The LVAD Market Size

The estimate of market size for LVADs depends on two factors:

1. Potential number of patients who are candidates for LVAD implant in both the BTT and DT indications
2. Clinical performance of LVADs which will drive market adoption.

The actual market and the rate of growth for LVADs for DT during clinical trials is an unreliable predictor of market growth following approval of the first suitable device for DT.

Market Size Estimates

Potential Market - USA

LVAD development has been driven by the gap between the number of donor hearts that become available in the USA each year and the estimated 50,000 to 60,000 patients annually that could benefit from a heart transplant. While the incidence of heart failure has increased, donor heart availability has fallen steadily over the last decade, so that transplants have fallen from a high of 2,363 in 1995 to 1,897 in 2003.\(^1\)

Estimates of the size of the LVAD market vary widely. The Thoratec 2002 annual report claims 100,000 p.a. for DT and 4-5,000 p.a. for BTT. Micromed state that 20,000-40,000 people annually could benefit from heart transplant. WorldHeart, on its website reports “More than 5 million people in the United States suffer from end-stage heart failure, with new diagnoses of more than 500,000 annually. …. Of those suffering from end-stage heart failure, more than 85% could experience near normal blood flow with left ventricle support.”

Renowned heart surgeon Michael DeBakey observed “By a conservative estimate more than 50,000 Americans could use a new heart but at most only 2,500 are available annually for cardiac transplantation”. Similarly leading LVAD implant surgeon O.H. (Bud) Frazier has quoted a figure of 60,000.\(^2\)

Many estimates fail to make the distinction between prevalence (the number of people having severe heart failure at any one time) and incidence (the number of people who develop severe heart failure annually and who thus constitute the ongoing market). Moreover, they do not mention that not all patients who “could use a new heart” are candidates for LVAD implantation.

Heart surgeon Glenn Pennington has analyzed the potential LVAD market.\(^3\) He begins from the position that 60,000 people die of heart failure in the US each year and that all of these could benefit from mechanical support. While this is higher than the mortality figure of 51,000 given for the year 2000 by the American Heart Association, it is not an unreasonable number to begin with, as candidates for implantation will die for reasons other than heart failure. Of the 60,000, he estimates that 30,000 are 75 years old and over and hence are currently ruled out as poor implant candidates by reason of age. His estimate of 50% of patients being 75 or older is higher than the national figures for heart failure indicate (32%). However the age distribution for end-stage heart failure should be more highly peaked with

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1. The Organ Procurement and Transplant Network run by the United Network for Organ Sharing http://www.optn.org/latestData/rptData.asp
age than the figure for HF in general, so 50% is a reasonable figure. The remaining 30,000 are divided into 4,000 heart transplant candidates and 26,000 who are not heart transplant candidates. He then further divides the 26,000 into 13,000 who are candidates for LVAD implantation and 13,000 who are not candidates because of irreversible organ deterioration, co-morbidities or other contraindications. To the remaining 13,000 he then adds 1,000 transplant candidates who can be identified as “less likely to receive a heart transplant” and 500 who while meeting all the criteria will still miss out for lack of a donor organ. Accordingly his final figure for likely LVAD demand is 14,500 p.a. for destination therapy in USA.

Pennington’s figure is subject to a cascade of errors.

- The starting figure of 60,000 may be low. Leading heart failure expert Lynne Warner Stevenson puts the prevalence of end-stage heart failure at between 100,000 and 150,000. The condition is widely accepted as having a 1 year mortality of around 50%. Simple mathematics then tells us that the incidence of end-stage heart failure must be between 50,000 and 75,000 p.a. So an upper incidence figure of 75,000 may be justified.
- The 50% excluded by reason of age may be high; however the percentage is bounded on the bottom by 32% and is unlikely to be lower than 40%.
- The current age restrictions may be relaxed as LVAD outcomes improve and the new devices like the VentrAssist prove less traumatic to implant.

Making the above allowances we arrive at an upper figure of 21,800 p.a., but we will use a slightly lower figure of 20,000 p.a. for the US market for destination therapy. In addition about half of all transplant candidates may be bridged, adding 1,500-2,000 p.a. for BTT. We thus arrive at a total figure of 21,500 p.a. for both bridge and destination indications. Note that the number of patients being placed on the transplant list (Europe and US) is growing, as LVAD for BTT becomes more acceptable. That is, physicians are starting to put patients on the transplant list who might not normally be put on the list, in the expectation that the patients may end up receiving an LVAD for a “long bridge”. Thus the number of BTT patients is expanding, but many of these should rightly be considered as DT patients.

The Bear Sterns analyst report of THOR in early 2007 estimated as follows

“5 million patients suffer congestive heart failure in the US. Of these, approximately 5% or 250,000 are termed class IV patients. Class IV sufferers are the sickest of these congestive heart failure patients and physically have multiple complex symptoms including, extreme shortness of breath even while at rest, swelling of limbs, lack of energy, abdominal swelling and chronic coughs. Approximately 50% of these class IV patients die within one year of class IV diagnosis status. Approximately 70% die within 5 years of class IV diagnosis. Each year there are an estimated newly diagnosed ~ 60,000 Class IV US patients who could benefit from a long term VAD device. But we estimate less than 10% of these eligible patients are receiving a VAD today. The primary reasons for the current low penetration rate are:

1) Thoratec’s current XVE VAD as well as other competing VADs are often too large for certain patients

4 23 Feb 2007, Bear Sterns
2) referring cardiologists have been somewhat reluctant to refer their patients on for LVAD therapy due to concerns over device durability, and higher post post-implant mortality rates compared to heart transplant.

3) the surgery required to implant the device is invasive and may not be suitable for these extremely frail, elderly patients with multiple co-morbidities.

The current patient pool could grow even larger in coming years. Helped by improved medical therapy and the benefits of cardiac resynchronization therapy devices (CRT-D), some portion of “VAD-eligible” patients have seen their historical progression delayed. While CRT-Ds have sustained the lives of patients from both sudden cardiac arrest and ventricular arrhythmias, CRT-D devices can only delay the progression for so long and patients will eventually progress onto severe congestive heart failure. At this point, these very sick patients require either a heart transplant or VAD therapy. But the possibility of heart transplant is limited in the US with approximately 3000 heart transplants being performed annually.”

The JP Morgan financial model for Thoratec estimates a potential US market for DT of about 25,000 patients but shows slow penetration until the HeartMate II is approved for DT after 2009.

**Outside USA**

Heart failure figures are generally not available to the same degree of detail for most other parts of the world as for the USA. However it is known that

- overall heart failure levels are similar across the western world
- heart failure is increasing across the developed world
- as shown in table below the number heart transplants in Europe approximately equals that in the USA, as would be expected given their similar populations
- just as for the USA, heart transplant rates are dropping around the world.

Putting these facts together we can reasonably conclude that the DT market for LVADs in Europe is of a similar size to that in the USA, ie: 20,000 p.a., with about half as many again in other developing markets (Asia, South America) for a ROW potential DT market of 30,000+ patients. A similar discussion applies for the BTT potential market, which is estimated at 4,000 p.a.

**World Market**

Outside Europe and USA, the potential markets for LVADs for DT may be large – especially with developing markets like China and India, but these markets will take a long time to develop, and therefore their contribution is ignored. Other developed markets (Australia, NZ, South Africa) are relatively small, and their contribution is ignored. Thus the overall developed world potential market is ~54,000 LVADs per year, of which approximately half are in the US.

There are some higher estimates – such as an early estimate by the National Institutes of Health of 100,000 potential DT patients per year. However, many of these “wet finger” guesses lack the rigor of estimation presented here.

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Drivers for Growth of LVAD Market

The key drivers of market acceptance of LVAD therapy are listed in Table 1. Of these, the most important is clinical acceptance of LVAD therapy, driven by excellent clinical results. First generation devices (Heartmate XVE and Novacor LVAS) had adequate results for BTT, but poor results for DT. It is expected that newer devices such as the Heartmate II and the VentrAssist will have adequate clinical performance to drive growth of the DT market, and early indications are encouraging.

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Status</th>
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<tr>
<td>Reliable, well performing product(s) with FDA approval.</td>
<td>HeartMate XVE inadequate. Novacor LVAS being withdrawn. Heartmate II BTT approval imminent, but not yet for DT.</td>
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<td>Excellent clinical results from multiple trials published by key opinion leaders in reputable scientific journals</td>
<td>Single small trial (REMATCH), mediocre results.</td>
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<td>Recommendations in clinical care guidelines from academic bodies (AHA, ACC)</td>
<td>LVADs mentioned in ACC/AHA guidelines as an option for treatment of advanced heart failure, but supporting evidence is poor.</td>
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<td>Therapy available from multiple device sourced from multiple companies</td>
<td>Only one company (Thoratec) with FDA approved device for DT.</td>
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<tr>
<td>Reimbursement</td>
<td>In place in USA for DT and BTT indications Patchy reimbursement elsewhere</td>
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<tr>
<td>Patient “gatekeepers” convinced of value of therapy</td>
<td>Heart failure cardiologists not yet convinced. Surgeons are positive, but don’t control patient flow.</td>
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<td>Therapy delivery possible by “average” practitioners</td>
<td>Devices still require superlative surgical and patient management skills, but improving.</td>
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<tr>
<td>A revenue and cost model which enables physicians and hospitals to run a profitable business</td>
<td>Unclear economics. Many hospitals would see LVADs as a “loss leader”. Cardiologists don’t know how to make money on LVAD therapy yet.</td>
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One of the key rivers for growth of the LVAD market in the US is the number of centers authorized by CMS (Centers for Medicare Services) to implant and bill for LVADs for the DT indication. At present, there are 69 centers authorized. However, CMS has a notice of proposed rule making in the public domain which seeks to increase the number of authorized centers, and change the criteria for eligibility from 15 LVAD experience to 10. In addition, there are moves towards allowing LVAD implantation for the DT indication in cardiac surgery centers that do not have a heart transplant program. As the number of centers grows from 69 to several hundred, it is believed that the number of LVADs implanted for DT will grow dramatically.

Clinical Performance of LVADs

BTT application of LVADs has been well accepted, and clinical results are encouraging.

Improved survival to transplant: In a nonrandomized study using concurrent controls Frazier et al. report outcomes for 75 LVAD patients and 33 controls. 71% of the

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LVAD patients (53 patients) survived to transplant as compared to 36% (12) of the controls. Similarly Sun et al\textsuperscript{7} report 70% survival to transplant among 95 patients implanted with LVADs, (mean duration of LVAD support 108 days), while, from a group of 53 patients, Vitali et al\textsuperscript{8} report a 71% survival to transplant. In a group of 264 patients Navia et al\textsuperscript{9} report 69% survival to transplant.

**No reduction in post-transplant survival.** Post-transplant has been shown to be as long as for patients bridged with an LVAD as for patients who have received a heart transplant without first receiving an LVAD\textsuperscript{10-11}. Indeed, in the previously mentioned study by Frazier et al, higher survival to 1 year (91% vs 67%) was recorded among transplant recipients, notwithstanding the longer waiting times experienced by patients who had received an LVAD.

**A consistent set of complications has been identified.** These include infection, device malfunction, bleeding, neurological disorder and multiple organ failure. Rates of complications are lower in later generation devices than earlier generation devices. Acceptable clinical management strategies have been developed and are in use.

**Survival over long periods has been documented.** DiBella at al\textsuperscript{12} reported support times of 662 and 1297 days and El-Banayosy et al\textsuperscript{13} of 670 days. The longest patients on the VentrAssist is almost 3 years. The longest patient on the Jarvik 2000 is almost 5 years, and on the Novacor LVAS is 7 years (two devices). Thus the potential for long term survival is being accepted.

**Satisfactory use of a rotary pump for bridge to transplant has been reported.**\textsuperscript{14} Overall the key metric of performance has been survival to transplant. This has consistently been reported at between 65% and 70%. The figure of 65% is usually taken as the Objective Performance Criterion (OPC) in design of clinical trials for an LVAD for the BTT indication. The VentrAssist CE Mark Bridge Trial reported a survival to transplant or continued eligibility for transplant at 154 days of 83.3% - statistically significantly higher than for first generation devices.

The DT application was first analyzed clinically in clinical trial called REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) funded primarily by the NIH. The REMATCH trial\textsuperscript{15} was a prospectively randomized trial of LVAD vs Optimum Medical Management (OMM) for end stage heart failure.

\begin{thebibliography}{99}
\bibitem{11} Schmid, C., et al., Outcome of patients surviving to heart transplantation after being mechanically bridged for more than 100 days. J Heart Lung Transplant. 2003. 22(9): p. 1054-8.
\end{thebibliography}
failure patients, and demonstrated clinical results which have led to DT approval for the Thoratec Heartmate XVE device, and growing acceptance in the clinical community of the DT concept. However, while the REMATCH trial showed that no patient with an LVAD died from heart failure, the overall survival rate was disappointing, with the high levels of device related failures and infection being obvious areas requiring improvement.

It appears therefore that the clinical elements are in place to drive adoption of LVADs for destination therapy, once the clinical result of trials are published.