American Enterprise Institute for Public Policy Research

No. 2 • January 2011

Health Policy Outlook

Are Medical Devices Turning the Corner against Heart Failure?

By John E. Calfee and Gabriel Sudduth

Despite the tremendous success modern medicine has had in treating coronary heart disease, heart failure has proved to be a formidable and significantly less treatable condition. The small drug armamentarium used to treat it is only modestly effective. Left ventricular assist devices, or "heart pumps," are proving to be the best available option for patients with advanced heart failure, and the technology has huge potential for improvement. The development and use of these devices are both at an early stage, however, and innovation could easily be slowed by the Food and Drug Administration (FDA) with unnecessary clinical requirements and other hurdles that retard device innovation and access.

The battle against coronary heart disease is one of the triumphs of modern medicine. Four decades or so ago, there were essentially no known preventatives or treatments for heart attacks and strokes. In the years since, numerous drugs, medical devices, and medical procedures have been developed to prevent or curtail cardiovascular disease and treat cardiovascular events when they occur. Among the drugs are beta blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), blood thinners, clot dissolvers, LDL cholesterol reducers, and aspirin (which was not widely recognized as a heart-attack preventative until the 1980s).[1] Prominent among medical devices are implanted heart defibrillators, pacemakers, and arterial stents. Procedures such as coronary artery bypass surgery and heart transplants are often effective in treating advanced heart disease. When augmented by prevention measures such as smoking cessation, these tools have had extraordinary effects. Since 1950, the mortality rate from coronary heart disease has dropped by over 60 percent, with most of the decline coming after 1970.[2] Roughly 85 percent of this improvement is due to medical treatments and preventatives, with the rest coming from lifestyle changes.[3]

John E. Calfee (jcalfee@aei.org) is a resident scholar at AEI. Gabriel Sudduth (gabriel.sudduth@aei.org) is a research assistant at AEI.

Heart Failure and Its Causes

These remarkable advances have left heart failure relatively untouched.[4] Heart failure occurs when a weakened heart can no longer pump enough

Key points in this *Outlook*:

- Heart failure is a devastating condition that has largely defied drug therapy.
- After several decades of slow development, left ventricular assist devices now offer hope to patients with advanced heart failure.
- Technology continues to improve rapidly, but unnecessary clinical requirements by the FDA could easily suppress future device innovation and access.

blood through the lungs and the rest of the body.[5] Sometimes referred to as congestive heart failure, it is caused mainly by heart attacks and other manifestations of coronary heart disease.[6] Heart failure has become common in our rapidly aging population, partly as a byproduct of increased survival rates from heart attacks.[7] It causes great discomfort, such as frequent shortness of breath and fatigue, and shortens life. Median survival after the onset of heart failure is less than two years for men and about three years for women.[8] Once admitted to a hospital for acute heart failure, the one-year mortality rate is about 30–50 percent.[9] Heart failure is very expensive, with estimated Medicare expenses of $39.2 billion in 2010.[10] As the single most common cause of hospitalization among the elderly,[11] it accounts for 6.5 million hospital days annually in the United States alone.[12]

Scientific advances in the past two decades have brought about a fundamental rethinking of the etiology and mechanisms of heart failure. Heart failure is now seen as a complex physiological sequence of events in which deleterious physical "remodeling," or reshaping, of the heart itself plays a central role.[13] Roughly speaking, heart failure begins with stress or injury to the heart muscles, usually provoked by genetics, coronary heart disease, or heart attacks.[14] After initial injury to the heart, the left ventricle is weakened and fluid accumulates in it. The shape and size of the ventricle changes in response to the stress. To compensate for weaker heartbeats, the kidneys reduce excretion to increase blood pressure. Further harm arises from biological imbalances that can cause heart cell death or damage cell structures, rendering them unable to produce sufficient energy. Overall, these diverse maladies perpetuate one another, and together they promote the progression of heart failure.

Drug Development for Heart Failure

In principle, each link in the progression of heart failure offers a target for drug therapy. In fact, each of the drug classes most widely used to treat heart failure (beta blockers, ACE inhibitors, and ARBs) targets a key component of the biological pathways that contribute to heart-failure progression. But these drugs were developed for other conditions, such as hypertension and arrhythmia. Only after a series of reversals in longstanding wisdom did they find a place as the best heart-failure treatments.

Many early treatments, for example, focused on stimulating the heart muscle with hormones similar to adrenaline. Studies eventually revealed that long-term use of such drugs actually increased mortality, although the drugs remain useful for short-term therapy.[15] Vasodilators, which expand blood vessels, were long considered the best way to reduce stress on the heart. Their use prompted closer examination of a related drug class, neurohormonal inhibitors, which had long been thought unhelpful for heart failure. Starting in the late 1980s, a series of clinical trials led ACE inhibitors (one type of neurohormonal inhibitor) to become central to heart-failure treatment.[16] Beta blockers, another staple in treating coronary heart disease, were once thought to be contraindicated for heart failure, but these, too, became standard heart-failure treatments based on clinical trials in the late 1990s.[17] Aldosterone antagonists, long used to treat hypertension, were once avoided in treating heart failure, but research has found that they are useful for many patients, and studies continue to explore expanded use.[18]

Treating heart failure with other established drug classes has proved unsuccessful. Of obvious interest is the statin class of cholesterol-reducing drugs such as Lipitor and Crestor, which address several specific biological mechanisms in heart failure.[19] A recent heart-failure trial of Crestor, the most powerful statin, failed to achieve success.[20] Research has also been unfruitful on noncardiac drugs whose approved indications are biologically related to the heart-failure cycle. For example, the tumor necrosis factor-alpha protein (TNF), deeply involved in rheumatoid arthritis, is also implicated in heart failure. But a leading TNF-inhibitor, the arthritis drug Enbrel, failed to reduce heart-failure mortality in a clinical trial.[21]

Finally, and most importantly, research to develop new drugs specifically for heart failure has been disappointing. One example is tezosentan, which targets endothelin, a hormone that promotes unhealthy vasoconstriction in heart failure, but it failed in clinical trials.[22] Numerous other targets are being addressed, particularly those involved in cell signaling, such as the beta-adrenergic receptors and calcium-handling proteins.[23] Significant success has yet to occur, however.

On the whole, today's mainstay heart-failure drugs have reduced hospitalization and mortality, but their benefits are modest.[24] Overall mortality and hospital readmission rates have remained high and largely unchanged in recent years.[25] Despite research expenditures that are often over $100 million per clinical trial,[26] nothing that has been achieved compares with the remarkable advances in treating coronary heart disease using medical devices.

Using Medical Devices to Treat Heart Failure

Medical devices used to treat heart failure fall into three categories: artificial hearts, defibrillators, and heart pumps. The most effective heart-failure treatment is a heart transplant, but the supply of hearts is extremely limited. Several decades of research on artificial hearts have moved slowly, and artificial hearts are mainly for temporary use while awaiting a transplant.[27]

A second category of medical devices is defibrillators, which target arrhythmia. Arrhythmia occurs when different compartments of the heart beat wildly or unevenly. Unchecked cardiac arrhythmia can develop at any moment and can cause sudden death. Implantable defibrillators detect and correct arrhythmias with electrical stimulation before sudden cardiac death occurs. Some implantable defibrillators can perform cardiac resynchronization therapy (CRT), in which electrical pulses stimulate the ventricles to beat in sync once again. CRT, often combined with defibrillation, can increase exercise capacity and survival.[28] Once used only in patients with moderate to severe heart failure,[29] combination CRT and defibrillation devices have recently been shown both to prevent death and to slow the progression of heart failure in mild cases.[30] Research also suggests that the use of CRT devices can promote a reversal of negative physical changes of the left ventricle.[31] Unfortunately, at least 25 percent of patients fail to respond to CRT.[32]

The third category of medical devices is heart pumps, which target the heart's limited pumping capacity. On this front, R&D has pursued several approaches. One is to thread a miniature pump into or near the heart through the femoral artery of the leg, as when performing an angiogram or inserting a stent. Examples include intra-aortic balloon pumps and Abiomed's Impella 2.5,[33] which are used temporarily before or after surgery on patients with severe heart failure.[34] Another approach is to develop more powerful devices to assume most of the burden of the left ventricle. These devices merit an extended discussion and form the focus of the rest of this *Outlook*.

The Advent of Left Ventricular Assist Devices

The most productive development of heart-failure devices has focused on assisting the left ventricle, which is the most powerful part of the heart and pumps blood throughout the body except to the lungs (which oxygenate blood pumped by the right ventricle). Advanced heart failure typically involves left ventricle contractile weakness.[35] Left ventricular assist devices (LVADs) take over most of the work performed by the left ventricle. In principle, this could accomplish two things. It could improve blood flow, thereby directly reducing mortality and morbidity, and it could permit the heart to recover physiologically, with the potential to reverse the heart-failure cycle.

The size and complexity of LVADs dictate that they be surgically implanted. In a typical LVAD, a tube carries blood from an opening in the lower left ventricle to an opening in the aorta, through which blood flows to most of the body. A pump, which in newer LVADs is about the size of a D battery and can be placed inside the tube itself, propels the blood through the tube. Power is electrical in newer devices but was originally mechanical. The FDA approves LVADs for two different uses: bridge-to-transplantation (BTT), that is, assistance until a heart transplant; and destination therapy (DT), or permanent assistance. The European Union (EU) makes no such distinction when approving LVADs.

LVAD development began in the 1970s in connection with the National Institutes of Health Artificial Heart Program.[36] Research has been dominated by private firms, however, including Jarvik Heart, MicroMed Technology, World Heart, and the Thoratec Corporation.[37] (See table 1 for dates of VAD development by Thoratec.)

Pursuing research through some three decades, Thoratec (based in Pleasanton, California) has had by far the greatest success in bringing various VADs to market. Its first generation of devices—PVAD, IVAD, and HeartMates IP, VE, and XVE—used a pulsatile method for pumping blood, using compression discs to push blood through the pump unit. The pulsatile style was adopted at least partly because a steady, nonpulsed blood supply to the muscles, brain, and other orgrans could prove harmful in unforeseen ways.[38] The HeartMate devices feature a proprietary texture that causes the blood to leave a deposit on surfaces that come in contact with it, making the surface resemble natural veins and arteries, which reduces the threat of clots.[39]

One of Thoratec's first devices (PVAD) was an external pump powered by air compression. Thoratec then developed a similar fully implantable version designed for the left ventricle exclusively, the HeartMate IP. A significant change in technology occurred in the next iteration of the device, VE (vented electric), in which an electrical motor powered the pump compression rather than air (though air compression remained a backup feature). Wires connected the internal pump to external batteries worn by the patient, which allowed for easy battery

exchange and free, unrestrained movement. Thoratec's last pulsatile device, HeartMate XVE, incorporated the same basic design with a number of improvements for better reliability and durability.[40]

Through much of this process, Thoratec also developed its second generation LVAD, HeartMate II. This model employs "continuous flow" technology in which blood is propelled constantly, nearly eliminating the pulse.[41] This completely electrical device (using a similar power system as that for VE and XVE) contains one moving part, the continuously turning impeller.[42] The pump is significantly smaller, quieter, and more durable than preceding models.[43] The HeartMate devices have proceeded through many improvements, some clearly targeted to extend trouble-free performance.[44] The HeartMate II has an estimated device life of nine years, although it may last longer.[45] Last July, former vice president Dick Cheney received a HeartMate II.[46] In a recent NBC News interview, he said it is a "wondrous device. It's really a miracle of modern technology, and I'm here today because we have that kind of technology."[47]

TABLE 1
THORATEC VENTRICULAR ASSIST DEVICE DEVELOPMENT DATES

Thoratec VAD Model	Start of Clinical Trials	FDA BTT Approval	FDA DT Approval	EU Approval
PVAD (external pump)	1976	1995	1998	1998
HeartMate IP (implantable pneumatic)	1985	1994	n/a	1994
HeartMate VE (vented electric)	1991	1998	n/a	1995
HeartMate XVE	n/a	2001	2003	2003
HeartMate II	2003*	2008	2010	2005

SOURCE: Thoratec Corporation, "Media Room," www.thoratec.com/about-us/media-room/index.aspx (accessed December 22, 2010); Thoratec Corporation, "History," http://phx.corporate-ir.net/phoenix.zhtml?c=95989&p=irol-history (accessed January 4, 2011); Thoratec Corporation, *2009 Annual Report* (Pleasanton, CA, 2009), http://phx.corporate-ir.net/phoenix.zhtml?c=95989&p=irol-reports (accessed January 12, 2011); Courtney J. Gemmato et al., "Thirty-Five Years of Mechanical Circulatory Support at the Texas Heart Institute: An Updated Overview," *Texas Heart Institute Journal* 32 (2005): 168–77; and James W. Long, "Advanced Mechanical Circulatory Support with the HeartMate Left Ventricular Assist Device in the Year 2000," *Annals of Thoracic Surgery* 71 (2001): 176–82.
NOTE: Trial initially began in 2000, but was halted to permit device redesign and resumed in 2003.

LVADs as Heart Failure Therapy

Clinical Trial Results for the HeartMate XVE and HeartMate II. Table 2 summarizes the results from two seminal clinical trials, one comparing the HeartMate XVE to "optimal medical management" (mainly drug therapy), and the other comparing the HeartMate II to the XVE.

The results are remarkable. The HeartMate XVE increased the two-year survival rate from 8 percent to 23 percent. The HeartMate II more than doubled that, to 58 percent. This sevenfold total improvement—from 8 percent to 58 percent—translates into a reduction in mortality of more than half, from 92 percent to 42 percent.

Figure 1 shows the results of HeartMate XVE and II clinical trials. What is striking is not only the reduction in mortality (the obverse of increased survival) but also the patterns through time. Several studies of HeartMate II patients demonstrate a dramatic slowdown in the probability of death after six months.[48] Thus, if patients survive six months after implantation, they have a very good chance of surviving several years with the device.

Also notable are improvements in quality of life shown in table 2, as measured by the "Minnesota Living with Heart Failure" questionnaire.[49] Although these gains are less dramatic than the gains in survival, they are nonetheless important. The average HeartMate II patient experienced dramatic decreases in severity of heart failure, going from New York Heart Association class III or IV heart failure to I or II. Moreover, 60 percent of these patients reported a moderate or greater increase in their exercise abilities.[50] Thus, LVADs can enable patients to live longer and with higher quality of life than today's best heart-failure medications can provide.

LVADs and the Heart. LVADs provide therapeutic benefits in two ways. The most obvious is to increase oxygen flow to the body and thereby maintain life and facilitate normal activities. But LVADs also affect the heart itself, which could prove to be even more important. A substantial and growing body of evidence indicates that by relieving the overburdened left ventricle, the LVAD initiates physiological changes that can lead to significant recovery in the heart, especially in the left ventricle itself.[51]

This raises the possibility of removing devices after the heart recovers, making LVADs a "bridge to recovery."[52]

LVADs, especially later-generation devices with the smaller pumps, can be "explanted" with little damage to the heart.[53] Limited but intriguing evidence indicates that some patients who use an LVAD for a year or more can maintain beneficial physiological changes following explantation, remaining largely free of recurrent heart failure after several years.[54] Nonetheless, whether explantation will prove to be a viable therapeutic course remains in doubt.[55]

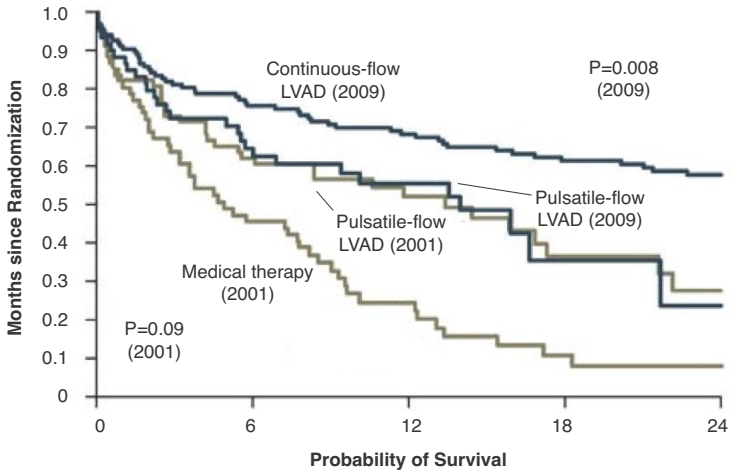
Potential harms from long-term LVAD use include right ventricular failure, calcium cycling, muscle contractile abnormalities, and aortic insufficiency.[56] These will have to be addressed through long-term studies. Whether these and other problems outweigh the benefits of either LVAD implantation or explantation remains to be seen.

TABLE 2
PROGRESS FROM OPTIMAL MEDICAL MANAGEMENT, HEARTMATE XVE AND II

	Treatment Options		
Endpoints	**Optimal Medical Management**	**HeartMate XVE**	**HeartMate II**
One-year survival rate	25%	52%	68%
Two-year survival rate	8%	23%	58%
One-year quality of life score (Minnesota Living with Heart Failure questionnaire)	58*	41*	34

SOURCE: Eric A. Rose et al., "Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure," *New England Journal of Medicine* 345 (2001): 1435–43; and Mark S. Slaughter et al., "Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device," *New England Journal of Medicine* 361 (2009): 2249.
NOTE: A lower score on the Minnesota Living with Heart Failure questionnaire corresponds with a better quality of life. * = The difference between these values was not statistically significant (p = 0.11).

FIGURE 1
SURVIVAL RATES IN LVAD CLINICAL TRIALS



SOURCE: James C. Fang, "Editorial: Rise of the Machines—Left Ventricular Assist Devices as Permanent Therapy for Advanced Heart Failure," *New England Journal of Medicine* 361 (2009): 2282–85.

LVAD Costs. As highly engineered devices requiring specialized implantations, HeartMate XVE and II are costly. The HeartMate XVE device alone costs $70,000 to $80,000.[57] HeartMate II, which has largely replaced it,[58] costs about $100,000.[59] The costs of implantation and immediate postoperative care are about $45,000.[60] Additional costs can arise from complications such as bleeding, infection, or sepsis.[61] Continuing costs include exams, batteries and other equipment, general maintenance, and drugs. Using data from the United Kingdom's National Health Service, Clegg et al. estimated monthly costs of about $2,500 compared to $800 for optimal medical therapy.[62]

Costs have been declining, however. For the HeartMate XVE, for example, hospital costs dropped by 40 percent after the pivotal clinical trial, as experience of implanting and managing the devices increased.[63] We can expect a similar pattern as hospitals and specialized heart centers gain experience with HeartMate II devices. Complications are also likely to decline, perhaps dramatically, with safer product design. For example, the HeartMate II does not require replacement nearly as often as the HeartMate XVE.[64] And patients receiving HeartMate implants after 2000 experienced significantly fewer adverse events than those receiving implants before 2000.[65] As medical experience with the devices has increased, so has patient safety.[66]

Set against LVAD costs are the costs of traditional heart-failure management, which consists mostly of prescribing an array of drugs, along with frequent hospitalization. In the non-LVAD group in the REMATCH trial of the HeartMate XVE,[67] the average cost of care in the last two years of life was more than $150,000, most of it coming in the last six months.[68]

Current and Expected LVAD Usage. Each generation of HeartMate devices, the most widely used LVADs, has been implanted more than its predecessor has. Since

FDA approval in 2001, more than six thousand HeartMate XVEs have been implanted worldwide.[69] The HeartMate II, first approved in the United States in 2008, already has over five thousand implants.[70] The potential market is much larger, however, especially when the next generation of LVADs (discussed below) becomes available. The estimated number of advanced-heart-failure patients in the United States who are potential candidates for HeartMate II ranges from ten thousand to two hundred thousand.[71] In the future, use of LVADs in patients with less-than-severe heart failure may provide patients with a chance for recovery and explantation.

A survey of treatment guidelines from leading cardiologist groups shows that LVADs are still gaining acceptance worldwide. Incorporation of LVADs into these groups' treatment guidelines will increase their use. The European Society of Cardiologists and the Cardiac Society of Australia and New Zealand have tepidly acknowledged that LVADs can provide long-term (DT) support, though the latter has embraced short-term LVAD use.[72] In this same vein, Scottish guidelines only recommend short-term use.[73] The Heart Failure Society of America recommends LVADs for BTT and DT.[74] In the United States, Medicare and private insurance generally cover LVADs for both BTT and DTT.[75]

The Next Generation of LVADs

Development of a third generation of LVADs is well underway (following on pulsatile and continuous-flow devices). Of the many improvements and changes being explored, two stand out. One is the use of magnetic levitation to suspend and rotate a disc that propels blood, with blood itself serving as the lubricant.[76] The second is the incorporation of transcutaneous energy transmission. This would permit the pump to be powered by a battery implanted in the body and charged wirelessly through induction. It would also eliminate open exit points in the skin for electrical leads, a source of infection and inconvenience in current devices.[77] Wireless LVADs have yet to reach clinical testing, but several LVADs with magnetic levitation are in testing or on the market in the EU.

Thoratec's third-generation LVAD, the HeartMate III, has been in laboratory and animal testing since at least 1998.[78] In addition to Thoratec, at least three other firms are involved: World Heart, HeartWare, and Terumo Heart. HeartWare and Terumo Heart already have third-generation devices on the market in Europe. Approved in Europe in January 2009, HeartWare's HVAD incorporates magnetic bearings, hydrodynamic suspension, and a small pump (about the size of a golf ball) implanted directly adjacent to the heart. Based on recently released clinical trial results, HeartWare plans to apply soon to the FDA for BTT approval and is planning DT trials in the United States.[79] Terumo Heart received EU approval for its DuraHeart LVAD in February 2007; it is in clinical trials in the United States for BTT.[80] In clinical trials, both of these devices had a one-year survival rate similar to that of HeartMate II.[81] Device malfunctions were rare, illustrating the technological progress in designing reliable devices.

The Significance of LVADs

The development of LVADs is typical of highly invasive medical devices in many respects. Cardiac stents, pacemakers, and defibrillators all required many years of testing before the FDA overcame serious doubts about their potential and approved first-generation devices. The improvements necessary for routine clinical use required many additional years. External defibrillators were developed in the 1950s, for example, while the first fully implantable defibrillator was not approved until 1985.[82] Eventually, these devices assumed a central role in treating coronary heart disease.

Ventricular assist devices, including LVADs, have followed a similar pattern, but they are still at an early stage of development, and advances have come, if anything, even more slowly. LVADs still reach only a few percent of advanced heart-failure patients, even though those patients face a bleak outlook in traditional medical care. But technical advances in materials, software, and miniaturization are advancing rapidly. The devices now in testing are quite different from anything yet seen in practice. In addition to the new LVADs just described, one small firm is testing a very small pump that can assist the left ventricle without artificial tubing.[83]

Many basic medical questions remain unresolved, the most important of which may be whether LVADs can lead to a resumption of normal cardiac functioning, perhaps after explantation of the device. This is an area in which medical devices are being used as research tools, with potential benefits for devices, drugs, and other heart-failure treatments. Thus, Mancini and Burkhoff noted that the "profound reverse remodeling routinely associated with [LVAD] use . . . further validates device-based approaches and should inspire research to find ways to make this recovery more complete and permanent."[84]

Should LVAD development continue to proceed along the lines of what has happened for earlier cardiac devices, the results could be remarkable. LVADs are highly invasive (like all cardiac devices), active (like defibrillators) rather than passive (like stents), electrically powered (like defibrillators and pacemakers), and continuously working (like pacemakers). Moreover, rather than just transmitting electrical pulses, as other active cardiac devices do, they are in constant motion, so even a brief failure could be fatal. The prospect that such devices could be used to treat thousands, possibly hundreds of thousands, of patients whose conditions have proved nearly intractable to decades of drug development is extraordinary. It marks a transition to a new stage for devices in medical practice.

LVADs and Public Policy

Complex, expensive medical devices like LVADs have implications for public policy in at least two ways. One pertains to costs and reimbursement. LVADs cost well over $100,000 including implantation and postoperative care, but they replace much of traditional therapy, which is also very expensive due to the nature of heart failure. Nonetheless, if LVADs become widely used—as is reasonably certain because of continuing technical advances—we can expect prices and reimbursement to be widely debated even if LVAD use is not constrained by reimbursement policies.

More importantly, the development of LVADs will be constrained by FDA regulation. The EU's medical device regulatory system, which is vastly different from ours, has usually approved LVADs more quickly than the FDA and makes no distinction between BTT and DT.[85] For example, the HeartMate II was fully approved in the EU in 2005, but not until 2008 for BT and 2010 for DT in the United States. In fact, the FDA has approved only six LVADs, of which four are successive generations of Thoratec's HeartMate line. Of the other two, one has been discontinued and the other is used only for pediatric BTT. The EU has approved all these devices plus five additional devices, three of which are in clinical trials in the United States for BTT and one of which is no longer available due to manufacturer bankruptcy. Moreover, development of the next generation of LVADs is proceeding more rapidly in the EU than in the United States. The EU's speed partly reflects far less stringent clinical-trial requirements (involving trial size, length, and complexity) for new device approvals. Yet there seems to be no evidence of undue safety problems with LVADs. As a result, further progress against heart failure depends not only on continued technical progress but also on changes in FDA policy that facilitate faster approval.

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