Aspirin and Hemocompatibility Events with a Left Ventricular Assist Device in Advanced Heart Failure

The *ARIES-HM3* Clinical Trial

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On Behalf of the ARIES Investigators

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Harvard Medical School

Disclosures

This presentation *will discuss off-label use* of the HeartMate 3

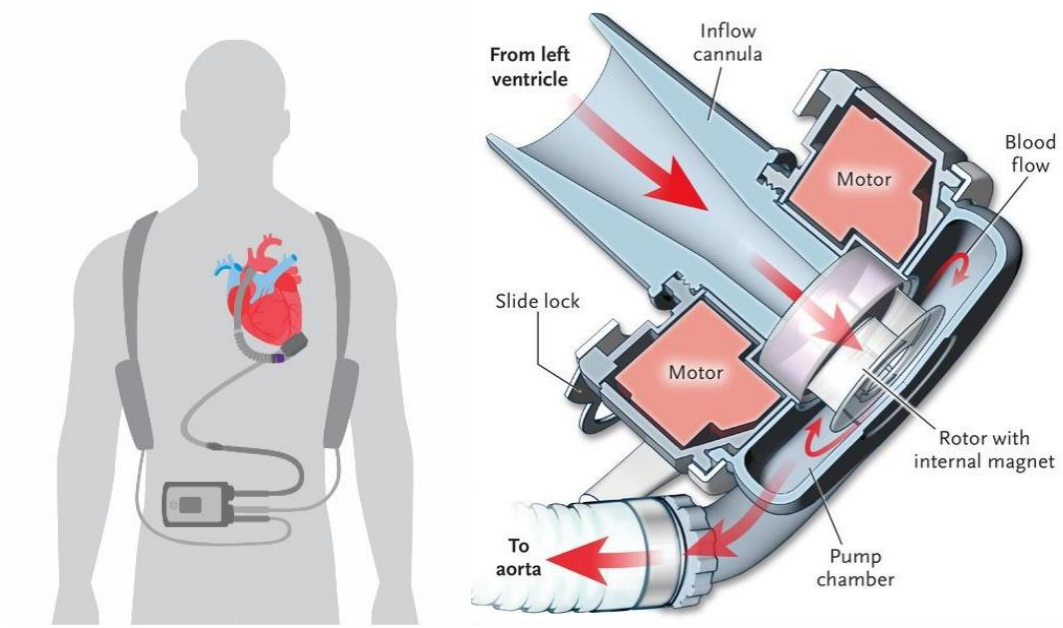
The ARIES HM3 Trial (NCT04069156) is funded and sponsored by Abbott, the manufacturer of the HeartMate 3 Left Ventricular Assist System

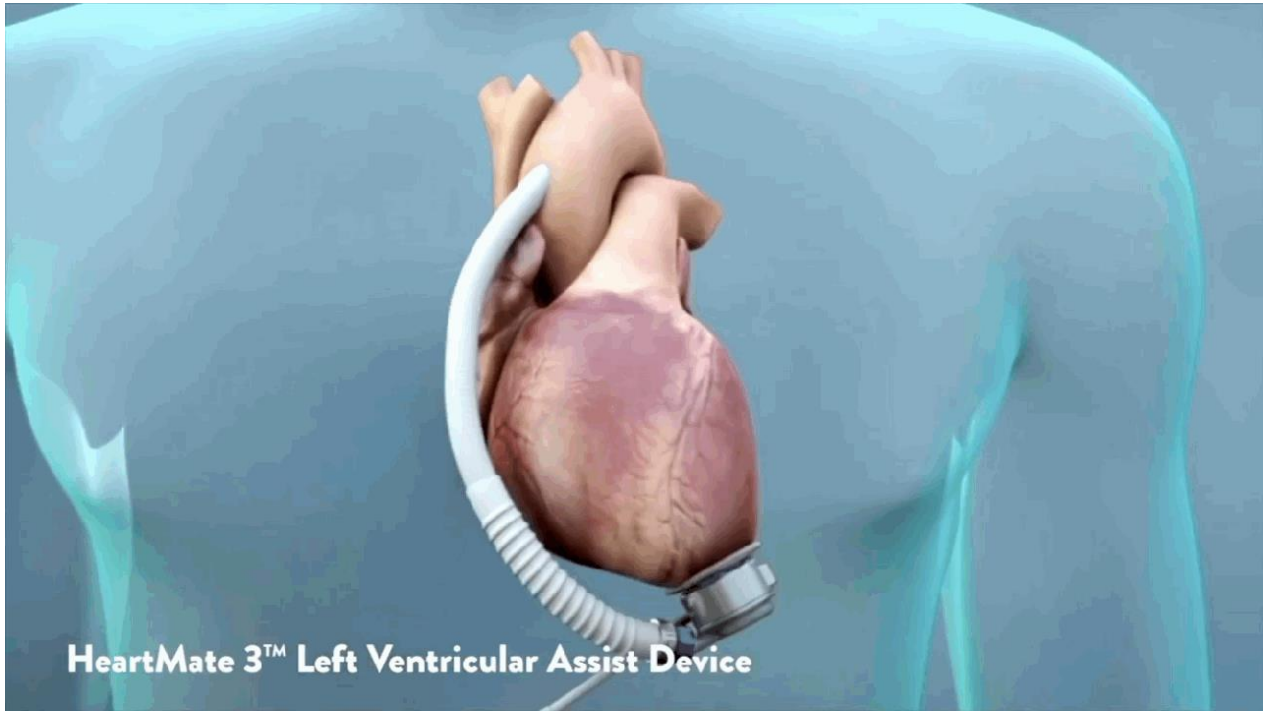
Dr Mehra reports payments made to his institution from Abbott for consulting, received personal consulting fees from Moderna, Paragonix and Natera.

He is an advisory board member for NuPulseCV, Leviticus, Transmedics and FineHeart.

ARIES

HeartMate 3 Left Ventricular Assist Device





The HeartMate 3 LVAD is a centrifugal-flow, fully magnetically levitated blood pump engineered to minimize destruction of red blood cells and thrombosis

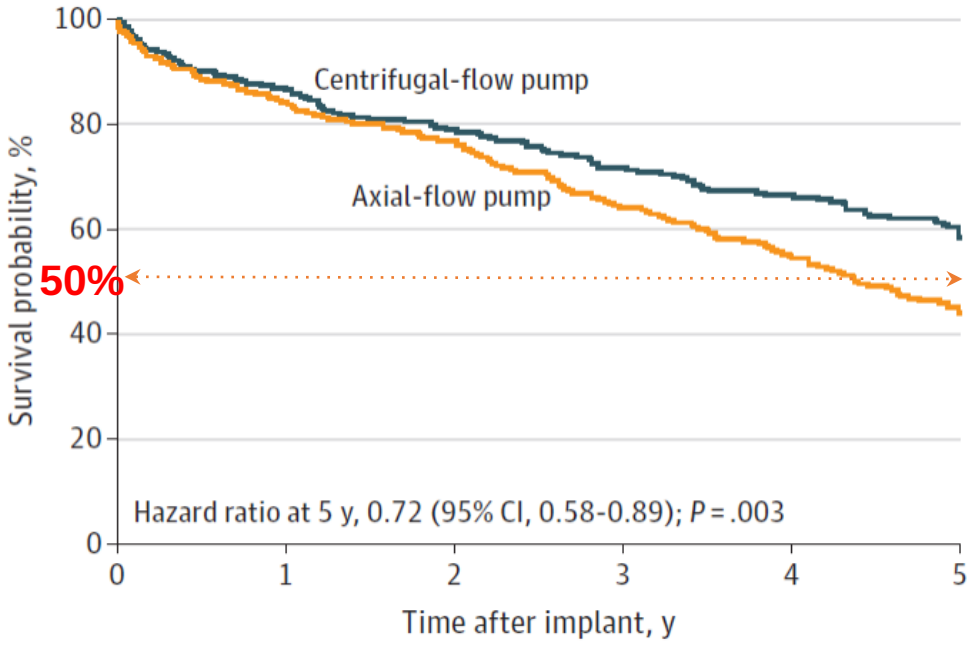
- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis

Bourque, Cotter, Dague, et al, *ASAIO J* 2016;62:375-83
Mehra, Naka, Uriel, et al, *N Engl J Med.* 2017; 376:440-450

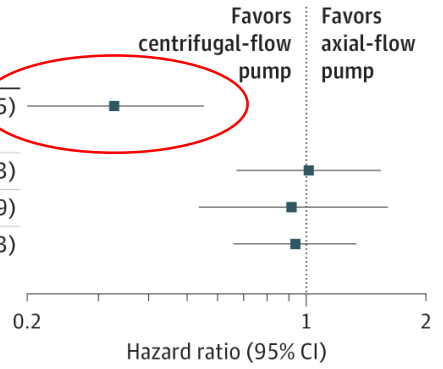
Mehra, Goldstein, Uriel, et al. *N Engl J Med.* 2018;378:1386-1395

A New Survival Benchmark with LVAD Therapy

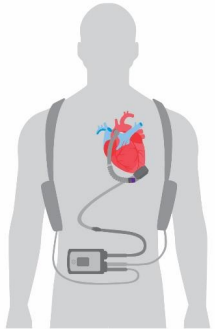
5-year survival of 58.4% with the centrifugal flow HeartMate 3 LVAD in advanced HF patients



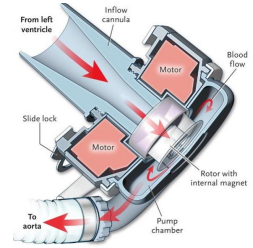
Cause of death	Difference, % (95% CI) %[a]	Hazard ratio (95% CI)	*P* value[b]
Hemocompatibility-related event (device thrombosis, stroke, bleeding)	-6.8 (-10.0 to -3.6)	0.33 (0.20-0.55)	<.001
Heart failure	0.6 (-2.9 to 4.1)	1.01 (0.67-1.53)	.95
Infection	-0.1 (-2.8 to 2.6)	0.92 (0.54-1.59)	.77
Other[c]	0.0 (-4.1 to 4.0)	0.94 (0.66-1.33)	.72

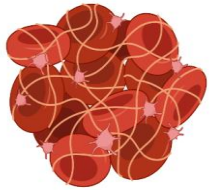


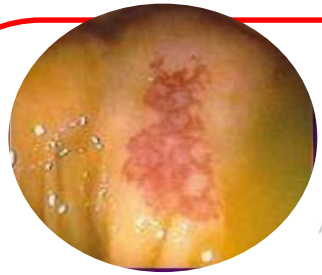
Mehra, Goldstein, Cleveland et al, *JAMA* 2022; 328(12):1233-1242

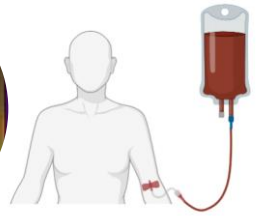


HEMOCOMPATIBILITY RELATED OUTCOMES

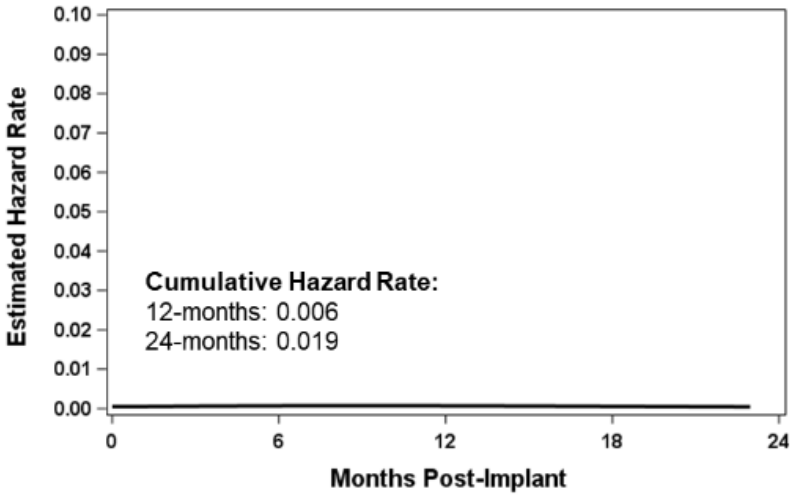




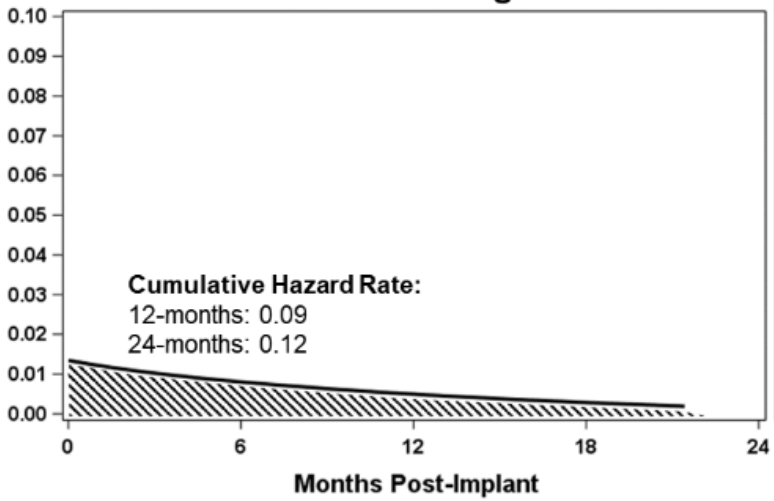




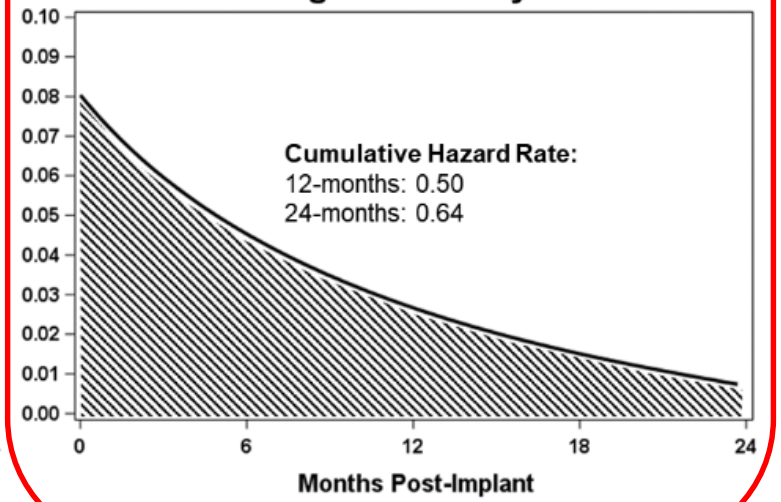
De Novo Pump Thrombosis



Ischemic or Hemorrhagic Stroke



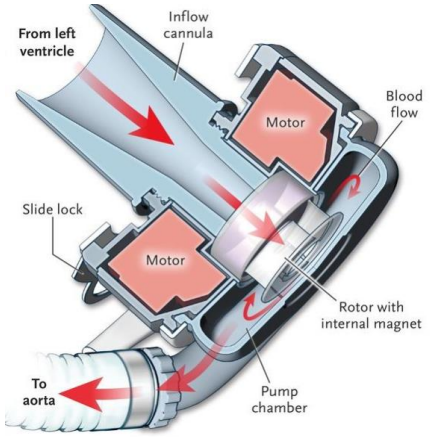
Bleeding Due to Any Cause



Opportunity to Reduce Residual Risk

Mehra MR, Crandall DL, Gustafsson F, et al., *Eur J Heart Fail*. 2021;23(7):1226-1237

Can aspirin be safely excluded from the antithrombotic regimen (*which includes Vitamin-K Antagonists*) in HM3 LVAD Patients?

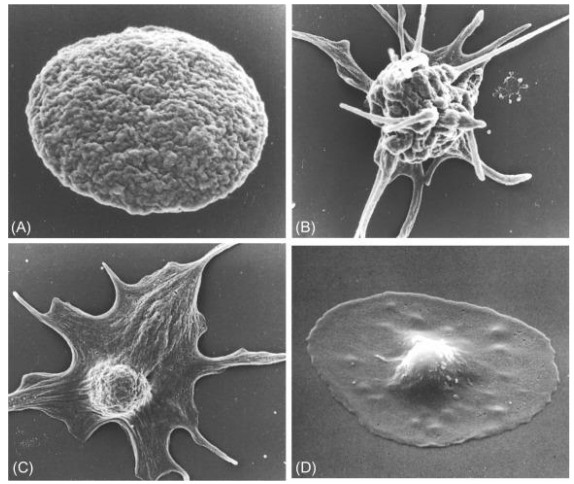


ACETYLSALICYLIC ACID

ACETYLATION → **COX-1 INHIBITION** → **PLATELET INHIBITION**

SALICYLATION → **COX-2 INHIBITION** → **ANTI-INFLAMMATION**

THROMBOSIS



Mehra MR, Crandall DL, Gustafsson F, et al., Eur J Heart Fail. 2021;23(7):1226-1237
Thomas, The Structure of Resting and Activated Platelets. Platelets 4th Ed. 2019, Pages 47-77

ARIES

International, Multicenter, Prospective, Randomized, Double-blind, Placebo-controlled Study

HYPOTHESIS

Exclusion of aspirin from the antithrombotic regimen of HM3 LVAD patients will not adversely affect safety or efficacy of the HM3 and may reduce non-surgical bleeding

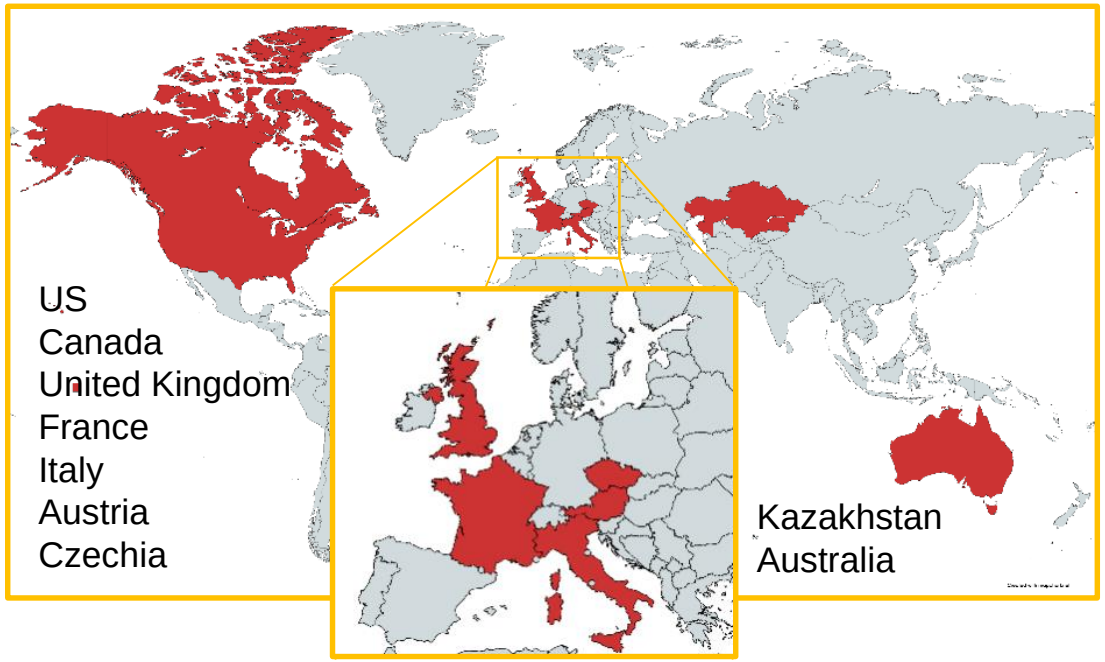
Antithrombotic Regimens

Aspirin (100mg) + Standard VKA (INR 2.0-3.0)

versus

Placebo + Standard VKA (INR 2.0-3.0)

Global Study of 51 centers in 9 countries



End Points

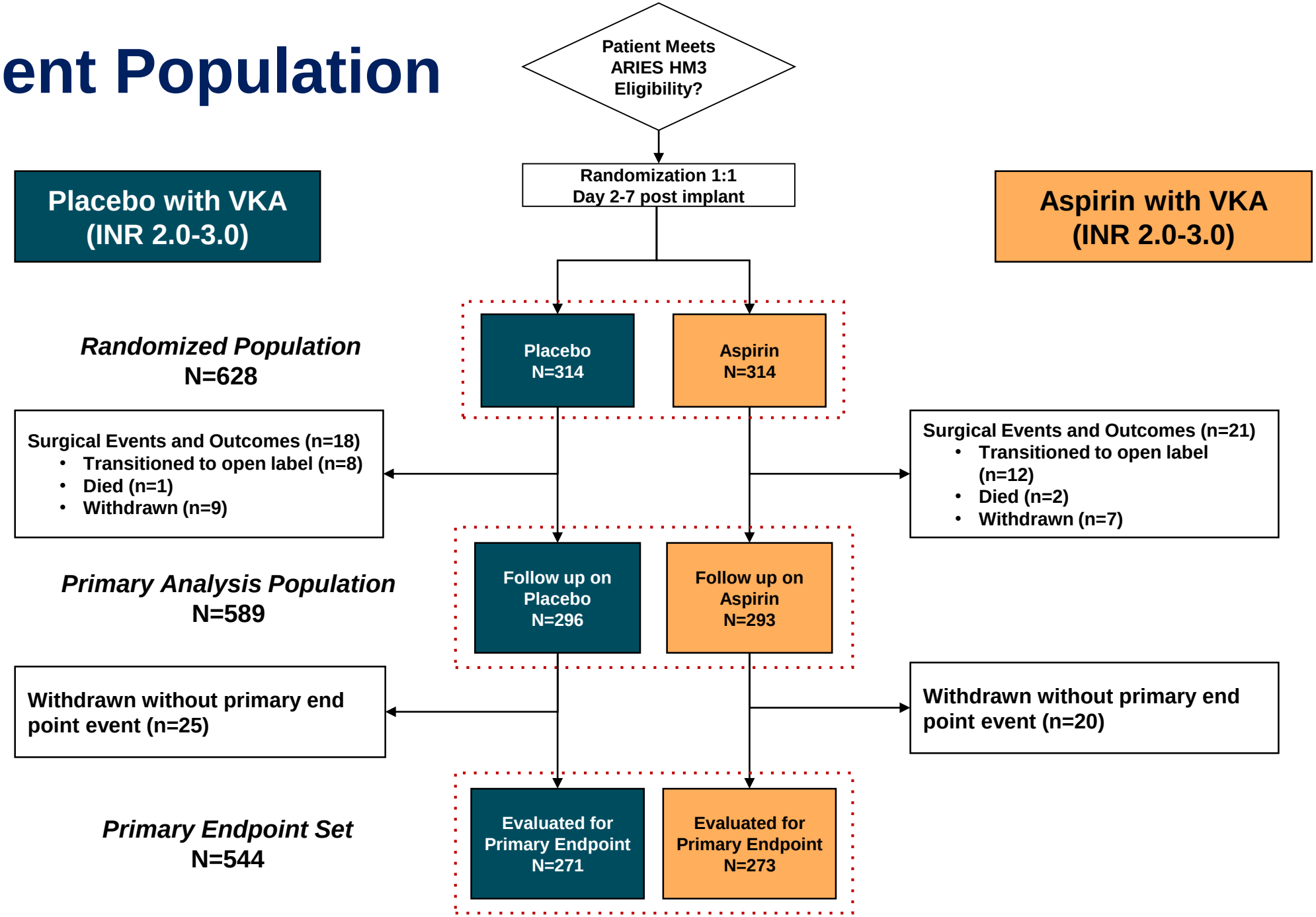
Primary: Survival free of any non-surgical[a] major hemocompatibility related adverse event[b] at 1-year post implant

[a] >14 days post implant. [b]Any Stroke, Pump Thrombosis, Major Bleeding, and Arterial Peripheral Thromboembolism

- The final sample size provided >90% power to assess the primary end point
- Non-inferiority met if the lower boundary of the one-sided 97.5% confidence limit was greater than the non-inferiority margin (-10%)

Principal Secondary: All Non-surgical Bleeding

Patient Population

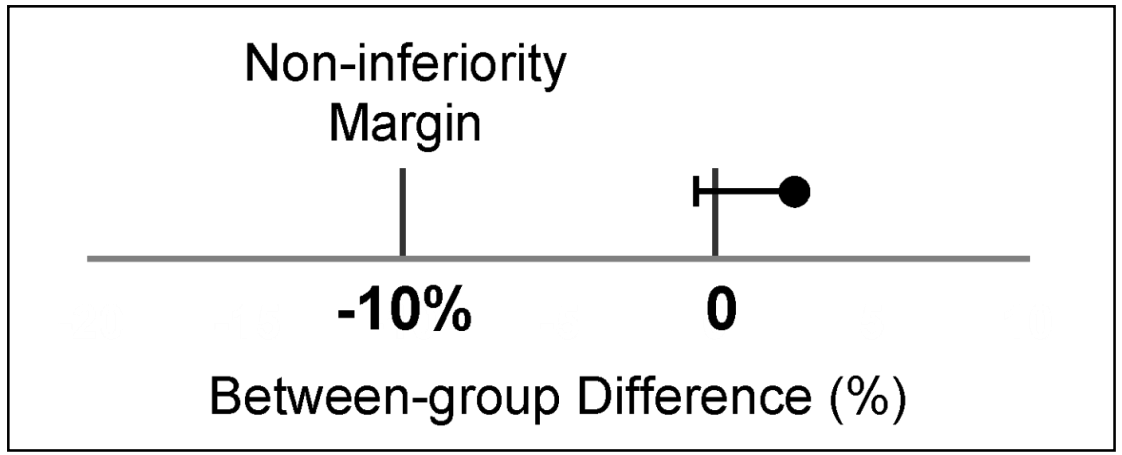


Baseline Characteristics

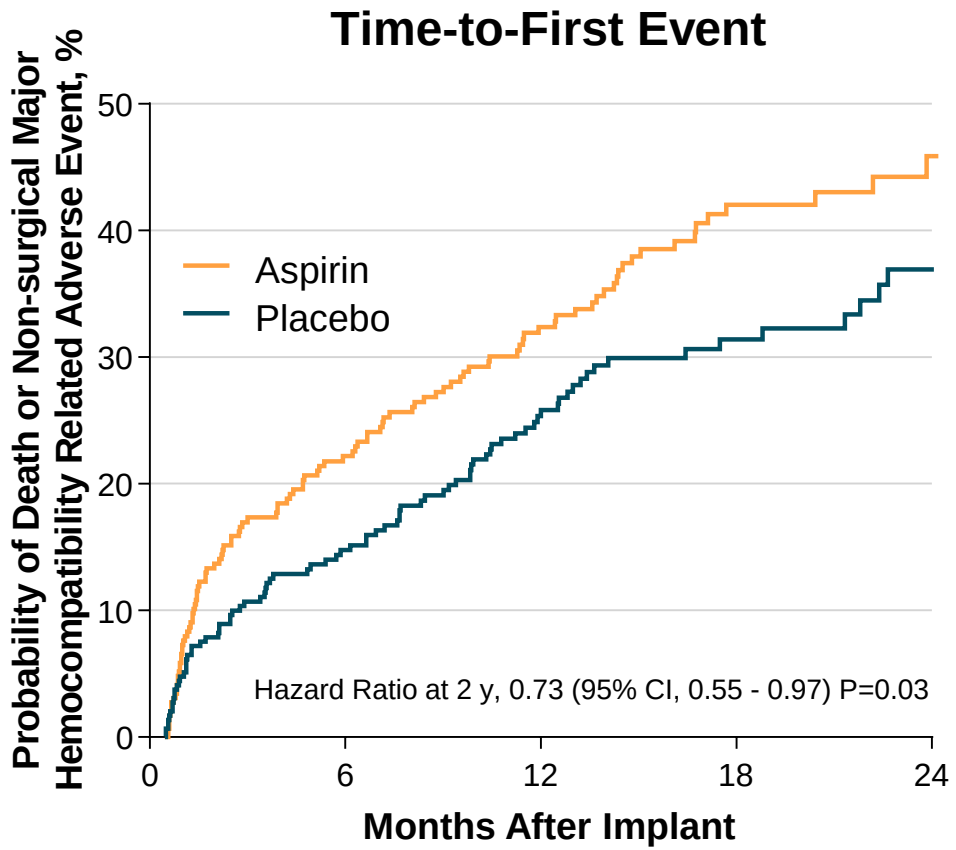
Characteristic	Placebo (N =296)	Aspirin (N =293)
Age – years, median (range)	60 (20-79)	59 (18-80)
Female sex – no. (%)	72 (24)	61 (21)
Race (white) – no. (%)*	179 (60.5)	181 (61.8)
Ischemic etiology of heart failure – no. (%)	106 (35.8)	101 (34.5)
History of atrial fibrillation – no. (%)	137 (46.3)	122 (41.6)
History of stroke – no. (%)	44 (14.9)	35 (11.9)
History of prior bleeding – no. (%)	17 (5.7)	12 (4.1)
History of diabetes mellitus – no. (%)†	134 (45.3)	106 (36.2)
Destination therapy goal of pump support – no. (%)	180 (60.8)	174(59.4)
INTERMACS profile – no. (%)		
1	12 (4.1)	18 (6.1)
2	76 (25.7)	75 (25.6)
3	133 (44.9)	133 (45.4)
4-7	75 (25.3)	67 (22.7)
Enrolled in North America – no. (%)	251 (85)	248 (85)

Primary End Point Analysis

	Placebo	Aspirin	Difference (Lower 97.5% CI)*	P-value*
Non-Inferiority Primary End Point Analysis	74.2 (201/271)	68.1 (186/273)	6.0% (-1.6%)	<.001



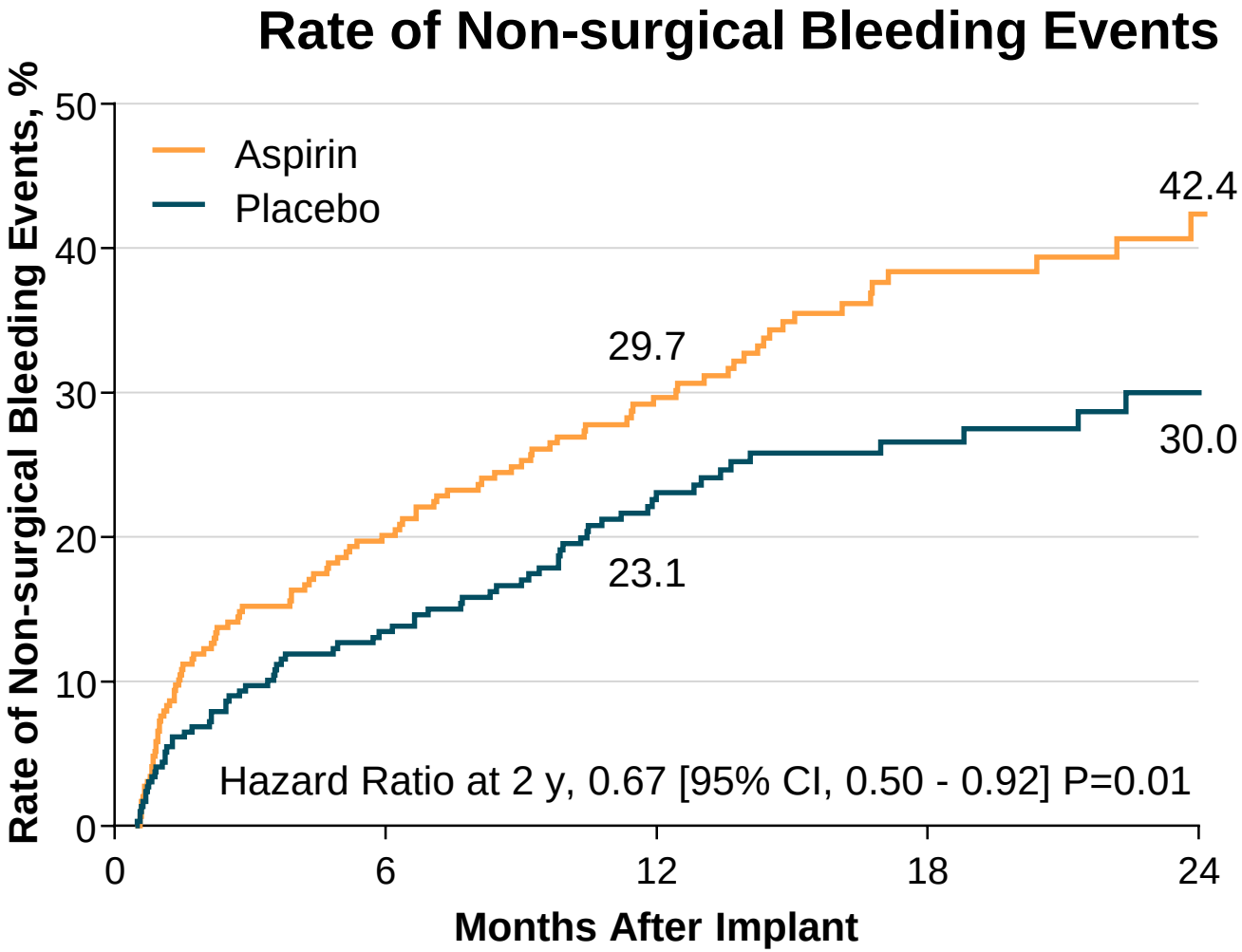
All sensitivity analyses concur with the primary analysis, including randomized population, worst case allocation of withdrawals, and impact of transition to open label



No. at Risk:

Placebo	296	221	161	84	44
Aspirin	293	205	146	72	33

Principal Secondary Endpoint



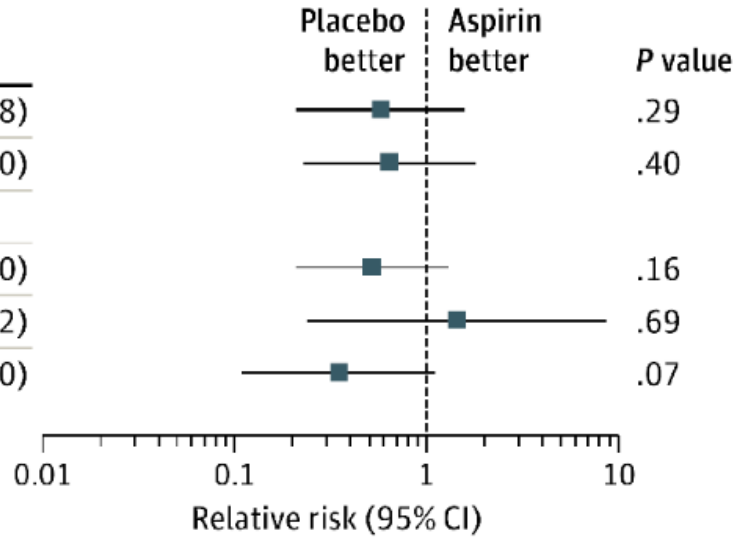
No. at Risk:					
Placebo	296	222	163	85	44
Aspirin	293	207	148	73	34

Secondary Endpoints – Total Events

For every 100 patients implanted with the study LVAD, aspirin exclusion prevents
14.5 major bleeding events in the first year

Safety Endpoints

Source	Events per 100 patient-years (No. of events): Placebo (n = 296; 366.41 patient-years)	Aspirin (n = 293; 351.64 patient-years)	Relative risk (95% CI)	*P* value
Thrombotic components of the primary end point	1.6 (6)	2.8 (10)	0.58 (0.21-1.58)	.29
Ischemic stroke[b]	1.6 (6)	2.6 (9)	0.64 (0.23-1.80)	.40
Ischemic stroke with hemorrhagic conversion[a]	0	0.3 (1)		
Any stroke	1.9 (7)	3.7 (13)	0.52 (0.21-1.30)	.16
Debilitating stroke	0.8 (3)	0.6 (2)	1.44 (0.24-8.62)	.69
Nondebilitating stroke	1.1 (4)	3.1 (11)	0.35 (0.11-1.10)	.07



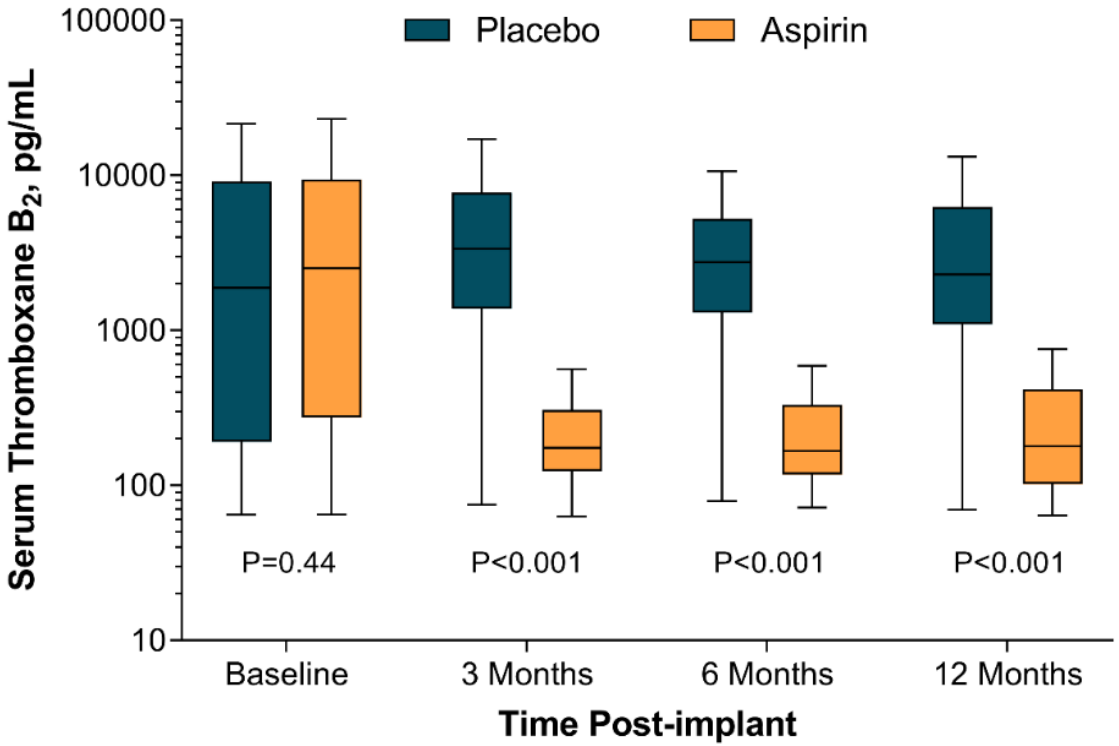
Mortality

	Placebo	Aspirin
12-month Mortality	4.3%	7.2%
24-month Mortality	12.3%	9.1%

There was no difference in mortality between Placebo and Aspirin.

HR [95% CI]: 0.90 [0.50 - 1.62] P=0.71

Efficacy of Antithrombotic Therapy



No. assessed:

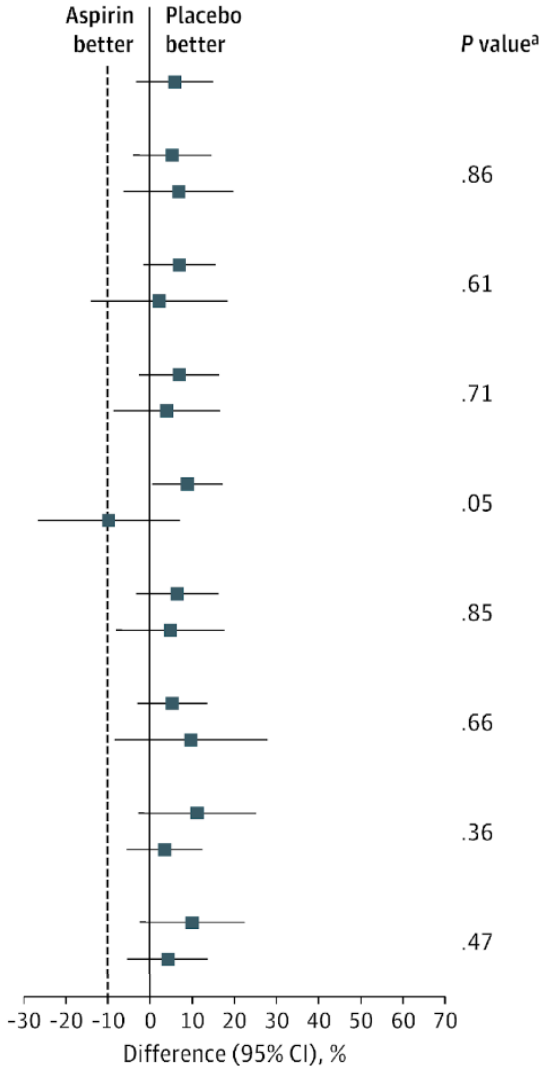
Placebo	223	198	162	149
Aspirin	213	180	156	120

Time in therapeutic range was not different between the two groups

	Placebo	Aspirin	P-Value
INR Median (IQR)	55.1% (39.5-73.9)	58.9% (39.5-69.0)	0.93

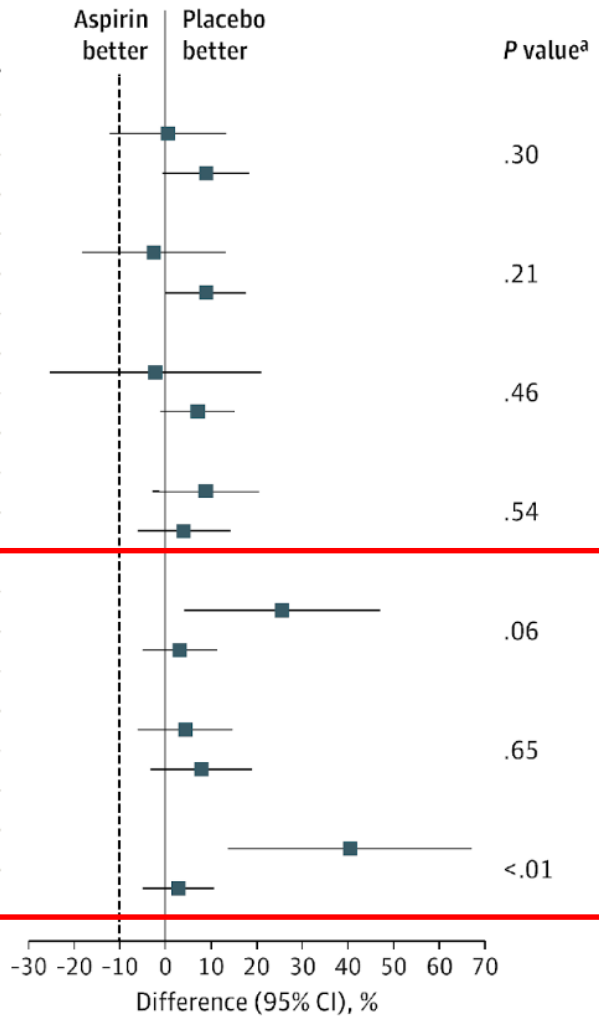
Important Patient Subgroups

Characteristic	Patients with treatment success, % (No./total No.)		Difference (95% CI), %	*P* value[a]
	Placebo	Aspirin		
Characteristic	74.2 (201/271)	68.1 (186/273)	6.0 (-1.6 to 13.7)	
Age, y				
<65	76.6 (131/171)	1.1 (123/173)	5.5 (-3.8 to 14.8)	.86
≥65	70.0 (70/100)	63.0 (63/100)	7.0 (-6.1 to 20.1)	
Sex				
Men	75.2 (155/206)	68.1 (147/216)	7.2 (-1.5 to 15.8)	.61
Women	70.8 (46/65)	68.4 (39/57)	2.3 (-13.9 to 18.6)	
Race				
White	75.1 (127/169)	68.0 (119/175)	7.1 (-2.4 to 16.7)	.71
Non-white	72.5 (74/102)	68.4 (67/98)	4.2 (-8.4 to 16.8)	
Region				
North America	74.1 (169/228)	65.1 (149/229)	9.1 (0.6 to 17.5)	.05
Europe, Australia	74.4 (32/43)	84.1 (37/44)	-9.7 (-26.6 to 7.3)	
Body mass index				
≤30	73.1 (125/171)	66.5 (109/164)	6.6 (-3.2 to 16.5)	.85
>30	74.4 (67/90)	69.4 (68/98)	5.1 (-7.9 to 18.0)	
Surgical technique[b]				
Sternotomy	73.0 (165/226)	67.5 (158/234)	5.5 (-2.9 to 13.9)	.66
Thoracotomy	81.8 (36/44)	71.8 (28/39)	10.0 (-8.2 to 28.2)	
Disease severity[c]				
INTERMACS 1-2	75.3 (61/81)	64.0 (55/86)	11.4 (-2.7 to 25.4)	.36
INTERMACS ≥3	73.7 (140/190)	70.1 (131/187)	3.6 (-5.5 to 12.7)	
History of diabetes				
Yes	70.8 (85/120)	60.6 (60/99)	10.2 (-2.3 to 22.7)	.47
No	76.8 (116/151)	72.4 (126/174)	4.4 (-5.2 to 14.0)	



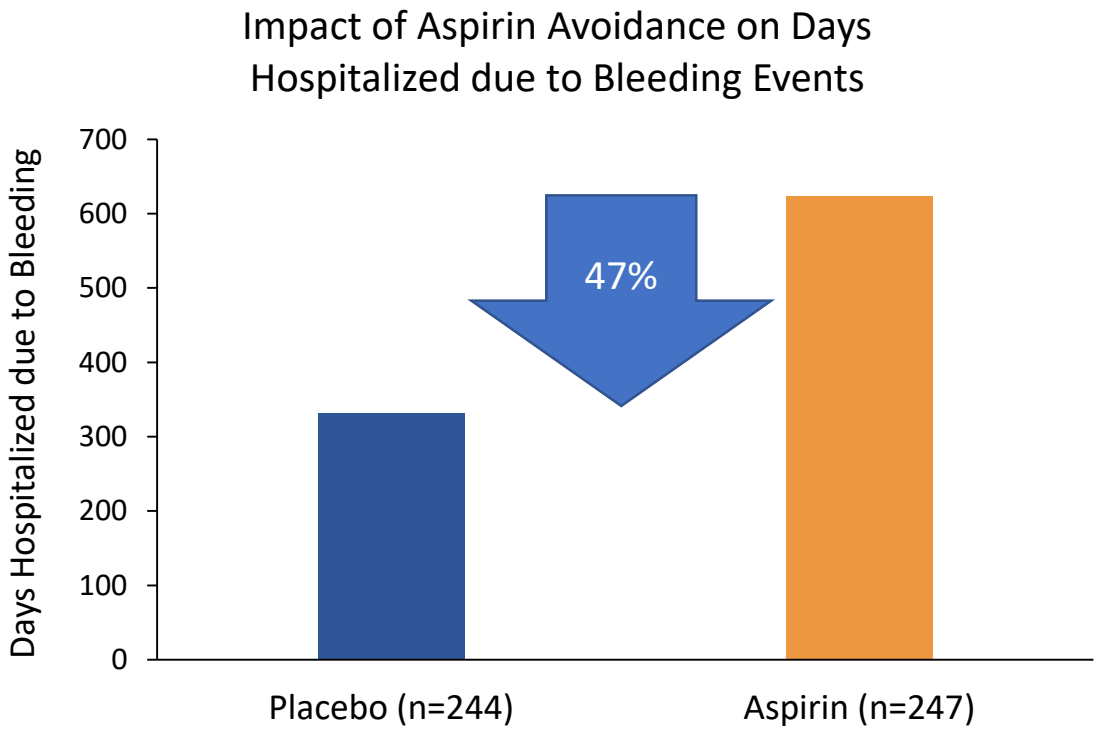
Important Patient Subgroups

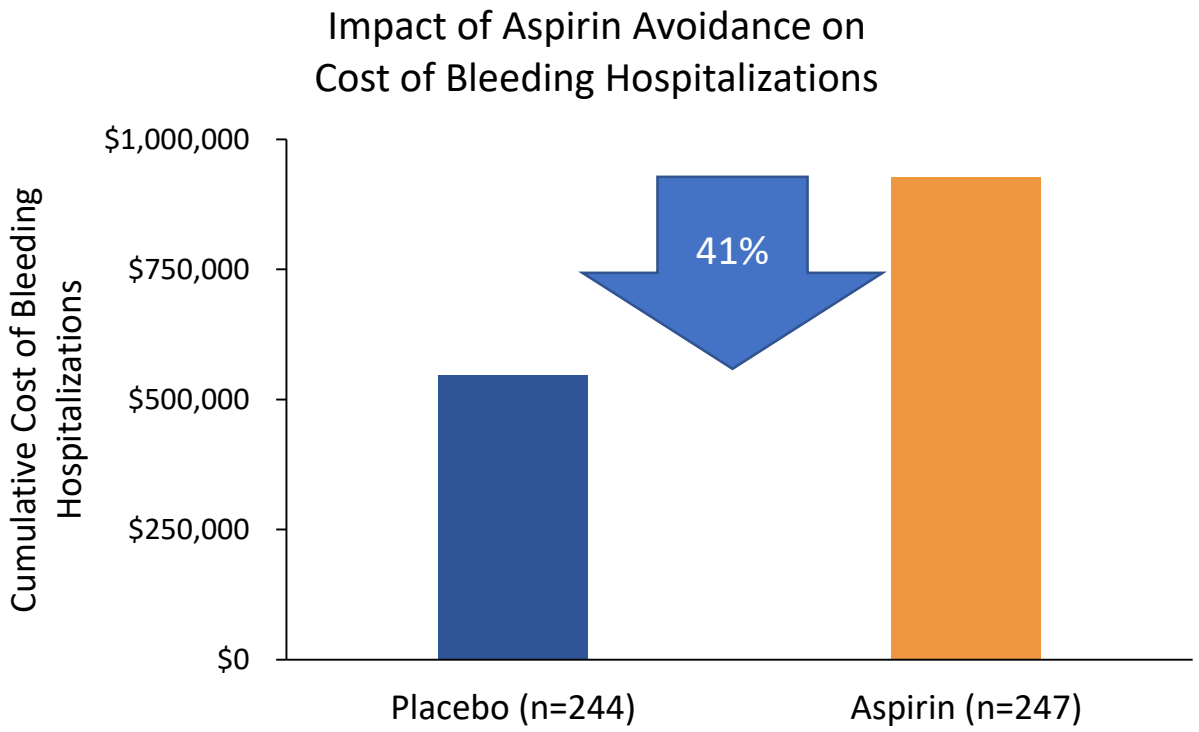
	Patients with treatment success, % (No./total No.)		Difference (95% CI), %	*P* value[a]
	Placebo	Aspirin		
Ischemic etiology of heart failure				
Yes	71.1 (69/97)	70.5 (67/95)	0.6 (-12.2 to 13.4)	.30
No	75.9 (132/174)	66.9 (119/178)	9.0 (-0.5 to 18.5)	
History of coronary stenting				
Yes	64.8 (46/71)	67.2 (45/67)	-2.4 (-18.1 to 13.4)	.21
No	77.5 (155/200)	68.4 (141/206)	9.1 (0.3 to 17.8)	
Coronary artery bypass procedure				
Yes	65.6 (21/32)	67.7 (21/31)	-2.1 (-25.3 to 21.1)	.46
No	75.3 (180/239)	68.2 (165/242)	7.1 (-0.9 to 15.2)	
Atrial fibrillation				
Yes	73.8 (93/126)	64.9 (72/111)	8.9 (-2.7 to 20.6)	.54
No	74.5 (108/145)	70.4 (114/162)	4.1 (-6.0 to 14.2)	
Prior stroke				
Yes	80.5 (33/41)	54.8 (17/31)	25.6 (4.3 to 47.0)	.06
No	73.0 (168/230)	69.8 (169/242)	3.2 (-5.0 to 11.4)	
History of thrombosis				
Yes	72.5 (108/149)	68.0 (100/147)	4.5 (-6.0 to 14.9)	.65
No	76.2 (93/122)	68.3 (86/126)	8.0 (-3.2 to 19.2)	
History of bleeding				
Yes	71.0 (22/31)	30.4 (7/23)	40.5 (13.8 to 67.2)	<.01
No	74.6 (179/240)	71.6 (179/250)	3.0 (-4.9 to 10.9)	



Hospitalizations and Cost Savings*

*US population only, US payer perspective only





Conclusions

- In patients with advanced heart failure receiving support from a fully magnetically levitated LVAD, aspirin is not required as part of an antithrombotic regimen that includes a Vitamin K Antagonist to preserve outcomes

- Exclusion of aspirin is associated with a significant decrease in bleeding events with no increase in risk of thrombo-embolic events

- Benefits of aspirin avoidance are associated with a decrease in hospitalization rates and cost of care due to bleeding complications.

Study Steering Committee

- Mandeep R. Mehra, MBBS, MSc (Chair)
- Ivan Netuka, MD, PhD
- Nir Uriel, MD, MSc
- Jason N. Katz, MD, MS
- Francis D. Pagani, MD, PhD
- Ulrich P. Jorde, MD
- Finn Gustafsson, MD, PhD, DMSci
- Jean M. Connors, MD

Data Safety Monitoring Board

- William Holman, MD (Chair)
- Kenneth Bauer, MD
- Stuart Russell, MD
- Daniel Heitjan, PhD

Clinical Events Committee

- Joseph Cleveland, MD (Chair)
- Joshua Willey, MD, MS
- Gregory Egnaczyk, MD, PhD
- Erin Coglianese, MD

We THANK all the patients, our investigators, clinical nurse coordinators, and allied health personnel for their dedication to the conduct of the ARIES HM3 Study

JAMA | Original Investigation

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The ARIES-HM3 Randomized Clinical Trial

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