Current risks of HeartMate II pump thrombosis: Non-parametric analysis of Interagency Registry for Mechanically Assisted Circulatory Support data

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BACKGROUND: Data from 3 institutions revealed an abrupt increase in HeartMate II (Thoratec) pump thrombosis starting in 2011, associated with 48% mortality at 6 months without transplantation or pump exchange. We sought to discover if the increase occurred nationwide in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data, and if so (1) determine if accelerated risk continued, (2) identify predictors, (3) investigate institutional variability, and (4) assess mortality after pump thrombosis.

METHODS: From April 2008 to June 2014, 11,123 HeartMate II devices were implanted at 146 institutions. Machine learning, non-parametric Random Forests for Survival was used to explore risk-adjusted thrombosis based on 87 pre-implant and implant variables, including implant date.

RESULTS: A total of 995 pumps thrombosed, with risk peaking within weeks of implant. The risk-adjusted increase in pump thrombosis began in 2010, reached a maximum in 2012, and then plateaued at a level that was 3.3-times higher than pre-2010. Pump exchange, younger age, and larger body mass index were important predictors, and institutional variability was largely explained by implant date, patient profile, and duration of support. The probability of death within 3 months after pump thrombosis was 24%.

CONCLUSIONS: Accelerated risk of HeartMate II thrombosis was confirmed by Interagency Registry for Mechanically Assisted Circulatory Support data, with risk subsequently leveling at a risk-adjusted rate higher than observed pre-2010. This elevated thrombosis risk emphasizes the need for improved mechanical circulatory support systems and post-market surveillance of adverse events. Clinicians cognizant of these new data should incorporate them into their and their patients’ expectations and understanding of risks relative to those of transplantation and continued medical therapy.

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thrombosis rose 3.8-fold from 2.2% (95% confidence interval [CI], 1.5%–3.4%) to 8.4% (95% CI, 5.0%–13.9%) by January 2013. The primary objective of the present study was to verify whether the increase in pump thrombosis risk occurred nationwide, using data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the largest United States registry of U.S. Food and Drug Administration (FDA)-approved ventricular assist devices,2 and if verified, to (1) determine if risk continued to rise, leveled at a new rate, or decreased, (2) identify patient and implant procedure predictors of pump thrombosis, (3) explore variability in risk of pump thrombosis among implanting centers, and (4) assess the effect of pump thrombosis on subsequent mortality.

Methods

Data

We were invited by the National Heart, Lung, and Blood Institute (NHLBI) and the FDA to independently investigate HeartMate II pump thrombosis using an identical INTERMACS data set provided to investigators within the INTERMACS enterprise, including Cleveland Clinic and NHLBI. Because of the public health importance of this study, the NHLBI considered the investigation of pump thrombosis a high-priority endeavor, and Cleveland Clinic Institutional Review Board approval was obtained for use of INTERMACS data, with patient consent waived.

Devices and patients

From April 2008 through June 2014, data were submitted to INTERMACS on 11,123 HeartMate II left ventricular assist devices (LVADs) implanted in 10,208 adult patients at 146 institutions. Mean age at implant was 57 ± 13 years, 21% were women, and 48% had ischemic and 48% non-ischemic cardiomyopathy (eTable 1, available on the jhltonline.org Web site). The device was implanted as permanent (destination) therapy in 41%, and in 400 instances, patients had been supported on different mechanical circulatory support device before a HeartMate II (eTable 2, available on the jhltonline.org Web site). Exploratory analyses of pre-implant variables revealed temporal trends: In recent years, more patients were men, older, and heavier, with more ischemic cardiomyopathy, previous coronary artery bypass grafting, renal and pulmonary failure, and prior LVAD support, but fewer biventricular devices were used (eFigure 1, available on the jhltonline.org Web site).

End points

The primary end point was HeartMate II pump thrombosis as defined by INTERMACS investigators.3 All pump thrombosis events were identified and adjudicated as described by Kirklin et al. Time zero was time of device implant. For analyses reported in this study, the HeartMate II device was the unit of analysis for pump thrombosis because each device was at risk of thrombosis from the moment of its implant to its explant. Thus, a given patient appeared in the analysis data set as many times as he or she underwent implantation of a new HeartMate II, in each case starting each device at its specific time zero. Pump thrombosis follow-up information was censored at device removal for reasons other than pump thrombosis and at cardiac transplant before pump thrombosis, death before pump thrombosis, and end of follow-up for the device.

The secondary end point was death after pump thrombosis while remaining on mechanical circulatory support. The common closing date for all analyses was September 30, 2014.

Statistical analysis

Time-related estimates

Non–risk-adjusted non-parametric estimates of pump thrombosis were generated for each implant year using the Kaplan-Meier estimator.4 Instantaneous risk was assessed by the temporal decomposition parametric hazard method.5 Details are available at http://www.lerner.ccf.org/qhs/software/hazard/.

Random Forests analysis

Machine learning Random Forests for Survival methodology6 (eAppendix 1, available on the jhltonline.org Web site) is related to recursive partitioning and classification and regression tree analyses,7 in which the variable that most widely separated devices that thrombosed from those that did not, based on the log-rank test, was used to split the data set into 2 device sub-sets (branches). In this instance, we included 87 pre-implant and implant variables, including date of implant (eAppendix 2, available on the jhltonline.org Web site), that could be used for making such a split.

The initial split of the so-called root into 2 branches is followed by more splits using the same method to create a classification tree. A tree “grown” by this method is known to be inherently unstable, and this can be demonstrated by growing trees from bootstrap samples of the original data set and noting that they split much differently. (A bootstrap data set is formed by random sampling of observations with replacement until a data set of equal size is generated; there will be some duplicated patients, and an average of 37% will not be picked.) To overcome single-tree instability, a forest of trees is grown from many bootstrap samples—2,000 in this instance—permitting an ensemble average to be formulated across these trees.8 Because the method is completely non-parametric, with no possibly restrictive underlying model assumptions, linear and non-linear relationships to pump thrombosis, along with complex interactions among variables with respect to it, can be robustly accounted for.

Because some values were missing for some variables, Random Forest imputation was used to maximize use of available data (eAppendix 1, available on the jhltonline.org Web site).6 Rather than p-values, 2 metrics of prediction accuracy were generated (eAppendix 1, available on the jhltonline.org Web site). The first ranks the importance of each variable in increasing the accuracy of predicting pump thrombosis using only observations for a given tree that were not selected by the bootstrap process (called variable importance).7–10 This method is equivalent to a single cross-validation, but in aggregate a 2,000-fold cross-validation. The second is a tree-building structural measure that quantifies the average level across all trees of branching before a variable is split (called “minimal depth,” although “minimal height” would make more sense).11,12 The closer to the trunk of the tree a variable is split, the more important that variable is for separating thrombosed devices from non-thrombosed devices. We have focused on variables with both high variable importance and low minimal depth.
Visualization of Random Forests predictions

We used variable dependence plots to visualize the relationship of variables to pump thrombosis. Variable dependence plots are based on predicting time-related curves of pump thrombosis for each device from all 87 variables (eFigure 2, available on the jhltonline.org Web site). Slices through these curves can be made to select values, for example, related to date of implant. To obtain smoothed estimates, we used a piecewise smoothing spline approach when dealing with ensembles of all observations.

Institutional variability

To determine how well the Random Forest method accounted for institutional variability in the occurrence of pump thrombosis, the observed number of thromboses for each institution was compared with the expected number predicted by the Random Forest. For this, the hazard of pump thrombosis was accumulated across each device’s implant duration as estimated from all trees in the Random Forest. The sum of these values across all devices implanted at a given institution constituted the institutional expected (E) number of pump thromboses. These were compared with observed (O) thromboses and expressed as O/E ratios and their 95% confidence limits (CLs).

Death after pump thrombosis

The probability of death after pump thrombosis while mechanically supported was estimated as described in eAppendix 3 (available on the jhltonline.org Web site) using a nested Kaplan-Meier method to account for patients who experienced more than 1 pump thrombosis.

Results

Temporal changes in the risk of pump thrombosis

Pump thrombosis occurred in 995 of the 11,123 HeartMate II devices. The non–risk-adjusted probability of pump thrombosis began to increase nationwide for devices implanted after mid-2010, reaching the highest values for those implanted in 2012 and 2013; 2014 values (half-year) tracked those for 2012 (Figure 1A). This resulted from a progressive increase in early instantaneous risk of pump thrombosis from 2010 through 2013, with a lower early peak in 2014 (Figure 1B), and simultaneously, starting in 2010, an elevation in late instantaneous risk of pump thrombosis (Figure 1C).

The risk-adjusted shape of the relationship of implant date to the probability of pump thrombosis from Random Forest analysis revealed an increase in pump thrombosis starting in 2010 that continued rising into 2012 (Figure 2A; device-level predicted data in eFigure 3, available on the jhltonline.org Web site). The early risk then appeared to plateau during 2013 and partial year 2014, but the underlying late risk of pump thrombosis was associated with a steady increased probability of thrombosis with longer duration of support. These 3 variables—date of implant, duration of support, and probability of pump thrombosis—are visualized as a surface in Figure 2B, which reveals (1) details of the change in pattern of thrombosis with calendar date starting in mid-2010; before that, the curve demonstrates a contour indicative of a constant low hazard (sometimes called “random failure”), (2) an increase in early risk of pump thrombosis within the first 12 months, (3) an increase in late risk of pump thrombosis, and (4) continued elevated risk above pre-2010 levels through mid-2014. The probability of pump thrombosis was progressively higher after each pump exchange (eFigure 4, available on the jhltonline.org Web site).

Predictors of pump thrombosis

In addition to the date of implant, the most important predictors of pump thrombosis and pump exchange were age at implant and body mass index (BMI; eFigures 5–7, available on the jhltonline.org Web site). Although the relationship was non-linear, patients younger than approximately 72 years experienced a higher risk of pump thrombosis (device-level data in eFigure 8, available on the jhltonline.org Web site) irrespective of whether their cardiomyopathy was ischemic (older patients) or non-ischemic (younger patients; Figure 3). Risk of pump thrombosis increased beyond BMI of approximately 25 kg/m², also in a non-linear fashion (Figure 4; device-level predicted data in eFigure 9, available on the jhltonline.org Web site).

Institutional variability in pump thrombosis

The number of implants varied widely (eFigure 10, available on the jhltonline.org Web site) among 146 implanting centers, as did number of documented pump thromboses (eFigure 11, available on the jhltonline.org Web site), which ranged from 0 (the most common finding) to more than 30. Over this wide range of observed pump thromboses, the expected number of thromboses for each center from the Random Forest analysis tracked well with the observed number (Figure 5A), indicating good calibration of the model to institutional experience, despite no institution-level variable being considered in the risk adjustment. However, 9 centers experienced more than the expected number of events (the lower 95% CL of O/E ratio was greater than 1.0), and 25 experienced fewer than the expected number of events (the upper 95% CL was less than 1.0; eFigure 12, available on the jhltonline.org Web site). Although some of these centers with fewer-than-expected number of events were high-volume centers with narrow 95% CLs and O/E ratios near 1.0, a number were intermediate-sized centers with O/E ratios considerably below 1.0 (Figure 5B).

Death after pump thrombosis

Of the 873 patients who experienced 995 pump thromboses, 292 died after pump thrombosis, while supported with that device or a subsequent HeartMate II, and before transplantation (if not destination therapy): 255 after 873 first thromboses, 31 after 110 second thromboses, 5 after 11 third
thromboses, and 1 after 1 fourth thrombosis. Probability of death at 1, 3, and 6 months, and at 1 year after the first thrombosis was 18%, 24%, 29%, and 37%, respectively (Figure 6). At these same time points, the likelihood of death after a second thrombosis was 32%, 44%, 47%, and 53%, respectively, and after a third thrombosis was 47%, 47%, 47%, and 47%, respectively. The competing opportunity of cardiac transplantation somewhat reduces the likelihood of dying on HeartMate II support (eFigure 13, available on the jhltonline.org Web site).

Discussion

Principal findings

The 3-institution report in the *New England Journal of Medicine* showed an abrupt, unexplained increase in HeartMate II pump thrombosis early after implant beginning in 2011 that was associated with 48% mortality within 6 months without pump exchange or transplant. Increased early pump thrombosis was confirmed in small single-center reviews and now from the INTERMACS registry, but rates of this rise and their subsequent trajectories have varied. This analysis of 11,123 HeartMate II implants from 146 centers with data captured in INTERMACS through mid-2014 demonstrates acceleration of pump thrombosis early after implant starting in mid-2010, with a peak in 2012 and plateau in 2013 at a rate 3.3-times higher than in the pre-market approval clinical trial and the pre-2010 era. Non-risk-adjusted actuarial data from the first half of 2014 suggested the risk of pump thrombosis might be declining; however, after adjusting for 87 variables and making no model assumptions, our Random Forest analysis predicts no decline below 2012 to 2013 levels as yet. The 95% CIs widen considerably for 2014 data, indicating increased
uncertainty of the results, but with great certainty the results do not suggest a return to pre-2010 rates. Additional follow-up and complete device information for 2014 and beyond is needed to be more certain of the trajectory.

In the 3-institution publication, a steep increase in pump thrombosis started in early 2011 from a stable baseline of 2.2% (95% CI, 1.5%–3.4%) at 3 months to 8.4% (95% CI, 5.0%–13.9%) by January 2013. In this INTERMACS analysis, a similar change in pump thrombosis occurred, although beginning a few months earlier, rising in unadjusted analysis from 1.7% (95% CI, 1.2%–2.5%) at 3 months in 2010 to 2.9% (95% CI, 2.3%–3.8%) in 2011 to 5.6% (95% CI, 4.7%–6.6%) in 2013, with CIs overlapping those of the 3-institution study.

A finding presented, but not emphasized, in the New England Journal of Medicine report was the doubling of late risk after early 2011. This doubling of late risk occurred in the INTERMACS data between 2009 and 2010, and the elevation has persisted. Thus, the entire profile of the instantaneous risk of pump thrombosis appears to have been elevated. As a consequence, the best current estimate is that up to 15% of HeartMate II pumps will be affected by thrombosis within 2 years of implant.

The INTERMACS data demonstrate that younger patients, irrespective of the etiology of their cardiomyopathy, are at higher risk of pump thrombosis than older patients, as are patients with a higher BMI.

Center-to-center variability in occurrence of pump thrombosis is partly explained by low institutional volume, date of implant, pump exchange, duration of support, and differences in patient characteristics. However, the Random Forest model identified a number of institutions that had fewer-than-expected pump thromboses, supporting the inference that there exist institutional factors affecting pump thrombosis beyond pre-implant and implant variables in the INTERMACS data set. Anti-coagulation strategy has been suggested as one of these institutional factors, but in our Cleveland Clinic experience, average international normalized ratio was higher in the era of increased pump thrombosis than in the earlier era of low occurrence of thrombosis.

Mortality after pump thrombosis without pump exchange or transplantation was 24% at 3 months and 29% by 6 months and even higher in patients who experienced another pump thrombosis after pump exchange.

**Causes and consequences of HeartMate II pump thrombosis**

The causes of accelerated risk of pump thrombosis starting in 2010 remain unknown. Manufacturing changes, including outflow graft and bend relief, inflow conduit, controller, and
Software changes, occurred during the time of accelerating risk. Clinicians, recognizing the accelerated risk, have modified their implant and management strategies, including orienting the inflow cannula to prevent partial or complete obstruction of pump inflow, early and more intense anticoagulation with heparin and anti-platelet agents, and maximizing flow through the pump by maintaining pump speed over 8,600 rpm. The effectiveness of these modifications is unknown, but they may account for flattening and possibly decreasing thrombosis risk.

It has been postulated that thrombosis rates are center specific and that close examination of clinical practice at centers with high and low occurrences of pump thrombosis may inform best-practice guidelines. Our results suggest that such an endeavor may be fruitful. An ongoing prospective observational trial sponsored by Thoratec is documenting the occurrence of HeartMate II pump thrombosis under strict adherence to implant, patient, and device management (Prevention of HeartMate II Pump Thrombosis through clinical management trial).

The increased risk of pump thrombosis in young and heavy patients is perplexing. We cannot find an easy explanation for either. It may be due to a less dilated ventricle and anatomic constraints that favor inflow cannula obstruction. Patients with a previous device are also at higher risk for pump thrombosis. This may relate to patient factors that promote pump thrombosis or to the fact that the pump is exchanged but not the inflow conduit and outflow graft. Further, the most common surgical approach to pump replacement is through a sub-costal incision that will not mitigate anatomic limitations, such as invagination into the ventricle, and may only temporarily relieve inlet obstruction. Complete replacement of the inflow conduit and outflow graft may be necessary to reduce the risk of thrombosis after pump exchange, but this introduces its own surgical risks.

Strengths and limitations

The strength of INTERMACS data is that they encompass nearly complete, nationwide, post-approval experience. The data are robust, with considerable effort made over the years to capture reliable data. However, recognizing and documenting pump thrombosis are limitations, mitigated by the careful reevaluation of this event as described by Kirklin et al.

Perhaps the most severe limitation is lack of device-level information about changes made to the HeartMate II inflow and outflow conduits, controller, and software. The data suggest that the most common location of thrombus is on the

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**Figure 4** Body mass index (BMI) at HeartMate II (Thoratec) implant and probability of pump thrombosis at 6 weeks, 3 months, 6 months, and 1 year after implant. Smoothing splines and 95% confidence bands are from the device-level predicted data in eFigure 9 (available on the jhltonline.org Web site).

**Figure 5** Observed versus expected HeartMate II (Thoratec) pump thromboses at each implant center based on Random Forest estimates from 87 variables. (A) Points represent implant centers shaded by volume, with darker gray indicating lower volume and lighter gray higher volume. Dashed line represents perfect agreement between observed and expected events. Implant centers above the line had fewer events than expected; those below experienced more events than expected. Note that over a wide range of outcomes, there is a generally close agreement between expected and observed events. (B) Observed-to-expected ratio (O/E) of pump thrombosis, ordered by center implant volume. Point estimates and 95% confidence limits are shown. Although most centers’ results have confidence intervals that cross 1.0, 9 have lower confidence limits above 1.0 and 25 have upper confidence limits below 1.0.
inflow side of the device at the inflow bearing. There are no data in INTERMACS on pump-pocket depth and angulation of the inflow cannula with respect to the body of the pump, which may predispose to pump thrombosis in this location.21,22

Unlike data used in the 3-institution study reported in the New England Journal of Medicine, INTERMACS does not capture long-term survival after transplantation; thus, we cannot provide a nationwide estimate of mortality after pump exchange or urgent transplantation for pump thrombosis.

Our investigation relies on non-parametric machine learning methodology to eliminate parametric model assumptions.23 Adjustment is made for all variables considered (non-parsimonious), but granularity of the INTERMACS data related to pump thrombosis and its management is limited. Validation of results, using for each tree the observations not used in constructing that tree, is built into the methodology, but we have no data beyond mid-2014 implants to verify our predictions. The penalty for Random Forest flexibility is that the resulting analysis can appear as a “black box.”14 Thus, we have provided graphs that peer into the black box to reveal relationships. However, the method is not immune to sample size, number of events, and richness of the data set. Random Forests also assumes “missing at random” when inputting missing values for variables.24

Regulatory implications

Device trials are expensive to complete and thus limited in size: only 325 devices were implanted in the HeartMate II bridge-to-transplant and destination therapy trials. Hence, detecting infrequent events, such as pump thrombosis, with limited follow-up is difficult. In addition, with expanded post-approval use, changes in the device, conduits, controller, and software, and changes in clinical care, unanticipated improvements or deterioration in clinical outcomes can occur. Recognizing changes in the safety of approved devices is of paramount importance for making informed health care choices.

INTERMACS and other national quality registries should be queried regularly for adverse events after device approval. Regulations requiring these queries, funding from government and industry, and commitment to rapid and reliable data input from implanting centers will be necessary for early detection of adverse event signals. Then, collaborative data analysis, information sharing, hypothesis generation, and clinical recommendations—as reflected in these 3 articles by Kirklin et al1, Jeffries et al,25 and Smedira et al—can proceed quickly. The evolution of our knowledge of HeartMate II pump thrombosis and the utility of the INTERMACS registry in providing these landmark data are of critical importance to inform clinicians, industry, the FDA, and NHLBI about appropriate design of clinical trials, eligible patient populations, and updated safety information.

Clinical implications

Nationwide, risk of HeartMate II pump thrombosis accelerated in 2010 and plateaued in 2013 at a level 3.3-times higher at 3 months than was observed in pre-market approval trials. Although pump exchange and urgent transplantation for bridge-to-transplant patients are options, mortality after pump thrombosis without these remains high. We thus recommend that patients with severe heart failure should receive a HeartMate II within the current FDA labeling, with informed consent providing the updated risks of adverse events. However, we acknowledge that for patients with severe heart failure, a HeartMate II implanted within current FDA indications is an important life-saving measure that improves survival and quality of life. Clinicians cognizant of these new nationwide data should incorporate them into their and their patients’ expectations and understanding of risks relative to transplantation and continued medical therapy.
Disclosure statement

R.C.S. is a member of the steering committee for Thoratec’s ROADMAP (Risk Assessment and Comparative Effectiveness Of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients) trial. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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Supplementary data

Supplementary material cited in this article is available online at www.jhltonline.org.

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