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DEVICES FOR MANY-FACETED HEART FAILURE

Corlnnova:

A Versatile Device Serves Many Heart Failure Patients

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Heart failure has come to the fore as an innovation and a puisition target for medical device companies at a time when the Heart Failure Society is working to create guidelines that support the use of devices in many groups of heart failure patients. The challenge remains: characterizing patients and understanding the best approach for them.

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hat's the biggest unmet need in cardiovascular disease? Heart failure, at least from the perspective of medical device company representatives who spoke on the panel "New Opportunities and Directions in Cardiovascular Medical Devices," which took place in April at the MedTech Strategist Innovation Summit in Dublin. Executives from Edwards Lifesciences, Johnson & Johnson, and Medtronic agreed that many patients with heart failure don't yet have access to the right therapy, because the disease is complicated in ways that we're only beginning to address.

Bruce Rosengard, MD, vice president and global lead for medtech for Johnson & Johnson's External Innovation group (and a cardiac surgeon), noted that, to begin with, "It's not one disease. It's really a syndrome, and in fact, heart failure is the end state of every form of cardiac disease: valvular disease, coronary disease, congenital disease, infectious disease, inflammatory disease, arrhythmic disease. All of them can lead to heart failure."

There are two major categories of heart failure between which patients are split about 50-50: heart failure with reduced ejection fraction (HFrEF), also known as systolic heart failure, and heart failure with preserved ejection fraction (HFpEF), or diastolic heart failure. But within those high-level distinctions are many gradations of disease, taking into account how, exactly, the heart is dysfunctional, and how the patient got there. Heart failure usually begins with some other condition—an earlier damaging myocardial infarction, an untreated arrhythmia or sleep apnea, or the slow accumulation of comorbidities like hypertension, coronary artery disease, and diabetes, which lead to vascular resistance.

Panelist Virginia Giddings, vice president of exploration for Edwards Lifesciences, pointed out that heart failure develops over many years, and it "is a very complex disease presenting with different phenotypes." Within the pathological state in which the heart is failing, there might be problems with the pump, the ventricles, the heart's muscle, or the valves, she said. There is right or left heart failure, and biventricular failure. Heart failure manifests in so many phenotypes because it arises from the interplay of structural and biological changes influenced by aging, one's genetic background, comorbidities, and lifestyle. "The physiology can be very different from one patient to another," Giddings said. Also on the panel was Chris Eso, vice president of corporate development for Medtronic, who said, "It is inevitable that companies that come to present to us say they're in heart failure. Our initial follow-up question is, 'Well, what patient type?' Because at the end of the day, there probably isn't one heart failure solution. It's a question of addressing all the different disease states that lead to heart failure."

In terms of the therapeutic development possibilities around heart failure, Giddings said, "The sky is the limit," and, she added, "the patient population is enormous."

Tailwinds for Heart Failure Innovators

In September, the Heart Failure Society of America reported that in 2021, heart failure, which affects approximately 6.7 million people over the age of 20, was responsible for 45% of all cardiovascular deaths, and the situation is worsening (see box, "In 2024, Heart Failure Has Become an Even Bigger Problem").

That same month, the society also issued a consensus document in the Journal of Cardiac Failure, to begin the process of creating guidelines for the use of medical devices in heart failure—not necessarily as a second-line alternative after guideline-directed medical therapy (GDMT) fails or is precluded, but right alongside medical therapy in the appropriate sets of patients. The authors make the case that devices can be beneficial because they might target specific physiological mechanisms of disease in ways that drugs can't, and they're also not, usually, subject to issues of adherence or metabolism the way drugs are.

The Heart Failure Society felt it necessary to take this step because device therapies, even when approved with evidence that they work, are underused or not used early enough. Thus the society wants to create, for heart failure device therapies, the kind of standardized, guidelines-based approach that governs drug therapy.

The authors contend that even when heart failure patients are managed by medical therapy, the residual risk of events (hospitalizations due to episodes of decompensation and death) is high enough to support combination approaches that include devices. But that's not the whole problem. The scientific statement cites real-world studies showing that 43% of eligible heart failure patients don't benefit from guideline-directed medical therapy for many reasons, including intolerance, nonadherence, inconsistent delivery, and the long-term cost of recurrent usage. Given that inadequate medical therapy confers an excess risk of all-cause mortality of 29% over two years (or higher—37% when the comparison includes only concurrent medication refills), the society has set out to create a care pathway and guidelines for the timely and judicious use of devices that target specific pathophysiological mechanisms, some already approved, and many more making their way through development.

This provides tailwinds for heart failure device developers, as do recent acquisitions by the some of the strategics mentioned above, whose spokespeople were clearly not talking through their hats when they said heart failure was a priority. In August, Edwards acquired, from **Genesis MedTech**, JC Medical, the maker of a transcatheter valve for the treatment of aortic regurgitation, a condition that drives the progression of heart failure, after previously announcing in July that it paid \$1.6 billion to acquire two other companies in the space (without disclosing what it paid for each). In the bundle was JenaValve, which Edwards bought for the potential of its transcatheter valve to treat aortic regurgitation, with FDA approval anticipated in late 2025 (see "TAVR Update: Market Leaders Medtronic and Edwards Look to Conquer New Indications and Solve Old Problems", MedTech Strategist, September 4, 2024). Endotronix was the second company purchased. It's Cordella sensor for monitoring pulmonary arterial pressure, which the FDA approved in June, provides an early warning of heart failure so clinicians can intervene in a timely fashion.

Johnson & Johnson had already staked a major claim to the space in December 2022 by acquiring Abiomed, the leader in mechanical circulatory support, in a deal that valued the acquisition target at almost \$17 billion. In August, it entered into a new device category for heart failure treatment by acquiring V-Wave for \$600 million up front with the possibility of additional regulatory and commercial milestone payments totaling \$1.1 billion. V-Wave is a leading player in the interatrial shunt space, having reported early results from its pivotal trial in April.

Figure 1 Mechanical Circulatory Support for Heart Failure

Category	Selected Company Examples
Left ventricular assist devices	FDA cleared: Abbott (<i>HeartMate 3</i>)
	In development: CorWave, Corvion Medical, EvaHeart
Total artificial heart (TAH)	SynCardia, only approved TAH in US. Carmat (<i>Aeson</i>) has CE mark.
	In development: BiVACOR (<i>BiVACOR</i>), Scandinavian Real Heart (<i>Realheart</i>)
Intraventricular flow accelerator	FineHeart (<i>FlowMaker</i>)
Balloon pump for counterpulsation	NuPulseCV (<i>iVAS</i> intravascular assist system)
Non blood-contacting biventricular support	CorInnova, Adjucor
Percutaneous ventricular assist devices	Abbott (Impella)
	Devices in development migrating from temporary support during high-risk PCI to heart failure: BrioHealth Solutions (<i>BrioVAD</i>), Magenta Medical (<i>Elevate</i>), Procyrion (<i>Aortix</i>), Puzzle Medical, Supira Medical

Source: "HFSA Scientific Statement: Update on Device Therapies in Heart Failure," Journal of Cardiac Failure, September 10, 2024; MedTech Strategist

These events are giving a muchneeded boost to a medtech development category that, while offering compelling products for an enormous market, is extremely challenging.

The Different Faces of Heart Failure: Opportunities and Challenges

Once, devices for heart failure fell into three basic categories: implantables for cardiac rhythm management (implantable cardioverter defibrillators or ICDs, and devices for cardiac resynchronization therapy or CRT); devices to manage fluid overload during acute decompensated heart failure; and mechanical circulatory support (artificial hearts or ventricular-assist devices) to sustain late-stage patients until a decision is made about a next step, such as a heart transplant.

The classic image of heart failure was the decompensated patient, breathless, swollen, and hospitalized frequently. While decompensation is a common latestage feature of all types of heart failure when it isn't under control, we now know that depending on the patient's disease, there are many more potential pathophysiological points of intervention, which device companies are now targeting.

There are programs addressing heart failure from a structural angle by repairing mitral or other damaged heart valves that exacerbate the problem, and others that attempt to reshape and/or remodel enlarged ventricles. Many companies are working to electrically modify pathways relevant to disease, at the level of cardiac cells, for example, to increase contractility, or by stimulating the autonomic nervous system or the respiratory system. Others are creating new heart pressure monitoring systems (Endotronix, for example) to signal worsening trends of heart failure to allow timely intervention, and, ultimately, a greater understanding of disease processes. (see Figures 1-3).

In addition, work is being done by companies on the front end of the problem, to diagnose and characterize heart failure patients, an unmet need that makes therapy development all the more challenging.

For example, while HFrEF, which is a dysfunction of the heart's pumping action, is easily diagnosed by the ejection fraction or how much blood is pumped out with each heart contraction, HFpEF, which represents at least half of all heart failure, is difficult to diagnose. HFpEF patients have a normal ejection fraction, but a dysfunction in the filling cycle of the heart. The current criteria for diagnosing HFpEF, in patients having shortness of breath during exertion and other signs of heart failure, include a normal left ventricular ejection

Figure 2 Selected Physiological Therapeutic Devices for Heart Failure

Physiological Approach	Selected Company Examples
Interatrial shunts	Adona Medical, Alleviant (<i>Alleviant System</i>), Corvia (<i>Corvia</i> Atrial Shunt), Edwards (<i>APTURE</i>), InterShunt Medical (<i>PAS-C Catheter</i>), NoYA MedTech (<i>NoYA</i>), Occlutech (<i>Atrial Flow Regulator</i>), V-Wave (<i>Ventura</i>)
Heart valves	Devices for the repair or replacement of heart valves, SAVR, and TAVR: Abbott (<i>Navitor</i>), Edwards (<i>Sapien S3</i>), Medtronic (<i>Evolut FX</i>)
	Transcatheter valves in development for aortic regurgitation: Edwards (JC Medical and JenaValve)
	Transcatheter edge-to-edge mitral valve repair: Abbott (<i>MitraClip</i>), Edwards (<i>PASCAL</i>)
	Tricuspid valve repair or replacement: Abbott (<i>TriClip</i>), Edwards (<i>EVOQUE</i>)
Neuromodulation, various	Baroflex activation: CVRx (Barostim Neo)
	Vagus nerve stimulation: LivaNova (VITARIA)
	Splanchnic nerve ablation: Axon Therapies (for HFpEF)
	Immunomodulation: Humanitas Research (<i>HF-ImMod</i>)
Electrophysiology modulation	Cardiac resynchronization therapy: Abbott, Biotronik, Boston Scientific, Medtronic.
	Cardiac contractility modulators: Berlin Heals (<i>C-MIC</i>), Impulse Dynamics (<i>IMPULSE Optimizer</i>)
Respiratory modulation	Phrenic nerve stimulation: Respicardia
Fluid volume management	Reprieve Cardiovascular
Reduction of pulmonary hypertension	Aria CV
Ventricular reshaping	Ancora Heart (<i>AccuCinch</i>); BioVentrix (<i>Revivent TC</i>), Cardiac Success (<i>VSling</i>)

Source: "HFSA Scientific Statement: Update on Device Therapies in Heart Failure," *Journal of Cardiac Failure*, September 10, 2024; *MedTech Strategist*

fraction (≥ 50%), evidence of abnormal left ventricular filling, increased filling pressures, and elevated levels of natriuretic peptides.

While transthoracic echocardiography is used to estimate intracardiac filling pressures, it requires expertise and is subject to intraoperator variability. Natriuretic peptides are easy to measure, but it's estimated that one-third of HFpEF patients have normal levels. Right heart catheterization is the gold standard in determining increased left ventricle pressure, but it's not undertaken lightly in a frail, elderly patient. The noninvasive diagnosis of HFpEF is an innovation target that one UK-based company, **Ultromics**, has taken on successfully with an AI application for echocardiography (see sidebar, "Ultromics: Successful Treatment Begins With Accurate Diagnosis").

The Swedish start-up **Acorai** is also developing an AI-enabled solution for heart failure; the company has developed a cluster of sensors for noninvasive pulmonary and cardiac pressure monitoring, which, as its founder Filip Peters says, "has been the Holy Grail of cardiology and particularly heart failure, for decades." We discuss Acorai below.

But Who Are the Patients?

With so much heterogeneity among patients, many unanswered questions remain. Which patients are right for the mechanism of action of which therapy? And in the end, how large is the market for that particular approach? How do you characterize patients and study them in clinical trials for the purpose of demonstrating benefit? Speaking at the Innovation Summit meeting mentioned above, Medtronic's Chris Eso said, "Any one of the new solutions might only be suitable for a smaller patient population. But we have to identify the right patients, period." This is an opportunity in and of itself; heart failure is ripe for innovation in the space of phenotyping tests.

The clinical experience of **Corvia** and V-Wave are illustrative of the challenges heart failure device developers face, as the first two companies in a new class of devices called interatrial shunts, a popular innovation space that has attracted at least seven start-ups so far. Elevated left atrial pressure is a feature in many heart failure patients and interatrial shunts create an opening in the septum between the left and right atria to shunt blood into the larger reservoir of the right atrium to relieve

In 2024, Heart Failure Has Become an Even Bigger Problem



 Approximately 6.7 million Americans over 20 years of age have heart failure (HF), and the prevalence is expected to rise to 8.7 million in 2030, 10.3 million in 2040, and 11.4 million by 2050.

 One in four will develop HF in their lifetime; the risk increases with obesity, hypertension, and clusters of comorbidities.

The proportion of younger patients with HF is increasing more than the share of older patients.

24-34% of the US population has pre-heart failure.

The incidence and prevalence of HF is higher among Black individuals compared with other racial and ethnic groups. The prevalence of HF has increased among Black and Hispanic individuals over time. HF mortality rates have been increasing since 2012. In 2021, HF contributed to more than 425,000 deaths in the US and accounted for 45% of cardiovascular deaths.

Black, American Indian, and Alaskan Native individuals have the highest all-cause age-adjusted HF mortality rates compared with other racial and ethnic groups. From 2010 to 2020, HF mortality rates have increased for Black individuals at a rate higher than for any other racial or ethnic group, particularly for individuals below the age of 65.

A greater relative annual increase in HF-related mortality rates has been noted for younger (35-64) compared with older (65-84) adults.

Rates of HF hospitalizations have increased since 2014. This increase was consistent between age groups and sexes, with the highest rates being among Black patients.

Source: Heart Failure Society of America, reported on September 24, 2024

the pressure. Both companies ran well-powered, high-quality randomized clinical trials, and both failed to prove their primary endpoints (of a reduction in heart failure events).

First, Corvia enrolled 626 patients in REDUCE-LAP HF II and randomized patients to either the Corvia Atrial Shunt, or a sham procedure. At two years, there was no difference in primary outcomes between the two groups. However, certain subsets of patients responded well to the therapy. Hence, Corvia is now running a second double-blinded, randomized, sham-controlled trial, RESPONDER-HF, and will study another 260 patients for two years, this time recruiting only certain patients with HFpEF (with an ejection fraction \geq 40% and further qualified by their hemodynamics during exercise) and HFmrEF (heart failure with mid-range ejection fraction), to try to determine which heart failure patients benefit from shunting.

Likewise, V-Wave enrolled 508 patients in its pivotal trial RELIEVE-HF. Heart failure patients with any ejection fraction were admitted, but randomization was stratified across patients with either reduced or preserved ejection fraction. As noted, the trial failed to achieve primary endpoints around the reduction of heart failure events, but demonstrated a 45% reduction in adverse cardiovascular events for HFreF patients, and a higher rate of harm to those with HFpEF.

The clinical community remains positive about the potential for these devices, although not enough patients have been studied yet to make pronouncements. Both **Occlutech** (with its *Atrial Flow Regulator*) and **Alleviant** (which creates a shunt without Depending on the patient's disease, there are many more potential pathophysiological points of intervention, which device companies are now targeting.

for such a heterogenous patient population. Further, current developers are challenged by the lack of a window into what, precisely, is happening with cardiac filling pressures as patients go about their lives. Adona Medical, profiled below, has designed its platform to address both shortcomings.

Addressing late-stage heart failure and cardiogenic shock, **CorInnova** hopes to disrupt the space with a novel, physiological, and non-blood contacting device. The start-up faces the rigorous PMA pathway for a first-of-its-kind device, but its CEO believes that the patient population it is initially targeting is well defined and large, with more to follow. We interview CorInnova below.

leaving a device behind) are currently enrolling for equally large and robust clinical trials, so we can expect some clarification within the next five years or so.

While incumbents are focused on determining which kinds of heart failure patients respond to interatrial shunting, Brian Fahey, PhD, the co-founder, president, and CEO of interatrial shunt newcomer **Adona Medical**, believes that's not the only challenge, and that today's "onesize-fits-all" approach to interatrial shunts isn't likely to be broadly effective

Figure 3 Selected Heart Failure Monitoring Companies

Category	Selected Company Examples
Invasive monitoring of surrogates for cardiac pressure (predicting congestion)	Two FDA-cleared stand-alone products: Abbott (<i>CardioMEMS</i>), Edwards (<i>Cordella</i>) Diagnostic companions to implanted CRT or ICD devices: Medtronic (<i>TriageHF</i>), Boston Scientific (<i>HeartLogic</i>), Biotronik (<i>HeartInsight</i>) In development: Fire1, Vectorious
Noninvasive surrogates for cardiac pressure monitoring	Acorai (SAVE sensor), Analog Devices (Sensinel), Bodyport, Cardiosense (Cardiotag), Zoll (Heart Failure Management System)

Source: "HFSA Scientific Statement: Update on Device Therapies in Heart Failure," Journal of Cardiac Failure, September 10, 2024; MedTech Strategist