Unexpected Abrupt Increase in Left Ventricular Assist Device Thrombosis
— Source link ⌴

Randall C. Starling, Nader Moazami, Scott C. Silvestry, Gregory A. Ewald ...+11 more authors

Institutions: Cleveland Clinic, Washington University in St. Louis, Duke University, University of Pennsylvania

Related papers:

- Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

- Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device

- An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial.

- Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure

- Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation

Share this paper: 🅕 🅣 🅛🅸🅽 ✉

2014

Unexpected abrupt increase in left ventricular assist device thrombosis

Randall C. Starling
Cleveland Clinic

Nader Moazami
Cleveland Clinic

Scott C. Silvestry
Washington University School of Medicine in St. Louis

Gregory Ewald
Washington University School of Medicine in St. Louis

Joseph G. Rogers
Duke University School of Medicine

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation

Authors

Randall C. Starling, Nader Moazami, Scott C. Silvestry, Gregory Ewald, Joseph G. Rogers, Carmelo A. Milano, J Eduardo Rame, Michael A. Acker, Eugene H. Blackstone, John Ehrlinger, Lucy Thuita, Maria M. Mountis, Edward G. Soltesz, Bruce W. Lytle, and Nicholas G. Smedira

ORIGINAL ARTICLE

Unexpected Abrupt Increase in Left Ventricular Assist Device Thrombosis

Randall C. Starling, M.D., M.P.H., Nader Moazami, M.D., Scott C. Silvestry, M.D.,
Gregory Ewald, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D.,
J. Eduardo Rame, M.D., Michael A. Acker, M.D., Eugene H. Blackstone, M.D.,
John Ehrlinger, Ph.D., Lucy Thuita, M.S., Maria M. Mountis, D.O.,
Edward G. Soltesz, M.D., M.P.H., Bruce W. Lytle, M.D.,
and Nicholas G. Smedira, M.D.

ABSTRACT

BACKGROUND

We observed an apparent increase in the rate of device thrombosis among patients who received the HeartMate II left ventricular assist device, as compared with preapproval clinical-trial results and initial experience. We investigated the occurrence of pump thrombosis and elevated lactate dehydrogenase (LDH) levels, LDH levels presaging thrombosis (and associated hemolysis), and outcomes of different management strategies in a multi-institutional study.

METHODS

We obtained data from 837 patients at three institutions, where 895 devices were implanted from 2004 through mid-2013; the mean (±SD) age of the patients was 55±14 years. The primary end point was confirmed pump thrombosis. Secondary end points were confirmed and suspected thrombosis, longitudinal LDH levels, and outcomes after pump thrombosis.

RESULTS

A total of 72 pump thromboses were confirmed in 66 patients; an additional 36 thromboses in unique devices were suspected. Starting in approximately March 2011, the occurrence of confirmed pump thrombosis at 3 months after implantation increased from 2.2% (95% confidence interval [CI], 1.5 to 3.4) to 8.4% (95% CI, 5.0 to 13.9) by January 1, 2013. Before March 1, 2011, the median time from implantation to thrombosis was 18.6 months (95% CI, 0.5 to 52.7), and from March 2011 onward, it was 2.7 months (95% CI, 0.0 to 18.6). The occurrence of elevated LDH levels within 3 months after implantation mirrored that of thrombosis. Thrombosis was presaged by LDH levels that more than doubled, from 540 IU per liter to 1490 IU per liter, within the weeks before diagnosis. Thrombosis was managed by heart transplantation in 11 patients (1 patient died 31 days after transplantation) and by pump replacement in 21, with mortality equivalent to that among patients without thrombosis; among 40 thromboses in 40 patients who did not undergo transplantation or pump replacement, actuarial mortality was 48.2% (95% CI, 31.6 to 65.2) in the ensuing 6 months after pump thrombosis.

CONCLUSIONS

The rate of pump thrombosis related to the use of the HeartMate II has been increasing at our centers and is associated with substantial morbidity and mortality.

From the Departments of Cardiovascular Medicine (R.C.S., M.M.M.), Thoracic and Cardiovascular Surgery (N.M., E.H.B., E.G.S., B.W.L., N.G.S.), and Quantitative Health Sciences (E.H.B., J.E., L.T.) and Kaufman Center for Heart Failure (R.C.S., N.M., E.H.B., M.M.M., E.G.S., N.G.S.), Cleveland Clinic, Cleveland; the Division of Cardiovascular Surgery (S.C.S.) and the Cardiovascular Division (G.E.), Barnes–Jewish Hospital, Washington University School of Medicine, St. Louis; the Cardiology Division (J.G.R.) and the Cardiovascular Surgery Division (C.A.M.), Duke University School of Medicine, Durham, NC; and the Divisions of Cardiology (J.E.R.) and Cardiovascular Surgery (M.A.A.), University of Pennsylvania, Philadelphia. Address reprint requests to Dr. Starling at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Desk J3-4, Cleveland, OH 44195, or at starlir@ccf.org.

THE HEARTMATE II (THORATEC), A small, axial-flow left ventricular assist device (LVAD), rapidly became integral to the treatment of patients with advanced heart failure.[1] Pivotal trials and postmarketing approval studies of the HeartMate II provide a reference occurrence of thrombosis of 2 to 4%[2-4]; however, an unexpected abrupt increase in the incidence of pump thrombosis was observed in a single-center quality review. To confirm that this finding was not an isolated phenomenon, two additional experienced centers pooled data to investigate the incidence of pump thrombosis and of elevated lactate dehydrogenase (LDH) levels as its clinical biomarker (indicating hemolysis), LDH levels that may presage thrombosis, and outcomes of thrombosis-management strategies.

METHODS

PATIENTS

A total of 895 HeartMate II LVADs were implanted in 837 patients at three institutions: Cleveland Clinic from October 2004 through February 2013 (296 devices in 280 patients), Washington University Barnes–Jewish Hospital from January 2004 through April 2013 (307 devices in 287 patients), and Duke University Medical Center from May 2005 through May 2013 (292 devices in 270 patients). At the three respective institutions, the mean (±SD) ages of the patients were 54±14, 54±13, and 58±14 years, with an overall average of 55±14 years; 19.3%, 16.4%, and 27.8% of the patients were women, with an overall average of 21.0%.

STUDY DATA

Limited, partially deidentified data were provided for analysis under data-use agreements and with approval from the institutional review board at each institution to use these data in research; the requirement to obtain informed consent from the patients was waived. Variables in common across the three institutions included the date of Heart-Mate II implantation, the number of HeartMate II devices each patient had previously received, age at each HeartMate II implantation, sex, bridge-to-transplantation versus destination therapy as the indication for mechanical circulatory support, and surgeon. The medical records of patients with confirmed or suspected pump thrombosis were scrutinized by investigators at each site to verify diagnostic evidence.

The electronic medical-records systems at the hospitals were queried to extract serial values of LDH during HeartMate II support. We obtained 12,379 LDH measurements for 568 devices (275 devices at Cleveland Clinic, 24 at Barnes–Jewish Hospital [only for some cases of confirmed thrombosis], and 269 at Duke University Medical Center). There were typically 12 to 24 LDH measurements per device (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

END POINTS

The primary end point was confirmed pump thrombosis. Secondary end points were confirmed plus clinically suspected pump thrombosis, elevated LDH levels, the pattern of LDH levels leading up to pump thrombosis, and outcomes after the management of pump thrombosis (pump replacement or explantation, urgent heart transplantation, medical treatment, or death).

Confirmed pump thrombosis was defined as a thrombus found on the blood-contacting surfaces of the HeartMate II, its inflow cannula, or its outflow conduit at pump replacement, urgent transplantation, or autopsy (Appendix S1 and Fig. S2 in the Supplementary Appendix). Suspected pump thrombosis was defined as a clinical diagnosis of pump-related malfunction in which the clinical or device variables suggested a thrombus on the blood-contacting surfaces of the pump, cannulae, or grafts (Appendix S1 in the Supplementary Appendix).

MANAGEMENT OF PUMP THROMBOSIS

Clinically suspected pump thrombosis was managed by means of intravenous anticoagulation therapy, thrombolytic agents, and antiplatelet therapy; pump replacement or explantation; or urgent heart transplantation. In general, centers followed the guidelines developed by a committee of clinical experts,[5] although the details of the approach and management strategies were specific to each institution and varied over time (Appendix S2 in the Supplementary Appendix).

FOLLOW-UP

Follow-up assessment of clinical outcomes and laboratory measurements occurred at intervals of 3 months or less after the device implantation. The common closing date for patients at the Cleveland Clinic was March 5, 2013; for those at

Barnes–Jewish Hospital, September 10, 2013; and for those at the Duke University Medical Center, May 16, 2013. The median follow-up at the three institutions was 7.8 months, 10.7 months, and 10.4 months, respectively; the three institutions had 278 patient-years, 376 patient-years, and 393 patient-years of follow-up data available for analysis, respectively.

STATISTICAL ANALYSIS

The risk of pump thrombosis was estimated from the pooled multicenter data and was also estimated separately for each institution. Kaplan–Meier,[6] parametric hazard,[7] and nonparametric random survival forest[8-10] analyses (Appendix S1 in the Supplementary Appendix) were based on data for unique devices rather than data for unique patients, with time zero defined as the date of implantation of each HeartMate II. Data were censored at transplantation, death, pump replacement, pump removal without replacement (allowed because of left ventricular recovery), and end of follow-up.

The date of implantation was incorporated into a parametric hazard model to identify a changing incidence of pump thrombosis across time. To corroborate parametric findings without making model assumptions, the data were also analyzed with the use of the random survival forest method (Appendix S1 in the Supplementary Appendix).

We hypothesized that the LDH level, which is indicative of hemolysis caused by thrombus formation in the pump, may independently corroborate an increasing incidence of pump thrombosis. Therefore, each patient's sequence of LDH measurements was scanned algorithmically for LDH levels of more than 1000 IU per liter. Single-sample spikes were ignored as probable sample hemolysis, although the algorithm included samples immediately proximate to death, urgent transplantation, device replacement, or explantation. These data were analyzed as time-related events, exactly as for pump thrombosis.

For confirmed thrombosis, a landmark analysis of LDH measurements was performed with the date of pump thrombosis set as time zero. The preceding 3-month longitudinal sequence of measurements for each device was connected by straight lines. A locally estimated scatterplot smoother (loess)[11] was then fitted to the ensemble of line segments.

Time zero for death after confirmed pump thrombosis was the date of suspected pump thrombosis, even if confirmation subsequently occurred at the time of pump replacement, urgent transplantation, or autopsy. Data were censored 30 days after transplantation or pump replacement to capture the risks of these procedures. The Kaplan–Meier method was used to estimate time-related mortality. For reference, the competing risk of death during HeartMate II support without pump thrombosis was generated.[12]

Data were analyzed with the use of SAS software, version 9.2 (SAS Institute), and R software, version 3.0.2.[13] For internal consistency, uncertainty of estimates is expressed uniformly by means of 95% confidence intervals or bands similar to ±2 SE.
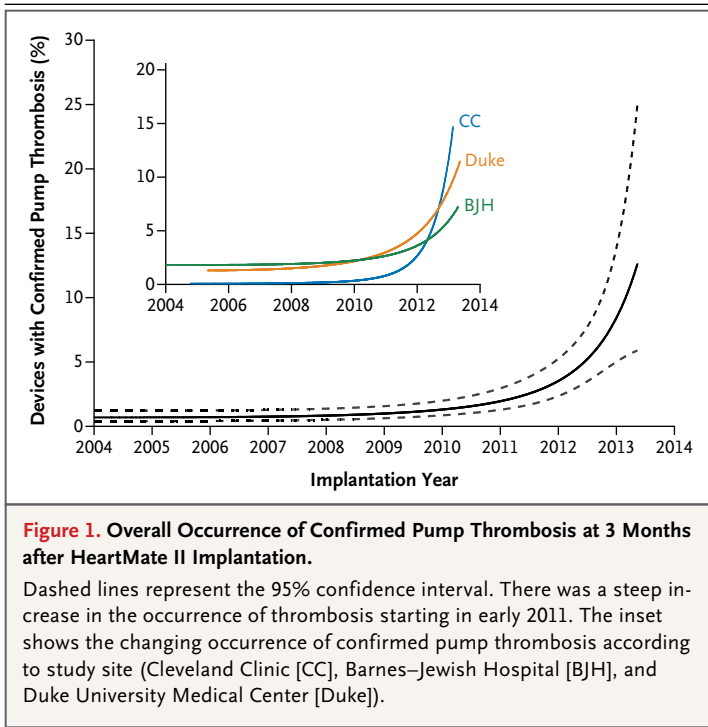
RESULTS

OVERALL INCIDENCE OF PUMP THROMBOSIS

A total of 72 confirmed pump thromboses were observed in 66 patients, and an additional 36 thromboses in unique devices were suspected. The risk of confirmed pump thrombosis peaked at 1.4% per month within 1 month after implantation before decreasing to a constant risk of 0.4% per month (Fig. S3A in the Supplementary Appendix), with estimated occurrences of pump thrombosis of 4.7% during HeartMate II support for 6 months, 7.5% during 12 months of support, and 12.3% during 24 months of support (Fig. S3B in the Supplementary Appendix). This pattern of risk was consistent among the three institutions (Fig. S4 in the Supplementary Appendix). It also characterized the combined risk of confirmed plus suspected pump thrombosis, which rose to 2.0% per month within 1 month after implantation, then fell to 0.7% per month after 6 to 8 months, with estimated occurrences of 7.1% during HeartMate II support for 6 months, 11.3% during 12 months of support, and 18.3% during 24 months of support (Fig. S5 in the Supplementary Appendix).

CHANGING INCIDENCE OF PUMP THROMBOSIS

The occurrence of confirmed pump thrombosis increased steeply after approximately March 2011, from 2.2% (95% confidence interval [CI], 1.5 to 3.4) at 3 months after implantation to 8.4% (95% CI, 5.0 to 13.9) by January 2013 (Fig. 1, and Table S1 and Fig. S6 and S7 in the Supplementary Appendix). A similar pattern was observed

Figure 1. Overall Occurrence of Confirmed Pump Thrombosis at 3 Months after HeartMate II Implantation.

Dashed lines represent the 95% confidence interval. There was a steep increase in the occurrence of thrombosis starting in early 2011. The inset shows the changing occurrence of confirmed pump thrombosis according to study site (Cleveland Clinic [CC], Barnes–Jewish Hospital [BJH], and Duke University Medical Center [Duke]).

at all three institutions (Fig. 1) and for multiple surgeons (Fig. S8 in the Supplementary Appendix).

The median time from implantation to confirmed pump thrombosis decreased from 18.6 months (95% CI, 0.5 to 52.7) before March 2011 to 2.7 months (95% CI, 0.0 to 18.6) during and after March 2011. What had been a constant risk of confirmed pump thrombosis of 0.4% per month (95% CI, 0.3 to 0.5) after implantation developed into an early hazard that peaked at 2 months and then fell to a sustained 0.6% per month (95% CI, 0.3 to 1.2) (Fig. 2); this risk was consistent across institutions (Fig. S9 in the Supplementary Appendix). This pattern of change in the incidence of confirmed pump thrombosis also characterized the rate of confirmed plus suspected events (Table S2 and Fig. S10, S11, and S12 in the Supplementary Appendix).

CHANGING OCCURRENCE OF ELEVATED LDH LEVELS

The graph of the occurrence of LDH levels above 1000 IU per liter within 3 months after implantation was nearly superimposable on the graph of the occurrence of confirmed pump thrombosis. The LDH data showed a parallel tendency for elevations to occur early after implantation beginning in approximately March 2011 (Fig. 3, and Fig. S13 in the Supplementary Appendix).

LDH LEVEL PRESAGING PUMP THROMBOSIS

On average, the LDH level increased from 540 IU per liter (95% CI, 388 to 695) to 1490 IU per liter (95% CI, 1350 to 1600) in the 6 weeks leading up to confirmed pump thrombosis. This finding was consistent across institutions (Fig. 4, and Fig. S14 in the Supplementary Appendix).

OUTCOMES AFTER PUMP THROMBOSIS

There were 72 pump thromboses in 66 patients. A total of 11 pump thromboses were managed by heart transplantation in 11 patients (1 patient died 31 days after transplantation). A total of 21 pump thromboses were managed by pump replacement in 19 patients (1 patient died >30 days after the pump replacement, and 1 underwent 3 replacements). Of 40 thromboses not managed by heart transplantation or pump replacement, 2 thromboses in 2 patients were managed with pump removal, because left ventricular function had improved; 38 pump thromboses were managed medically in 38 patients (4 of whom had undergone prior device replacement), of whom 19 died. Medical management included the augmentation of anticoagulation therapy and thrombolytic agents, which in some cases was effective and stabilized the patient's clinical course; however, some patients elected withdrawal of care on the basis of futility.

As compared with mortality during HeartMate II support among patients without confirmed pump thrombosis, the actuarial mortality after confirmed pump thrombosis at various time points was higher: 6.9% (95% CI, 5.4 to 8.8) versus 17.7% (95% CI, 9.7 to 30.1) at 30 days, 9.7% (95% CI, 7.9 to 11.9) versus 22.4% (95% CI, 13.0 to 35.8) at 60 days, 12.2% (95% CI, 10.1 to 14.6) versus 27.4% (95% CI, 16.6 to 41.5) at 90 days, and 16.8% (95% CI, 14.3 to 19.6) versus 35.6% (95% CI, 22.9 to 50.7) at 180 days (Fig. S15A in the Supplementary Appendix). There was considerable variation in outcomes (Fig. S15B in the Supplementary Appendix), depending on candidacy for urgent transplantation or pump replacement. Mortality at 6 months among patients treated with device replacement or transplantation was similar to that among patients who did not have device thrombosis (Fig. 5), but mortality was 48.2% (95% CI, 31.6 to 65.2) among patients with device thrombosis who were not treated with these methods, and this elevated mortality was consistent across institutions (Fig. S15C in the Supplementary Appendix).
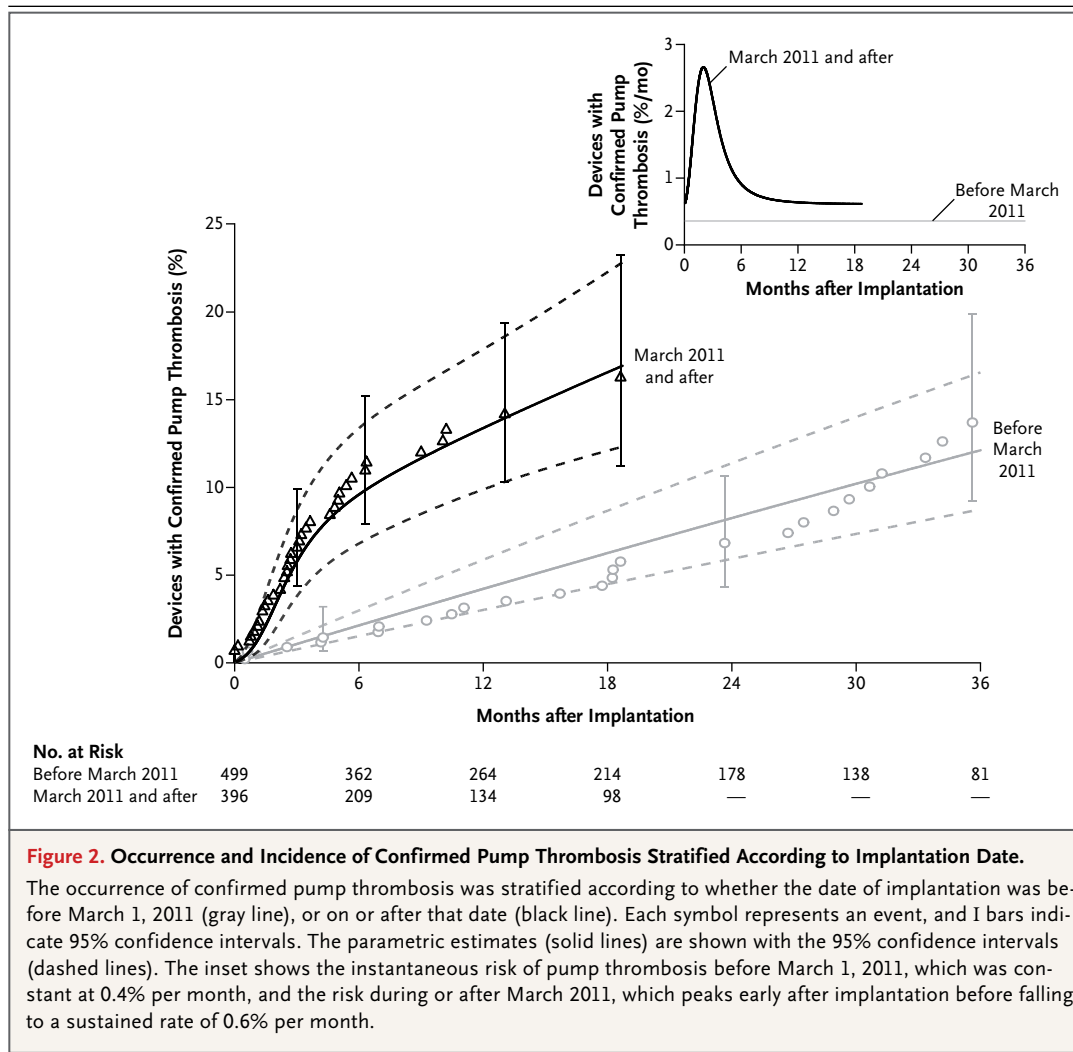
Figure 2. Occurrence and Incidence of Confirmed Pump Thrombosis Stratified According to Implantation Date.

The occurrence of confirmed pump thrombosis was stratified according to whether the date of implantation was before March 1, 2011 (gray line), or on or after that date (black line). Each symbol represents an event, and I bars indicate 95% confidence intervals. The parametric estimates (solid lines) are shown with the 95% confidence intervals (dashed lines). The inset shows the instantaneous risk of pump thrombosis before March 1, 2011, which was constant at 0.4% per month, and the risk during or after March 2011, which peaks early after implantation before falling to a sustained rate of 0.6% per month.

DISCUSSION

Approval of the HeartMate II by the Food and Drug Administration (FDA) has had a substantial impact on the care of patients with advanced heart failure. LVAD therapy is an important advance that is used to prolong survival and improve quality of life. Refinement of all therapeutic innovations evolves as clinicians gain experience with and an understanding of device-associated complications and their management.

The rate of pump thrombosis with the Heart-Mate II began increasing in March 2011 and had not plateaued as of mid-2013. Confirmed pump thrombosis occurs early and peaks 1 month after implantation, with a reduction in risk by 6 months. This rate exceeds the rates previously observed at our centers and reported in clinical trials.[14] The

incidence of elevated LDH levels mirrors this increased rate, making it a useful clinical biomarker of hemolysis associated with pump thrombosis. Patients with pump thrombosis have increased morbidity and substantially increased mortality unless the pump is replaced or cardiac transplantation is performed.

The initial analysis that revealed this sudden increase in the incidence of pump thrombosis was a clinical quality review at a single center (Cleveland Clinic). To confirm and strengthen those findings, we pooled data from two additional experienced LVAD centers and found similar results. The initial findings at the Cleveland Clinic were immediately sent to Thoratec and to the FDA. Statisticians at the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) conducted an analysis of 6251
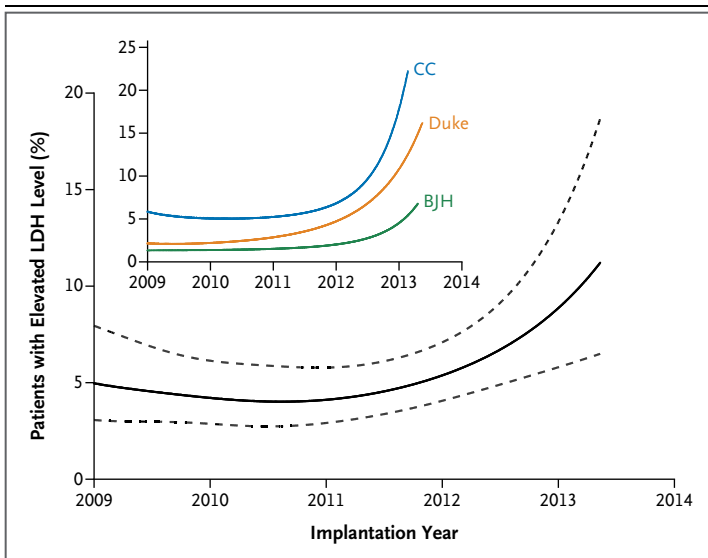
Figure 3. Elevated Lactate Dehydrogenase (LDH) Levels within 3 Months after HeartMate II Implantation.

The overall estimate of the percentage of patients with LDH levels of more than 1000 IU per liter within 3 months after the implantation of a Heart-Mate II is shown, without regard to diagnosis of confirmed or suspected pump thrombosis. The parametric estimate is shown (solid line) with the 95% confidence interval (dashed lines). The occurrence of elevated LDH levels increased steadily starting in 2011, which was similar to the pattern observed for pump thrombosis. The inset shows changes in occurrence according to study site.
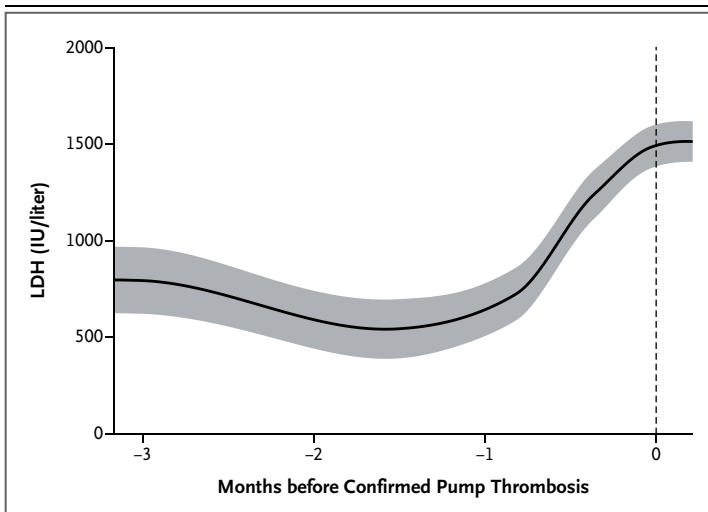

Figure 4. LDH Values before Confirmed Pump Thrombosis.

The time of pump thrombosis (time zero) is shown at the right side of the graph, and LDH values up to 3 months before confirmed thrombosis are shown. The solid line represents the estimate of the LDH level, as generated by the locally estimated scatterplot smoother (loess), and the gray band represents the bootstrapped 95% confidence interval.

implantations performed from April 1, 2008, to September 1, 2012, and found that the occurrence of pump thrombosis increased from 2% before May 2011, to 5% from May onward.[15] This observation is reported on the INTERMACS website.[15]

The INTERMACS captures data on the occurrence of suspected pump thrombosis on the basis of device replacement or death attributable to thrombus. Our study also included 11 of 66 patients with device thrombosis (16.7%) who were rescued with urgent heart transplantation. Examination of the incidence of device thrombosis with the use of the implantation date as a continuous variable and with a description of outcomes after therapeutic intervention provides a more complete picture of the scope and risks of device thrombosis. Thus, we believe the INTERMACS data may not accurately reflect the actual occurrence of pump thrombosis and its risks. Although the INTERMACS is a valuable resource, event reporting is voluntary, and definitions of adverse events are evolving. By combining data from three high-volume institutions, we reduced the likelihood that our observations are an isolated single-center effect related solely to the management approach.

We found that a sharp rise in LDH levels occurring within the first weeks after implantation often preceded and heralded confirmed pump thrombosis. Our findings are consistent with those of the University of Michigan.[16]

Pump function and reliability are related to the complex interaction between implantation techniques[17] and anatomical constraints; patient-level factors such as infection, bleeding, and adequacy of anticoagulation; pump settings; and device design and manufacturing.[18] During the course of the study, implantation techniques did not change, and we could find no association between pump thrombosis and the surgeon performing the implantation (Fig. S8 in the Supplementary Appendix). Design changes, including modification of the outflow graft and bend relief, inflow conduit, and software, were introduced during the study period but, to our knowledge, have not been directly linked to pump thrombosis.

We have collectively observed, most commonly at explantation, that there is a deposition of material (fibrin and denatured protein) in proximity to the inflow bearing (Fig. S2 in the

Supplementary Appendix), which depends on fluid for lubrication and flow to dissipate heat. Heat generation and the subsequent deposition of fibrin around the bearing narrows the inflow pathway, increasing shear stress on the red cells and, if the deposition is large enough, decreasing the ability of the pump to unload the left ventricle. The bearing–fibrin deposition theory could explain the hemolysis that develops as thrombus deposition begins, escalates into frank pump thrombosis, and culminates in hemodynamic compromise. We theorize that the changes occur in three stages: the initial stage is hemolysis with thrombus deposition but no hemodynamic compromise (thrombus formation); this may progress to hemolysis and abnormal pump function (incomplete thrombosis); and ultimately, complete thrombosis and pump stoppage may occur.

Any perturbation that might reduce flow and heat dissipation from the bearing, or inadequate anticoagulation, might represent precipitating conditions. Known clinical factors that might transiently impair flow include the development of aortic regurgitation, arrhythmias, kinking of the inflow graft because of bending, and hypovolemia. As of this writing, the exact cause of the increased rate of pump thrombosis remained unknown.

This is a three-institution retrospective study with known inherent limitations. However, unlike INTERMACS, we have extensive data on LDH levels and can carefully scrutinize patient records. The definitions of confirmed and suspected pump thrombosis have been revised recently by the INTERMACS steering committee to reflect elevated LDH levels as a marker of hemolysis.[16] These definitions were not available prospectively for this study but were used in the individual review of potential cases of pump thrombosis. This may explain differences between our data and INTERMACS reported events. However, it is possible that we underdiagnosed pump thrombosis before 2011, and clinically evident pump thrombosis does not develop in all patients with increased LDH levels. In addition, in the case of patients who died with the LVAD in situ, if an autopsy was not performed, visual confirmation could not take place.

Anticoagulation protocols changed during the course of this analysis, with some variation among institutions (Table S4 in the Supplemen-
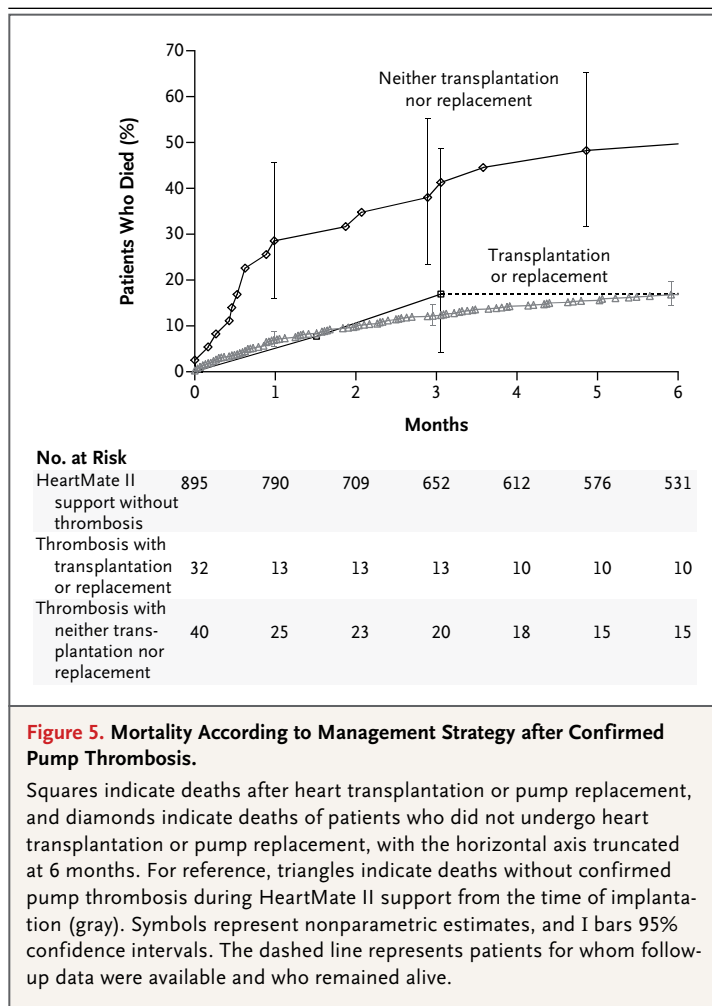

No. at Risk

HeartMate II support without thrombosis	895	790	709	652	612	576	531
Thrombosis with transplantation or replacement	32	13	13	13	10	10	10
Thrombosis with neither transplantation nor replacement	40	25	23	20	18	15	15

Figure 5. Mortality According to Management Strategy after Confirmed Pump Thrombosis.

Squares indicate deaths after heart transplantation or pump replacement, and diamonds indicate deaths of patients who did not undergo heart transplantation or pump replacement, with the horizontal axis truncated at 6 months. For reference, triangles indicate deaths without confirmed pump thrombosis during HeartMate II support from the time of implantation (gray). Symbols represent nonparametric estimates, and I bars 95% confidence intervals. The dashed line represents patients for whom follow-up data were available and who remained alive.

tary Appendix). Nonetheless, our data suggest that the HeartMate II may have a more narrow tolerance with respect to thrombus formation than originally understood and may be vulnerable to the timing and intensity of anticoagulation.

In conclusion, we observed an increasing incidence of early thrombosis with the HeartMate II that is associated with substantial morbidity and mortality. Costly device replacement or urgent transplantation can be lifesaving, although with morbidity. Further investigation of predisposing patient and device factors and preventive and therapeutic strategies are urgently needed to resolve this important safety issue. We recognize that LVADs provide life-sustaining treatment for many patients with advanced heart failure. However, recommendations for LVAD therapy should account for this updated risk–benefit profile.

Note added in proof: Pursuant to a data-sharing agreement with the University of Pennsylvania, we have completed a preliminary analysis of 150 unique devices (placed between November 1, 2005, and September 3, 2013) in 148 patients who had 15 thrombotic events (closing date, October 28, 2013). Similar to the findings in our study, the event rate has increased abruptly and unexpectedly, with a rate of confirmed thrombosis that continues to rise.

REFERENCES

1. Kirklin JK, Naftel DC, Kormos RL, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant 2013;32:141-56.
2. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2011;57:1890-8. [Erratum, J Am Coll Cardiol 2011;58:2142.]
3. 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.
4. 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.
5. Goldstein DJ, John R, Salerno C, et al. Algorithm for the diagnosis and management of suspected pump thrombus. J Heart Lung Transplant 2013;32:667-70.
6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
7. 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.
8. Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS. Random survival forests. Ann Appl Stat 2008;2:841-60.
9. Ishwaran H, Kogalar UB. Random survival forests for R. R News. Vol. 7. No. 2. October 2007:25-31 (http://www.r-project.org/doc/Rnews/Rnews_2007-2.pdf).
10. Breiman L. Random forests. Mach Learn 2001;45:5-32.
11. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 1979;74:829-36.
12. Nonparametric estimation. In: Andersen PK, Borgan Ø, Gill RD, Keiding N. Statistical models based on counting processes. New York: Springer-Verlag, 1993:176-330.
13. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2013 (http://www.R-project.org).
14. Summary of safety and effectiveness data. Table 8 — serious adverse events as of September 14, 2007 (http://www.accessdata.fda.gov/cdrh_docs/pdf6/P060040b.pdf).
15. Initial analyses of suspected pump thrombosis. 2013 (http://www.uab.edu/medicine/intermacs/images/INTERMACS_PI_and_Website_Notice_9-6-2013_2.pdf).
16. Shah P, Mehta VM, Cowger JA, Aaronson KD, Pagani FD. Diagnosis of hemolysis and device thrombosis with lactate dehydrogenase during left ventricular assist device support. J Heart Lung Transplant 2013 August 19 (Epub ahead of print).
17. Taghavi S, Ward C, Jayarajan SN, Gaughan J, Wilson LM, Mangi AA. Surgical technique influences HeartMate II left ventricular assist device thrombosis. Ann Thorac Surg 2013;96:1259-65.
18. Steffen RJ, Soltesz EG, Miracle K, Lee S, Mountis M, Moazami N. Incidence of increases in pump power utilization and associated clinical outcomes with an axial continuous flow ventricular assist device. J Heart Lung Transplant 2013 September 25 (Epub ahead of print).

Copyright © 2013 Massachusetts Medical Society.