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**REPRIEVE CARDIOVASCULAR:** IMPROVING THE FRONT-LINE THERAPY FOR ACUTE DECOMPENSATED HEART FAILURE

Reprieve Cardiovascular’s Guided Diuretic Therapy for fluid overload optimizes diuretics, today’s front-line therapy for acute decompensated heart failure, in a way that promises to be faster, safer, and, in the long run, more helpful for patient management than drugs on their own.

Reprieve Cardiovascular Inc. was launched just five months ago to address the leading cause of hospital admissions among older patients: acute decompensated heart failure (ADHF). In the US, one million patients with ADHF end up in the hospital each year.

Although the start-up hasn’t been in business long, it has hit the ground running because the technology at the heart of its novel heart failure therapy has already been used in 20,000 patients, 2,000 within clinical trials in Europe, for a different clinical indication. “That’s an important advantage,” says CEO and co-founder Jim Dillon, “because it translates to manufacturing experience and an incredible safety profile.”

Reprieve Cardiovascular’s core technology was developed by the team behind RenalGuard Solutions Inc.; Howard Levin, MD, a heart failure cardiologist who created and leads the medical device incubator Coridea, and Andrew Halpert, an electrical engineer who worked on Coridea’s start-up CHF Solutions Inc., which developed an ultrafiltration system to alleviate fluid overload in chronic/rescue heart failure patients.

RenalGuard developed a medical device to protect the kidneys of patients who receive contrast agents during imaging procedures in cardiac catheterization labs. Contrast is toxic to kidneys, so the team developed a system that dilutes contrast and increases urine output to decrease its contact with kidney cells. Before imaging procedures, patients receive an injection of a diuretic. The RenalGuard system then constantly measures urine output and reinfuses an equal volume of hydration fluid.

The use of RenalGuard in the cath lab led to an insight that was the impetus for the creation of Reprieve Cardiovascular: “The maintenance of intravascular volume generated significantly more urine output per amount of diuretic given, that is, the diuretic efficiency was markedly better in those patients,” says Howard Levin. RenalGuard thus emerged as an adjunctive treatment for ADHF, where diuretics constitute the chief therapy for the management of fluid overload.

The use of diuretics is challenging, says Levin, who describes the “over-under” of ADHF.
including the kidneys. As renal protective mechanisms kick in, the body retains more sodium and water, creating a vicious cycle.

Too little diuresis is also undesirable, because a patient who is not properly decongested remains in an unhealthy state that increases the length of stay and the likelihood of readmission to the hospital.

Clinicians and hospitals thus perform a challenging balancing act around the health of heart failure patients and the economics of healthcare. If ADHF patients stay in the hospital for too long, profitability is impacted under bundled payment models, and there is an additional opportunity cost for keeping an ICU bed occupied by an unprofitable patient. But if patients are released too soon, they are more apt to return to the hospital. Under Medicare’s Hospital Readmissions Reduction Program, more than half of health systems have to pay penalties for heart failure readmission rates above a certain threshold (too many patients coming back too soon). They also stand to gain from increased reimbursement if their readmission rates are much lower than the benchmark.

Levin points out that 90% of all heart failure admissions are due to volume overload, not pump failure. “Patients have too much volume on board. They’re short of breath, have impaired organ function, and are at risk of having an adverse event that you can’t prevent by adjusting their meds on an outpatient basis and sending them home.”

Levin noted that patients being treated with RenalGuard for contrast induced nephropathy had much larger and prolonged response to diuretics than expected. For this and other physiological and clinical reasons, he saw an opportunity to help remove excess fluid in heart failure patients who are more resistant to diuretics.

RenalGuard’s management team made the decision to form a new heart failure-focused company to help its platform evolve into a new market with the right clinical—and financial—support. The strategy appears to be working; Abiomed Inc. came in on a $7 million financing round in August.

Figure 1
Reprieve Cardiovascular Optimizes Diuretics to Precisely Control Decongestion

<table>
<thead>
<tr>
<th>Current Platform</th>
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<tbody>
<tr>
<td>• Current device platform.</td>
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<tr>
<td>• CE-Marked for “fluid balancing.”</td>
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<tr>
<td>• HF application functional with current device technology.</td>
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<tr>
<td>• Expanding inpatient and potential outpatient site of care.</td>
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<tr>
<th>Theranostics – in Development</th>
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<tbody>
<tr>
<td>• Real-time diagnostics: sensors built into urine collection set.</td>
</tr>
<tr>
<td>• Front-line therapy: combination of sensor readings with urine output data to optimize therapeutic decongestion.</td>
</tr>
<tr>
<td>• Iterate treatment algorithm with machine learning and artificial intelligence.</td>
</tr>
</tbody>
</table>

Source: Reprieve Cardiovascular
reduced congestion. The therapy was associated with an improvement in the signs and symptoms of heart failure, and there was an increase in diuretic efficiency, all patients felt better after the therapy, and there was improvement in the signs and symptoms of congestion. The therapy was safe, with no procedure-related side effects. “These effects, which were much bigger than we expected, came as a positive surprise,” he said, when presenting the results at the European Society of Cardiology’s Heart Failure congress in May 2018.

A second trial in Europe, called Target II, was designed to determine whether the safety net the system offers in terms of maintaining a healthy fluid balance would enable rapid but safe fluid removal in patients given a high initial dose of diuretic. The study is still ongoing, but early results have shown an improvement in diuretic efficiency as demonstrated by a doubling over the baseline level of net fluid loss within 24 hours. “The studies in Europe have confirmed the diuretic efficiency of urine removal in diuretic-resistant heart failure patients,” says Dillon.

While initial development efforts are focused on improving the way patients are treated today—that is, in the hospital, with diuretics—the company is already working on a new theranostics platform that marries simple front-line diagnostics with therapy to improve overall patient management. The third generation system will incorporate sensors that monitor sodium and other parameters in urine as well as machine learning to help clinicians answer three relevant questions, says Andrew Halpert: “Does the patient have enough retained kidney function in order to benefit from diuretic therapy, or do they need more aggressive therapy? Is the current fluid removal rate too high or too low? Is the current diuretic dose too high or too low?” Clinicians have never had this information before, and without it, valuable time is lost. Even at highly regarded centers, says Dillon, it can take days for clinicians to figure out the right dose of diuretic to get patients headed in the right direction. “We are trying to get to the point where you can answer those questions within hours, so the clinician can optimize the diuretic dose and fluid removal rate within hours,” he says.

The answers to these questions will not only make treatment in the hospital setting more efficient and predictable, they will also help clinicians better manage patients on diuretics at home. And the information will underpin a new delivery strategy—guided diuretic therapy on an outpatient basis, with the goal of keeping heart failure patients out of the hospital in the first place. This is an opportunity that has already been enabled by companies developing implantable heart failure sensors like Medtronic PLC’s Chronicle and CardioMEMS from Abbott Laboratories Inc., and digital apps like Bluetooth-enabled weight scales, all aiming to give early signs of impending ADHF.

As to how Reprieve Cardiovascular’s new offering will fit into the workflow of hospitals, Levin says “We are automating, in a real-time fashion, the front-line therapy that they are already comfortable with. We are not changing the standard of care, we are making it better.”

It’s too soon to discuss pricing, but Dillon relates it to the hourly costs of a patient in an intensive care setting. “It is fair to say that the first generation off-the-shelf Reprieve commercial system would cost less than a couple of hours in the ICU.”

In five short months, Reprieve Cardiovascular has advanced swiftly. The next move is the completion of Target II, and the beginning of an early feasibility study in the US. The FDA has granted approval for the company to study 40 patients at five sites, which will help it rapidly iterate its protocol and technology and get it closer to its ultimate goal of benefitting millions of patients worldwide.