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SUMMARY

Pulsatile and continuous flow devices are both expected to have a role, but the biggest market will go to continuous/ axial flow devices. However, sales of these devices is unlikely to take off until there is an approved continuous flow device for destination therapy, and sources do not believe anything currently in trials is likely to be the winner. Continuous flow devices have design issues, but they are generally considered safe. The major cardiac device companies are interested in LVAS, and they are likely to buy smaller companies to get into the market – but not until the products are developed further. The major companies just do not view current devices as ready for prime time, but they are watching the space.

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LEFT VENTRICULAR ASSIST SYSTEMS

To check on the outlook for Left Ventricular Assist Systems (LVAS), 16 experts in the field were interviewed as well as several industry sources. There are two types of LVAS – pulsatile and continuous flow. The term "axial flow device" is preferred over continuous flow device because experts are finding that continuous flow devices actually have some pulsatility. However, the names are still being used rather interchangeably, though centrifugal pumps (e.g., Ventracor's VentrAssist and Arrow's CorAide) differ from the true axial flow pumps (e.g., Micromed Technology's DeBakey, Berlin Heart's Incor, and Jarvik's Jarvik 2000).

PULSATILE VS. AXIAL/ CONTINUOUS FLOW

Opinions varied as to which technology is most likely to prevail – pulsatile or continuous flow. However, most sources believe there will be a role for both, with the larger market going to axial/continuous flow devices. Pulsatile devices will continue to be used primarily for bridge-to-transplant, and axial/continuous flow will address the much larger destination therapy market.

Doctors were divided as to which technology will prevail. However, most sources believe there is a role for both types of devices.

Axial/continuous flow devices will prevail:

➢ *Dr. Ed Savage, Rush Presbyterian:* "I think you are going to see that the **axial flow devices are going to take over** when they're approved. There are some problems with them. For example, there is thrombosis with the DeBakey device, though I've heard they've solved that or made it better. I don't know if there is a final answer…The newer generation LVADs being developed are all continuous flow devices – which may be able to contribute some pulsatility."

➢ *Dr. Gary Ott, Portland Heart Clinic:* "**I think the future will be continuous flow, but maybe *not* with this generation of devices**. I see the future as better devices, and we'll use them in people who are not candidates for transplant. Once proven, they'll be an alternative to transplantation, but that's still two generations away. The heart transplant is still the gold standard. Send someone home, and they have a life and can go swimming, which is not possible with the current devices…The company that wins will have an axial flow device because the other ones are just too bulky. We surgeons love making big incisions and fixing the problem, but for patient acceptance and doctor acceptance, the smaller, sexier devices win. The winner will be a Jarvik, DeBakey, or a derivative of those. Everyone thought when Novacor came out, it would be the one, but the tide changed completely when the results came in. For destination therapy, it is more attractive to look at axial flow devices because of their size.

They are not so cumbersome, and they are built for patients who are semi-ambulatory already. So the two types of devices have two separate areas of use…We had a patient who got such good results (with an axial flow device), that it became destination therapy by default. He was a truck driver from Tennessee who was passing through our state. He got the device and went home. He didn't want it taken out, and he didn't want a transplant…The majority of the axial flow devices are not intended to take patients who are at death's door and give total output from the heart. They've been better at true assistance – helping someone who still has a little bit of heart function. In that situation they're going to do very well."

➢ *Dr. James Stringham, University of Utah:* **"Continuous flow is the future**. No one will put in a short-term pump when the longer-term pumps are available."

➢ *Dr. Mehmet Oz, Columbia University:* "Both will play a role, but continuous flow will be the most used eventually…Safety is not an issue with the continuous flow devices."

➢ *Dr. Eric Rose, Columbia University:* "Continuous/axial flow devices will probably replace pulsatile devices in the future, but there may be room for both as well…If I were a company entering the field now, I would develop continuous flow devices."

Pulsatile will continue to dominate:

➢ *Dr. Brad Rosengard, Papworth Hospital, London:* "It is not clear that the field is moving away from pulsatile. There is a lot of hype in the field, but only small improvements… REMATCH was supposed to support destination therapy, but most patients are dead in two years…Pulsatile is good if the destination is the grave since that device is only intended to last two years…**I'm not sure axial flow will last**. Either it needs to be implanted across the aortic valve or above the aortic valve."

➢ *Dr. J. Yasha Kresh, Drexel University, Philadelphia:* **"Continuous flow (axial flow) devices are not going to replace pulsatile devices in the future**. The 'experts' refer to the continuous flow devices as 'ventricular assist devices' as opposed to 'ventricular replacement devices,' the implication being that the continuous flow devices will be used to treat patients who still have some (albeit suboptimal) ventricular (cardiac) function. The distinction may be somewhat theoretical since continuous flow devices are still capable of generating 10 L/min flow. In part, this is related to the desire to have some native pulsatility such that these devices are behaving as augmenters elevating the underlying cardiac output. The concern is that our organism evolved where the blood pressure is pulsatile and the reflex systems that regulate our blood pressure are conditioned to experience a degree of pressure pulse."

A role for both:

➢ *Dr. Christiano Caldeira, University Hospitals, Cleveland:* "**Both will be used in the future.** Pulsatile is a field that is slowly maturing…The (pulsatile) devices perform well, but they are very large and only usable for short periods of time. Bridge will shake down to only a couple of players… Continuous flow is smaller but more complicated. Transplant patients will remain pulsatile candidates. The market for continuous flow is larger."

➢ *Dr. Mithan Sukumar, Oregon Health & Science University:* "It's almost like asking which car is going to be the best. **We need both of them**…When there is no function of the heart, when the heart has given up the ghost, we use a pulsatile device – almost like a replacement device. Continuous flow devices are called assist devices because some function of the heart is still there."

➢ *Dr. O. H. (Bud) Frazier, Texas Heart Institute:* "There are **different roles for different technologies**…Continuous flo w pumps can be implanted easily and safely in very sick patients. With the last three I put in, the patients already had incisions in their chest. Continuous flow pumps are very beneficial to critically ill people. On the other hand, continuous flow pumps are only assist devices; the heart has to have enough capability so that it can contribute whereas pulsatile pumps can work in patients with no pumping capability…I think continuous flow pumps have tremendous potential. We use them in England, where they don't transplant patients over the age of 60…It's clear the primary role of continuous flow pumps will be as assist devices, but the patients in England did very well with them in lieu of a transplant."

➢ *Dr. John Conte, Director of Heart/Lung Transplantation at Johns Hopkins University:* "One's an apple, and one's a watermelon. They are tremendously different. I suspect that the axial flow devices will get approved in time and will be used, but I think there are going to be problems with them, and there will be a learning curve. So, **both will find a niche**. My suspicion is that more pulsatile devices will be used for destination therapy…It makes sense to me that something that is moving 60 times a minutes is going to last longer than something moving 10,000-12,000 rpms. There would be less damage to blood cells, less wear and tear…Axial flow patients are smaller, and to maintain some kind of pulsatility in the circulation, they don't empty the left ventricle out totally, so they are more of an assist device than a replacement device. That's the important distinction when trying to determine the best device."

➢ *Dr. Pierre Theodore, a cardiac surgeon at Johns Hopkins University:* "Continuous flow devices will probably have a role with patients with limited left ventricular function. With more heart failure patients being diagnosed, I wouldn't be surprised to see **more and more continuous flow devices** in place…Chances are the future will be smaller, more efficient,

self-contained pulsatile devices – maybe a third, fourth, or fifth generation implantable AbioCor device or a small, percutaneously delivered axial flow device that even a non-surgeon might be able to place…Long-term efficacy remains to be seen with every device."

➢ *Dr. H. J. Patel, University of Michigan:* "There are **pros and cons to both**…The lack of a transcutaneous energy source is a problem with any of these devices…My preference is pulsatile devices, and we have more experience with those, but we recently obtained access to the DeBakey device, and I don't know which will be better in the long term…I think axial flow devices probably are safe. The body gets used to not having flow beyond a certain point, and we've certainly had patients on the devices for months who don't appear to have any sign of end-organ impact."

PULSATILE DEVICES

Among the advantages cited for pulsatile devices were:

- **Mimic the heart/circulation.** An expert said, "Pulsatile devices really mimic the circulation closely. They kind of replace the left ventricle, and that's important in sicker patients."
- **Experience.** There is simply more data on these devices than on axial/continuous flow devices.
- **Valves.** This is in contrast to continuous flow devices, which depend on motor function to prevent backflow.
- **Low energy.**
- **Low mechanical failure.** An expert said, "Devices with an external drive are less prone to mechanical failure."
- **Good flow.** An expert said, "Pulsatile devices are good for people who have no circulation because they deliver more flow."

Disadvantages to pulsatile devices include:

- **Infection.** An expert said, "None is completely contained. All have drive lines or communications lines, which are always a source of infection. Virtually all get infected within three months of implantation."
- **Hard to implant**. A surgeon said, "The first HeartMate was simple, with a minimal chance of failure. The second generation device has had a lot of mechanical failure problems."
- **Bulky.** An expert said, "For the moment, they are more mechanically complicated, bulkier, and require drive lines that get infected quickly." Another doctor said, "Pulsatile devices are prone to mechanical failure."
- **Thrombosis.** A doctor said, "In coronary arteries where there is a long blood path – all the way to the aortic valve – a clot can form in the patient's bloodstream because of loss of pulsatility."
- **Exercise tolerance.**
- **Auto regulation in the brain.**
- **Visceral organs.** An expert said, "Visceral organs have been designed to accept pulsatile flow, and it's an unnatural thing to run around with no pulse."

The leaders in pulsatile devices were identified as Thoratec's HeartMate and World Heart's Novacor, and there are few other players in the wings. Following are comments by sources on each of these devices.

ABIOMED'S AbioCor

This is the first totally artificial heart. It is pulsatile and transcutaneous. Comments included:

- "We're supposed to be in that trial…but there are a lot of issues with this device. People who need total artificial hearts are few and far between."
- "This is a short-term device for acute perioperative cardiac dysfunction. You can use it for a week – at most 10-14 days – for a patient to recover from surgery and get transferred to another medical center."

ARROW'S LionHeart

Arrow does not have a well-defined presence in this area, though it has both a pulsatile and a continuous flow product. Sources were not particularly excited about LionHeart. The lack of enthusiasm either related to (a) an opinion that the device is too far from the U.S. market to follow closely, or (b) a belief that it is too problem-prone.

Among the comments about Arrow and LionHeart were:

- "I've seen Arrow used, but I know very little about it."
- "Arrow has a lot of potential, but it isn't approved yet…The Arrow pump is very similar to the Thoratec pump. It was developed by the same guy, so it's basically a pump that's a pusher plate pump, but all the electronics are internal, so nothing is outside. That is going to be one of the keys – if not the key – to the long-term pump. There's a drive line that exists, and by having everything contained, once the surgical wound heals, there is less chance of infection. One of the biggest problems with LV devices is infection and either bleeding or thrombosis…Arrow has limited data, but the advantage is that the Arrow device is fully implantable."
- "We haven't used LionHeart at our center, but there has been reasonable success with it at other centers."
- "Arrow's LionHeart hasn't done well in its first clinical trial. Why? It's a whole lot of hardware. It's complex. It's a big operation. And they had high mortality in their first few patients. When I first saw the whole thing, I thought it was a great idea – fully implantable and known and proven technology – but I guess they've had a lot of problems with it."

➢ "The Arrow devices haven't been widely used…All of these devices have been put together by relatively small companies and without a large industrial base. And they are going to face more difficulties."

➢ "LionHeart is big and bulky but totally implantable."

➢ "LionHeart is different technology altogether…LionHeart got the idea of including the compliance chamber and the transcutaneous power…We could have done that in the 1970s, but we didn't see any virtue in that if we'd have to vent it anyway. I'm glad they did it, but it is basically nothing new…Both LionHeart and Novacor still have some strokes associated with them."

➢ "Transcutaneous energy transfer (TET) will likely become more important in the future."

➢ "TET will decrease the infection rate of the devices since no cables need to protrude through the skin, but as with most things, this benefit comes at a cost. With the pulsatile devices, there must be a compliance chamber which requires periodic refilling with air, partially negating the sterility issue. Secondly, these devices have no external cables (the advantage of TET systems), and thus have no means for back-up energy delivery. Without that, it is hard to see how they can have a back-up system if there is any device malfunction. The HeartMate has the potential for hand pumping through the driveline until help (new batteries, new controller, etc.) can arrive. Finally, the mechanics of transferring energy through the skin requires a relatively stable alignment of the sending and receiving TET coils ('antenna'). Since this is such a critical piece of device function, I think that it is a matter of time before complications arise because the patient dislodges the coil in their sleep and dies of pump failure or thrombosis. I think that TET needs to be proven reliable before it can be truly adopted by numerous companies and physicians."

THORATEC

HeartMate

This is the only device with FDA approval for destination therapy. The lack of a transcutaneous energy transfer capability is a problem for Thoratec, but the company has an implantable version in development. Comments about HeartMate included:

➢ "HeartMate is approved for destination therapy, but I think **it is inferior to the other devices** because of mechanical failure, which is a big Achilles heel. It's a complex device…The Thoratec people came out with their first device five years ago…and it went through the skin to plug into the heart. The pump chamber was external, which is not good for long-term support. People can get around, but they have a pounding against their chest, etc. **The company is in the process of clinically testing an implantable device**. That is actually a simple device, and the pump has been proven long-term, so the new Thoratec pump may be able to last longer with less thrombosis."

➢ "Even though (Dr.) Eric Rose – and the Columbia team – did well to organize the REMATCH trial, which led to FDA approval, there hasn't been a stampede of patients or doctors to use the device**. It's good but not quite there yet**…There is some interest in HeartMate-III, but meanwhile the HeartMate-VE has to soldier on…Because of the rotational motor, the HeartMate is bulky and more trouble, and it has bearings that wear down. But the thing works, and it saves lives… HeartMate had a fast start because of low thromboembolism. That was the primary reason it got off the ground faster than Novacor, the rates of which weren't acceptable. All the trials have been done with HeartMate, so approval for destination was with HeartMate data, not Novacor data."

➢ "HeartMate came out with a newer version in the past year or so that is **quite durable**. We've placed it in a number of patients, and we've seen it last a while."

➢ "Mechanical dysfunction is an issue, and so is the size of the device. Infections are the biggest problem."

➢ "HeartMate would be very good if it were totally implantable."

➢ "HeartMate is **the market leader because it was the first one to get approved.** Is it the best pump out there? It depends on who you're asking and the criteria you're using. I like it. It's a very simple pump, and I use it as our number one pump.

- Anyone who says one pump is better than another is wrong. I've used HeartMate, Novacor, Thoratec, and Abiomed, and I'm about to start using Micromed…You tell me the patient, and I'll tell you what to use.
- HeartMate is the one we'd use for destination therapy right now, but we're going to be using the Novacor, and we're going to do a head-to-head trial between Novacor and HeartMate for destination therapy.
- HeartMate is easy to put in. It is a major operation, but it is relatively easy to put in.
- The disadvantages are that it wears out, there is an external drive line, and it can't be used for everyone – patients have to be a certain size."

HeartMate-III

This implantable, rotary, centrifugal pump started preclinical trials around the first of the year. This sealed (fully implantable) system has no mechanical bearings, a flow capacity of 2-12 L/min, a weight of 500 gm, and a volume of 195 cc.

Thoratec IVAD

This implantable, pneumatic, pulsatile VAD was mentioned by a couple of sources, but it does not appear to be gaining popularity. A source said, "It's somewhat less expensive than HeartMate, and it works well, but it is impossible to go home on one; they're too big."

WORLD HEART

Novacor

This electromagnetically driven pump provides circulatory support by taking over part or all of the workload of the left ventricle. It has been implanted in more than 1,480 patients, with no deaths attributed to device failure. Some recipients have lived with their original pumps for as long as four years. Novacor is approved for bridge-to-transplant in the U.S. and Canada. In Europe, it is approved for both destination and bridge-to-transplant therapy. In Japan, it is approved for use in cardiac patients at risk of imminent death from non-reversible left ventricular failure for which there is no alternative except heart transplantation.

The INTREPID trial has stopped enrolling patients, but at least 37 patients (33 in the U.S. and 4 in Canada) were enrolled, and those patients continue to be monitored. The primary endpoint is all-cause mortality at six months. World Heart submitted Novacor to the FDA for destination therapy before completion of this trial, using a Bayesian statistical analysis of all Novacor patients, and is awaiting an FDA decision. World Heart also intends to conduct a pivotal trial in about 30 centers in the U.S., comparing Novacor to the approved HeartMate-XVE for destination therapy.

Novacor II (HeartSaverVAD)

This miniaturized bearing-less, pulsatile, fully implantable device is in the early stages of development. It uses a transcutaneous energy lead from the external battery pack to the implanted controller/standby battery and pump. Comments included:

- "This is less prone to mechanical failure (than HeartMate), but there is a higher incidence of thromboembolism with it than with HeartMate."
- "Many people in the field have the feeling that Novacor is a sturdier pump (than HeartMate), but that remains to be seen."
- "Novacor has some intuitive advantages – fewer moving parts and monitor functions plus instant rotation, but it's a linear up and down piston."

CONTINUOUS/AXIAL FLOW DEVICES

Continuous flow used to connote non-pulsatility, but the thinking on this has changed, and sources all agreed that continuous flow devices have some pulsatility, depending on the action of the patient's heart. The main characteristic of axial flow pumps is their small size. They are about 80% smaller and up to 90% lighter than available, approved, pulsatile devices. Instead of an abdominal pocket, they can be implanted above the diaphragm just below the heart.

A source summed up these devices well: "Axial flow pumps produce non-pulsating flow. In reality, however, the flow, as well as the pressure in the great vessels, show some degree of pulsatility. Depending on the volume in the left ventricle and the ability of the heart to build up pressure, the blood stream into the pump is pulsatile and therefore the flow coming out of the pump is as well." Another doctor commented, "If you run at a sweet spot (4 instead of 6 liters), you can develop some pulse…I think in non-pulsatile pumps, we can achieve some pulse by running them smart."

*The **advantages** cited for axial/continuous flow devices were:*

- **Small size.** An expert said, "Many non-pulsatile devices are considerably smaller, even tiny, like the size of a thumb." Another surgeon said, "The small size offers an opportunity for minimally invasive implantation."
- **Implantation.** This reportedly is easier with axial devices, especially in small patients, though there are "pitfalls" to implantation of these devices that don't exist with pulsatile devices.
- **Few moving parts.** This means less concern with wear and tear, durability, and breakage. An expert said, "As a result, perhaps their durability will be better. With fewer large moving parts, there is less to break." Another doctor said, "Hopefully, they'll be less prone to failure."

*The **disadvantages** cited for axial/continuous flow devices were:*

- **Infection.** Sources agreed ***all*** devices have this problem.
- **Flow.** A source said, "The concern with axial flow is whether the devices are going to be able to deliver adequate flow for people with severe heart failure who don't need just a boost but need almost a mechanical replacement."
- **Energy requirements.** A doctor commented, "They require more energy."
- **Complications (backflow and thrombosis).** Continuous motor function is required to prevent backflow, so if an axial device fails, the potential exists for backflow. A doctor commented, "Imagine what backflow would do to heart function!" Another expert said, "If you lose power, you have thrombosis and the possibility of backflow." Another source said, "We traded clotting something off for pushing thrombosis out…Before, pumps stopped. Now, we get embolisms…I'd rather have something clot off than embolize."
- **Lack of long-term data.** A doctor said, "No one knows what the long-term consequences are for pulsatile flow devices. There are quite a few devices now that have been working for years with no consequences, but each person has a slightly different residual function of the heart."
- **Need for some heart function.** A patient has to have some heart function to use an axial flow device.
- **Lack of good animal models.**

- **Size.** The smallness of these devices is both a plus and a minus. A source said, "Size does matter, but the alternatives bring new issues. No one can say it is easy to re-do a HeartMate…The (pulsatile) devices are marvelous, but they require big surgery…and continuous flow devices are smaller surgery."

The leaders in continuous flow devices were identified as Micromed and Jarvik Heart, but there are several other devices on the horizon, and sources believe the field is still wide open. A source said, "None of these is FDA approved yet. They are still in clinical trials. There isn't enough data to say objectively which is better yet." Another source commented, "Jarvik and DeBakey are the two out front. Patient selection is still being learned, but, for the right patient, they are very attractive. The right patient is the one who is not dying in front of you, someone slipping into heart failure that allows elective intervention." A third expert said, "People are always trying to compare this and that device. They're all about the same. There are minor advantages of one over the other, but it's mainly a Ford vs. a Chevrolet difference. The main thing is to introduce it properly, work on the cost, and deal with the regulatory problems, and it will result in tremendous patient benefit in the future. But there is no competition between the different technologies. The competition is really the education of the cardiologists and an interface with the regulatory system to accelerate usage."

Continuous Flow Devices in Development

Company	Device	Number of patients tested	Type of bearing
Arrow	CorAide	1	Centrifugal – blood-fed journal bearing
Berlin Heart	Incor	71	Axial – magnetic bearings
Jarvik Heart	Jarvik 2000	65	Axial – blood immersed bearings
Micromed	DeBakey	200+	Axial – blood immersed bearings
Terumo	DuraHeart	0	Centrifugal – magnetic levitated
Thoratec	HeartMate-II	10	Axial – blood immersed bearings
Ventracor	VentrAssist	2	Centrifugal – hydrostatic levitated impeller

Do Thoratec, World Heart, Arrow, etc., need a larger partner to make these devices commercially successful? Sources don't think so, but they acknowledged that it is an expensive and time-consuming process getting these devices FDA-approved.

Following are comments by sources on each of these devices:

ARROW

Sources also were not very excited about Arrow's CorAide axial flow device. They pointed out that it is too far from market and too uncertain. However, CorAide does have one key advantage – transcutaneous energy. A source said, "Transcutaneous is a big deal. Most REMATCH complications came from infections due to the line. So, there is a good reason for Arrow to stay in the race."

While Arrow may have an advantage with its transcutaneous energy system, that is not one of the key features described by a expert talking about the characteristics wanted in continuous flow devices. He cited:

- Pumps with design features that may decrease the risk of infection – pumps with less motion within the patient, fully implantable devices, and smaller pump designs.
- Increased durability to decrease the rate of re-operation, something he said is both important and achievable.
- Modulation of the host immune system, though that is further in the future.
- Anti-staphylococcus vaccines.
- Device coatings that discourage bacterial adhesions, colonization, and growth or that encourage a host immune response.
- Novel therapies to prevent bacterial adhesion, quorum sensing and biofilm formation.

JARVIK HEART'S Jarvik 2000

A source said, "Jarvik…has a lot of potential because of its size, but I think getting people through the safety trials has been a problem because of distribution."

MICROMED TECHNOLOGY'S DeBakey

This device has a CE Mark, and the company is working on expanded indications in Europe. In the U.S., a feasibility trial has been completed, and a 19-patient pivotal trial is underway. The company has an IDE, and a randomized trial of destination therapy has been submitted to various IRBs. Comments on this device include:

- "We are starting to use the DeBakey. It probably has a role in patients with limited left ventricular function."
- "DeBakey is going to be more widely available (than Jarvik). When it first came out, the trials were in Germany, and there were some problems with thrombosis, but things are supposed to be better now, and the data is improving."
- "The advantage to this device is that smaller patients can get it, it can be explanted, patients are less aware of it, and it is less expensive (than other continuous flow devices)."

- "The DeBakey and the HeartMate-II are similar."
- "We are about to start using the Micromed device. It is for short-term recovery. It is very easy to use, easy to put in and take care of, but the patients are limited. They have to stay in bed right now…The advantage is that it is small. The disadvantage is that it appears that with all of these centrifugal pumps you may not be able to completely support the circulation. It's an assist as opposed to a replacement, and the long-term data is not there yet."
- "Micromed is the current leader in continuous flow technology."

TERUMO'S DuraHeart

Early animal studies look good, and a human trial is expected to begin soon in Europe.

THORATEC'S HeartMate-II

The initial European experience with this device in 2001 was less than satisfactory: Pump thrombosis occurred in 6 of 9 patients, and two of these also had intermittent hemolysis. As a result, Thoratec voluntarily stopped the trial in 2002 to make design changes. The textured coating was removed from inside the pump, new software was written, and new anti-coagulation guidelines were designed. Since these changes, no pump thrombosis has been seen in animal tests. A seven-patient U.S. study was initiated in late 2003, and the company hoped to restart the European study in 2004.

VENTRACOR'S VentrAssist

Several sources suggested that this Australian company bears watching. The VentrAssist is a third-generation system. It's small, weighs 298 gm, with a volume of 122 cc and a maximum output of 10 L/min. As of October 2003, three patients had been implanted, and all were doing well. The company intends to apply for a U.S. IDE this year (2004), with a trial likely to start here in early 2005.

MARKET OPPORTUNITY

The market for bridge-to-transplant is, obviously, limited by the hearts available for transplant, and sources do not expect this to increase much above the current 2,500 annually in the U.S. The market for destination therapy is huge, with 500,000 new cases of heart failure diagnosed each year in the U.S. and an aging population. The actual market is more limited by the device design than the patients. The European market is considered to be quite separate from the U.S. market, and there are European companies there working quite independently on these devices.

Comments on the market opportunity included:

- "The market is potentially huge."
- "I don't know if the number will be 10,000, 15,000, 20,000, or 50,000. My fear is that anybody who does surgery is going to say, 'I'm going to put in these LVADs for less than ideal indications – for bypass surgery, valves, etc.' The FDA worries about who will be the gatekeeper. A lot of people want to pay the $100,000 for grandma who isn't doing too well."
- "There are a fair number of patients who could be considered for destination therapy…The biggest difference between the U.S. and Japan is that it will be easier to get devices implanted in other countries. I'm not sure there will be an increase in numbers used here, in percentage terms, but there may be a fair number of patients eligible."
- "It would be a big, big market if you had a functional assist device that was easy to maintain."
- "The market is about 15,000 in the U.S."
- "The opportunities in Europe and Japan are just as large as in the U.S."
- "The outlook for these devices in Europe and Japan will depend more on how these countries 'manage' end-stage heart failure care. There are aggressive transplant/VAD centers in Germany, but they may still limit the use to younger/healthier patients. The situation in Japan is a bit more complex; it may, in fact, be even more 'VAD-friendly' because transplantation is a problematic issue (there). There are inherent problems in the recognition (legally and socially) of brain death. Unless things have changed in Japan in recent years, they are probably looking for all types of alternatives to transplantation. In addition, I would imagine that the average Japanese is smaller than the average American, so the newer rotary devices could fit better."
- "The leaders in continuous flow technology are either the DeBakey or Jarvik 2000 devices. They are ahead in Europe and are closer to approval, although that is just a guess. It seems as if Thoratec got a late jump, especially in the U.S., where the others already have many implants and big centers involved that can keep up the implantation rate to get approval."

The big cardiac companies – Guidant, Medtronic, Johnson & Johnson, etc. – are interested in this space, but sources believe they are waiting for a smaller company to do the R&D and prove the technology before they buy in. And that is exactly what they are expected to do if and when the devices appear to have large-scale commercial appeal. One source said, "I asked Medtronic, and officials there told me they are interested but are waiting for the market to mature, and then they will buy a smaller company." Another source said, "The big guys are not interested yet because the market is not there.

Other treatments for Class III heart failure are improving, and the devices have a way to go." A third source said, "The big guys have people like me watching out, but all the products have defects, and there is no long-term data on continuous flow." A fourth said, "The big companies may be taking a wait-and-see attitude…The biggest obstacle for the little guys is the FDA. That's expensive and time-consuming, and their capital is limited." A fifth doctor said the big companies aren't interested yet "because the market is too open, and too much of a 'niche' market to get the big guys involved. Reimbursement for VADs is relatively anemic for the hospitals; they are performed at relatively few centers, affect relatively few patients, and are not likely to generate huge profits for these companies compared to other endeavors that they could get involved with."

THE MEDICAL COMMUNITY AND REFERRALS

Cardiac surgeons believe in the value of LVAS, but other doctors still have not accepted the technology. Cardiologists are not referring enough patients, and they are not referring them soon enough. In part, this is due to drugs and other devices that compete for the same patients – and the doctors would rather try a drug or less-invasive device first. Thus, LVAS is still considered an option-of-last-resort by most doctors. Sources agreed that a serious education effort is needed to convince doctors and patients that these devices are beneficial, spurring referrals. However, sources do not think this is going to happen until and unless axial flow assist devices are approved for destination therapy.

- *Dr. Theodore*: "In centers like ours, the medical community is firmly behind it. At the same time, we need to graduate as an industry to where patients are referred for mechanical devices prior to the point where they're at multi-organ dysfunction end-state heart failure. At that point, there is no therapy that will save patients. Although we are used to the idea of prosthetic devices – no one blinks twice when their aunt gets an artificial hip – this is a new and emerging technology."

- *Dr. Conte*: "The average working internist doesn't have a clue (about these devices). It's becoming more mainstream in cardiology, but to a very limited degree. Ninety-nine percent of cardiologists don't have a clue about how they work, so I doubt very much that they will be well-accepted until physicians have patients involved with them."

- *Dr. Frazier:* "Right now, I could put a Jarvik pump in every patient who is homebound with heart failure, but we can't do that (because of reimbursement). Our cardiologists understand it, but the regulatory agencies don't. The bureaucrats are the big barrier."

- *Dr. Caldeira*: "This is a major problem. The timeframe for referrals also is an issue. Referrals need to be sooner as with ICDs. When patients are NYHA Class III is the time to put a device in. But there are a lot of medication trials ongoing, and CRT (cardiac resynchronization therapy) is available – all competing for patients."

- *Dr. Rose*: "The medical community is still taking a wait-and-see approach, but it's very early in the game."

- *Dr. Kresh:* "Many of the cardiologists are on the verge of adopting/embracing this technology. They see many patients suffering because they cannot get a transplant, and medical therapy is so limited. Our center is getting a few calls for destination therapy already. If the cardiologists jump on board, it is only a matter of time before the internists/family doctors join along because these are some of their most difficult patients to treat."

CMS REIMBURSEMENT

Lack of favorable Medicare reimbursement also has dampened enthusiasm for these devices. Several sources pointed out that their hospitals were losing money by implanting an LVAS, but still implant devices – occasionally – because it is good medicine for the right patient. Medicare was paying about $70,000 for a pulsatile device, while the cost to the hospital was about $90,000. An expert said that one reason for the low CMS reimbursement was that CMS was undercounting the patients getting LVAS because the hospitals are not using the correct codes when filing claims. He said, "CMS said most bridges are not being put in Medicare patients…and that may be due to wrong coding."

Reimbursement for continuous flow devices also has been an unprofitable procedure for a hospital, and total artificial hearts currently are excluded from Medicare coverage.

CMS has proposed a national coverage decision that will increase reimbursement by 30% for all ventricular assist devices implanted for destination therapy; the rule will go into effect on October 1, 2004. Destination devices would be reimbursed under DRG 103, which covers heart transplants. Currently, destination therapy is reimbursed under DRG 525, which covers the implantation of heart assist devices. A Thoratec official said, "The current median reimbursement to those 68 centers recognized by CMS for destination therapy reimbursement is approximately $96,000. Based on our preliminary analysis of this CMS proposal, we believe the median reimbursement would increase by around 30% to approximately $125,000, with certain centers qualifying for levels significantly higher."

In Europe, reimbursement also has become an issue. A German doctor said, "In 2004, we started a DRG-type system in Germany…The government knows it can't ignore this field…or the newspapers will be full of scandals of people dying…We are interested in what the U.S. is doing because the problem will be similar in Germany…In the U.K. and France reimbursement also will be difficult…but in Germany we will have a system to take care of most situations."

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