not experience noticeable symptoms due to AF, others have fatigue, weakness, lightheadedness, shortness of breath, or chest pain. Palpitations – sensations of a racing, uncomfortable, or irregular heartbeat – are also quite common. Symptomatic AF is widely recognized as leading to reduced patient **quality of life**, functional status, and cardiac performance.[23]

Importantly, one of the most common presentations for AF is stroke. In fact, AF is the heart condition that most commonly causes stroke.[24] Because the atria are fibrillating and not contracting, the flow of blood in the atria can become sluggish, especially in certain parts of the left atrium. This blood can coagulate leading to the formation of a clot. If a clot is dislodged and pumped out of the heart to the brain, it can cause a stroke. As a result, many patients with AF are treated by physicians for stroke using medicines that prevent the blood from clotting easily. Since these medicines can lead to the side effect of bleeding, a consequence is that physicians sometimes occasionally need to treat patients for a side effect of the stroke treatment itself.

In general, younger patients tend to have more "palpitations symptoms" which cause them to seek medical care. Older patients tend to have few (or no) symptoms of palpitations, but may be more compromised by fatigue. Patients with preexisting cardiac disease, such as heart failure, in which the heart does not function well at baseline, can become severely ill if they develop AF, sometimes resulting in the need for acute hospital care.

Clinical outcomes

Importantly, clinical outcomes are different from symptoms. Outcomes generally refer to hard data points associated with a disease that can be measured. The two most important types of clinical outcomes to consider are **morbidity** and mortality. Morbidity refers to the severity of the disease and its associated complications. Measures of morbidity may be evaluated using quality-of-life questionnaires, or they can be assessed by more specific endpoints such as distance walked in six minutes, hospital admissions, or a clinical event which does not cause immediate death (e.g., stroke, heart attack). Mortality refers to the death rate associated with a disease. Clinical outcomes are particularly important as they often serve as endpoints for clinical trials, since they can be assessed more easily and objectively than symptoms and have a direct impact on cost.

In the AF example, key clinical outcomes to address are the morbidities associated with AF, their likelihood of occurrence, and what factors have the greatest impact on them (e.g., age).

Working Example
Clinical outcomes associated with atrial fibrillation

Morbidities

One of the most frequent reasons that patients come to the emergency room for evaluation is palpitations. Although a number of rhythm disturbances can cause palpitations, AF is one of the most common. AF not only causes an irregular heartbeat, but can result in a rapid heart rate of up to 180 beats per minute, which can make patients feel nauseated and short of breath. These symptoms often improve with treatment by intravenous medications that slow AV conduction and reduce the heart rate. Episodes of AF are extremely scary and have a major impact on quality of life. They also result in a large number of emergency room visits each year.

In addition to acute symptoms with accelerated ventricular rates, AF can lead to a four- to five-fold increase in the risk of stroke.[25] The risk of stroke due to AF increases with age, rising from 1.5 percent for patients in their 50s to 23.5 percent for those in their 80s.[26] Overall, the annual risk of stroke in patients with AF ranges from 3–8 percent per year, depending on associated stroke risk factors[27] – a rate that is roughly five times higher than the rate of stroke in patients without AF.[28] As a result of this risk, one of the most common reasons for hospitalization each year is the need to anti-coagulate

the patient and reduce the rate of stroke, driving huge impact on patients and the healthcare system.

Beyond the risk of stroke, AF is widely believed to reduce the heart's pumping capability by as much as 20–30 percent. As a result, AF (combined with a rapid heart rate over a sustained period of time) can lead to congestive heart failure (CHF). More directly, patients with existing heart failure often decompensate when they develop AF, requiring prolonged hospitalization.

Mortality

AF is also associated with an increased risk of death. According to the Framingham Heart Study, AF leads to a doubling of mortality in both sexes. After making adjustments for comorbidities, the risk remains 1.5 times higher in patients with AF. This increased rate of mortality is mainly due to strokes, progressive ventricular dysfunction and heart failure, and increased mortality from coronary events.[29]

Economic impact

At this stage of the biodesign innovation process, the focus of economic research should be on understanding the overall costs of the disease on the system at large, including the annual cost of treatment, hospitalization, and lost productivity due to absenteeism from work. Consider these costs at the system level, not necessarily for individual treatment alternatives. More detailed analysis of costs and healthcare payments will be performed as part of 2.2 Existing Solutions, 2.4 Market Analysis, and 4.3 Reimbursement Basics.

Be diligent in trying to understand the distribution of costs. Is the primary expenditure for acute or chronic medications, a device-based treatment, or a major surgery? Does the treatment of symptoms require hospitalization, or is this type of care mainly provided in the outpatient setting (which can be more cost effective)? Remember to take into consideration the life-long costs of care, as well as those associated with episodes such as hospitalization. The answers to these questions may reinforce the presence of **value** signposts (as described in 1.2 Needs Exploration), which signal that innovators may be able to create increased value for the stakeholders affected by AF in addressing the defined need. The potential value associated with a need is explored further in 2.4 Market Analysis, with the economic data gathered as part of disease state analysis acting as an important input.

For AF, innovators should look at the aggregate, system-level cost of AF on an annual basis, the treatment-related annual cost of AF, the annual cost of hospitalization, and the annual cost of lost productivity from absenteeism due to AF.

Working Example

Economic cost of atrial fibrillation

According to study published in 2011, AF costs the US healthcare system up to $26 billion each year. This retrospective, observational cohort study, based on administrative claims from the MarketScan Commercial and Medicare Supplemental research databases from 2004 to 2006, estimated that more than 460,000 hospitalizations per year cite atrial fibrillation as the primary diagnosis. The authors also concluded that AF contributes to 80,000 annual deaths.[30]

Just under three-quarters of total annual AF costs are associated with patient hospitalization. Another 23 percent is spent on outpatient care and testing. And 4 percent goes to outpatient prescription drugs.[31] Hospital costs are high among AF patients because they often require readmission. As the US population ages, costs associated with AF are expected to increase significantly.

Optimizing disease state research

The approach to disease state research described in this chapter is applicable no matter where in the world innovators intend to work. Just keep in mind that certain aspects, such as epidemiology, pathophysiology, clinical outcomes, and the economic impact of a disease, can vary dramatically by geographic setting. For example, a global registry of more than 14,000 patients spanning North America, Latin America, Europe, the Middle East, Africa, India, China, and other parts of Asia,

demonstrated that hypertension was the most common risk factor for AF, present in 62 percent of patients worldwide. But its prevalence ranged from 41.5 percent in India to 80 percent in Eastern Europe. Rheumatic heart disease was present in only 2.1 percent of North American AF patients, compared to 15.3 percent in both the Middle East and China, 22.0 in Africa, and 30.9 percent in India. In Africa, more than 5 percent of AF cases were associated with pericarditis or endomyocardial fibrosis, while these conditions were present in less than 1 percent of patients in the other locations.[32] Innovators are advised to understand the leading research in the field at large, as well as disease information that is specific to the location they are targeting.

As innovators perform disease state research, they also should be careful not to lose sight of the human side of the disease. Studying clinical presentation as part of this recommended research approach provides a good start; but even this line of inquiry can tend to be rather scientific. To gain a full appreciation of a disease, it can be helpful for innovators to understand the emotional toll it takes on patients, their families, and the providers who care for them. The following quote from an article by one AF patient underscores how significant the disease burden can be:[33]

> *I never knew when an episode would strike – while washing the dog, walking, talking on a conference call, sitting in a meeting – so I was always afraid. My heart was like a flopping fish inside my chest. I would get so dizzy and lightheaded that I thought I would pass out. I was paralyzed and scared. When it was over, I was so wiped out that all I could do was crash. Life with atrial fibrillation wasn't normal . . .. My family was scared [too] and wouldn't let me out of their sight. We traveled together in the motorhome [for recreation]. . .. We planned our route to be near hospitals, and I knew every hospital along the way. You can't imagine, unless you've lived through it, the toll that atrial fibrillation takes. It takes a huge physical toll and a huge emotional toll, not just on you, but on your whole family, too. Worst of all is the financial toll – huge medical bills, inability to get insurance once you have atrial fibrillation, lost time from work and lost income, and for some people, lost jobs and careers and even lost houses and life savings.*

The human aspects of a disease may not be relevant to every need. However, in some cases, it can provide important insights about need criteria that potential solutions should addresses. It also expands the innovators' understanding of key stakeholder (see chapter 2.3) and promotes a stronger sense of **empathy** for those affected by the disease.

In terms of the mechanics of performing disease state research, it is best to give priority to professional medical resources (textbooks, **peer-reviewed** medical journals, and websites targeted toward physicians and backed by accredited medical institutions). Peer-reviewed medical journals are usually the most up-to-date resources. However, not all medical journals are necessarily equal – just because an article is published in a medical journal does not make it fact. The higher the quality of the medical journal, the more likely the research design, process, and conclusions are accurate. One method to evaluate the credibility of a journal is to review its "impact factor." The impact factor, a measure of the frequency with which the "average article" in a journal has been cited in a particular year or period, is often used as an indicator of the importance of the journal to its field.[34] A "citation impact" can be used to measure the significance of an individual work or author. Impact factor and citation impact information is available on the Thomson Reuters Web of Knowledge, in its annual *Journal Citation Reports*.[35] Other tools, such as Google Scholar, also provide some information on citation frequency. No matter how credible the journal or its authors, innovators are advised not to accept any information blindly. Always search back for any original references that are available and try to triangulate data via multiple sources.

When searching, it is often valuable to start with a series of general searches (e.g., on "atrial fibrillation") using the sources outlined in the Getting Started section. Then, specific gaps in available information can be addressed through additional, increasingly directed data searches (e.g., annual cost of

hospitalization for atrial fibrillation) until innovators have a thorough understanding of the space. In addition to moving from general to more specific inquiries, another helpful approach for completing disease state research is to look up references cited in some of the most informative documents and then to find and review the listed papers, especially the peer-reviewed ones. Lastly, analyst reports can be invaluable for understanding hard-to-find economic impact data, which is usually important for discerning the economic impact of a disease.

Summarizing the data

When summarizing what has been learned about a disease state, innovators should strive to keep the target audience in mind. Write the overview in an appropriate manner (i.e., not too technical if intended for potential investors, but adequately scientific if targeted to clinicians). Additionally, make sure to cite the sources of all statistics, study results, and clinical outcomes, as well as the source of interviews with physicians or other experts. Unless this information is sourced, the credibility of the research is subject to question. If conflicting information is uncovered during the research process, give priority to data from peer-reviewed medical journals or other similar resources, as noted above.

The case example on The Foundry and Ardian, Inc. describes how one team approached the challenge of disease state research.

FROM THE FIELD — THE FOUNDRY AND ARDIAN

Using disease state research as a building block for an innovative therapy

As part of its efforts to identify its next new project, medical device incubator The Foundry routinely looks at disease states not adequately served by existing technologies. The company identifies clinical needs internally and also evaluates ideas presented by other innovators. Years ago, as the team debated its next focus area, serial entrepreneurs Howard Gelfand and Mark Levin came to The Foundry with a novel idea. Levin, a heart failure cardiologist, and Gelfand, a biomedical engineer, had studied the interactions between the kidney and central nervous system that help the body regulate blood pressure and fluid balance. They believed that blocking the activity of the renal nerves[36] could positively affect three major disease states: heart failure (HF), hypertension (HT), and chronic kidney disease (CKD). In particular, having previously invented a dialysis-like device to remove excess fluid from patients in congestive heart failure, Gelfand and Levin hypothesized that preventing the transmission of signals along the renal nerves could help HF patients offload the fluid that builds up in the lungs and causes these individuals to be repeatedly hospitalized with shortness of breath. The entrepreneurs had even proposed a solution – an implantable neurostimulator or drug pump that could block renal nerve activity. They dubbed their concept renal denervation.

While the need for better solutions for fluid-overloaded HF patients was compelling, the complex physiology involved in targeting the renal nerves, combined with an implantable solution, sounded too much like “a science project” to Foundry partner Hanson Gifford. Partner Mark Deem, however, was not dissuaded. Intrigued by the idea of manipulating the renal nerves to influence other body systems, Deem set aside Gelfand and Levin’s possible solution and dove into disease state research to better understand the mechanisms of action related to the need.

Rather than starting with an investigation of heart failure or hypertension, Deem focused on the neurophysiology of the kidney and the integrated processes that help the body control blood pressure and fluid to maintain

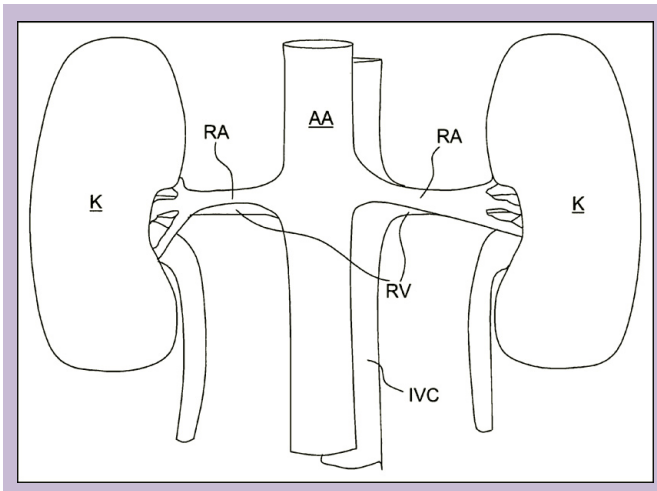

FIGURE 2.1.5
The first drawing from a seminal Ardian patent reflects the fact that the team's focus was grounded squarely in the disease state (from US utility patent 7,653,438-14).

homeostasis (see Figure 2.1.5). "I wanted to understand how the renal nerves play into this thing," Deem said. He began by accessing relevant journal articles via Medline. Describing his process, Deem explained, "When I'm working in body systems that I don't know well, I keep an excel spreadsheet of keyword searches as I work. The first column contains my exact search term, complete with quotes and Booleans. The second column is the number of hits, and the third is the number of relevant hits. Then I go one row per citation with title and author columns and a notes box I use to capture a three line synopsis that summarizes what I got out of the paper." According to Deem, this system keeps his research organized, prevents him from re-visiting papers he has already reviewed as he follows interesting citations, and helps him identify the best keyword strings. In the journal articles, Deem also highlights passages and uses margin notes to summarize key points. "I highlight what I think is important initially, but I often need to go back when I realize that actually different information is important. The margin notes help me quickly find the most relevant information in the paper."

Ultimately, Deem's Medline searches led him to papers written by Dr. Gerald F. DiBona, professor and vice chairman of the Department of Internal Medicine at the University of Iowa College of Medicine. "He was the guy who has produced the largest body of work on renal neurophysiology in the world," Deem recalled. "And there was this one 'magnum opus' of a paper that had hundreds of citations. And for easily a month to two months, I just sat with that one paper. I'd read that paper and then I'd hit a brick wall. And there'd be a citation there. So, I'd go back to this huge bibliography, and I'd go pull that paper. And so I had the floor of an office basically covered with Gerry's paper and all of the citations from Gerry's paper, trying to build a fundamental understanding of the neurophysiology of the kidney and how that influenced hypertension and heart failure."

Through his research, Deem learned that in response to a decrease in blood pressure, a drop in sodium, or signals from the sympathetic nervous system, special cells in the kidneys generate a chain of neurohormonal responses that raise blood pressure by constricting the blood vessels, stimulating the heart to pump harder and faster, and causing the body to retain water and salt.[37] Although designed to maintain homeostasis, these regulatory mechanisms are chronically hyperactivated in some patients, causing the sustained high blood pressure, fluid overload, and dangerous sequelae that are the hallmarks of heart failure, hypertension, and chronic kidney disease.[38,39] Accordingly, blocking renal sympathetic activity could interrupt this cycle and have a dramatic effect on these disease states.

Following this deep dive into the literature, Deem was ready to test what he had learned by talking to doctors in the field. "I tend not to just go and try to sit down with docs and just ask them a bunch of questions," he explained. "Personally, I find it more useful to wait until I am very conversant about the anatomy and physiology that we're talking about. Otherwise, we can't really have a discussion, and I can't challenge them. And a huge amount of us being successful at what we do is being able to challenge the docs on the dogma of the clinical practice in the area that we're in. We say, 'Why is it that

way?' and 'Couldn't it be this way?' And you can't do that unless you understand the system you are questioning." In line with this approach, Deem did not reach out to Gerry DiBona until he had read "everything I could find," he recalled. Describing their conversation, he continued, "We got pretty deep into the physiologic details, and he finally asked me who I had studied with. When I told him I'd just been reading up on it, he kind of laughed. I thought it was a pretty cool compliment."

Subsequent to speaking with DiBona, Deem also mentioned the concept of renal denervation as a treatment for heart failure to a practicing nephrologist. This conversation led him to an important historical precedent that served as early proof of concept and helped validate the proposed mechanism of action. Specifically, he was guided to a 1956 study of a now outdated procedure in which portions of the sympathetic nerve chain controlling the kidneys were surgically removed. While high risk, the surgery had been shown to slow progression of heart failure, resolve congestive symptoms, reduce blood pressure in 30–50 percent of cases, and increase survival. Deem also found more recent studies that concluded that surgical denervation (severing the renal nerves, as in kidney transplantation) was well-tolerated, increased urine output, and made it nearly impossible to induce or maintain a hypertensive state.

While Deem's research validated the role of the renal nerves in all three disease states, The Foundry team initially focused on heart failure. "Although kidney disease is a terrible disease, it was unclear that there would be a significant market there. So that was out from the get-go. Between heart failure and hypertension – well, we really went back and forth on that a lot," Deem remembered. Ultimately the preclinical focus by Levin and Gelfand on heart failure, and the fact that it was a huge medical opportunity that The Foundry had considered before, biased the team to focus on this space.

Gifford, who had worked in cardiovascular devices prior to forming The Foundry, provided the relevant disease state research on heart failure. With this condition, the patient's heart muscle cannot pump enough blood to meet the body's needs or keep up with the return of blood to the heart. Because of this, patients feel tired or weak. They also experience fluid build-up and swelling in the abdomen and extremities due to ineffective circulation. Fluid also backs up in the lungs, causing shortness of breath, especially upon exertion or when lying down. Doctors categorize heart failure patients as Class I through Class IV according to the severity of the symptoms,[40] and patients in the more advanced stages of the disease tend to be unstable, suddenly worsening (acute decompensated heart failure) and then improving temporarily after treatment with drugs and diuretics in the hospital.

With regard to clinical outcomes, 40 percent of Class IV patients are hospitalized at least four times a year, most often because of shortness of breath due to fluid overload. Late-stage heart failure has a 50 percent 5-year mortality.[41] Epidemiological research at the time indicated that there were five million HF patients and one million HF-related hospitalizations in the US each year.[42] The economic impact was significant; heart failure is one of the most resource-intensive conditions with direct and indirect costs in the United States estimated at $39.2 billion in 2010.[43]

While the compensatory hormonal responses that Deem had studied were meant to improve perfusion in HF patients, they ultimately put more stress on the heart and caused it to become even less efficient.[44] As noted, medications could help, but as heart failure advances these drugs often become ineffective.[45] Based on their improved understanding of the disease area, The Foundry team refined its direction, focusing on a way to offload fluid longer term than drugs to get congestive HF patients into a more stable, more medically manageable state in order to reduce the length and frequency of hospitalizations. Deem and his colleagues founded Ardian, named for the phonetic pronunciation of RDN for **r**enal **de**n**e**rvation, in January of 2005 to formally pursue this need.

Over time, as the team progressed, the solution evolved from an implantable device to a catheter-based treatment that would quiet the renal nerves using energy. Although the team believed the approach was technically sound, as they moved closer to their first-in-human milestone CEO Andrew Cleeland and other members of the team began to worry about the fragility and unpredictability of heart failure patients as a study group. Deem explained: "The big problem with heart failure is that you have patients who are Class II, and then they progress rapidly to Class IV. You get them in the hospital and pump them full of meds, you get the water off, and they go back to Class III. And then they go to II, and then they're back to IV. I mean, it's called 'unstable heart failure' for a reason. These patients are really hard to characterize, and it's difficult to build a study around that." Denise Zarins, Ardian's VP of R&D added, "We were worried that if we took them when they were in a decompensated state, with all that fluid on board, even having them lie down for a procedure could be difficult."

Going back to Deem's deep research and the effect of the renal nerves on all three disease states, Cleeland and the team realized that they could change the trial design for the first-in-human study to treat patients with HT resistant to drugs rather than heart failure. Describing the decision as "an evolution of thought," Cleeland explained, "Our [initial] goal was just to show that we could safely denervate a human being – not that we were going to cause a specific physiologic response. So we thought, maybe we should begin with the HT population because they are relatively healthier and more robust. Hypertension leads to heart failure, it leads to stroke, it leads to everything else, and it is the precursor." On the other hand, hypertension can be managed with safe, inexpensive drugs in many patients, so it wasn't clear that the risks of an interventional procedure would be justified. If the company was going to focus on treating hypertension, the procedure would need to be extraordinarily safe.

The results of the first trial not only demonstrated safety and proof of denervation, but were highly encouraging, as HT patients in the study experienced significant blood pressure reductions, with very few complications. Accordingly, while the team had planned to continue its HT study, and also start pilot studies in two HF groups (chronic and acute decompensated), the HF study arms "dropped by the wayside pretty quickly when the team started seeing 20–30 point reductions in blood pressure," recalled Deem. Convinced that they were onto something, the Ardian team decided to change its primary indication to HT.

Ardian's first pivotal trial, called Symplicity HTN-2, supported the decision to pursue hypertension. This study involved more than 100 patients in 24 centers in Europe, Australia, and New Zealand. The primary endpoint was office blood pressure as measured six months post treatment. Patients randomized to renal denervation therapy plus antihypertensive medications achieved a significant reduction in mean blood pressure (–32/–12 mmHg) at six months, whereas patients in the control group (randomized to receive antihypertensive medications alone) had blood pressures that did not vary from baseline (+1/0 mmHg).[46] In addition, over 20 percent of treated patients were able to decrease their hypertension medications or reduce their dosage at the six-month point when physicians were allowed to change their prescription regimens.[47] Based on the results of this study, Ardian received a CE mark for its technology and began commercializing the product in Europe. Shortly thereafter, the company was acquired by Medtronic.

As part of the strategy to bring the technology to the US, Medtronic worked with the FDA to design and launch another pivotal trial, known as HTN-3. In this blinded, randomized controlled study of more than 500 treatment-resistant hypertension patients, renal denervation met its primary safety endpoint, but did not show a significant difference from a sham intervention for lowering office systolic blood pressure through 6 months

among patients who continued taking their anti-hypertensive medications.[48]

These results underscore the fact that a complicated disease process, such a sympathetic overactivity, can be unpredictable and difficult to study. In this case, several of the key issues affecting the outcome of the trial were directly related to disease factors, including the impact of medication roll-in and demographic mix on treatment results, as well as the extent of renal artery sympathetic nerve response to ablation energy.

Following the announcement of the HTN-3 results, Medtronic reconfirmed its commitment to the technology and indicated that it would continue working with the FDA to prepare for additional US trials.[49] In response to the HTN-3 data, one of the team's top priorities was to return to disease state research to expand its understanding of hypertension in different populations and the most effective way to study the link between the disease and renal denervation.

Online Resources

Visit www.ebiodesign.org/2.1 for more content, including:

Activities and links for "Getting Started"

- Assess anatomy and physiology
- Understand the pathophysiology of the disease
- Understand clinical presentation
- Assess clinical outcomes
- Gather epidemiology data
- Evaluate the economic impact
- Assess and summarize the information

Videos on disease state research

CREDITS

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