

PERSPECTIVE

# What is the truth behind pump thrombosis in the HeartMate II device? A National Heart, Lung, and Blood Institute perspective based on data from the Interagency Registry for Mechanically Assisted Circulatory Support



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The clinical community faces major issues in caring for the 100,000 to 300,000 advanced heart failure patients in the United States.<sup>1</sup> For these patients, left ventricular assist devices (LVADs) may provide life-saving options for use as destination therapy or as a bridge to heart transplantation. Emerging and changing patterns of adverse events in continuous-flow LVADs present challenges to optimizing use of LVADs in this very ill population. These patterns have only recently been uncovered following more widespread use as compared with the controlled clinical trials, in which they performed admirably.

In this issue of the journal, Kirklin et al<sup>2</sup> and Smedira et al<sup>3</sup> report on parallel analyses of HeartMate II pump thrombosis data derived from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry. Kirklin and colleagues report a reversal in the first half of 2014 of a trend that had been increasing over the previous several years. They hypothesize that modifications in anti-coagulation therapy, among other strategies, are working to reduce the apparent increases in pump thrombosis observed between 2010 and 2013. Smedira and colleagues report a flattening of the pump thrombosis rate, but suggest that clinicians may reconsider and recalibrate their decision thresholds for recommending device implant, transplant and medical therapies.

As this collaboration evolved, the National Heart, Lung, and Blood Institute (NHLBI), along with the NHLBI-appointed study chair for INTERMACS, further explored the same INTERMACS data sets to give perspective to the 2 analyses described. Modeling choices within the analyses were assessed along with the uncertainty of statistical estimates of recent trends. Different approaches to estimating the magnitude of risk in the presence of censoring events are described. Consideration of these approaches is important for interpretation of the trends described and critical to making research and clinical decisions involving patients receiving these devices. The results of this collaborative approach demonstrate the capabilities and limitations of INTERMACS for capturing important trends in ventricular assist device (VAD) utilization and outcomes. They also show how these data may be used in concert with data from other reliable sources to inform public health, regulatory and research decisions.

## Sensitivity of recent trends to modeling choices

What is the truth behind the recent trends? Are thrombosis rates increasing, decreasing or relatively unchanged? These questions are important for the evaluation of equipoise for possible clinical trials as well as physician recommendations for individual patients. The following discussion is based on thrombosis risk within 3 months after implant, because every VAD recipient in the data set had at least 3 months of follow-up time available (a complete description of the data set is provided by Kirklin et al). Also, if a recent reduction

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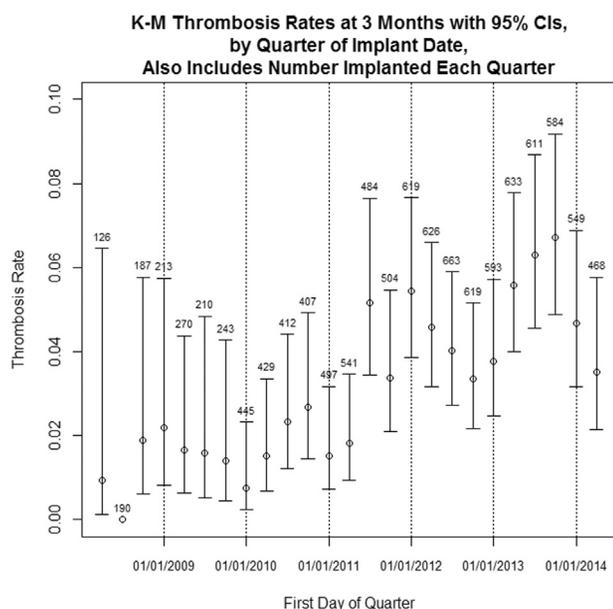
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in thrombosis rates has occurred, this will likely be reflected first in shorter follow-up periods due to less recent follow-up for longer periods; for instance, 2014 implants cannot provide full information for the 1-year follow-up in this data set. Other follow-up times beside the 3-month period may show different risk profiles over time.

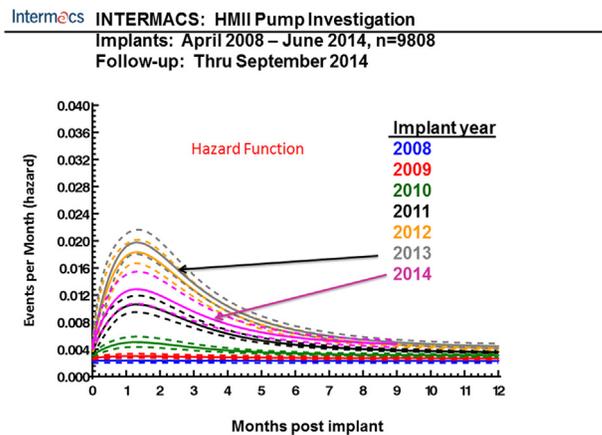
Figure 1 shows 3-month thrombosis rates computed for each quarter during the implant period. For the set of HeartMate II VADs implanted in a given quarter, a Kaplan–Meier analysis was conducted, and point estimates (shown by circles) and 95% confidence intervals for the probability of thrombosis within 3 months are plotted. In addition, the graph shows the number of implants performed in each quarter. Although the graph shows all 11,123 pumps, the general trends were also observed in the subset of 9,808 primary pumps.

Although the confidence interval for any given quarter may be relatively wide, there is a definite impression of an increase in 3-month thrombosis rates beginning in mid-2011 and rising throughout 2013 with a plateau or decline in early 2012 and 2014. This analysis does not account for covariates that may affect the temporal pattern, and it treats each quarter’s data separately, thus generating wide confidence intervals. Statistical modeling of the trend with respect to implant date may productively be used to address both of these shortcomings.

Both analyses by Kirklin et al<sup>2</sup> and Smedira et al<sup>3</sup> use statistical models of risk over calendar/implant time. Kirklin et al provides a parametric hazard rate model yielding the curves shown in Figure 5 of their report and reproduced here as Figure 2. The graph shows the estimated hazard rate curves by year for initial pumps. The fitted hazard curves can be used to estimate 3-month thrombosis probabilities (estimate =  $1 - e^{-AUC}$ , where AUC is the area under each curve between 0 and 3 months determined from visual inspection of the curves). This approach yields 3-month



**Figure 1** Kaplan–Meier estimates of thrombosis rates within 3 months of implant with 95% confidence intervals and the total number of implants in each quarter ( $N = 11,123$ ).

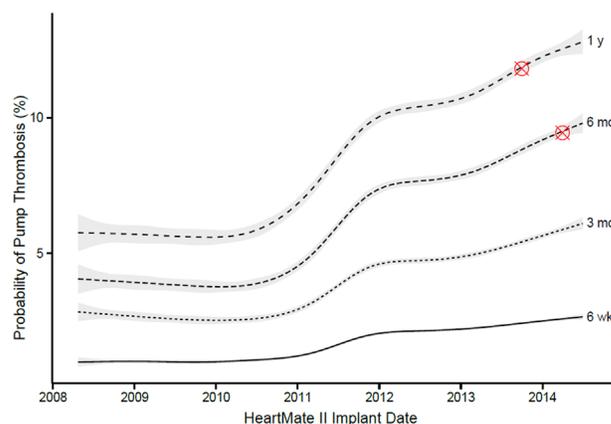


**Figure 2** Parametric modeling of thrombosis hazard rate, by year, as shown by Kirklin et al.<sup>2</sup>

probabilities of approximately 0.7%, 0.9%, 1.5%, 2.6%, 4.4%, 4.7% and 3.2% for Years 2008 through 2014, respectively. Although confidence intervals for these point estimates are not provided, the estimates suggest there was an increase beginning around 2010 and peaking in 2013, with a decline in 2014.

Smedira et al provide a similar analysis in Figure 1B of their report using the same parametric methodology<sup>4</sup> employed by Kirklin et al.<sup>2</sup> The 2 analyses are not identical, primarily because different modeling assumptions are presented; however, the general trend of increasing early hazard through 2013, with a suggestion of decline in 2014, is reflected.

In addition to this parametric approach to produce hazard functions, Smedira et al<sup>3</sup> employ a more recently developed random forests approach<sup>5</sup> to investigate the thrombosis rate question. Estimates for the probability of thrombosis for 1.5, 3, 6 and 12 months after implant are shown in Figure 2A of their study and reproduced here as Figure 3. In Figure 3, the confidence intervals are very tight, and the graph suggests the 3-month risk has not reversed but may in fact still be increasing, and more so for the longer follow-up periods.



**Figure 3** Variable dependence of implant date with respect to the probability of HeartMate II pump thrombosis, from bottom to top, at 6 weeks, 3 months, 6 months, and 1 year, as shown by Smedira et al. Red points mark the limits of follow-up data. Confidence bands are shown with light shading.

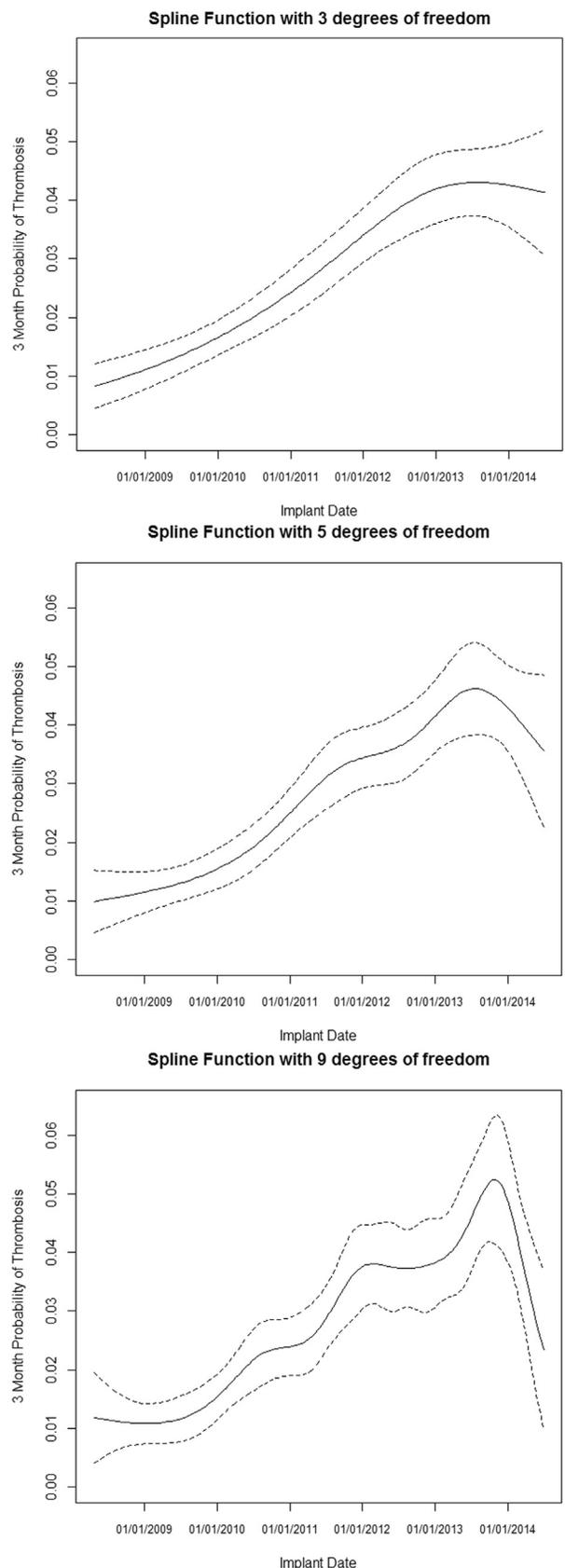
Are these analyses contradictory? Some major differences in modeling are noteworthy. For the curves in Figure 2, the model is based on a parametric estimation and the accuracy of the estimate and associated confidence intervals requires the model to be a reasonably good approximation to the true, underlying relationship. However, this parametric approach allows for a very rich set of potential models, and the discussion by Kirklin et al suggests the models do reproduce the data relatively well. Also, Figure 2 is based on only primary pumps. Given that subsequent implants have higher thrombosis risk,<sup>2,3</sup> the absolute probabilities in Figure 2 likely understate the risk in a population in which 12% to 13% of individuals have at least 2 implants. Finally, the model to produce Figure 2 does not incorporate covariates, such as age, race, gender, body mass index (BMI) and pump count (i.e., primary, second, third or fourth pump implanted). These factors may affect the risk profile and change the shape of the hazard function if their distributions change over time.

The analysis for Figure 3 differs in some ways. First, it is based on all pumps (not just primary) and, consequently, may reflect a higher overall level of risk and different risk profile over time. Also, the graph is based on a non-parametric curve—one that is not assumed to be of a specific shape determined by a small number of graphical parameters. In addition, the curve can reflect the presence of interactions between implant time and other covariates that need not be explicitly modeled. In addition, the curve reflects the actual distribution of covariates in the population. If those with secondary pumps are more represented in 2013 and 2014, then this will produce a rise in this curve that would not be reflected in the shape of the curves for Figure 2.

Finally, modeling choices may heavily influence the interpretation of implant date on risk. Figure 4 shows curves for 3 semi-parametric models we generated that model the hazard rate as a parametric function of age at implant date, white race, gender and pump count, and a non-parametric function of implant date. Mathematically:

$$\log \lambda(t; \text{age, race, gender, implant date}) = \log(\lambda_0(t)) + \beta_1 \text{age} + \beta_2 \text{if white} + \beta_3 \text{if male} + \beta_4 \text{pump number} + f(\text{implant date})$$

where  $\lambda_0(t)$  is a baseline hazard at time  $t$  and  $f(\ )$  is a non-parametric spline function fit by the data. The degree of complexity for  $f(\ )$  is determined by a degrees-of-freedom parameter. The 3 graphs in Figure 4 correspond to 3, 5 and 9 degrees of freedom and show the estimated probability of thrombosis within 3 months as a function of implant date for a 59-year-old, white male who received his first pump. What is noteworthy is how the shape and interpretation of the graph changes depending on how much flexibility is given in modeling the effect of implant date. The top figure suggests the risk plateaued in early 2013 and perhaps has continued to decline, although there are wide 95% confidence intervals that would give one pause before decisively concluding that the risk declined in 2014. The bottom figure corresponds to a less restrained modeling of implant date (9 degrees of freedom) that more closely tracks



**Figure 4** Models for effect of implant date on probability of thrombosis within 3 months of implant for a 59-year-old, white male receiving his first HeartMate II pump. Models differ by degrees of freedom used to model implant date. Top, middle and bottom figures correspond to 3, 5 and 9 degrees of freedom, respectively.

the minor variations over time in Figure 1 and gives the impression that risk had dramatically improved in 2014, although the confidence intervals are still relatively wide. The middle figure, with an intermediate level of flexibility (5 degrees of freedom), gives an intermediate interpretation that risk has declined somewhat. These figures show modeling decisions that may heavily influence the interpretation and suggest the data are not sufficiently strong to make unambiguous conclusions regarding declining risk in 2014.

In an effort to ascertain what degree of flexibility best fits these data, we performed a cross-validation approach based on 1,000 bootstrap samples to determine the number of degrees of freedom yielding best performance. For a given bootstrap sample, we fit models with 2, 3, ..., 8 and 9 degrees of freedom and applied the models to the cases omitted from the bootstrap sample and obtained C-statistics—a measure of model performance for Cox models.<sup>6</sup> The model with 3 degrees of freedom had the highest C-statistic performance averaged over the 1,000 bootstraps. This model corresponds to the top graph in Figure 4 and supports the more cautious interpretations regarding the improvement in risk.

## Magnitude of risk

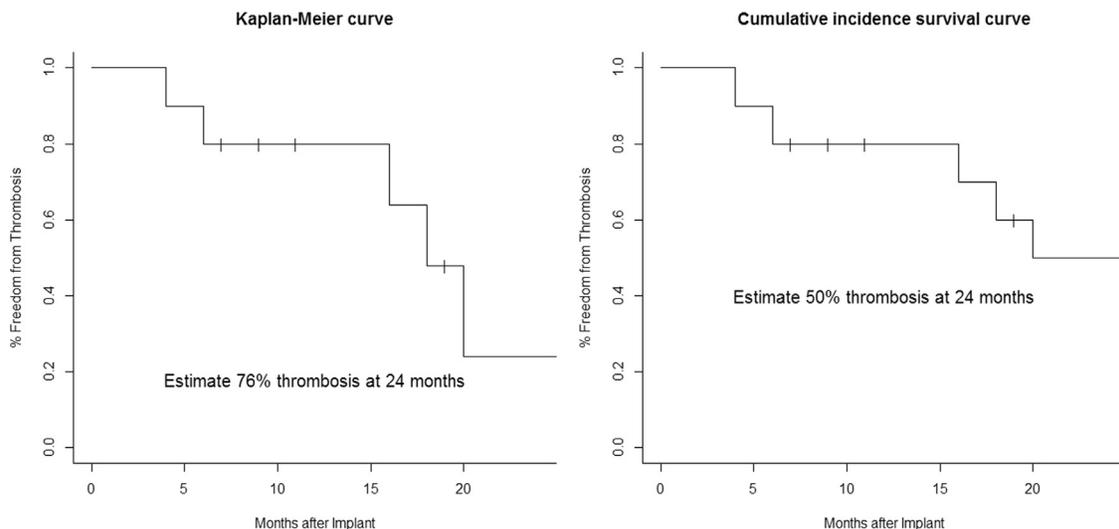
A second major issue is the magnitude of risk, its estimation and interpretation. When considering time to thrombosis for a given pump, the events of death, transplant and pump removal preclude the pump continuing to be at risk for thrombosis when these events occur for reasons unrelated to thrombosis. In statistical terms, these are referred to as competing risks for the outcome of thrombosis.<sup>7</sup> Because these competing events preclude the event of subsequent thrombosis for a given pump, it is appropriate to end follow-up observation for the pump/person experiencing a competing event.

Under these circumstances, the usual Kaplan–Meier estimates of thrombosis risk have an altered interpretation when individuals having these competing risks are treated in

the same way as an individual censored for insufficient follow-up time. For example, Person A has a transplant 8 months after implant and Person B has only 8 months of follow-up (without any events) when the analysis is conducted. The usual Kaplan–Meier approach treats both Persons A and B as censored after 8 months of follow-up, although Person B could, in principle, still have a pump-related thrombosis at some time after 8 months, whereas Person A will not. By treating these censored individuals equivalently, the Kaplan–Meier estimates for a given follow-up time now have the interpretation of the probability of thrombosis in a population that is not subject to the competing risks of death, transplant or removal unrelated to thrombosis, and the estimates will exceed what is observed in a population that is subject to these competing risks.

An alternative method for estimating the risk of thrombosis with competing risks involves a cumulative incidence approach. The cumulative incidence estimated thrombosis risk corresponds to what would be seen in a population that is subject to competing events, and hence is lower than that corresponding to Kaplan–Meier because some individuals who would have had a thrombosis instead first have another event that precludes thrombosis.<sup>7–9</sup>

The following simplified example, similar to that of Grunkemeier et al,<sup>10</sup> illustrates the differences in approaches. Consider 10 people implanted with pumps and each is followed for 24 months. Five recipients have pump thrombosis at 4, 6, 16, 18 and 20 months, respectively, after implant. Two individuals die, 1 at 7 months and 1 at 19 months, and 2 undergo transplant (1 at 9 months and 1 at 11 months), with none of these 4 events related to thrombosis. The tenth individual lives past 24 months without any of these events occurring. Figure 5 shows both Kaplan–Meier and cumulative incidence survival curves through 24 months. All outcomes at 2 years are known; that is, for each individual we know whether or not a thrombosis event occurred. The actual proportion free of thrombosis is 50% in this sample. The cumulative incidence estimate is 50%, matching the observed proportion, as will be the case when the outcome at a given follow-up time is known for each



**Figure 5** Kaplan–Meier and cumulative incidence estimates of freedom from thrombosis in a simple example.

pump; that is, there is no censoring due to insufficient observation time. In contrast, the Kaplan–Meier estimated thrombosis rate is 76% at 2 years. This example shows the difference in estimated rates can, in principle, be substantial.

Figure 6 shows Kaplan–Meier and cumulative incidence curves we constructed for freedom-from-thrombosis estimates for all primary implants in our data set. For short follow-up periods (e.g., 3 or 6 months), the difference between the 2 methods is negligible; however, for longer periods (e.g.,  $\geq 24$  months), the differences can be relatively large. At 24 months, the Kaplan–Meier estimate is 89% and the cumulative incidence estimate is 92%. Although the absolute difference is only 3%, the Kaplan–Meier approach overestimates the cumulative incidence by about 33% in relative terms. At 36 months, this relative overestimation is closer to 50%. As an aside, it is noted that, in discussing the recent trends in 3-month thrombosis rate, we used Kaplan–Meier approaches and other methods that similarly overlook the competing risks. We did perform complementary analyses that incorporated competing risks; these did not change our conclusions as the follow-up period considered was only 3 months and the difference was negligible.

The differences between Kaplan–Meier and cumulative incidence approaches may be important for interpreting thrombosis estimates. The cumulative incidence estimate and observed proportion of thrombosis from a cohort that has complete or nearly complete follow-up at a given time should be relatively close. However, estimates from the Kaplan–Meier procedure will overestimate if competing risk events are treated as if censored for lack of follow up. Also, these differences may be important when comparing data sets from different sources. Registries, individual centers, industry records and clinical studies may all provide estimates that are potentially tabulated differently. Part of the difference observed between estimates may arise from the different methods used for computation. The cumulative incidence should be reported for studies involving longer

follow-up times and a non-negligible prevalence of competing events.

## Conclusions

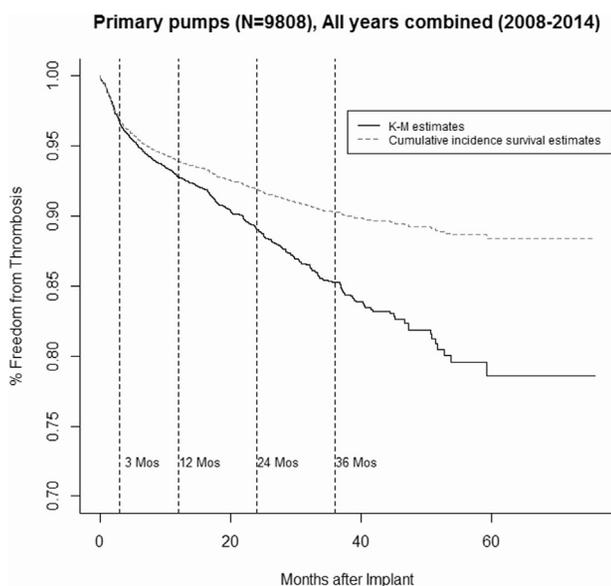
Based on the 2 outstanding analyses and the NHLBI's own consideration of the >10,000 HeartMate II implants and reflections on the limitations of the statistical approaches, we conclude:

- Kirklin et al, Smedira et al and our own analysis support the findings suggesting that risk of thrombosis has increased from levels seen during the 2008 to 2010 period, with the highest rates observed in 2013.
- Although some evidence suggests that thrombosis risk declined in 2014, the conclusions depend on model specification. Moreover, the data may not be complete enough for unambiguous conclusions regarding 2014 rates. The analyses by Smedira et al suggest risk may be increasing. Clearly, there is a need for longer follow-up and adjudication of the 2014/2015 experience, along with updated analyses.
- Assessing the magnitude of risk can be complicated by the presence and treatment of competing risks. Traditional Kaplan–Meier assessment of risk can overestimate the thrombosis risk in a population that is subject to competing risks of death, transplant and removal of implants for reasons unrelated to thrombosis. Risk estimates from various sources (e.g., clinical studies, center experiences and registries) may be computed in different ways, and the treatment of competing risks may account for some of the differences among estimates.

## Next steps

Despite the frequency of pump thrombosis in the HeartMate II, and other reported serious adverse events associated with this and other currently marketed LVADs,<sup>11–15</sup> these devices continue to extend and save lives of advanced heart failure patients. Continued vigilance and institution of best clinical practice is needed with regard to risk mitigation as are observational studies to further inform these practices.

Analyses and descriptions of the emerging challenge of pump thrombosis have been made possible due to the availability of INTERMACS data and the efforts of a broad group of collaborators associated with the INTERMACS enterprise. Although randomized clinical trials are considered the “gold standard” for testing the benefit of an intervention, the work on the HeartMate II thrombosis issue demonstrates the value of a registry that has been in existence for nearly a decade for dynamically following trends in device design, patient selection, management practices and emerging adverse events. INTERMACS data are also an important resource and can be used to formulate new hypotheses that may be tested in randomized clinical trials or when utilizing other approaches. Other device performance investigations are ongoing within INTERMACS.



**Figure 6** Kaplan–Meier and cumulative incidence estimates of freedom from pump thrombosis applied to primary pumps.

As novel design innovations available in the next generation of devices reach the marketplace, new and potentially unanticipated challenges will emerge. How and when will these be identified? Accurately determining the safety and efficacy of therapies is the underpinning of clinically oriented scientific ventures. Development of evidence that will guide wise therapeutic decisions and recommendations is essential. The INTERMACS registry is clearly an invaluable resource for evaluating emerging trends and for continuing to promote dialogue among clinicians, academicians, government and industry as to important choices related to the use of this technology.

## Disclosure statement

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## References

1. Starling RC, Gorodeski EZ. Potential population for long-term use of left ventricular assist devices. In: Kormos RL, Miller LW, editors. *Mechanical circulatory support: a companion to Braunwald's heart disease*. Philadelphia: Elsevier; 2011. p. 1-10.
2. Kirklin JK, Naftel DC, Pagani FD, et al. Pump thrombosis in the Thoratec HeartMate II device: an updated analysis of the INTERMACS registry. *J Heart Lung Transplant* 2015;34:1515-26.
3. Smedira NG, Blackstone E, Ehlinger J, et al. Current risks of HeartMate II pump thrombosis: nonparametric analysis of INTERMACS data. *J Heart Lung Transplant* 2015;34:1527-34.
4. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc* 1986;81:615-24.
5. Ishwaran H, Kogalur UB, Blackstone EH, et al. Random survival forests. *Ann Appl Stat* 2008;2:841-60.
6. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models—issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87.
7. Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: Wiley; 1980. p. 163-71.
8. Gooley TA, Leisenring W, Crowley J, et al. Estimation of failure probabilities in the presence of competing risks: new representation of old estimators. *Stat Med* 1999;18:695-706.
9. Southern DA, Faris PD, Brant R, et al. Kaplan–Meier methods yielded misleading results in competing risk scenarios. *J Clin Epidemiol* 2006;59:1110-4.
10. Grunkemeier GL, Anderson RP, Miller DC, et al. Time-related analysis of nonfatal heart valve complications: cumulative incidence (actual) versus Kaplan–Meier (actuarial). *Circulation* 1997;96(suppl):S7011-4.
11. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;357:885-96.
12. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;361:2241-51.
13. Pagani FD, Miller LW, Russell SD, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol* 2009;54:312-21.
14. Fraser CD Jr, Jaquiss RDB, Rosenthal DN, et al. Prospective trial of a pediatric ventricular assist device. *N Engl J Med* 2012;367:532-41.
15. U.S. Food and Drug Administration. FDA safety communication. Serious adverse events with implantable left ventricular assist devices (LVADs). August 5, 2015. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm457327.htm/>.