Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work

STUDY DEVICE

The HeartMate 3 Left Ventricular Assist Device (HM3 LVAD) is a centrifugal, magnetically levitated pump. It is intended for implantation in the patient's thorax. This centrifugal-flow pump was designed to reduce shear stress on blood elements by incorporation of a magnetically levitated rotor and wide blood-flow paths. The pump automatically ramps rotor speeds to create an artificial pulse to modulate flow to mimic native contractility and discourage stasis and reduce the risk of thrombogenesis. The pump has been approved for long-term use in the United States since 2018.

STUDY ORGANIZATION AND CONDUCT

Study Steering Committee

Mandeep R. Mehra, MBBS, MSc, FRCP (Chair)	Brigham and Women's Hospital, Boston, MA
Ivan Netuka, MD, Ph.D.	IKEM, Prague, Czech Republic
Nir Uriel, MD, MSc	New York Presbyterian—Columbia University Medical Center, New York, NY
Jason Katz, MD	Duke University Hospital, Durham, NC
Francis Pagani, MD, Ph.D.	University of Michigan, Ann Arbor, MI
Ulrich Jorde, MD	Montefiore Medical Center, New York, NY
Finn Gustafsson, MD, Ph.D.	Rigshospitalet, Copenhagen, Denmark
Jean Connors, MD	Brigham and Women's Hospital, Boston, MA

Clinical Events Committee (CEC)

Joseph Cleveland, MD (Chair)	University of Colorado, Denver, CO
Erin Coglianese, MD	Massachusetts General Hospital, Boston, MA
Gregory Egnaczyk, MD	The Christ Hospital, Cincinnati OH
Joshua Willey, MD	Columbia University, NY, NY

Data Safety Monitoring Board (DSMB)

William Hollman, MD (Chair)	University of Alabama at Birmingham, Birmingham, AL
Kenneth Bauer, MD	Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
Stuart Russell, MD	Duke University Hospital, Raleigh, NC
Daniel Heitjan, Ph.D.	Southern Methodist University; University of Texas Southwestern Medical Center, Dallas, TX

Study Sites

Below is a list of principal investigators of the 51 sites enrolling subjects to this study. Of the 51 sites enrolling subjects, 49 randomized subjects.

Principal Investigators	Research Coordinator	Site Name, Location
Jerry Estep Edward Soltesz (Current PI)	Barbara Gus	The Cleveland Clinic Foundation Cleveland, OH
Peter Ivak	Zuzana Tučanová	IKEM Prague Prague, Czech Republic
Jay Bhama Bryan Barrus John Ransom (Current PI)	Amy Bland	Baptist Health Medical Center Little Rock, AR
Jennifer Cowger	Kelsey Neaton	Henry Ford Hospital Detroit, MI
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Omar Saeed Daniel Goldstein (Current PI)	Magdalena Mamczur-Madry	Montefiore Medical Center - Moses Division Bronx, NY

Principal Investigators	Research Coordinator	Site Name, Location
Rebecca Cogswell	Julie Longman	University of Minnesota Medical Center Fairview, Minneapolis, MN
Samer Najjar Farooq Sheikh (Current PI)	Megan Fuller	Washington Hospital Center Washington, DC
Ashwin Ravichandran	Regina Margiotti	St. Vincent Hospital, Indianapolis, IN
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Eugene Chung	Mary Kreimer	Christ Hospital, Cincinnati, OH
Anita Phancao	Isabel Vital	Miami Transplant Institute- Jackson Memorial, Miami, FL
Jennifer Conway	Tara Pidborochynski	University of Alberta Hospital Edmonton, Canada
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Anelechi Anyanwu	Deniz Akkoc	Mount Sinai Hospital New York, NY
Anna Mara Scandroglio	Alessandro Ortalda	Ospedale San Raffaele Milano, Italy
Mary Keebler	Abbey Sung	University of Pittsburgh Medical Center, Pittsburgh, PA
Sriram Nathan	Isabella LeFebvre	Memorial Hermann Hospital Houston, TX
Craig Selzman	Ashley Elmer	University of Utah Hospital Salt Lake City, UT
Jeffrey Alexis Igor Gosev	Solomiya Rachynska	University of Rochester Medical Center, Rochester, NY
Nasir Sulemanjee	Don Lobacz	Aurora Medical Group Milwaukee, WI
Christopher Hayward	Emma Norris	St. Vincent's Hospital, Sydney Darlinghurst, Australia
David D'Alessandro	Tracy Crosby	Massachusetts General Hospital Boston, MA
William Hiesinger	Rachelle Villanueva	Stanford University Medical Center, Palo Alto, CA
Pavan Atluri	Kunal P Shah	Hospital of the University of Pennsylvania, Philadelphia, PA
Sern Lim	Annette Nilsson	Queen Elizabeth Hospital, Birmingham, United Kingdom

Principal Investigators	Research Coordinator	Site Name, Location
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John Entwistle	Linda Hosler	Thomas Jefferson University Hospital, Philadelphia, PA
Andreas Brieke	Emanuel Gebreab	University of Colorado Hospital Aurora, CO
Robert Adamson	Donna Small	Sharp Memorial Hospital San Diego, CA
David Dean	Kristi Picardi	Piedmont Heart Institute Atlanta, GA
Pierre Dos Santos	Philippe Prunier	Hopital Haut Leveque Pessac, France
Douglas Horstmanshof James Long	Dellia Dion	Integris Baptist Medical Center Oklahoma City, OK
Sanjeev Gulati	Krystal G Winkler	Carolinas Medical Center Charlotte, NC
Peter Eckman	Sarah Schwager	Minneapolis Heart Institute Minneapolis, MN
Jacob Abraham	Sarah Jackson	Providence Heart & Vascular Institute, Portland, OR
Clement Delmas	Solange Adjanor	CHU Rangueil Toulouse Toulouse, France
Antone Tatooles	Colleen Gallagher	Advocate Christ Medical Center Oak Lawn, IL
Scott Silvestry	James Duryea	Advent Health Orlando Orlando, FL†
David Kaye	Jia Tang	The Alfred Hospital Melbourne, Australia†

Note: Sites with two names have co-principal investigators (PIs). Current PIs are noted in cases where the previous PI has left, and previous PIs are also listed. †Enrolled but did not randomize patients.

Role of the Study Sponsor and Investigators

(a) **Trial Design**: The Steering Committee and Sponsor designed the ARIES HM3 trial with feedback from the US FDA.

(b) **Site Selection**: The Sponsor selected centers based on established site qualification procedures. Qualification visits were conducted to ensure that investigators were qualified by training, education and experience and had adequate resources, staffing and facilities to conduct the trial.

(c) **Patient Assessment, Enrollment, Site Supervision & Data Collection**: The Sponsor was responsible for training the clinical sites on patient eligibility assessment, enrollment procedures, and data collection requirements; once trained, site personnel were responsible for conducting these activities under supervision of the principal investigator. The steering committee provided supplemental training on equipoise within the study at predetermined investigator meetings.

(d) **Data Analysis**: The Sponsor was responsible for analyzing the study data per the pre-specified Statistical Analysis Plan (SAP) and an independent statistician was responsible to the Steering Committee for verifying the results of the primary end point, including sensitivity analyses, and major adverse events.

(e) **Manuscript Writing, Revision and Publication Decisions**: The manuscript writing, revision and decision to submit the paper for publication were driven by the Steering Committee members along with the authors; the manuscript was written by the first author, all versions fully controlled by him in collaboration with the other authors; the Sponsor assisted with data requests under the direction of the steering committee. The decision to submit the paper rested with the steering committee.

Eligibility Criteria

Inclusion Criteria

1. Subject will receive the HeartMate 3 per standard of care (SOC) in accordance with the approved indications for use in the country of implant.

2. Subject will receive the HeartMate 3 as their first durable VAD.

3. Subject must provide written informed consent prior to any clinical investigation related procedure.

4. In patients of childbearing capability, subject will not be currently pregnant or breastfeeding and on appropriate contraception.

Exclusion Criteria

1. Post-implant additional temporary or permanent mechanical circulatory support (MCS).

2. Post-implant Investigator mandated antiplatelet therapy for other conditions (including mandated presence or absence of antiplatelet agent).

3. Patients who are nil per os (NPO) post-implant through day 7.

4. Subjects with a known allergy to acetylsalicylic acid (aspirin).

5. Participation in any other clinical investigation(s) involving an MCS device, or interventional investigation(s) LIKELY to confound study results or affect study outcome.

6. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

Adverse Event Definitions

Serious Adverse Events

If an adverse event meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

   1. a life-threatening illness or injury, or
   2. a permanent impairment of a body structure or a body function, or
   3. in-patient hospitalization or prolongation of existing hospitalization, or
   4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
   5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

Note: All adverse events, independent of seriousness, are included in the primary analyses. Instances limited to serious adverse events are limited to eTable 4.

1. Bleeding

VAD-IMPLANT-RELATED BLEEDING:

VAD-implantation-related bleeding (includes concomitant cardiac or non-cardiac surgical procedures) that requires:

- Reoperation after closure of incision or incisions used to implant the VAD for the purpose of controlling bleeding
- If ≥ 50 kg, ≥ 4U packed red blood cells (PRBC) within any 48-hour period during first 7 days post implant.
- If < 50 kg, ≥ 20 cc/kg packed red blood cells (PRBC) within any 24-hour period during first 7 days post implant.
- Or any transfusion from 8-14 days

or exhibits:

- Chest tube output > 2L within a 24-h period

MODERATE:

Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for a Severe or Surgical Bleeding Definitions but meets the following criteria:

- requiring nonsurgical, medical intervention by a healthcare professional;
  and
- leading to hospitalization or increased level of care (unscheduled clinical visit or use of emergency services).

SEVERE:

- Type A: (Meets any of the below)
  - Overt bleeding plus hemoglobin drops of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding
- Type B: (Meets any of the below)
  - Overt bleeding plus hemoglobin drops 5 g/dL or greater (provided hemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental, nasal, skin, or hemorrhoid)
  - Hypotension attributable to bleeding and requiring intravenous vasoactive agents for hemodynamic support
  - Intracranial Hemorrhage that does not meet the definition of hemorrhagic stroke
- Type C1: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- Type C2: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

2. Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g., diminished VAD flow, oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:

- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

3. Device Thrombosis

Device thrombosis is an event in which the pump or its conduits contain a thrombus that results in or could potentially induce circulatory failure. Suspected device thrombus is an event in which clinical or pump parameters suggest thrombus on the blood

contacting components of the pump, cannula, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:

- Presence of hemolysis
- Worsening heart failure or inability to decompress the left ventricle
- Abnormal pump parameters

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:

- Treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
- Pump replacement
- Pump explantation
- Urgent transplantation (UNOS status 1A)
- Stroke
- Arterial non-CNS thromboembolism
- Death

Confirmed device thrombus is an event in which thrombus is confirmed by the Sponsor's returned product analysis to be found within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can also be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

4. Hemolysis*

A plasma-free hemoglobin value that is greater than 40 mg/dl, concomitant with a rise in serum LDH above three times the upper limit of normal, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant.

*Hemolysis in the presence of worsening heart failure or inability to decompress the left ventricle or abnormal pump parameters should be reported as suspected device thrombosis, not as hemolysis

5. Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater

than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

6. Hypertension

Blood pressure elevation of a mean arterial pressure greater than 110 mm Hg, despite anti-hypertensive therapy.

7. Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pump Infection

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection

Infection of blood-contacting surfaces of the LVAD documented by positive site culture.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

8. Myocardial Infarction

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction

The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

Non-Perioperative Myocardial Infarction

The presence at > 7 days post-implant of two of the following three criteria:

- Chest pain, which is characteristic of myocardial ischemia,
- ECG with a pattern or changes consistent with a myocardial infarction, and
- Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

9. Neurologic Dysfunction

Any new, temporary or permanent, focal or global neurological deficit, ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as defined below:

- Transient ischemic attack*, defined as an acute transient neurological deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI)
- Ischemic Stroke*: a new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit, or a clinically covert ischemic stroke seen by surveillance imaging, without clinical findings of stroke or at the time of event recognition.
- Hemorrhagic Stroke*: a new acute neurologic deficit attributable to intracranial hemorrhage (ICH), or a clinically covert ICH seen by surveillance imaging, without clinical findings of ICH at the time of event recognition.
- Encephalopathy: Acute new encephalopathy** due to hypoxic-ischemic injury (HIE), or other causes, manifest as clinically evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic

evaluation to be attributable to acute global or focal hypoxic, or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.

- Seizure of any kind
- Other neurological event (non-CNS event): examples include neuro muscular dysfunction or critical care neuropathy

*Modified Rankin Score (MRS) will be used to classify the severity of all strokes. MRS will be captured at baseline, the time of stroke, and at 60 days post-stroke. MRS will be determined by an independent assessor, defined as an independent, trained, and certified clinician. Severity will be defined as disabling (MRS > 3) or nondisabling (MRS ≤ 3). MRS is defined below.

**Acute encephalopathy is a sign or symptom of some underlying cerebral disorder and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

10. Renal Dysfunction

Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction

Abnormal kidney function requiring dialysis (including hemofiltration) in Subjects who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL sustained for over 48 hours.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

11. Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for reoperation or temporary intubation for diagnostic or therapeutic procedures.

12. Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction requiring RVAD implantation or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 14 days at any time after LVAD implantation. To compare to prior studies, this study will begin collecting details of events involving nitric oxide or inotropic therapy for a duration of more than 7 days, whereas reportable right heart failure will begin at 14 days of therapy.

To further stratify right heart failure (RHF) events, the following criteria will be used to identify a sub-category of persistent, clinically significant RHF events:

- Death due to right heart failure or
- RVAD or
- Hospitalization with primary diagnosis of decompensated heart failure with evidence of right heart support or
- Post-discharge inotropes or
- > 30 consecutive days on inotropes.

13. Arterial Peripheral Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) Standard clinical and laboratory testing
2) Operative findings
3) Autopsy findings

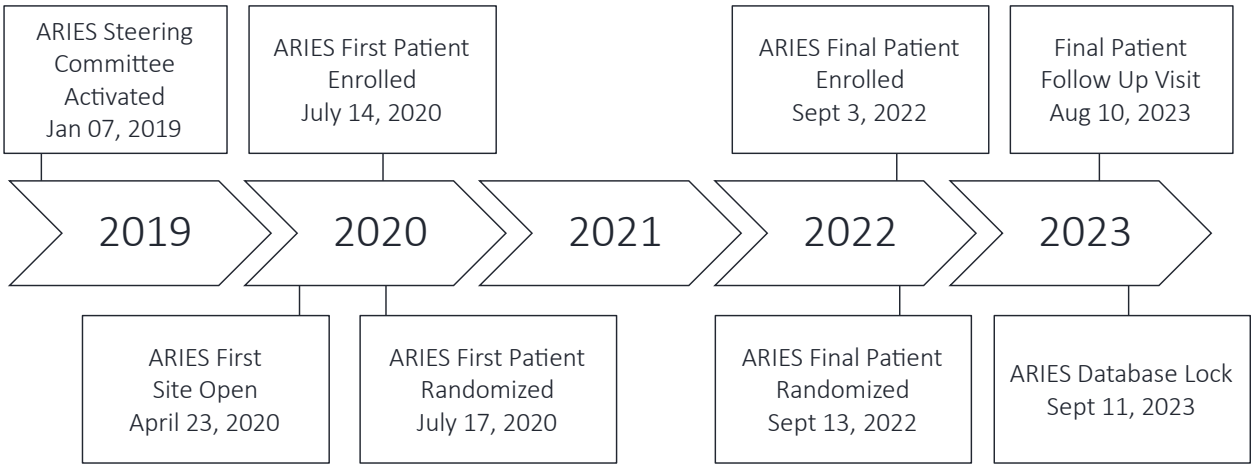
This definition excludes neurological events.

14. Venous Thromboembolism Event

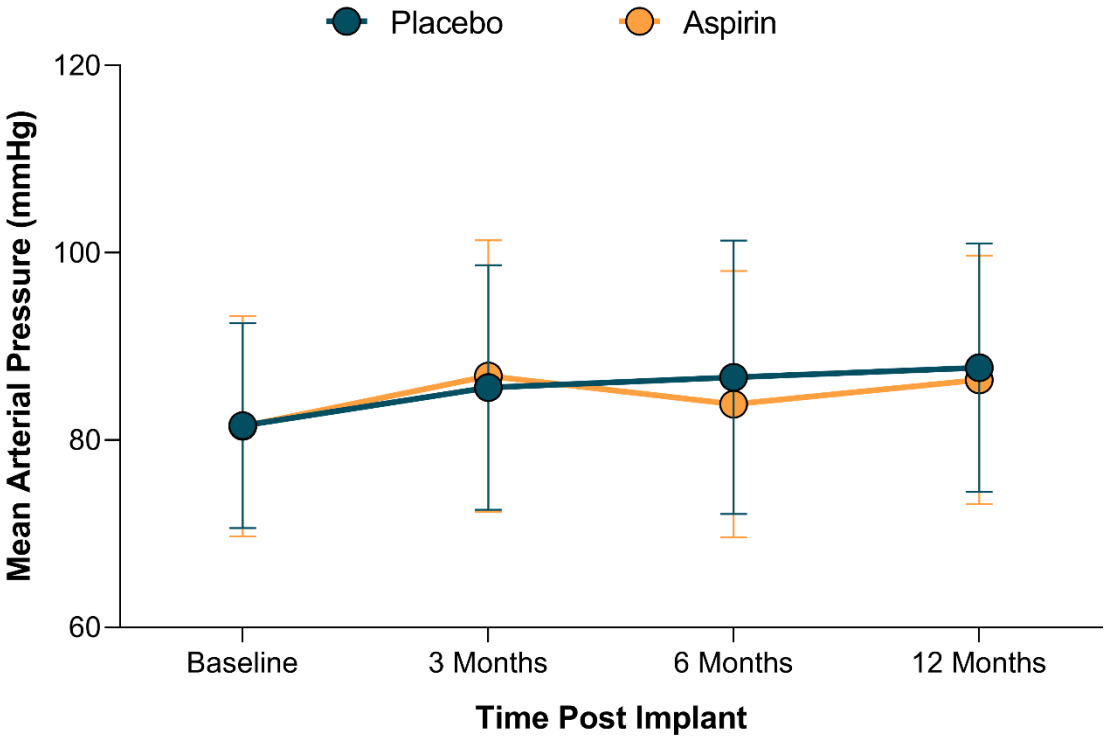
Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

SUPPLEMENTARY FIGURES

eFigure 1. Timeline of the ARIES HM3 Trial Conduct

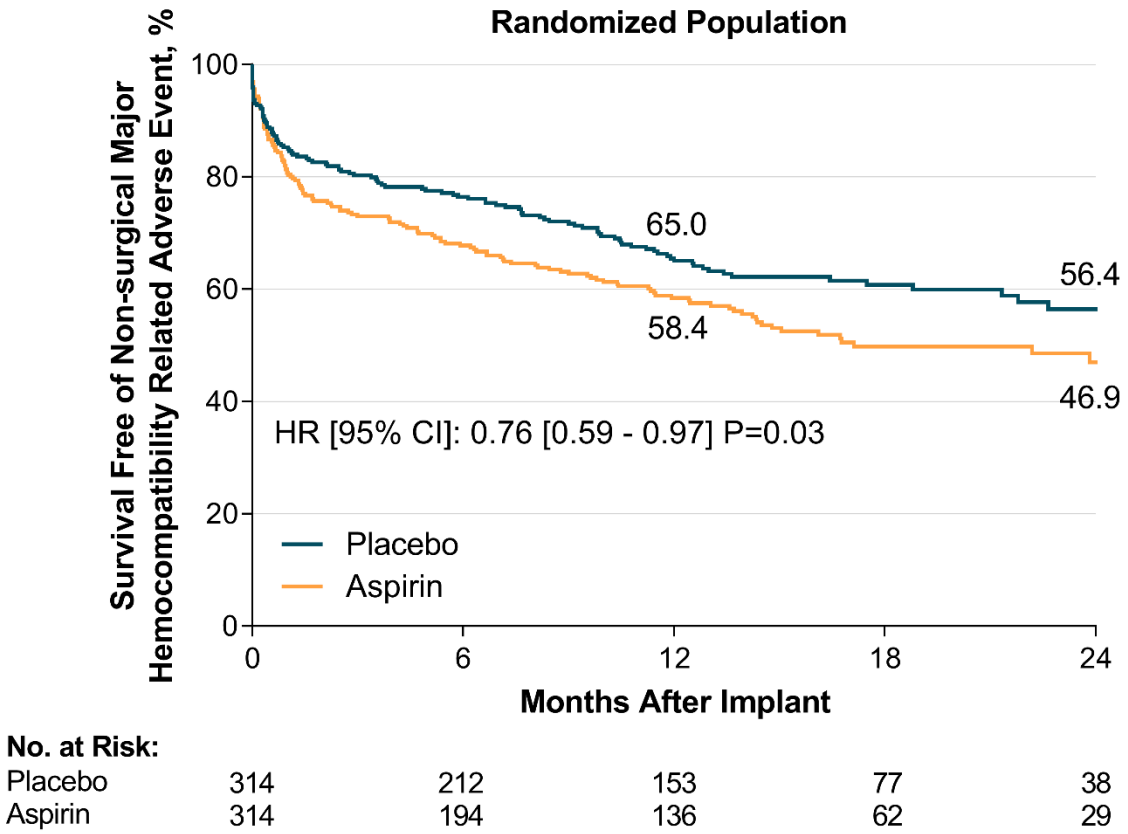


eFigure 2. Mean Arterial Pressure (MAP) over Study Follow-up Period (Principal Analysis Population)



No. :				
Placebo	296	281	252	231
Aspirin	293	266	246	221

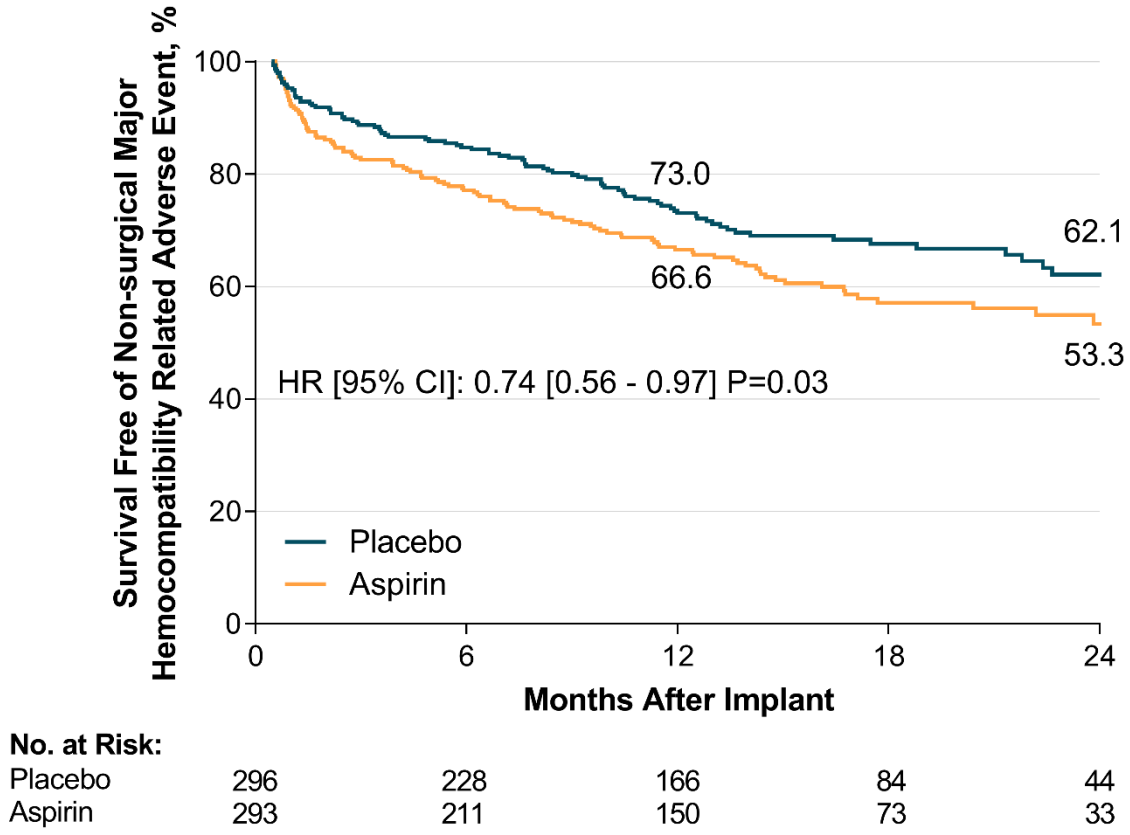
eFigure 3. Primary End Point Sensitivity Analysis (Randomized Population)



No. at Risk:					
Placebo	314	212	153	77	38
Aspirin	314	194	136	62	29

The randomized population includes all randomized patients and includes all events, including both surgical events (within 14-days of LVAD implant) and events occurring after transition to open label.

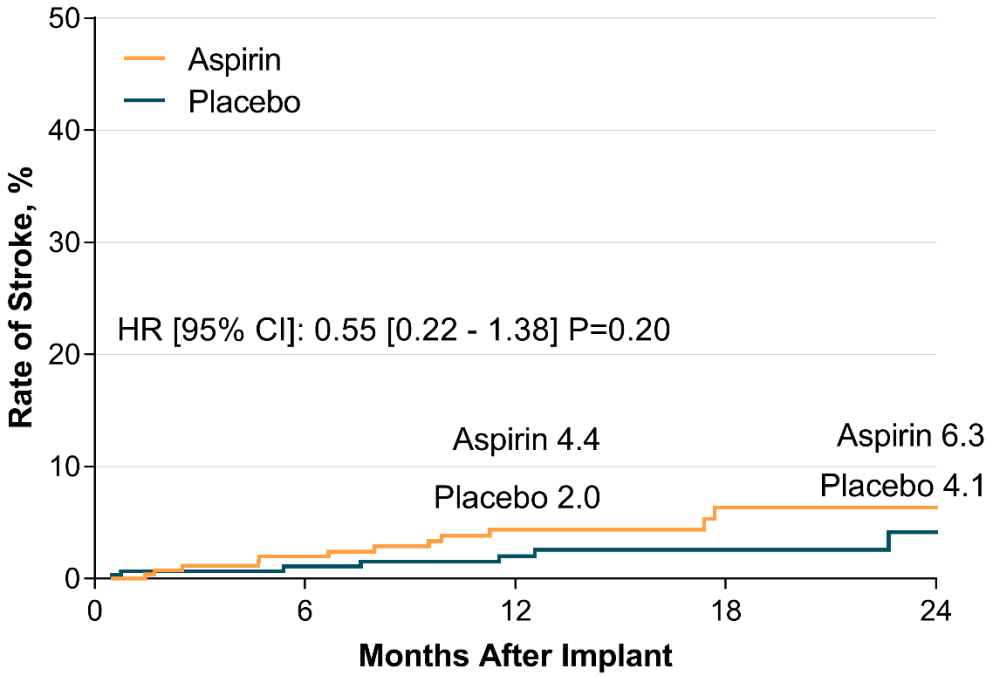
eFigure 4. Primary End Point Sensitivity Analysis Including Follow Up Beyond Transition to Open Label (Principal Analysis Population)



No. at Risk:					
Placebo	296	228	166	84	44
Aspirin	293	211	150	73	33

This sensitivity analysis includes follow up of patients beyond transition to open label. Transition to open label is when administration of the blinded treatment arm medication (placebo or aspirin) ceases and a regimen prescribed by their doctor is instituted which contains the known presence or absence of aspirin.

eFigure 5. Rate of Stroke (Principal Analysis Population)

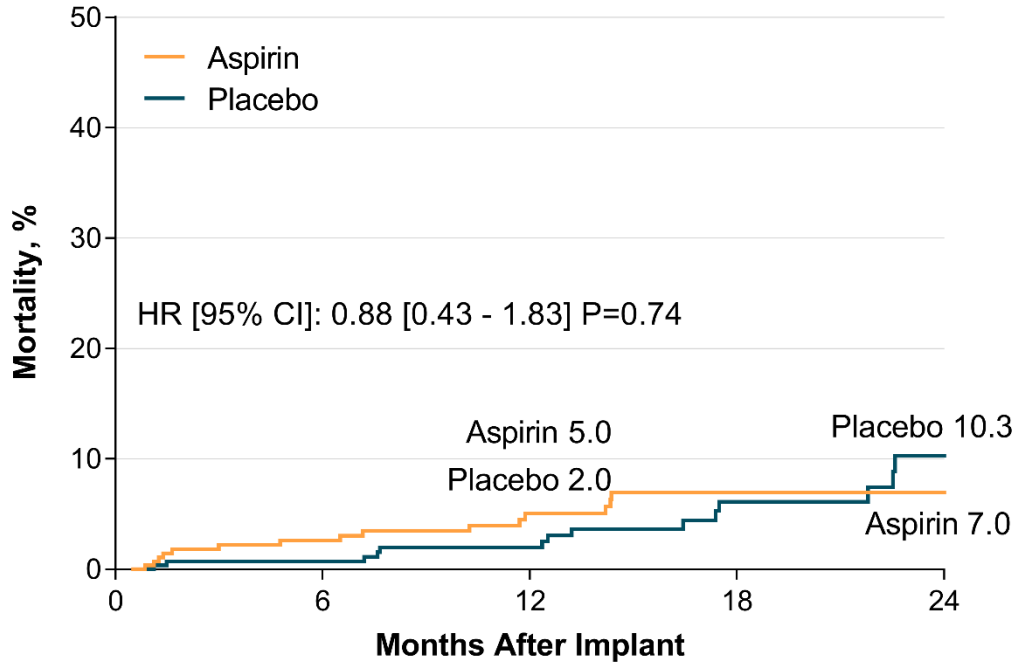


No. at Risk:

Placebo	296	240	186	101	52
Aspirin	293	227	170	89	46

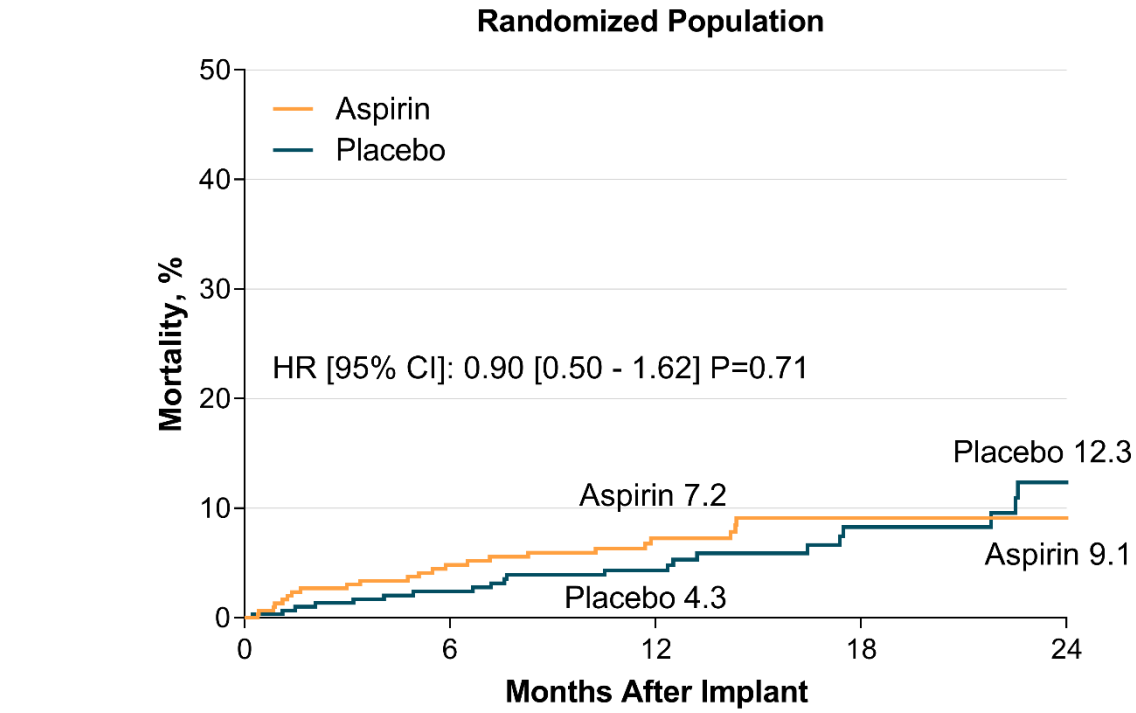
Stroke includes ischemic, hemorrhagic, and ischemic with hemorrhagic conversion.

eFigure 6. Mortality Rate (Principal Analysis Population)



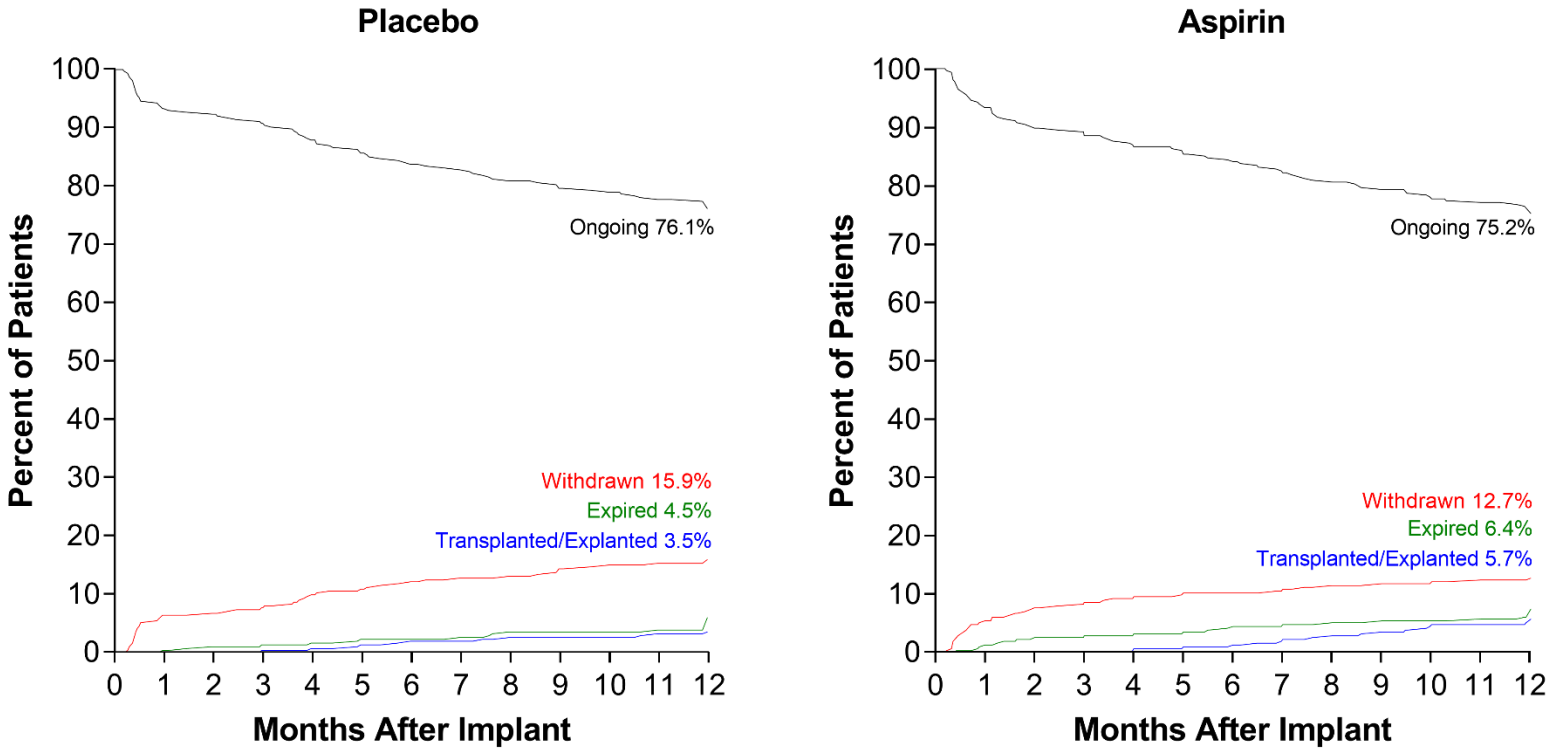
No. at Risk:					
Placebo	296	241	188	103	53
Aspirin	293	230	174	93	48

eFigure 7. Mortality Rate (Randomized Population)

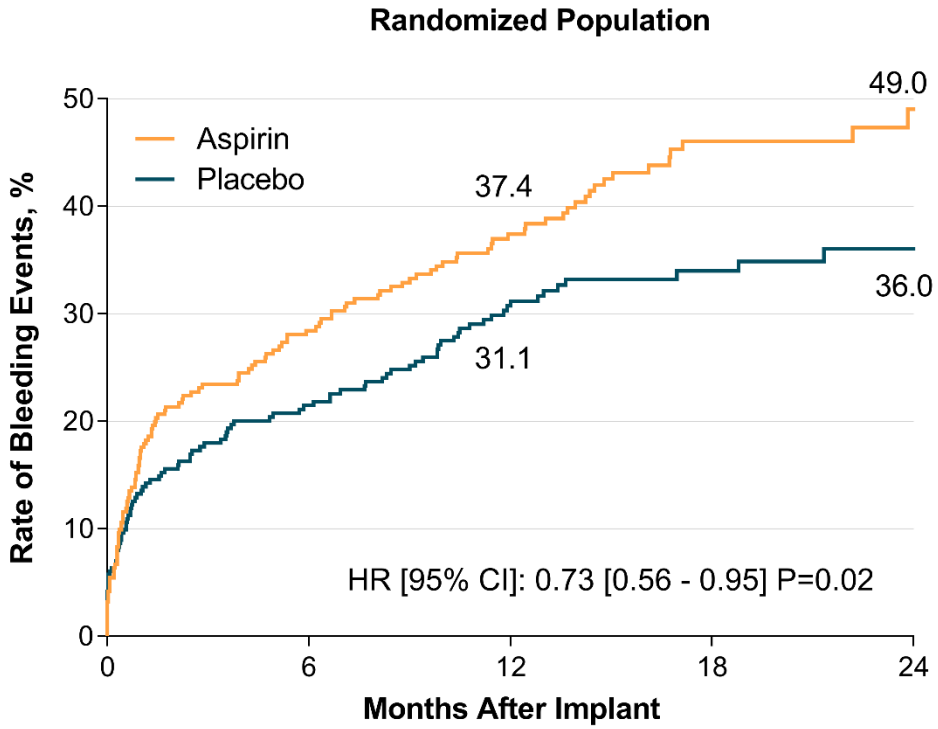


No. at Risk:					
Placebo	314	263	203	103	53
Aspirin	314	264	196	94	48

eFigure 8. Competing Outcomes (Randomized Population)

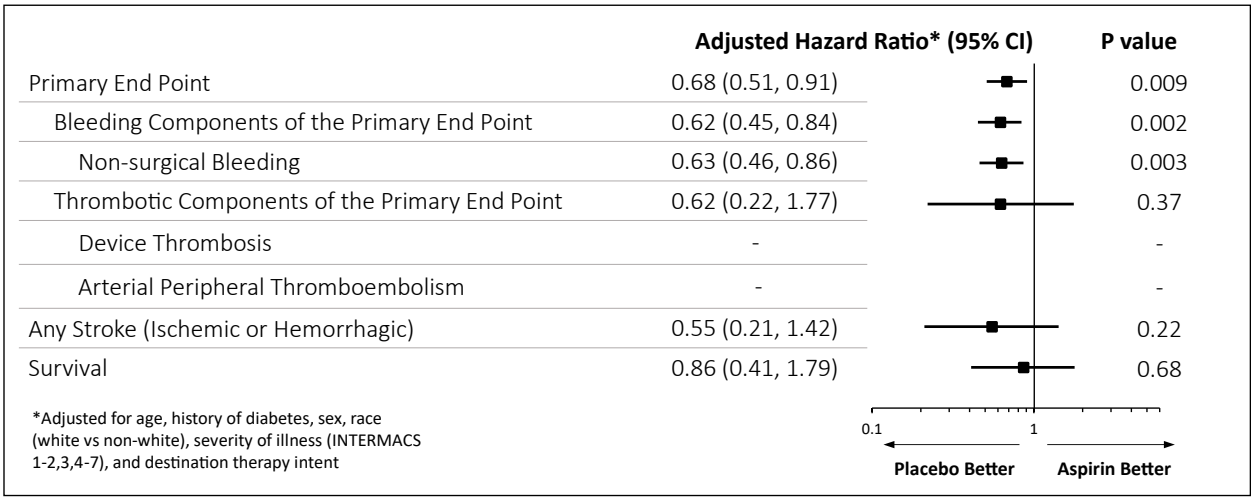


eFigure 9. Rate of Bleeding Events (Randomized Population)



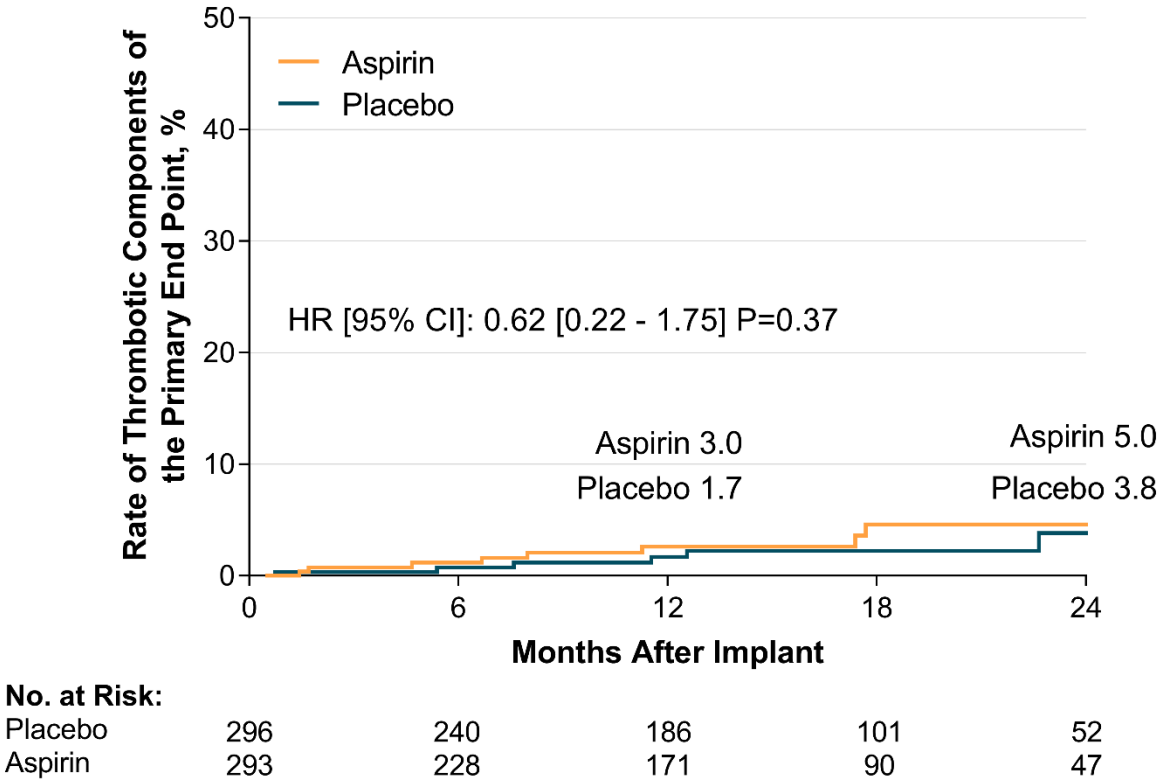
No. at Risk:					
Placebo	314	216	158	79	39
Aspirin	314	197	139	63	30

eFigure 10. Adjusted Hazard Models (Principal Analysis Population)



Cox proportional hazard models were constructed to develop hazard ratios which were adjusted by clinical factors known to impact hemocompatibility related adverse events, specifically age, history of diabetes, sex, race, severity of illness, and destination therapy. Adjusted hazard ratios were all consistent with the primary analyses.

eFigure 11. Rate of Thrombotic Components of the Primary End Point (Principal Analysis Population)

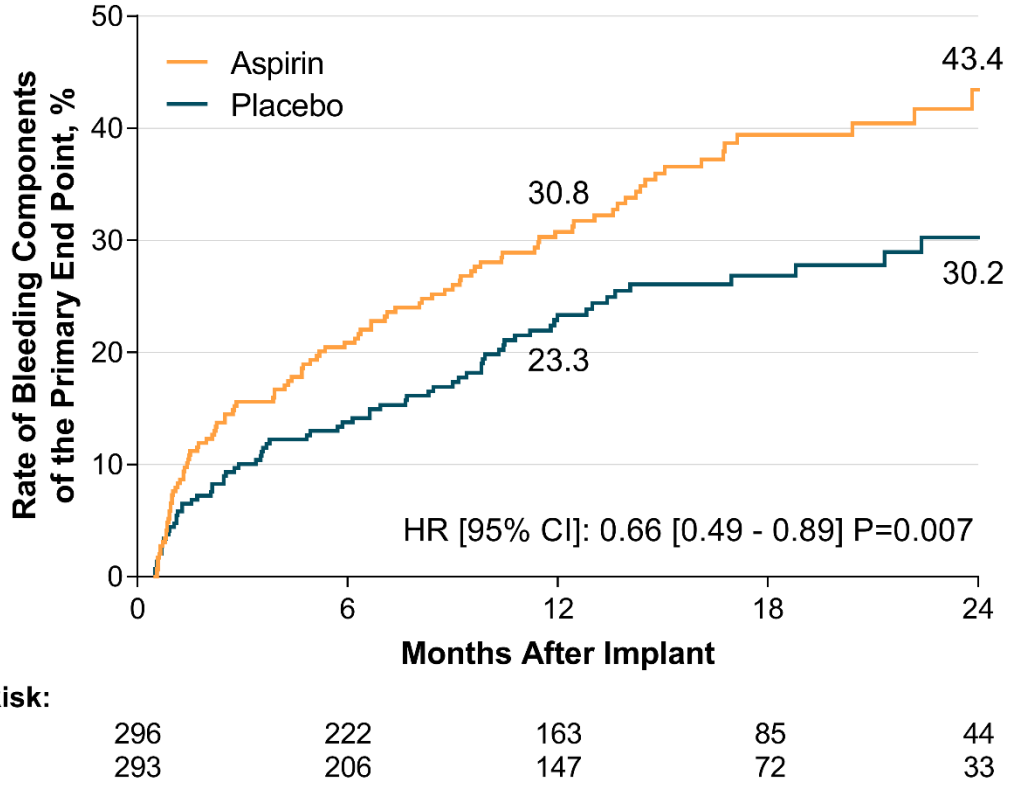


No. at Risk:

Placebo	296	240	186	101	52
Aspirin	293	228	171	90	47

Thrombotic components of the primary end point include ischemic stroke, ischemic stroke with hemorrhagic conversion, pump thrombosis, and arterial peripheral thromboembolism.

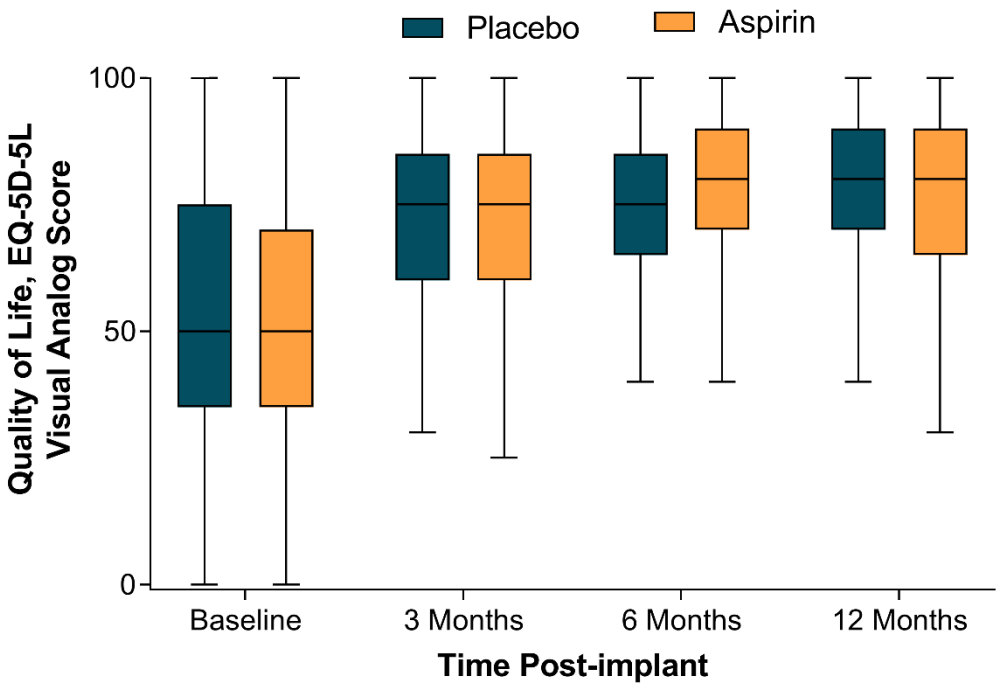
eFigure 12. Rate of Bleeding Components of the Primary End Point (Principal Analysis Population)



No. at Risk:					
Placebo	296	222	163	85	44
Aspirin	293	206	147	72	33

Bleeding components of the primary end point, which include hemorrhagic stroke, ischemic stroke with hemorrhagic conversion, and non-surgical bleeding, were lower in the placebo arm than the in the aspirin arm (P=0.007 by log-rank).

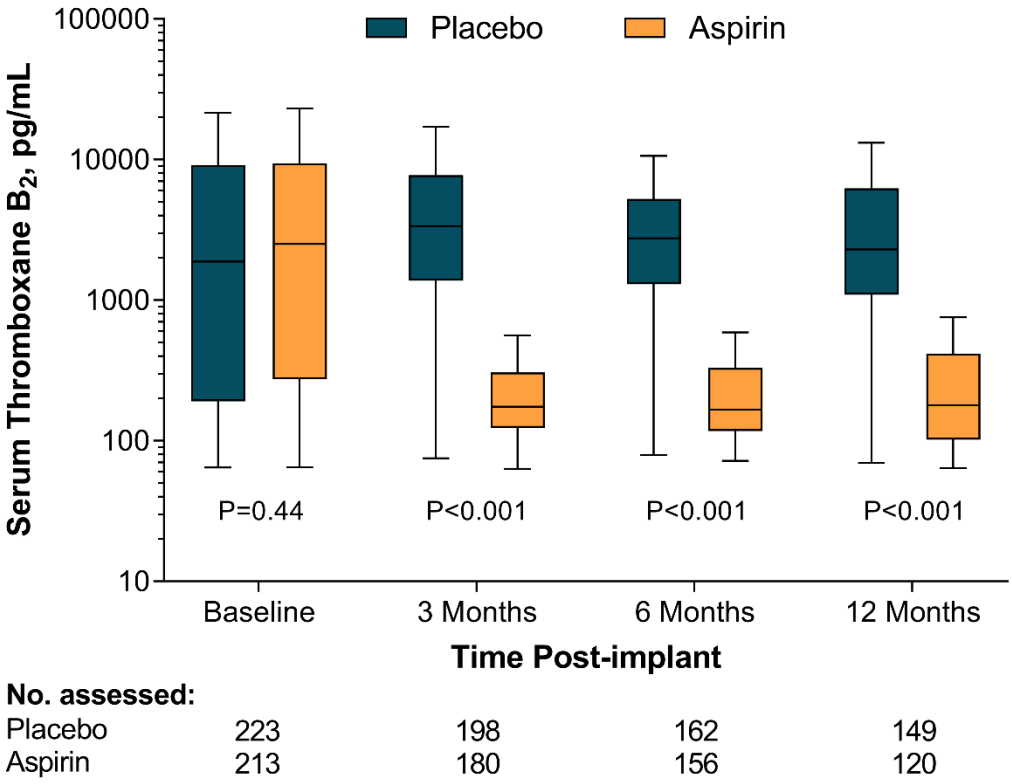
eFigure 13. Quality of Life (Principal Analysis Population)



No. assessed:				
Placebo	294	272	247	229
Aspirin	290	260	244	223

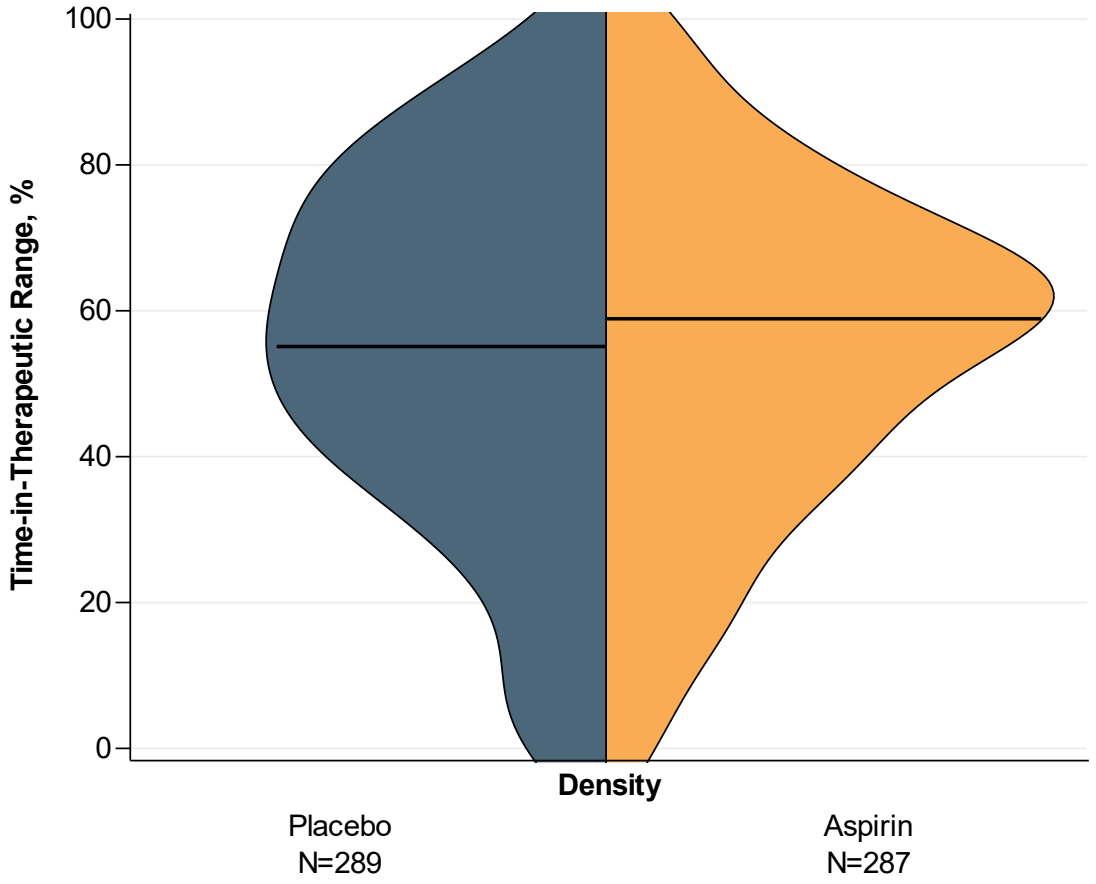
Quality of life was measured by the EuroQOL 5 dimension, 5 levels, visual analog scale. Response rates were high and similar between the two groups, therefore imputations for missing values were not performed.

eFigure 14. Aspirin response (US-based Patients Only)



Aspirin effect is shown biochemically by measurement of serum thromboxane B_2 levels (3A). In patients randomized to aspirin, reduced thromboxane B_2 levels are shown, which indicate aspirin effect and no change was seen in placebo patients. Patients transitioned to open label are excluded from thromboxane B_2 analysis.

eFigure 15. Vitamin-K Antagonist Management (Principal Analysis Population)



The VKA use, as assessed by TTR, was similar between placebo (55.1% (Q1 39.5, Q3 73.9)) and aspirin (58.9% (Q1 39.5, Q3 69.0)) groups. VKA therapy was managed to patient-specific international normalized ratio (INR) target ranges (INR 2-3) by serial measurement of INR over time. VKA dose adjustments were performed per site-specific protocols. Serial INR measurements are summarized as time-in-therapeutic range (3B; TTR), defined as the number of person-days within the patient-specific therapeutic range divided by the total number of person-days on VKA, for both arms. There was no difference between the two arms in management of VKA regimens (P=0.93). TTR is shown as a density plot with the horizontal line indicating the median.

SUPPLEMENTARY TABLES

eTable 1. Reasons for Patient Withdrawal (Principal Analysis Population)

Reason for Withdrawal	Placebo Arm (N =296)	Aspirin Arm (N =293)
Withdrawn without Primary Endpoint Event before 12-Months		
Subject and/or Family Request Withdrew Consent	12	9
Subject Never Started Treatment Arm Medication	1	1
Subject Non-Compliance	6	7
Subject Participation Terminated by Investigator	2	1
Other	4	2
Total	25	20
Withdrawn prior to Completing 12-Months[a]		
Subject and/or Family Request Withdrew Consent	4	2
Subject Non-Compliance	1	2
Subject Participation Terminated by Investigator	3	1
Other	2	2
Total	10[b]	7[b]
Withdrawn after Completing 12-Months		
Subject and/or Family Request Withdrew Consent	5	1
Subject Non-Compliance	0	2
Subject Participation Terminated by Investigator	4	2
Other	2	1
Total	11	6

[a]Patients who experienced a primary endpoint event, or transition to open label prior to withdrawal are accounted allocated to primary endpoint failures and successes respectively in the binary primary end point calculation.

[b]There was one subject in each the placebo and aspirin arms of the study that were transitioned to open label prior to their withdrawal. Within the consort diagram (Figure 1), these patients are accounted as "Transitioned to open label prior to 12 months without a primary endpoint event," the status that informs their allocation for the primary end point analysis.

eTable 2. Transition to open label within 12-months (Principal Analysis population)

	no. **Placebo N=296**	no. **Aspirin N=293**
Transition to open Label	39	52
Transition to open label after experiencing primary end point event[a]	25	37
Transition to open label without experiencing primary end point event[b]	14	15

[a]Patients who transition to open label after experiencing a primary end point event contributed to the primary end point calculation as a failure.

[b]Patients who transition to open label without experiencing a primary end point event contributed to the primary end point calculation as a success. In most cases, aspirin was avoided after transition to open, 61.5% in placebo and 75% in the aspirin group.

eTable 3. Reasons for transition to open label within 12-months (Principal Analysis Population)

	no. **Placebo N=39**	no. **Aspirin N=52**
Due to adverse event	33	42
Bleeding	21	30
Neurologic Dysfunction	1	5
Hemolysis	1	0
Respiratory Failure	3	2
Other Adverse Event	7	5
Patient non-compliance	3	8
Other	3	2

eTable 4. Additional Laboratory Values (Principal Analysis Population)

Additional laboratory values	Placebo Arm (N =296)	Aspirin Arm (N =293)
Laboratory values		
Serum sodium – mmol/liter	135 (133, 138) [294][a]	136 (132, 138) [292][a]
Blood urea nitrogen – mg/dL	25 (18, 35)	25 (18, 37)
Serum creatinine – mg/dl	1.27 (0.96, 1.65)	1.30 (1.00, 1.61)
Aspartate transaminase – U/L	25 (19, 35)	26 (20, 36) [290][a]
Alanine aminotransferase – U/L	25 (17, 44)	27 (18, 41) [290][a]
Lactate dehydrogenase – U/L	261 (201, 366) [216][a]	266 (216, 342) [230][a]

[a]In instances where data may be missing for some subset of patients, total numbers are provided as [N] to describe the population where the specific data point is available.

eTable 5. Major Adverse Events during the First 14-days Post-LVAD Implant (Randomized Population)

	Events no.	Subjects no. (%)	Events no.	Subjects no. (%)
Major adverse events during the first 14-days post-LVAD implant[a]	**Placebo (n=314)**		**Aspirin (n=314)**	
Arterial peripheral thromboembolism	5	4 (1.3)	2	2 (0.6)
Bleeding	35	30 (9.6)	37	36 (11.5)
VAD-implant related (Surgical)	32	28 (8.9)	31	31 (9.9)
Moderate[b]	1	1 (0.3)	5	5 (1.6)
Severe[c]	2	2 (0.6)	1	1 (0.3)
Stroke	2	2 (0.6)	4	4 (1.3)
Ischemic stroke with hemorrhagic conversion	0	0 (0.0)	1	1 (0.3)
Ischemic stroke	2	2 (0.6)	3	3 (1.0)
Total	**42**	**35 (11.1)**	**43**	**41 (13.1)**

[a]Major adverse events occurring within the first 14-days post implant were not included in the primary end point analysis but are included in the randomized population sensitivity analysis.

[b]There were 5 moderate bleeding events (4 epistaxis, 1 gastrointestinal bleed) that do not meet the VAD implant related bleeding definition but are conservatively classified as moderate bleeding events by the clinical events committee. The sixth moderate bleeding event is a pre-existing, recurrent gastrointestinal bleed, and therefore was not attributed directly to the VAD implant.

[c]There were 3 severe bleeding events (gastrointestinal bleeding n=2, worsening of pre-existing subdural hematoma n=1) that did not meet the VAD implant related bleeding definition.

eTable 6. Sensitivity Analyses of Primary End Point

Sensitivity analyses for the primary end point	Success Rate (Population)		Difference (Lower 97.5% CL)	P-value
	Placebo	Aspirin		
Randomized Population Analysis[a]	65.0 (n=314)	58.4 (n=314)	6.6 (-1.3)	<0.001
Worst-case allocation of withdrawals in the Primary Analysis population[b]	67.9 (n=296)	70.3 (n=293)	-2.4 (-9.8)	0.02
Transition to open label analysis in the Primary Analysis population[c]	72.3 (n=271)	66.2 (n=272)	6.2 (-1.6)	<0.001

Impact of the Stratification of Randomization by Site on the Primary Endpoint[e]

Analysis Method	Difference of Proportions, %	Lower 97.5% Confidence Limit, %
Primary Endpoint Farrington-Manning (Unadjusted)	6.0	-1.6
GLM (Adjusted by site)	6.2	-2.2
GLM (Adjusted by site, grouping small sites)	6.1	-2.2

[a]Randomized population includes all patients randomized within the study, n=314 in each arm, and all major hemocompatibility related adverse events, including VAD implant related bleeding. Time-to-event analysis with testing for non-inferiority against a margin of 10% performed using the Com-Nougue method.

[b]Worst-case scenario allocation of withdrawals in the Principal Analysis population was performed for patients who were withdrawn without a prior primary end point event, specifically all placebo patients are counted as failures whereas aspirin patients are included as successfully meeting the primary end point.

[c]Transition to open label is when administration of the blinded treatment arm medication (placebo or aspirin) ceases and a regimen prescribed by their doctor is instituted which contains the known presence or absence of aspirin.

[e]The impact of the stratification of randomization by site on the primary endpoint was assessed by Generalized Linearized Model (GLM) using binary distribution and identity link function for difference of proportions. Adjustments were made by site using all sites as well as by grouping of small sites.

eTable 7. Adjudicated Causes of Death (Principal Analysis population)

Adjudicated Cause of Death	No. (%)	
	Aspirin Free (N=296)	**Aspirin-Based (n=293)**
Total Deaths	**21 (7.1)**	**22 (7.5)**
Hemocompatibility Related	5 (1.7)	3 (1.0)
Bleeding	1 (0.3)	-
Hemorrhagic Stroke	1 (0.3)	-
Intracranial Hemorrhage	1 (0.3)	2 (0.7)
Ischemic Stroke with Hemorrhagic Conversion	1 (0.3)	1 (0.3)
Thrombo-embolic Cerebral and Mesenteric Ischemia with Shock	1 (0.3)	
Non-Hemocompatibility Related	11 (3.7)	12 (4.1)
COVID-19 Pneumonia	1 (0.3)	-
Driveline Exit Site Infection	1 (0.3)	-
Encephalopathy	1 (0.3)	-
Infection	1 (0.3)	1 (0.3)
Intestinal Ischemia	-	1 (0.3)
LVAD Disconnect	1 (0.3)	-
LVAD Outflow Graft Anastomotic Dehiscence	-	1 (0.3)
Multi-organ failure	-	1 (0.3)
Right Heart Failure	2 (0.7)	3 (1.0)
Sepsis	3 (1.0)	4 (1.4)
Shock	-	1 (0.3)
Suicide	1 (0.3)	
Inconclusive for Hemocompatibility Relatedness	5 (1.7)	7 (2.4)
Cardiac Arrest	-	1 (0.3)
Multi-organ failure		1 (0.3)
Unknown	5 (1.7)	5 (1.7)

eTable 8. Other Serious Adverse Events[a] (Principal Analysis Population)

Serious Adverse Events	Events no.	Subjects no. (%)	Events no.	Subjects no. (%)
	Placebo (n=296)		Aspirin (n=293)	
Cardiovascular Events				
Cardiac Arrhythmia[b]	31	27 (9.1)	46	26 (8.9)
Atrial Fibrillationc	28	27 (9.1)	19	16 (5.5)
Right Heart Failure	27	22 (7.4)	18	15 (5.1)
Hypertension	13	9 (3.0)	10	10 (3.4)
Major Infection	260	127 (42.9)	244	136 (46.4)
Neurologic Dysfunction other than stroke				
Transient Ischemic Attack	2	2 (0.7)	5	5 (1.7)
Encephalopathy	12	12 (4.1)	5	5 (1.7)
Seizure	2	2 (0.7)	6	5 (1.7)
Other	8	8 (2.7)	11	8 (2.7)
Renal Dysfunction	26	21 (7.1)	8	7 (2.4)
Hepatic Dysfunction	9	9 (3.0)	5	4 (1.4)
Respiratory Failure	28	25 (8.4)	23	17 (5.8)
Hemolysis	2	2 (0.7)	1	1 (0.3)
Venous Thromboembolism	5	5 (1.7)	6	6 (2.0)

[a]Serious adverse events include those that: a)led to a death, b) led to a serious deterioration in health of the subject, that either resulted in: a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, c) resulted in chronic disease or d) led to fetal distress, fetal death or a congenital abnormality or birth defect. **Note:** A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE. All adverse events, irrespective of seriousness, in the primary analyses of the study, including the primary end point and major adverse events analysis.

[b]Requires clinical compromise. Includes both ventricular and supraventricular arrhythmias.

[c]Includes both with and without clinical compromise.

eTable 9. Hemocompatibility Score (Randomized Population)

	No. (%)	Score	No. (%)	Score	P-Value
	Placebo (N= 314)		Aspirin (N= 314)		
Patients with No Events – Total Score 0	**225 (71.7)**	**-**	**198 (63.1)**	-	0.03
Tier I (Mild) – 1 point each					
<=2 gastrointestinal or other bleeding episodes (>30 days postimplant)	59 (18.8)	59	86 (27.4)	86	
Suspected pump thrombosis (successfully medically treated)	-	-	-	-	
Non-stroke-related neurological events (hemocompatibility etiology or inconclusive)	8 (2.6)	8	10 (3.2)	12	
Arterial thromboembolism not resulting in organ loss	5 (1.6)	6	2 (0.6)	2	
Tier II (Moderate) – 2 points each					
>2 gastrointestinal or other bleeding	8 (2.6)	16	8 (2.6)	16	
Nondisabling stroke (hemorrhagic or ischemic)	7 (2.2)	14	13 (4.1)	28	
Tier IIIA (Moderate to Severe)					
Arterial thromboembolism resulting in organ loss	-	-	-	-	
Pump malfunction attributable to pump thrombosis leading to reoperation for removal or replacement	-	-	-	-	
Tier IIIB (Severe) - 4 points each					
Disabling stroke	4 (1.3)	16	4 (1.3)	16	
Death attributable to a hemocompatibility etiology or inconclusive (unknown or multiple causes)	11 (3.5)	44	11 (3.5)	44	
Total	89 (28.3)	163	116 (36.9)	204	

eTable 10. Post-discharge Hospitalizations (Principal Analysis Population)

Post-Discharge Hospitalization[a] Reasons	No. (%)[b] N=279	Events per 100 pt-yrs (no. events)	No. (%)b N=281	Events per 100 pt-yrs (no events)	Relative Risk (95% CI) ‡	p-Value
	Placebo (N= 279)		Aspirin (N= 281)			
Hemocompatibility Related	38 (13.6)	14.7 (51)	72 (25.6)	28.4 (95)	0.52 (0.37,0.73)	<0.001
Major Hemocompatibility Related Hospitalizations	37 (13.3)	14.4 (50)	67 (23.8)	26.6 (89)	0.54 (0.38,0.77)	<0.001
Bleeding	35 (12.5)	13.6 (47)	62 (22.1)	23.9 (80)	0.57 (0.40,0.81)	0.002
Severe Bleeding	27 (9.7)	9.5 (33)	48 (17.1)	17.7 (59)	0.54 (0.35,0.83)	0.005
Moderate Bleeding	12 (4.3)	4.0 (14)	17 (6.0)	6.3 (21)	0.64 (0.33,1.27)	0.20
GI Bleeding	24 (8.6)	9.8 (34)	43 (15.3)	17.4 (58)	0.57 (0.37,0.86)	0.009
Stroke	3 (1.1)	0.9 (3)	8 (2.8)	2.7 (9)	0.32 (0.09,1.19)	0.09
Ischemic Stroke Without Hemorrhagic Conversion	3 (1.1)	0.9 (3)	5 (1.8)	1.8 (6)	0.48 (0.12,1.93)	0.30
Ischemic Stroke With Hemorrhagic Conversion	-	-	1 (0.4)	0.3 (1)	-	-
Hemorrhagic Stroke	-	-	2 (0.7)	0.6 (2)	-	-
Pump Thrombosis	-	-	-	-	-	-
Arterial Peripheral Thromboembolism	-	-	-	-	-	-
Myocardial Infarction	1 (0.4)	0.3 (1)	-	-	-	-
Venous Thromboembolism	-	-	1 (0.4)	0.3 (1)	-	-
Transient Ischemic Attack	-	-	2 (0.7)	0.6 (2)	-	-
Other Hemocompatibility Related AEs	1 (0.4)	0.3 (1)	3 (1.1)	0.9 (3)	0.32 (0.03,3.10)	0.33
Major Infection	65 (23.3)	33.8 (117)	77 (27.4)	36.2 (121)	0.93 (0.72,1.20)	0.60
Cardiovascular Related	60 (21.5)	32.7 (113)	56 (19.9)	32.9 (110)	0.99 (0.76,1.29)	0.95
Right Heart Failure	8 (2.9)	2.9 (10)	3 (1.1)	1.5 (5)	1.93 (0.66,5.65)	0.23

[a]Post-discharge refers to discharge from the index LVAD implant hospitalization. Only hemocompatibility related, infection and cardiovascular related hospitalizations are shown. Reasons not shown include hypertension, non-cardiovascular organ dysfunction, neurologic dysfunction other than stroke or TIA, and other.

[b]Only subjects who were discharged from their index hospitalization prior to transition to open label are included. ‡ < 1 indicates placebo better, > 1 indicates aspirin better.

eTable 11. Impact of Aspirin Avoidance on Cost using a Centers for Medicare and Medicaid Services basis in US Dollars (Principal Analysis Population, US-based patients)

	Total Estimated Cost for Bleeding Events (CMS Cost Basis, USD)	average cost per bleeding event	Average cost per study patient over the first-year post-implant	Cost of Bleeding Hospitalization for 1000 LVAD implants over the first-year post-implant
Aspirin N=244	$927,040	$13,836	$3,799	$3,799,344
Placebo N=247	$546,947	$13,674	$2,214	$2,214,362
Cost savings for Placebo	$380,092	$163	$1,585	$1,584,982

In this cost analysis, the published Gaussian model estimation using medicare average reimbursement from Mehra, et al,[1] was used to calculate an average cost for each bleeding hospitalization occurring within the first-year post-implant for US-based mITT patients in the ARIES HM3 study. Note that only US patients were used for this analysis. Costs are adjusted for inflation (2017-2023) using the US Bureau of Labor Statistics Medical Consumer Price Index.

[1] Mehra MR, Salerno C, Cleveland JC, et al. Healthcare Resource Use and Cost Implications in the MOMENTUM 3 Long-Term Outcome Study. *Circulation*. 2018;138:1923-1934.

eTable 12. Impact of Aspirin Avoidance on Hospitalizations Days Saved due to Non-surgical Bleeding (Principal Analysis Population, US-based patients)

	Hospitalization days due to bleeding events in first year post-implant	Hospitalization days for bleeding per 100 LVAD patients over a median follow up of 14 months
Aspirin N=244	624	256
Placebo N=474	331	134
Difference	293	122