



Industry Updates

HeartMate II Post-marketing Clinical Studies to Further Establish and Expand LVAD Therapy

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Introduction

The number of patients with end-stage heart failure (HF) benefiting from mechanical circulatory support based therapy is rapidly growing. Over the last 2 decades the therapy has been rapidly evolving particularly since the introduction of continuous flow ventricular assist devices (CF-LVAD) which addressed several limitations of the first generation pulsatile devices. According to the sixth INTERMACS registry annual report, the 12 and 24 months overall actuarial survival of CF-LVAD was 80% and 70% respectively.¹ Survival rates remained unchanged over the past 6 years. The adverse events associated with CF-LVAD have been dramatically reduced when compared to rates associated with the previous generation pulsatile flow devices. The burden of adverse events associated with CF-LVAD decreased over the last 6 years and quality of life improvement at 12 and 24 months remained consistent. According to the report, while the proportion of patients implanted while stable on inotropic support has significantly increased in the last era (2011-2013), the expansion into INTERMACS levels 4 and higher remains limited to 20%.

In order to further reduce the adverse events associated with LVAD and expand the access to the therapy, Thoratec Corporation sponsored and conducted several post-marketing studies. These studies are focused on improving clinical outcomes, expanding mechanical circulatory support patient population and advancing clinical science. These studies are either Thoratec or single and/or multi-center investigator sponsored studies. A summary of the Thoratec sponsored studies and the multi-center investigator sponsored studies and their anticipated impact is described.



Studies Focused on Expanding LVAD Patient Population

ROADMAP (Risk Assessment and Comparative Effectiveness Of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients)

While LVAD therapy is well established for the treatment of advanced HF patients requiring intravenous inotropic support, its role in ambulatory non-inotrope dependent HF patients is still unknown. To help characterize and define the patients who benefit from LVAD therapy instead of remaining on optimal medical management, the ROADMAP study was designed and conducted. ROADMAP is a prospective, multi-center, non-randomized, controlled observational study of 200 patients with advanced Class III or ambulatory Class IV symptoms who meet the current FDA indications for LVAD and who are either maintained on optimal medical management or receive a HeartMate II. The primary endpoint of ROADMAP is a composite of survival on original therapy and improvement in 6 minute walk distance of ≥ 75 meters at 12 months. In addition several secondary endpoints will be assessed and these include a risk stratified subgroup analysis of the primary endpoint and temporal analysis of primary endpoint at 6, 12, 18, and 24 months, accuracy of prognostic survival risk models including Seattle Heart Failure Model and HeartMate II Risk Score, quality of Life using the EQ-5D-5L Health Utility Index, depression using Patient Health Questionnaire-9, questionnaire on patient decisions related to LVAD therapy versus optimal medical therapy. Additional information on ROADMAP can be found on [ClinicalTrials.gov](#) (identifier: NCT01452802). As of July 2013, the study was fully enrolled with 97 patients received a HMII and 103 patients were on optimal medical management. Study results will be presented at major conferences in the near future.

SEE-HF (Screening for Advanced Heart Failure Treatment)

The objective of SEE-HF, a Thoratec sponsored study, is to determine the proportion of HF patients followed in outpatient CRT/ICD clinics who are NYHA Class III-IV with LVEF $\leq 40\%$ and who have an indication without contraindication for heart transplantation and/or DT LVAD. It is hypothesized that among all CRT and/or ICD patients with NYHA III-IV HF, with LVEF $\leq 40\%$, the number of patients who have an indication without contraindication for heart transplant or LVAD is between 7 and 13% ($10 \pm 3\%$). The data from this study will help identifying patients in CRT/ICD clinics who may benefit from early consultation with an advanced HF cardiologist. Additional information on SEE-HF can be found on [ClinicalTrials.gov](#) (identifier: NCT01626404). The study is currently enrolling at 8 European sites.

Studies Focused on Improving Clinical Outcomes

TRACE (STudy of Reduced Anti-Coagulation/Anti-platelet Therapy in Patients with the HeartMate II LVAS)

Despite current recommendations to treat LVAD patients with both warfarin and aspirin, those who bleed often require a reduction in their antithrombotic



therapies. To document and characterize patients who can be safely managed with a reduced anti-thrombotic (RT) therapy, TRACE was initiated in the US and Europe. An RT is defined as aspirin only; warfarin or vitamin K antagonist only, or no anti-platelet and anti-coagulation. The primary study endpoint is the rate of thromboembolic (i.e. ischemic stroke, transient ischemic attack, or pump thrombosis) and hemorrhagic events (i.e. bleeding and hemorrhagic stroke). The secondary endpoint is to characterize the patient population who can be safely maintained on RT. Additional information on TRACE can be found on [ClinicalTrials.gov](#) (identifier: NCT01477528). Enrollment in the study was completed as of July 2013 and enrolled 203 patients from 9 US sites (100 patients) and 9 European sites (103 patients). While in the US the reason for RT initiation was in response to bleeding events, in Europe all HeartMate II patients are managed without anti-platelet agents. Because of the resulting inherent difference in the patient populations, the results from both cohorts are being analyzed and reported separately. Initial results from the study were presented at the 2014 ISHLT conference.

As reported by Katz et al., in the first year of RT, among the US cohort there were 29 bleeding events, 6 ischemic and 0 hemorrhagic strokes and 4 pump thrombosis events.² The freedom from bleeding, ischemic stroke, hemorrhagic stroke, and pump thrombosis were 66%, 94%, 100%, and 95%, respectively. These initial results suggest that reducing anti-thrombotic therapies on a chronic basis in response to persistent non-surgical bleeding events may be safe in selected patients.

As reported by Netuka et al., in the first year post-RT (vitamin K antagonist only), in the European cohort freedom from ischemic stroke, hemorrhagic stroke, and device thrombosis post initiation of RT therapy were 95%, 98%, and 96% respectively.³ Nine patients (12%) experienced a bleeding event while on RT therapy. It is important to note that while no anti-platelet therapy was used, the median INR was 2.3. The preliminary results from the European TRACE cohort suggest that in selected patients, single therapy with relatively high INR target is associated with a low risk of bleeding and thromboembolic events.

SSI (Driveline **S**ilicone **S**kin Interface Registry)

Single center experience has suggested reduction in driveline infection rates after changing the surgical tunneling technique to keep the entire driveline velour portion in the subcutaneous tunnel. This results in a Silicone-to-Skin Interface (SSI) at the exit site. To assess the long term freedom from driveline infection associated with this technique, a multi-center SSI registry was initiated and conducted. It is hypothesized that the modified tunneling technique is associated with at least 50% reduction in driveline infection at one year post implant when compared to the velour-to-skin method used in the HMII Destination Therapy (DT) trial. The study includes a retrospective and a prospective cohort which are independently powered to achieve the study primary endpoint. Additional information on TRACE can be found on [ClinicalTrials.gov](#) (identifier: NCT01577433). As of July 2013, enrollment of 400 patients from 15 US sites was completed.



Dean et al. reported on results from the retrospective cohort at the 2014 ISHLT conference.⁴ The actuarial freedom from driveline infection was 93% and 84% at 12 and 24 months respectively. These rates are significantly lower when compared to the corresponding rates in the HMII DT trial of 77% and 65% at 12 and 24 months post implant. These results suggest that leaving the entire driveline velour portion below the skin is associated with a significant reduction in driveline infection when compared to results from the HMII DT trial.

RESIST (**RE**duce Driveline Trauma Through **Stab**lization and Exit **Site** Management)

Driveline infections in patients with LVADs are usually secondary to trauma to the exit site. The percutaneous lead management kit (PLMK) was developed for the HeartMate II LVAD using commercially available components for driveline stabilization and management. The purpose of the RESIST study was to evaluate the wearability and usability of the PLMK for a minimum of 30 days. Additional information on RESIST can be found on ClinicalTrials.gov (identifier: NCT01485666). The study completed enrollment of 50 patients from 5 US sites. Stahovich et al. presented results from the study at the 2014 ISHLT conference.⁵ At 30 days, significantly more patients found the PLMK to be extremely comfortable (80% vs. 37%, $p < 0.001$) and extremely effective at stabilizing the driveline (82% vs. 40%, $p < 0.001$) compared to before the PLMK. Ease of use was similar for PLMK compared to before (72% vs. 57%, $p = 0.19$). Dressing change frequency was a minimum of 6-7 days or more for 85% of the patients, which was less frequent than their standard of care. There were 4 patients (8%) who stopped using the kit within the first 30 days due to skin irritation ($n = 3$) and driveline infection ($n = 1$). The PLMK is easy to use, increases patient comfort, and increases driveline stability with a dressing change frequency of 6-7 days. This kit may therefore help reduce the risk of trauma to the exit site, increase patient compliance, and reduce the risk of driveline infections.

PREVENT (**PREVEN**tion of HeartMate II Pump **Thrombosis** Through Clinical Management)

Pump thrombosis is a complex and multi-factorial adverse event. Patients may present with a variety of symptoms including power elevations, isolated rises in serum lactate dehydrogenase, clinically significant hemolysis, failure to adequately unload the left ventricle or worsening HF. The factors that may contribute to this adverse event could be pump-related, patient-related, or management related. In addition, patient profiles and management protocols vary from center to center, resulting in significant variability in reported pump thrombosis rates. To reduce such variability a set of standard practices for surgical implantation and patient management were developed. These standardized practices are based on the HMII instruction for use with modifications derived from clinical practice. The impact of these standard practices on the incidence of HMII pump thrombosis will be assessed by PREVENT, a prospective, non-randomized multi-center study. The primary endpoint of PREVENT is the incidence of confirmed pump thrombosis within three months of HMII implantation. The secondary endpoints consist of the



incidence of confirmed pump thrombosis within six months of HMII implantation, incidence of suspected pump thrombosis (including unexplained hemolysis) within three and six months of HMII implantation, incidence of pump exchange, urgent transplantation or death due to pump thrombosis within three and six months of HMII implantation, and analysis of risk factors for pump thrombosis. Additional information on PREVENT can be found on [ClinicalTrials.gov](#) (identifier: NCT02158403). The PREVENT study is currently enrolling and will enroll up to 300 subjects from up to 20 sites.

Studies Focused on Advancing Clinical Science

RESTAGE-HF (REmission from Stage D Heart Failure)

RESTAGE-HF is a multi-center study sponsored by the University of Louisville and funded by Thoratec. The study was designed to determine the proportion of subjects treated with a standardized LVAD plus pharmacologic recovery and testing protocols who experience sufficient cardiac reverse remodeling to enable LVAD removal and remain free of mechanical circulatory support or heart transplantation for one-year post-LVAD removal. The secondary endpoints consist of the time course of reverse remodeling on a left ventricular assist device, the time course and sustainability of reverse remodeling following LVAD explantation, the predictors of recovery and device removal, changes in functional capacity and quality of life. Additional information on RESTAGE-HF can be found on [ClinicalTrials.gov](#) (identifier: NCT01774656). The study is currently enrolling at 6 US sites.

Conclusion

Over the last decade significant improvements in survival and quality of life associated with the HeartMate II have been consistently achieved and demonstrated through the HMII BTT, DT, and post-approval trial data.^{6,7,8} To further expand the patient population who benefit from a HeartMate II device and to establish best practices for implant techniques and patient managements tailored to reduce adverse events, Thoratec sponsored and funded several post-marketing studies. Results from these studies will soon be published in peer reviewed journals and positively impact clinical practices.

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