

Současná evidence a nové trendy v léčbě pacientů s dlouhodobou mechanickou srdeční podporou

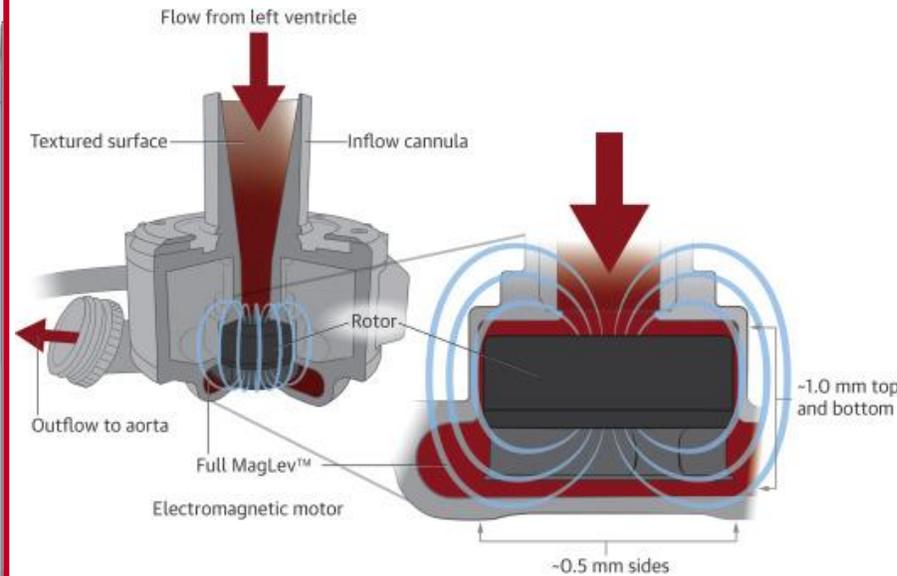
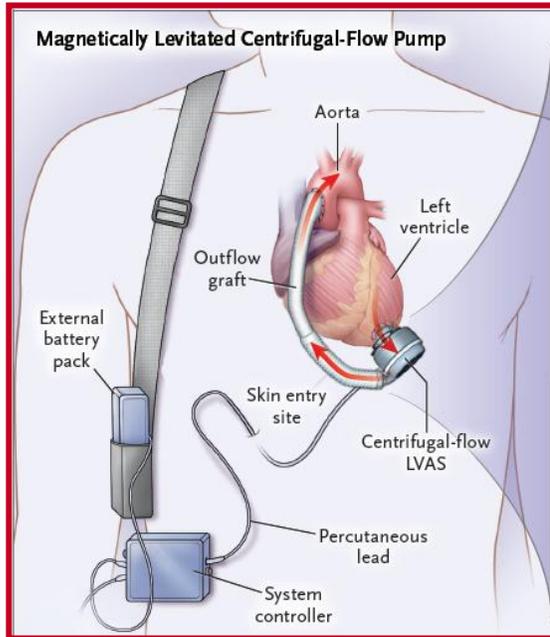
prof. MUDr. Ivan Netuka, Ph.D.

Klinika kardiovaskulární chirurgie

Institut klinické a experimentální medicíny, Praha



A New Survival and Functional Status Benchmark with Contemporary LVAD Therapy



Key Attributes

Enhanced “Thrombo-resistance”

- Near Elimination of Pump Thrombosis
- Low Stroke Rates



Improved Survival

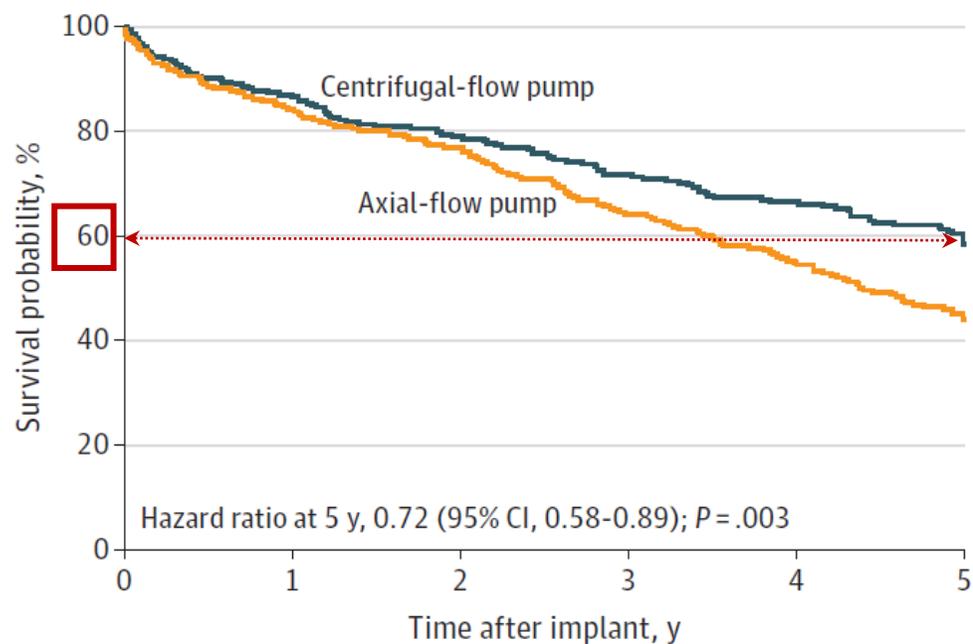
Netuka I. et al. *J Am Coll Cardiol.* 2015;66:2579-2589.

Mehra MR. et al. *N Engl J Med.* 2019;380:1618-1627.

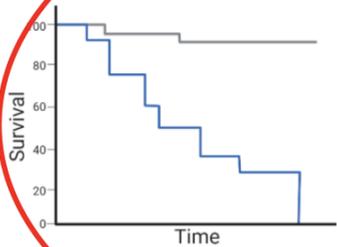
5-year survival of 58.4% and excellent functional capacity on the centrifugal flow HeartMate 3 pump in advanced HF patients irrespective of therapeutic intent

Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial

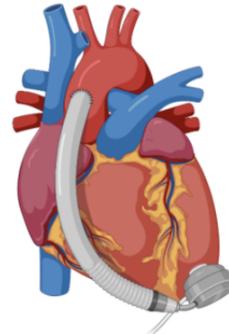
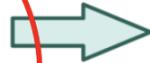
Mandeep R. Mehra, MD, MSc; Daniel J. Goldstein, MD; Joseph C. Cleveland, MD; Jennifer A. Cowger, MD, MS; Shelley Hall, MD; Christopher T. Salerno, MD; Yoshifumi Naka, MD, PhD; Douglas Horstmanshof, MD; Joyce Chuang, PhD; AiJia Wang, MPH; Nir Uriel, MD, MSc



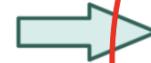
EXPECTED OUTCOMES IN ADVANCED HF PATIENTS



- Median survival **<1 year** in those dependent on iv inotropic therapy
- Median survival **<2 years** in ambulatory advanced HF not yet on inotropes



LVAD THERAPY



LONG TERM BENEFITS OF LVAD THERAPY

SURVIVAL



Median survival of
5 years

FUNCTIONAL STATUS



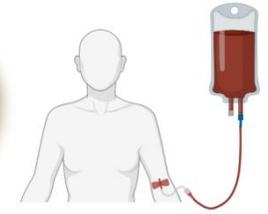
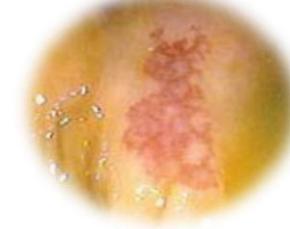
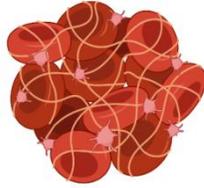
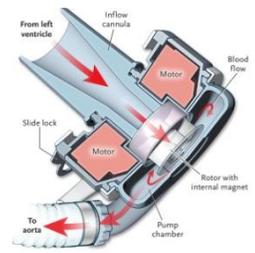
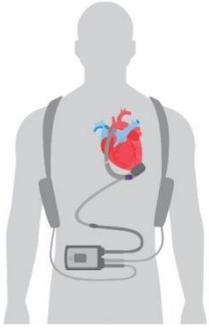
- **NYHA class I-II** in 75-80% at 2 years
- **2.5 fold** improvement in 6MWD (to >300 meters at 2 years)

QUALITY OF LIFE

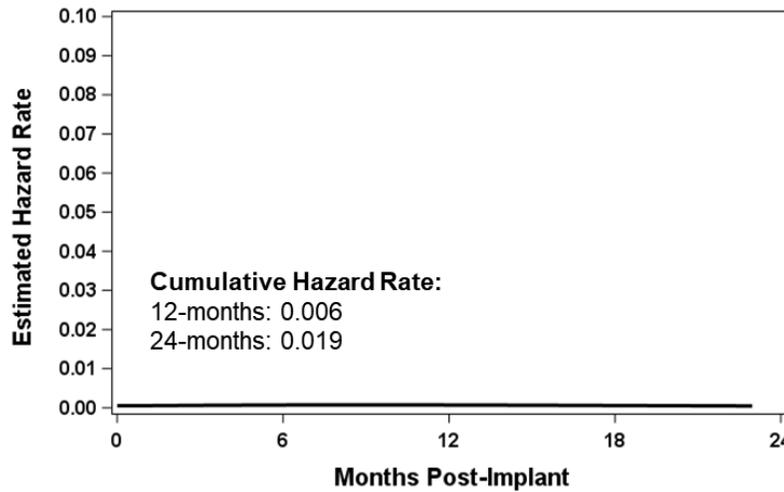


- **>75% increase** in KCCQ score (+30 points)

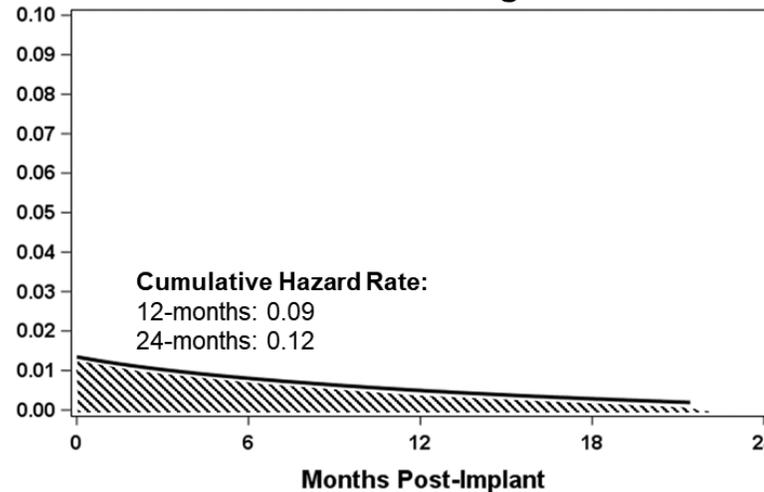
HEMOCOMPATIBILITY RELATED OUTCOMES



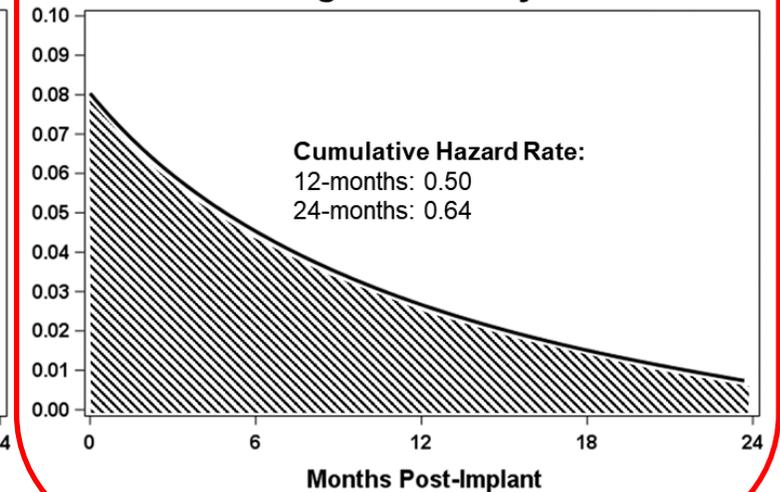
De Novo Pump Thrombosis



Ischemic or Hemorrhagic Stroke



Bleeding Due to Any Cause



Opportunity to Reduce Residual Risk

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

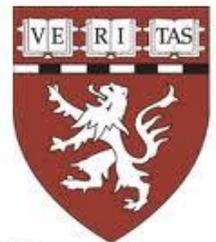
The ARIES-HM3 Clinical Trial

Mandeep R. Mehra, Ivan Netuka, Nir Uriel, Jason N. Katz, Francis D. Pagani, Ulrich P. Jorde, Finn Gustafsson, Jean M. Connors, Peter Ivak, Jennifer Cowger, John Ransom, Aditya Bansal, Koji Takeda, Richa Agarwal, Mirnela Byku, Michael M. Givertz, Abbas Bitar, Shelley Hall, Daniel Zimpfer, J David Vega, Manreet K. Kanwar, Omar Saeed, Daniel J. Goldstein, Rebecca Cogswell, Farooq H. Sheikh, Matthew Danter, Yuriy Pya, Anita Phancao, John Henderson, Daniel L. Crandall, Kartik Sundareswaran, Edward Soltesz and Jerry D. Estep

On Behalf of the ARIES Investigators



ARIES



HARVARD
MEDICAL SCHOOL

ARIES

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

HYPOTHESIS

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

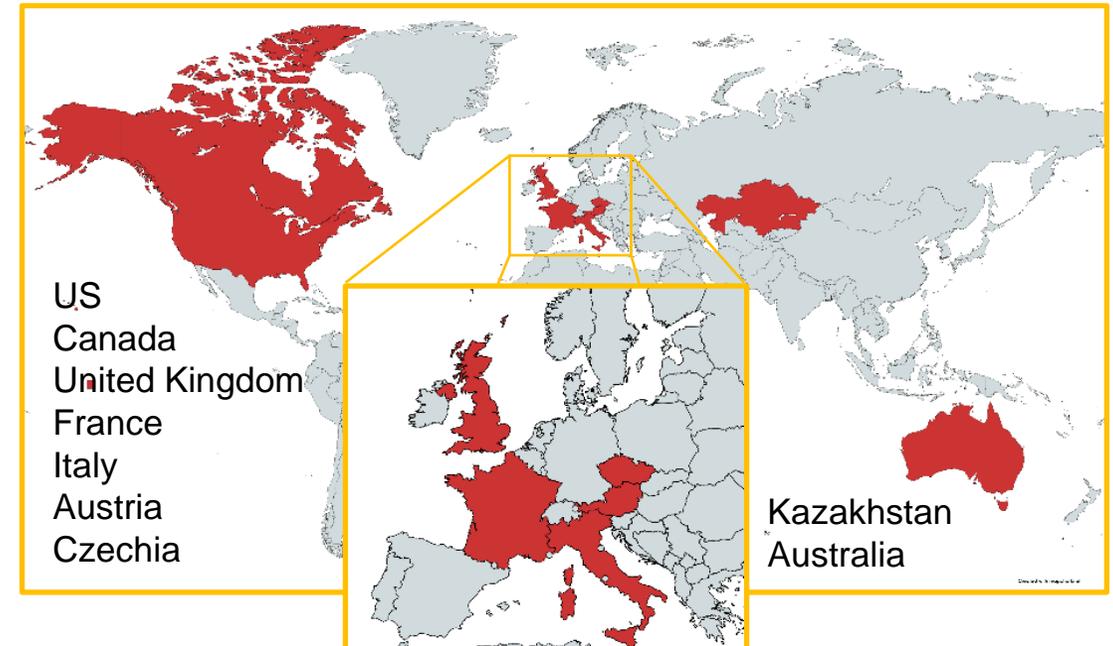
Antithrombotic Regimens

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

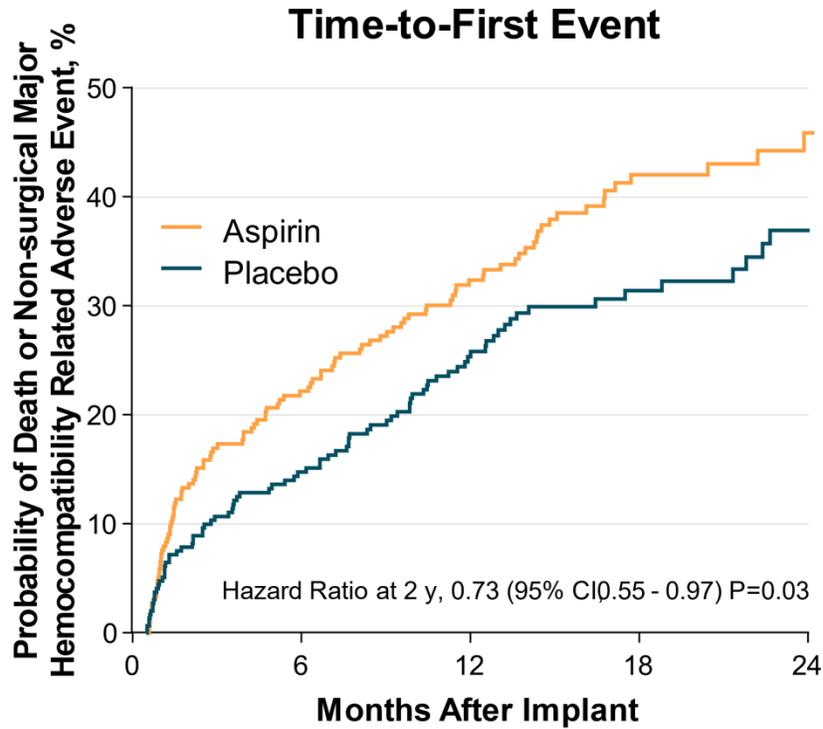
^a >14 days post implant. ^bAny Stroke, Pump Thrombosis, Major Bleeding, and Arterial Peripheral Thromboembolism

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

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

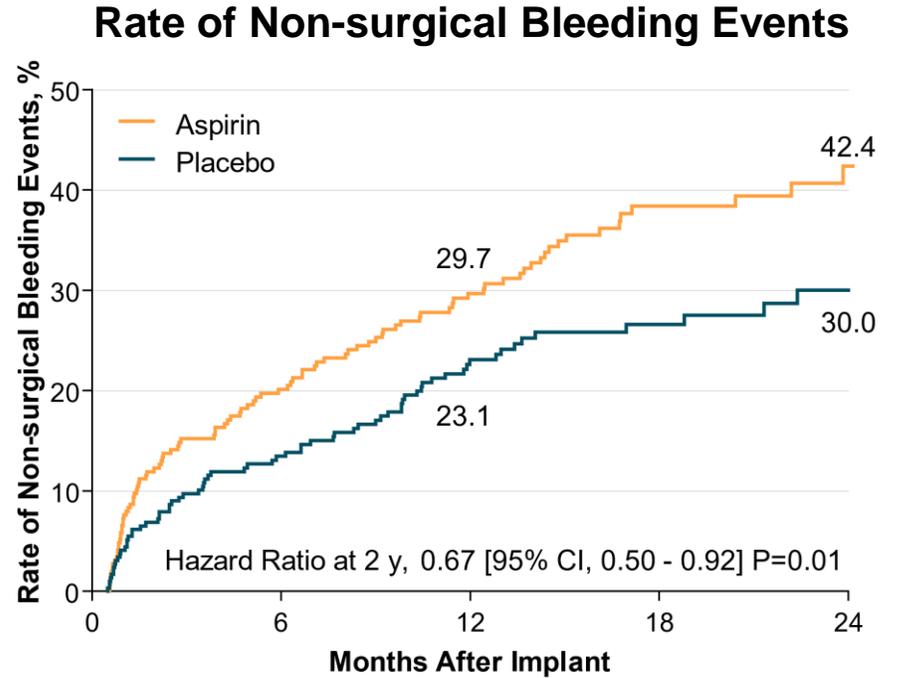
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No. at Risk:

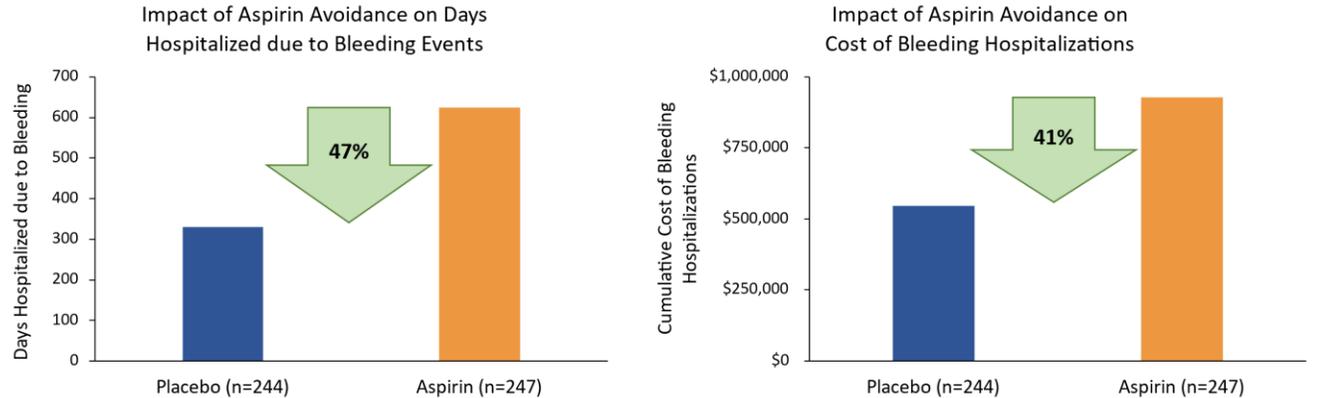
	0	6	12	18	24
Placebo	296	221	161	84	44
Aspirin	293	205	146	72	33



No. at Risk:

	0	6	12	18	24
Placebo	296	222	163	85	44
Aspirin	293	207	148	73	34

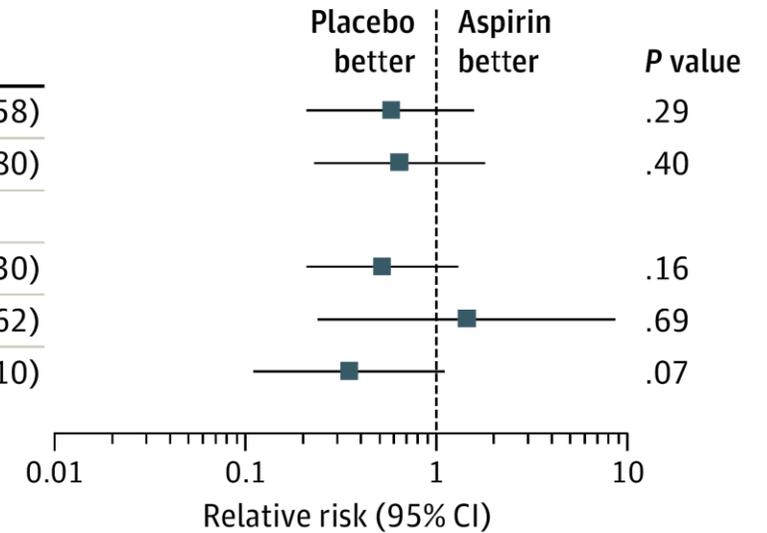
Hospitalizations and Cost of Care



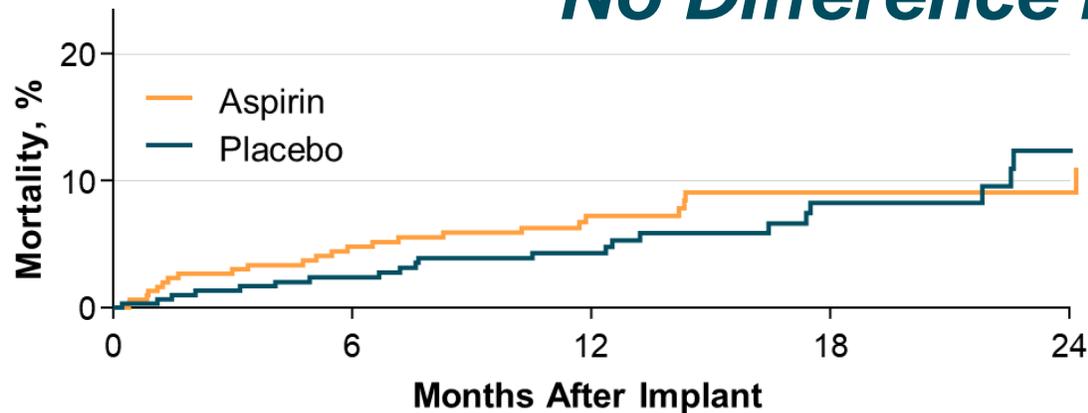
Safety Endpoints

No Increase in Thrombosis

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)
Thrombotic components of the primary end point	1.6 (6)	2.8 (10)	0.58 (0.21-1.58)
Ischemic stroke ^b	1.6 (6)	2.6 (9)	0.64 (0.23-1.80)
Ischemic stroke with hemorrhagic conversion ^a	0	0.3 (1)	
Any stroke	1.9 (7)	3.7 (13)	0.52 (0.21-1.30)
Debilitating stroke	0.8 (3)	0.6 (2)	1.44 (0.24-8.62)
Nondebilitating stroke	1.1 (4)	3.1 (11)	0.35 (0.11-1.10)

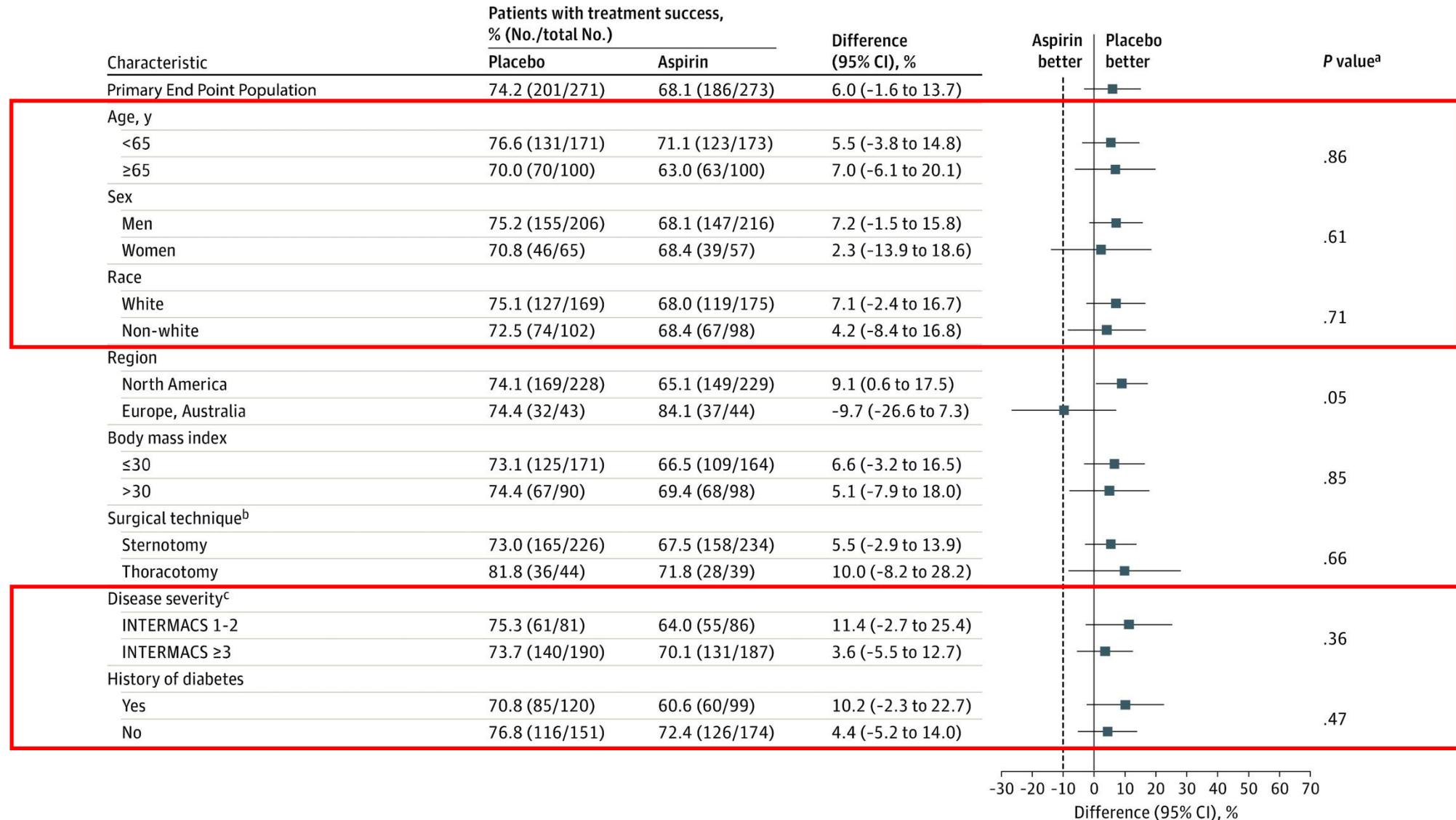


No Difference in Mortality

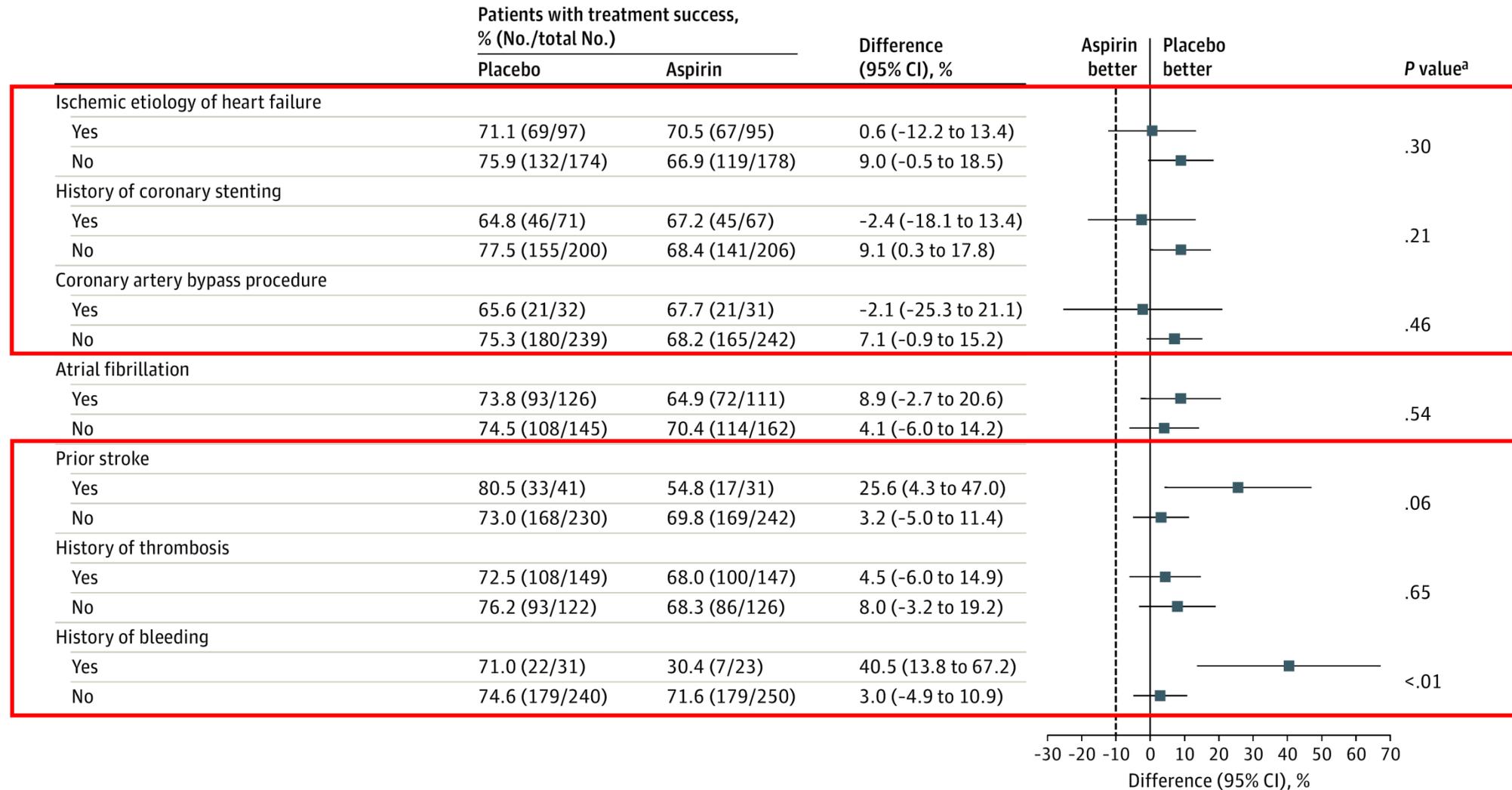


HR [95% CI]: 0.90 [0.50 - 1.62] P=0.71

Important Patient Subgroups



Important Patient Subgroups



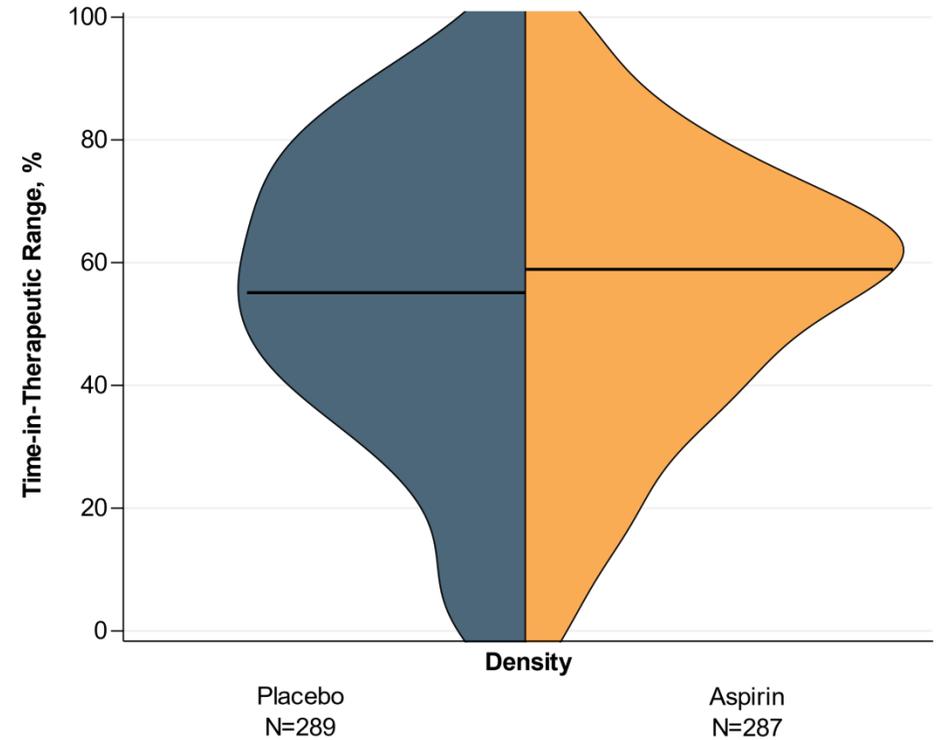
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JAMA. 2023;330:2171-2181.

Vitamin-K Antagonist Management

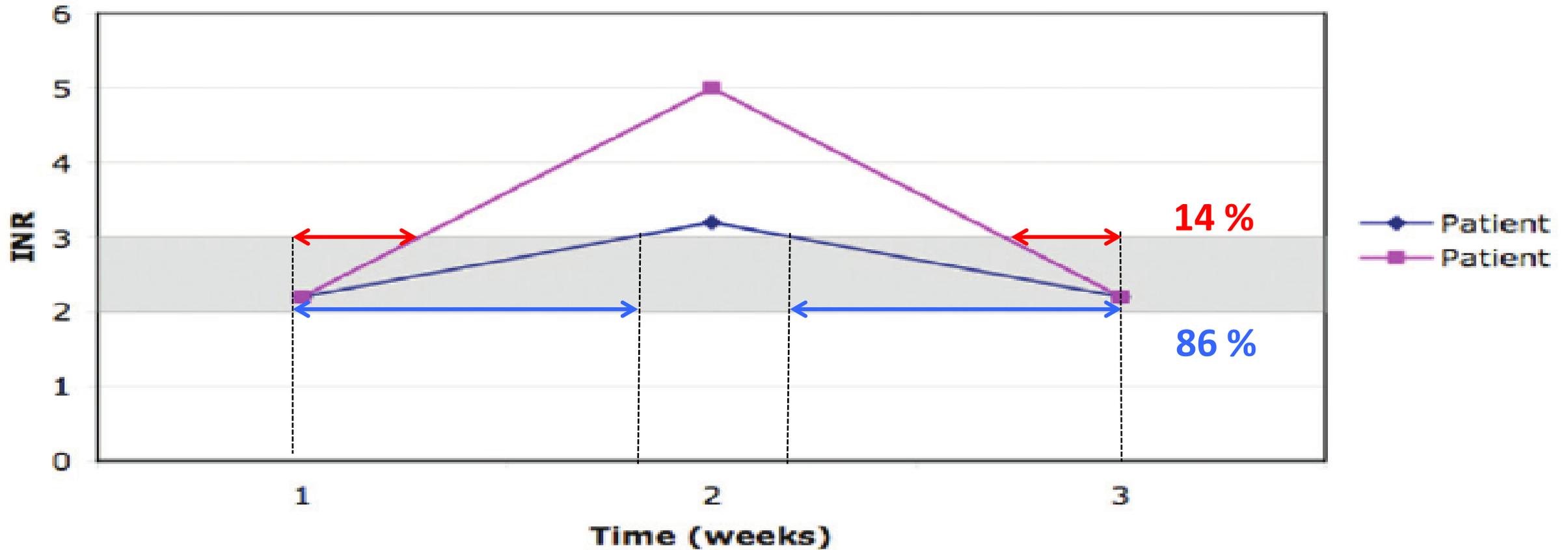


Target Therapeutic Range INR 2.0 - 3.0

Time in Therapeutic Range (TTR) 56%

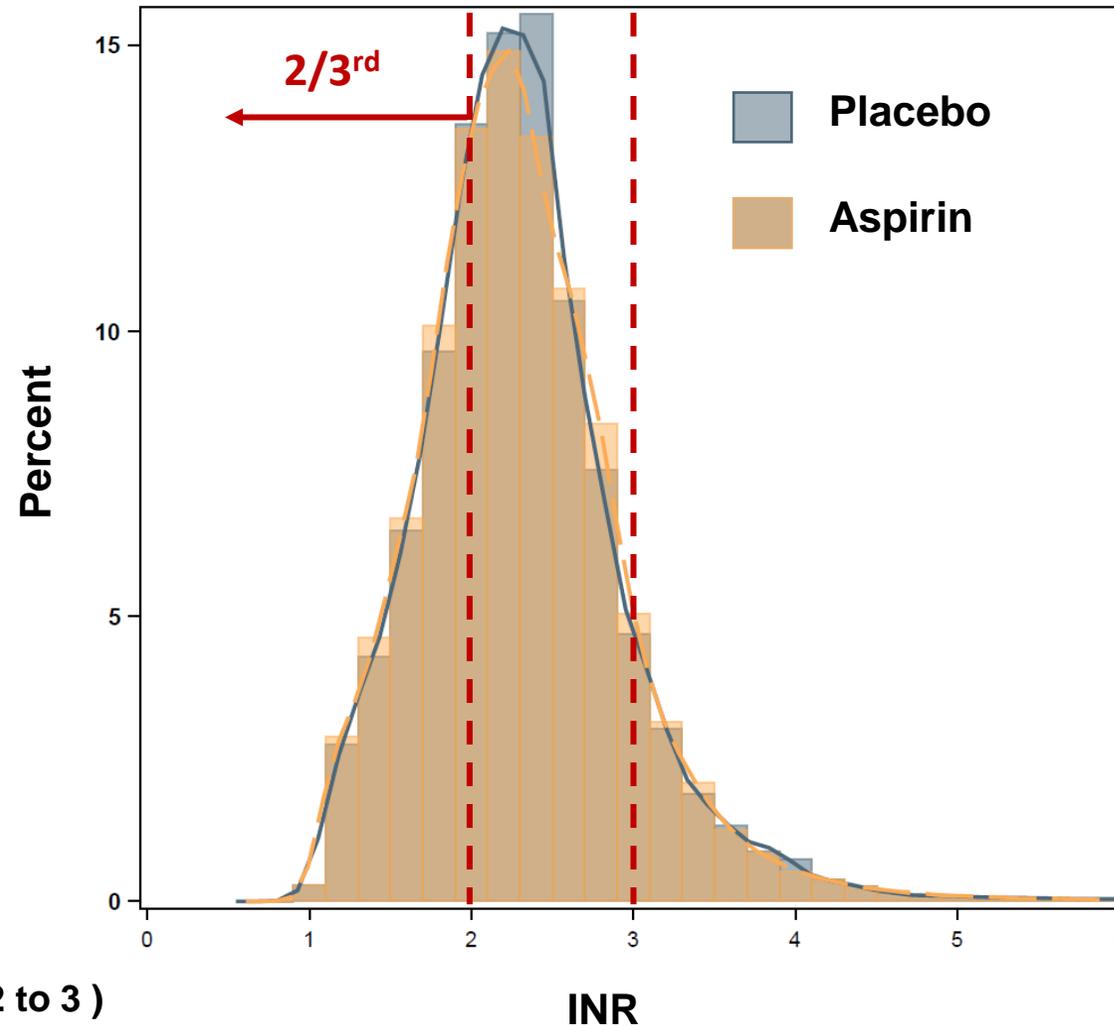
TTR – time in therapeutic range

Rosendaal method of linear interpolation



INR Distribution within follow-up period

Implant to 12-months Follow-up

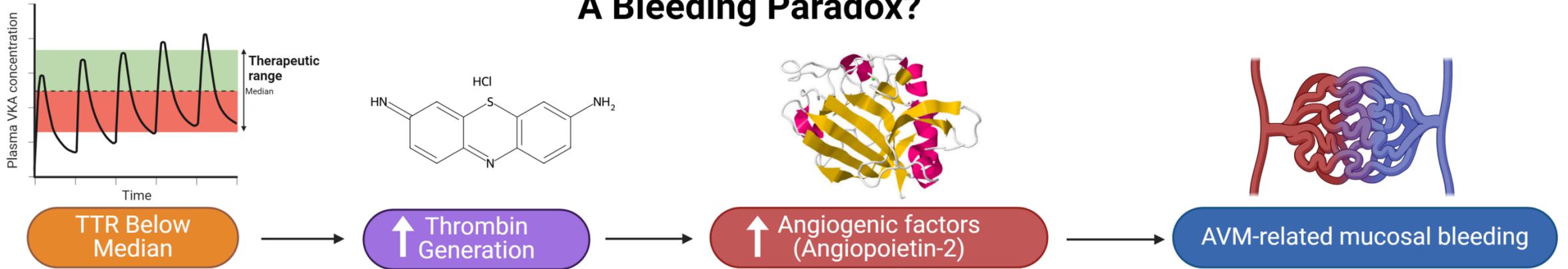


*TR=Therapeutic Range (INR from 2 to 3)

N=277 Placebo, N=277 Aspirin Patients

Strategies to Mitigate Bleeding Complications with the HM3 LVAD

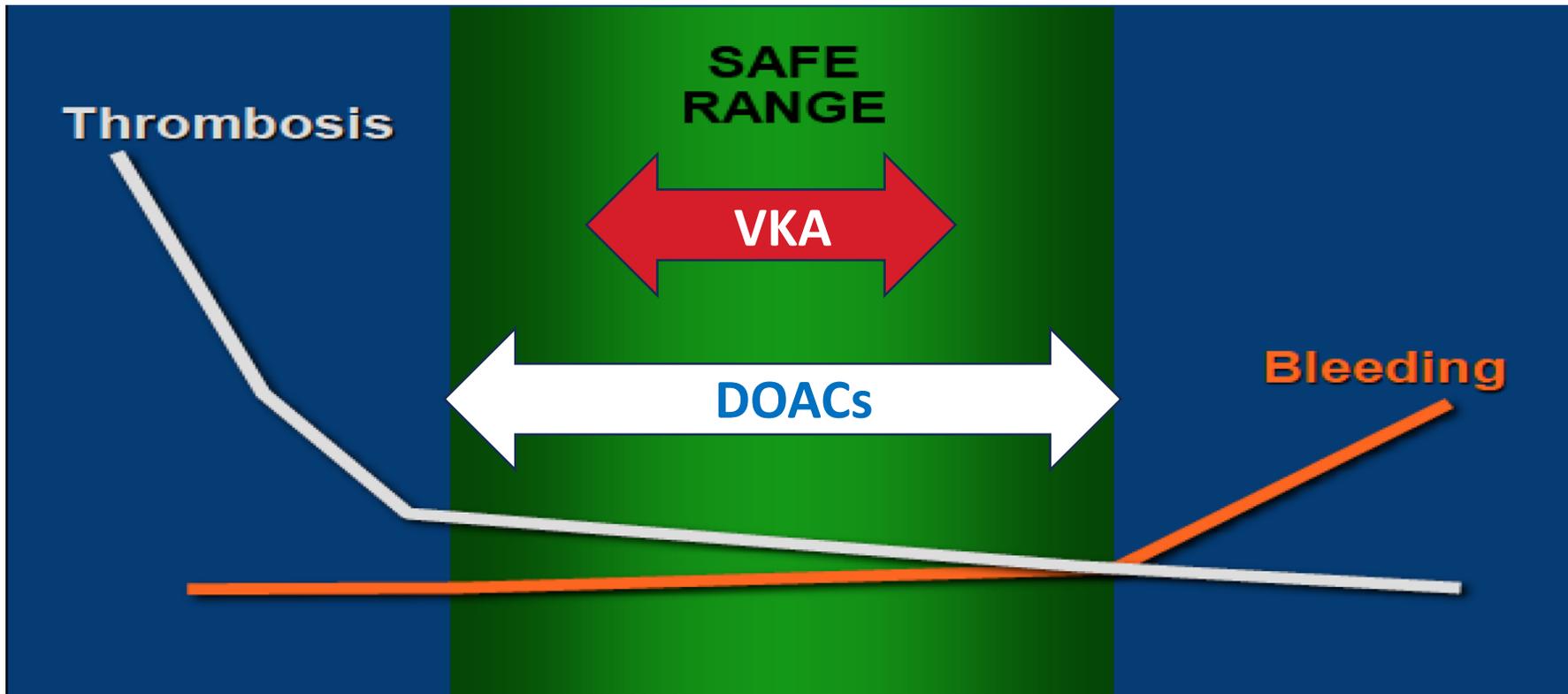
A Bleeding Paradox?



VKA, Vitamin K Antagonist; HM 3, HeartMate 3; DOAC, Direct Oral Anticoagulant; INR, International Normalized Ratio; TTR, Time in Therapeutic Range; AVM, Arteriovenous Malformation.

Direct oral anticoagulants and anticoagulants and LVADs

- Vitamin-K Antagonist (VKA) remains suboptimal and resource intensive
- Direct oral anticoagulants (DOACs) alternative with a potential of better compliance and no additional monitoring for dose adjustments



A Prospective Randomized Trial of Direct Oral Anticoagulant Therapy with A Fully Magnetically Levitated LVAD

The DOT-HM3 Study

Ivan Netuka, Zuzana Tucanova, Peter Ivak, Stanislav Gregor, Dushan M. Kolesar, Tomas Marek, Vojtech Melenovsky, Jana Binova, Zora Dorazilova, Marketa Hegarova, Martina Podolec, Hynek Riha MD, Jean M. Connors and Mandeep R. Mehra



Direct Oral Anticoagulant Therapy With the HeartMate 3 LVAD (DOT-HM3) Trial

Study Aim

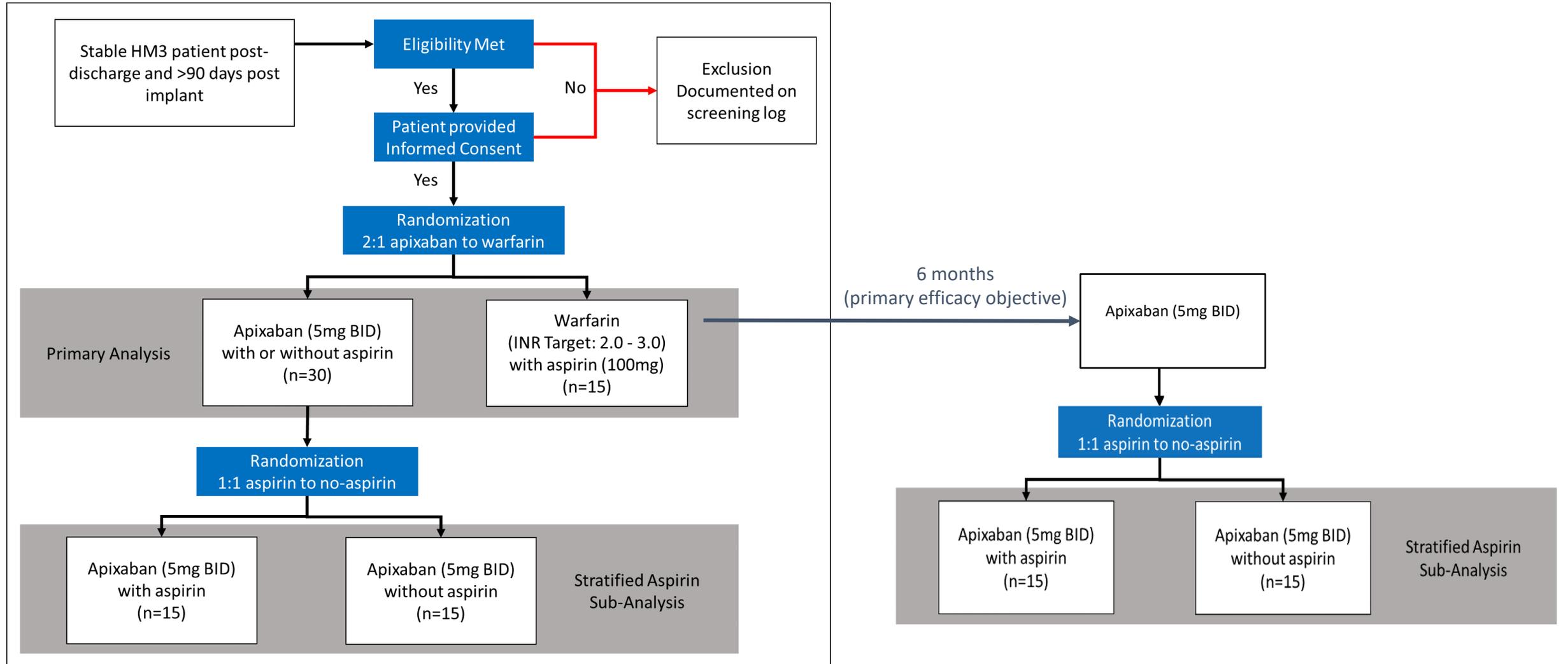
- Prospective, single-center, randomized, safety and feasibility trial of apixaban anticoagulation in patients on HeartMate 3 LVAS (*Clinical Trials.gov NCT04974684*)

Primary Endpoint

- The primary safety endpoint was survival-free of pump thrombosis, disabling stroke, or major bleeding at 3 months post-randomization.
- If no safety concerns, clinical outcomes were mandated at completion of 6-month follow-up.
- Heart transplantation was considered success, and other withdrawals, a failure.

Funding: Investigator-initiated study supported by an institutional grant by Abbott (USA). The sponsor was not involved in the design, execution, analysis or presentation and publication decisions of the study

DOT-HM3 Study Design



Clinical Outcomes (6-months)

CLINICAL OUTCOME (6-months)	APIXABAN + 100mg ASA N=15	APIXABAN Alone N=16	Warfarin + 100 mg ASA N=14
Cumulative Follow-up (pt/days)	2338	2656	2338
Primary outcome: Patient survival-free of pump thrombosis, disabling stroke, or major bleeding (HTx considered success and other withdrawal a failure)	13/15 (86.7%)	15/16 (93.7%)	12/14 (85.7%)
Individual Components			
Thromboembolism (pump malfunction, stroke or arterial thromboembolism) at 6 months	0	0	0
Major bleeding	1 (Gastrointestinal)	0	2* (uterine)
Withdrawals (without a primary event or transplantation)	1	1	1
Heart transplants	4	2	1

* 2 uterine bleeding events occurred in 1 patient (treated as a single count in the primary endpoint)

A Prospective Randomized Trial of Direct Oral Anticoagulant Therapy with A Fully Magnetically Levitated LVAD: The DOT-HM3 Study

Ivan Netuka, MD, PhD¹, Zuzana Tucanova, MD¹, Peter Ivak, MD, PhD¹, Stanislav Gregor, PharmD¹, Dushan Michael Kolesar, MD¹, Tomas Marek, MD¹, Vojtech Melenovsky, MD¹, Jana Binova, MD¹, Zora Dorazilova, MD¹, Marketa Hegarova, MD, PhD¹, Martina Podolec, MD¹, Hynek Riha MD, PhD¹, Jean M. Connors, MD², Mandeep R. Mehra, MD, MSc²

¹Institute for Clinical and Experimental Medicine, Prague, Czech Republic, ²Brigham and Women's Hospital and Harvard Medical School, Boston, MA

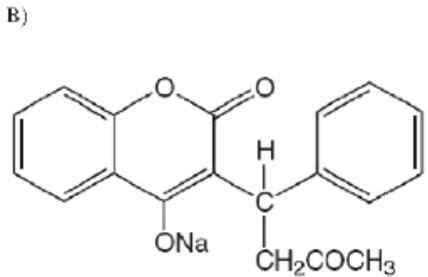
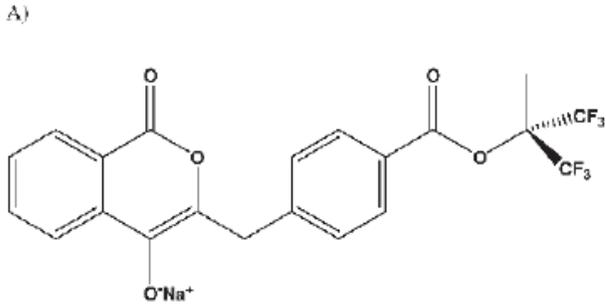
Direct Oral Anticoagulants in LVAD

- 3 “exploratory safety trials”
- \cong 150 total patients
- Apixaban
 - a) DOT HeartMate 3 Study (NCT04974684), n= 45 (5mg BID)
 - b) DOAC LVAD (NCT04865978), n=30 (5 mg BID)*
 - c) APIXI-VAD (ACTRN12621000956808), n=30 (2.5 mg BID)
- Bridge to transplant reversal concerns
- Early versus Late use concerns
- Practice change will require a well-powered RCT
- Clinical comfort will drive eventual practice

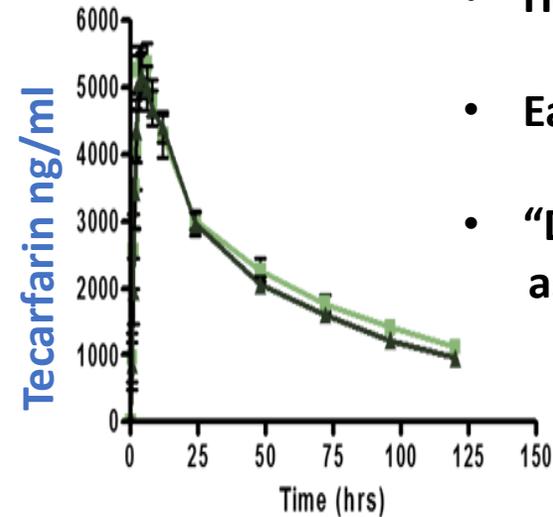
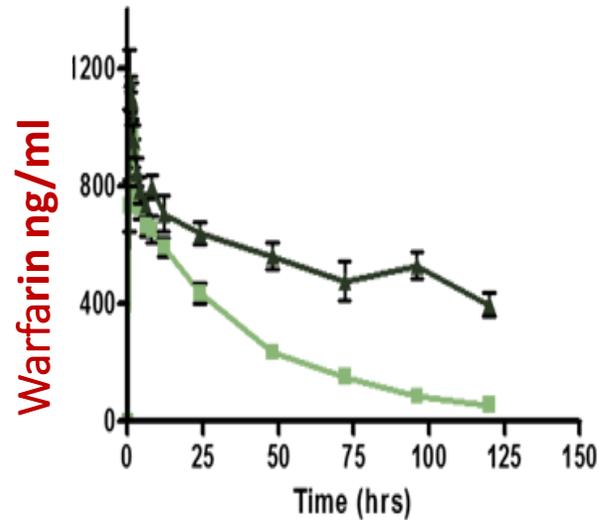
Tecarfarin versus Warfarin: TEC-LVAD Trial

A Novel Vitamin K Antagonist?

Tecarfarin



Warfarin



PRE Fluconazole
Post Fluconazole

- Preserved benefits of Warfarin
- Heightened attained TTR
- Ease in a spectrum of designations
- “DOAC like” dosing & monitoring associated QoL

Fluconazole is broad CYP450 inhibitor incl. CYP2C9

Tecarfarin Pivotal Trial Design for LVAD Patients

*TEC*arfarin Anticoagulation and *H*emocompatibility in *LVAD* Patients (*TECH-LVAD*)

A randomized, single-blind, phase 3 pivotal study to evaluate the efficacy and safety of tecarfarin compared to warfarin in patients with an approved left-ventricular assist device



Planned
Enrollment
N = 440

Patients implanted with an approved LVAD and older than 18 years of age.

R
1:1
Randomization

Tecarfarin (n = 220)

Treatment for 53 weeks

Warfarin (n = 220)

Primary Endpoint:

Hierarchical Composite

- Death
- Stroke
- Device Thrombosis/Thromboembolus
- Major Non Surgical Hemorrhage
- Moderate Non Surgical Hemorrhage
- TTR

Hemodynamic Sensors Guided LVAD Timing & Management

Use of a Pulmonary Artery Pressure Sensor to Manage Patients With Left Ventricular Assist Devices

Vinay Thohan, MD; Jacob Abraham MD, PhD; Adam Burdorf, DO, MS; Nasir Sulemanjee MD; Brian Jaski, MD; Maya Guglin MD, PhD; Francis D. Pagani MD, PhD; Himabindu Vidula MD, MS; David T. Majure MD, MPH; Rebecca Napier, MD; Thomas J. Heywood, MD; Rebecca Cogswell MD; Nicholas Dirckx MPH; David J. Farrar PhD; Stavros G. Drakos MD, PhD; on behalf of the INTELLECT 2-HF Investigators*

HeartMate™ LVAD

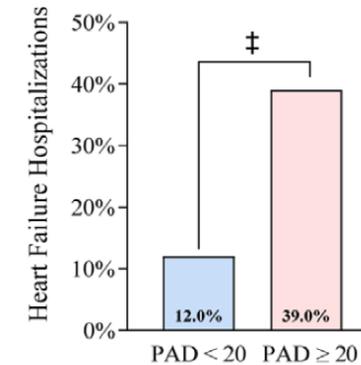
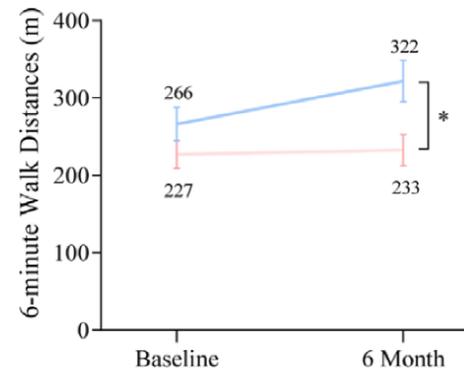
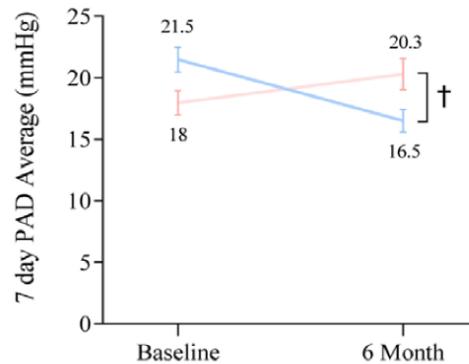


CardioMEMS™-HF System

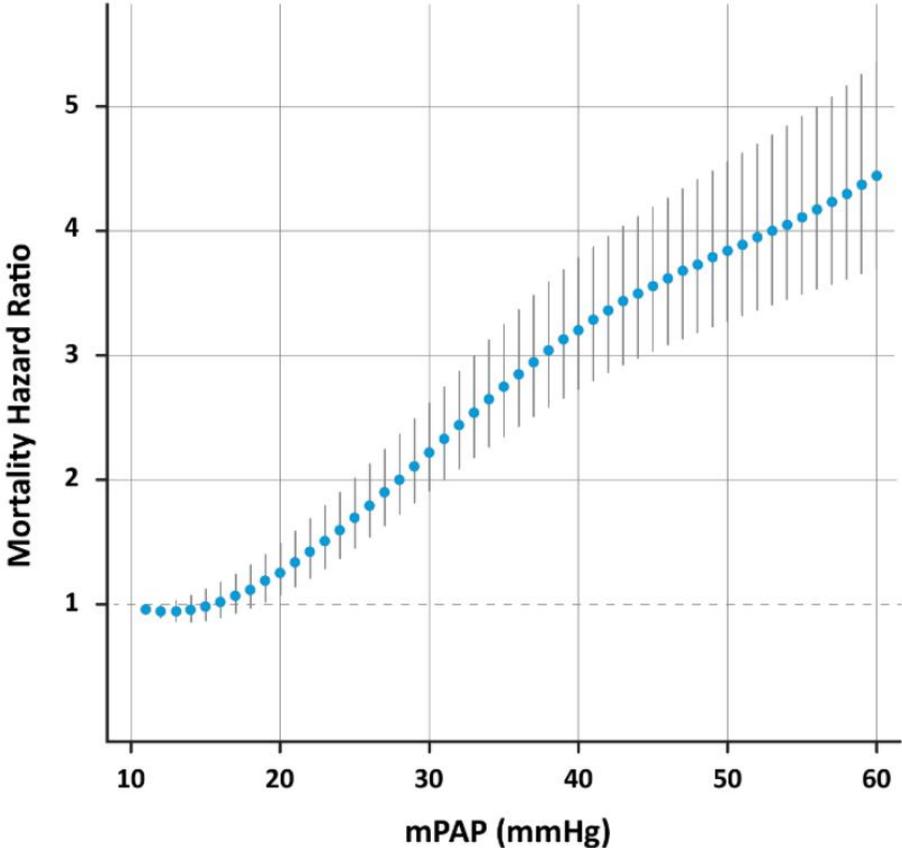


101 Total Patients with Both Devices

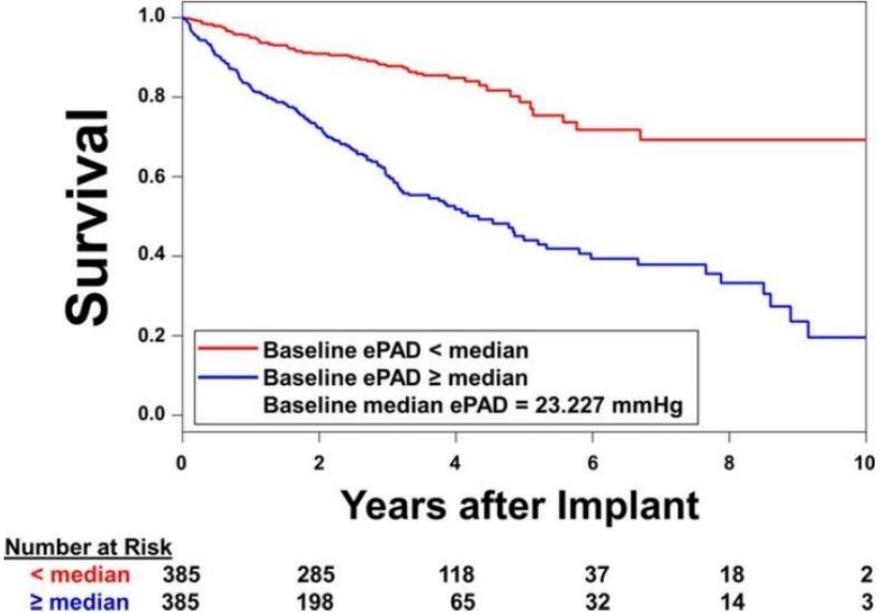
	PAD (mmHg)	6MWD (m)
Responder	↓	↑
Non-Responder	↑	↓



Hemodynamic Sensors Guided LVAD Timing & Management



RELATIONSHIP BETWEEN ESTIMATED PULMONARY ARTERY DIASTOLIC PRESSURE (EPAD) AND MORTALITY



Hemodynamic Sensors Guided LVAD Timing & Management



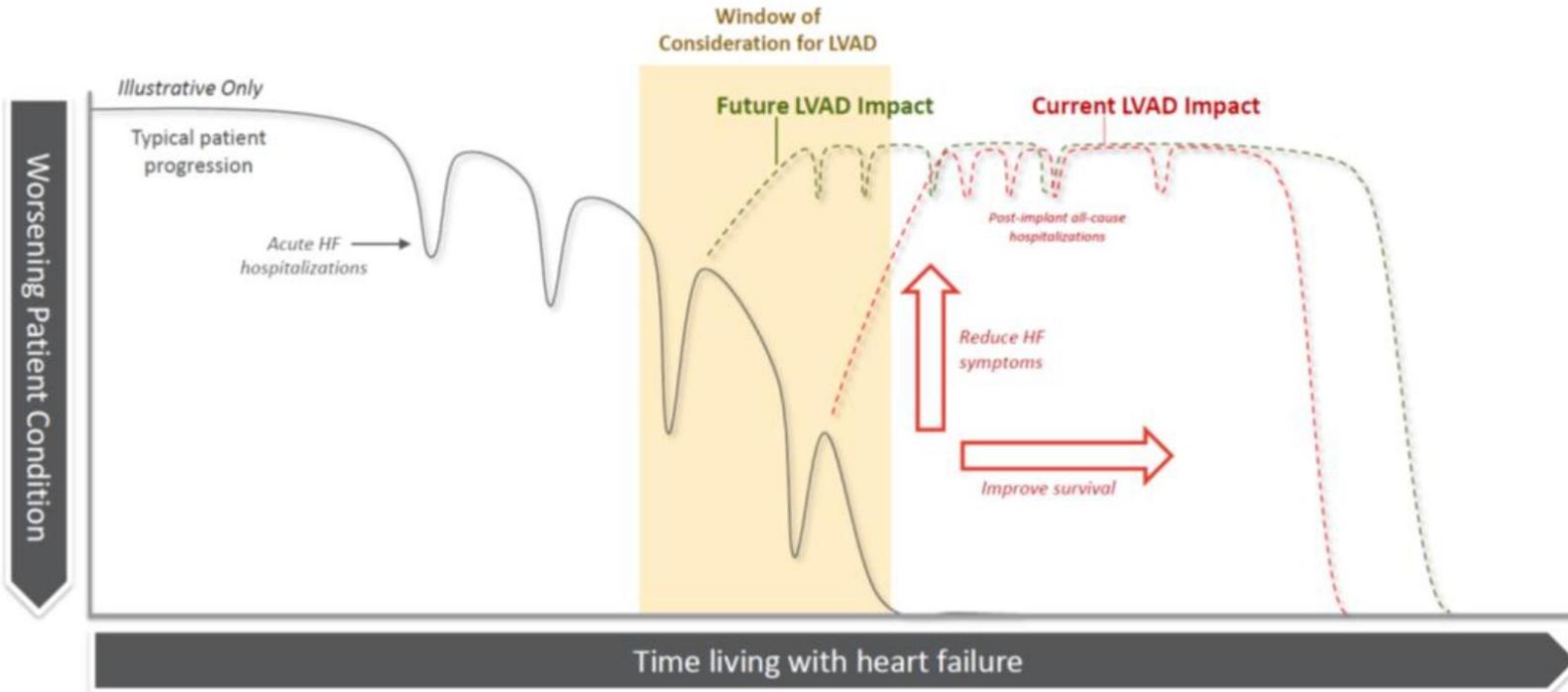
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Trial to Evaluate Safety And Effectiveness of Mechanical Circulatory Support in Patients With Advancing Heart Failure (TEAM-HF)

CardioMEMS™ HF System

HeartMate™ 3 LVAD

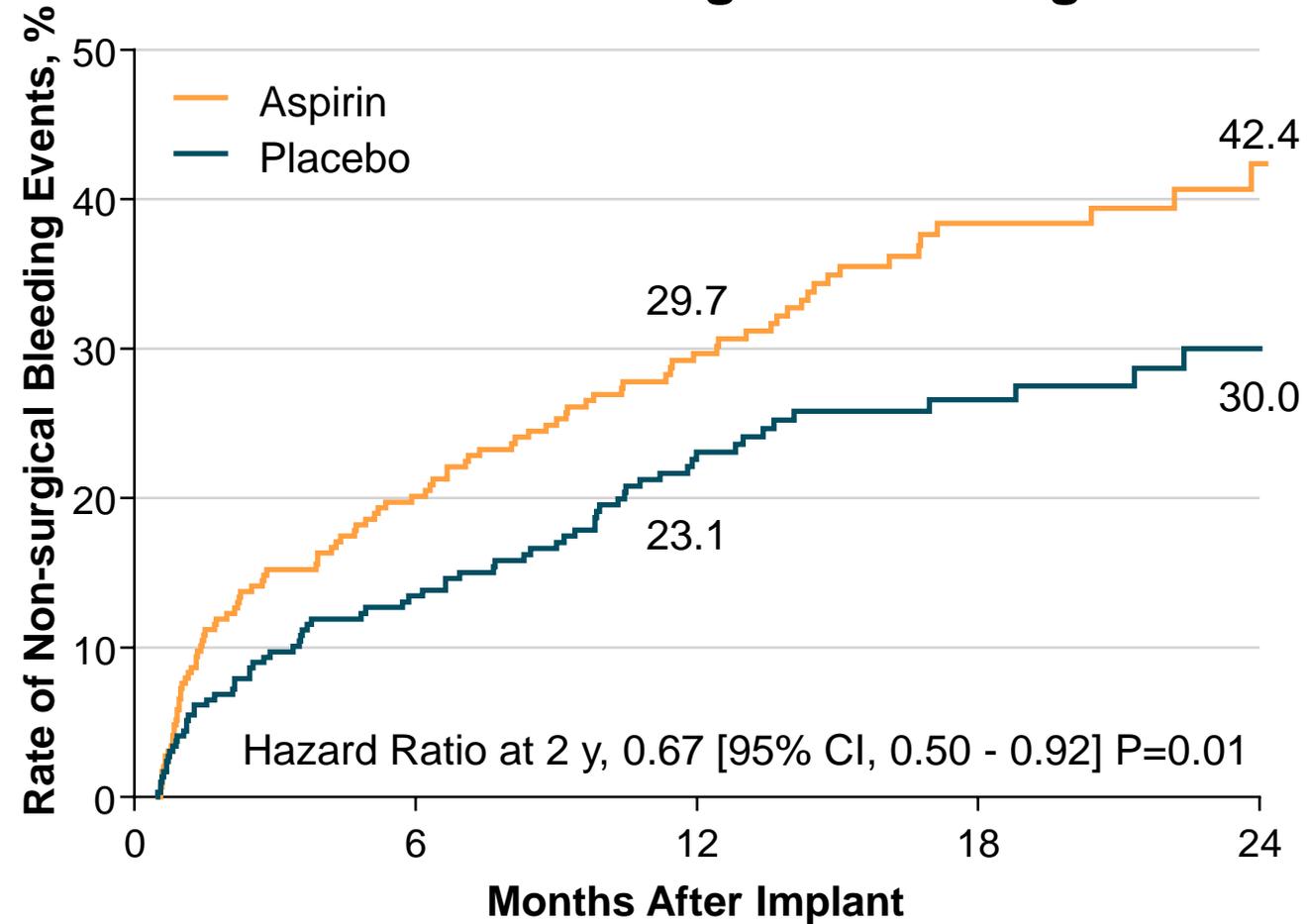


Conclusions

- LVADs – game-changer in HF patients prognosis with significant survival benefit
- 5-years survival above 60% with improved functional capacity and QoL
- Accomplishments in addressing residual risks (bleeding AEs)
- Signal of DOACs (Apixaban) safety use
- Exploratory trial with more stable VKA (TECH-HM3 Tecarfarin)
- Potential of advancing the therapy with currently existing technology

Principal Secondary Endpoint

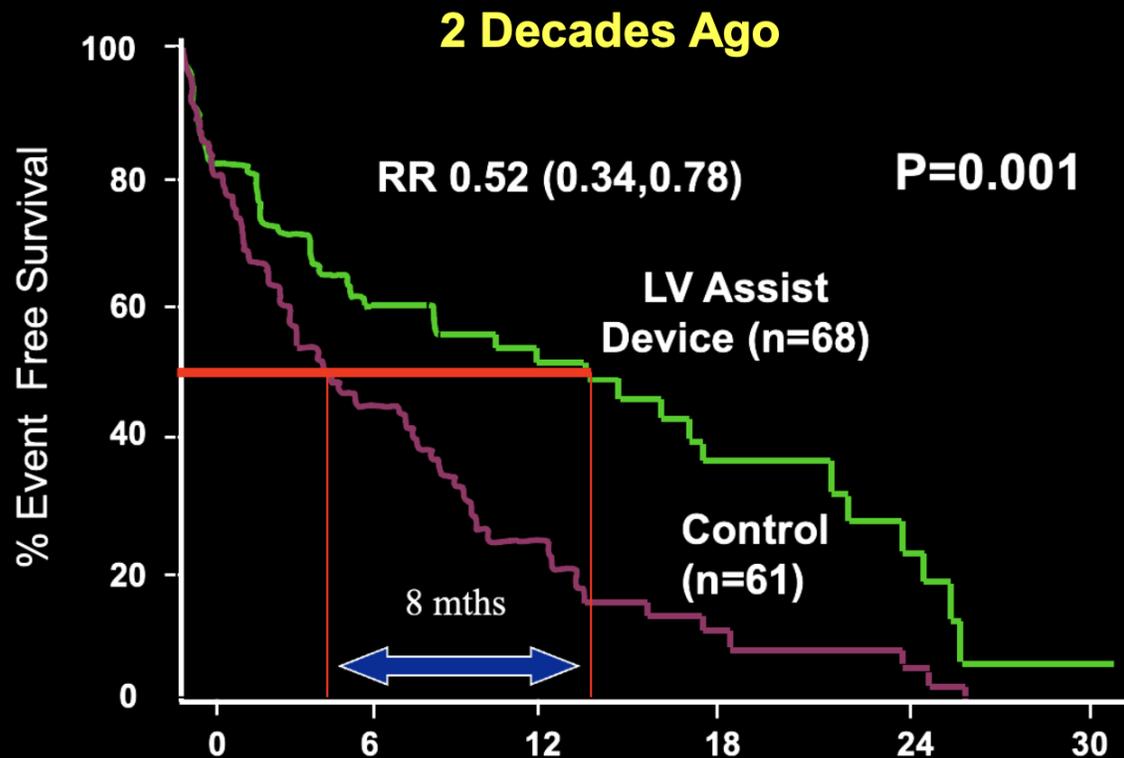
Rate of Non-surgical Bleeding Events



No. at Risk:

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Aspirin	293	207	148	73	34

The “Base Case” of Continuous Inotropic Support Median Survival <12 months



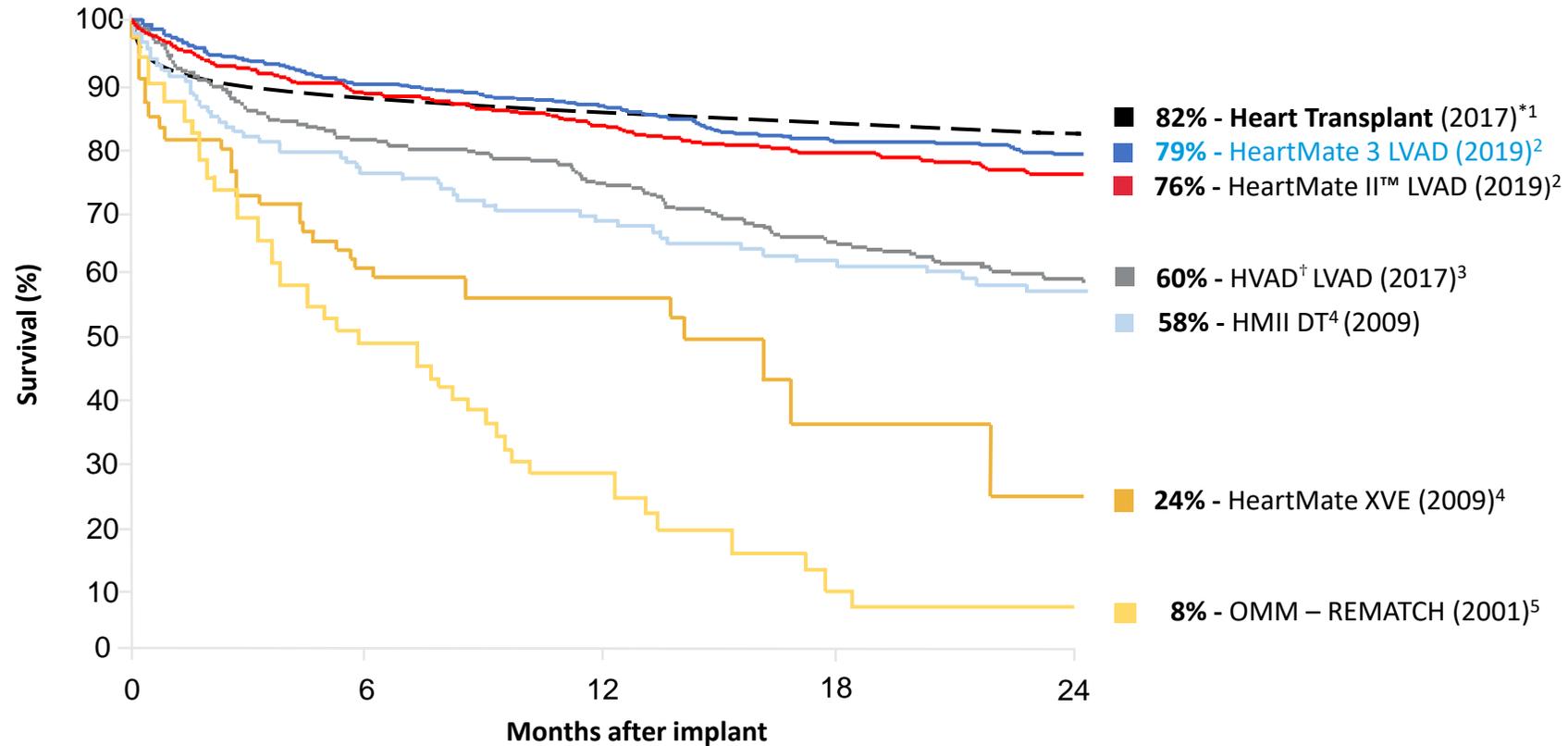
1. *Circulation: Heart Failure* 8.5 (2015): 880-886.
2. *Journal of Cardiac Failure* 27.9 (2021): 974-980.
3. *The Journal of Heart and Lung Transplantation* 39.7 (2020): 721-724.
4. *Journal of Cardiac Failure* 28.12 (2022): 1683-1691.

Contemporary Outcomes

Study	Study type	Time period	Patient population	Survival
¹ Hashim et al.	Retrospective cohort, single center	2007-2013	197 ambulatory patients on iv inotropes, 57% palliative (8% declined LVAD therapy), 30% bridge therapy	Median survival: 9.0 months (IQR: 3.1–37.1), actuarial 1-year survival of 47.6%, and 2-year survival of 38.4% for palliative group
² Rao et al.	Retrospective cohort, single center	2010-2016	373 ambulatory patients on iv inotropes, 34% palliative, 66% bridge therapy	Mean survival: 6.2 months (SD 6.6) for palliative group, 8.6 months (SD 9.3) for bridge group who did not receive surgical therapy
³ Fendler et al.	Randomized stepped-wedge trial, multi-center	2015-2017	248 patients being evaluated for DT-LVAD, 15% declined, 15% deemed ineligible	1-year survival 50% for decliners, 60% for ineligible patients
⁴ Sami et al.	Retrospective cohort, 2 centers	2015-2019	248 ambulatory patients, on palliative iv inotropes	Median survival: 5.9 months (IQR 1.7–15.8), 1-year survival of 30%

Improvement in ICD, Palliative Care, Medical Therapy

Impact of advancing technology and best practices



Based on published data from multicenter experience and separate studies, which may involve different patient populations and other variables. Not a head to head comparison. Data presented for informational purposes only.

*82% 2-year survival for adult heart transplants patients between 2009 and 2015¹

References: 1. Lund LF, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report—2017; Focus theme: allograft ischemic time. *J Heart Lung Transplant.* 2017;36:1037-1046. 2. Mehra MR, Uriel N, Naka Y, et al. A Fully Magnetically Levitated Ventricular Assist Device-Final Report. *N Engl J Med.* 2019. 3. Rogers JG, Pagani FD, Tatroles AJ, et al. Intrapericardial Left Ventricular Assist Device for Advanced Heart Failure. *N Engl J Med.* 2017;376:451-60. 4. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med.* 2009;361:2241-2251. 5. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med.* 2001 Nov 15;345(20):1435-43.

DOT-HM 3 Study

Entry Criteria

HeartMate 3 LVAS

- INR 2.0-3.0 + ASA 100mg*

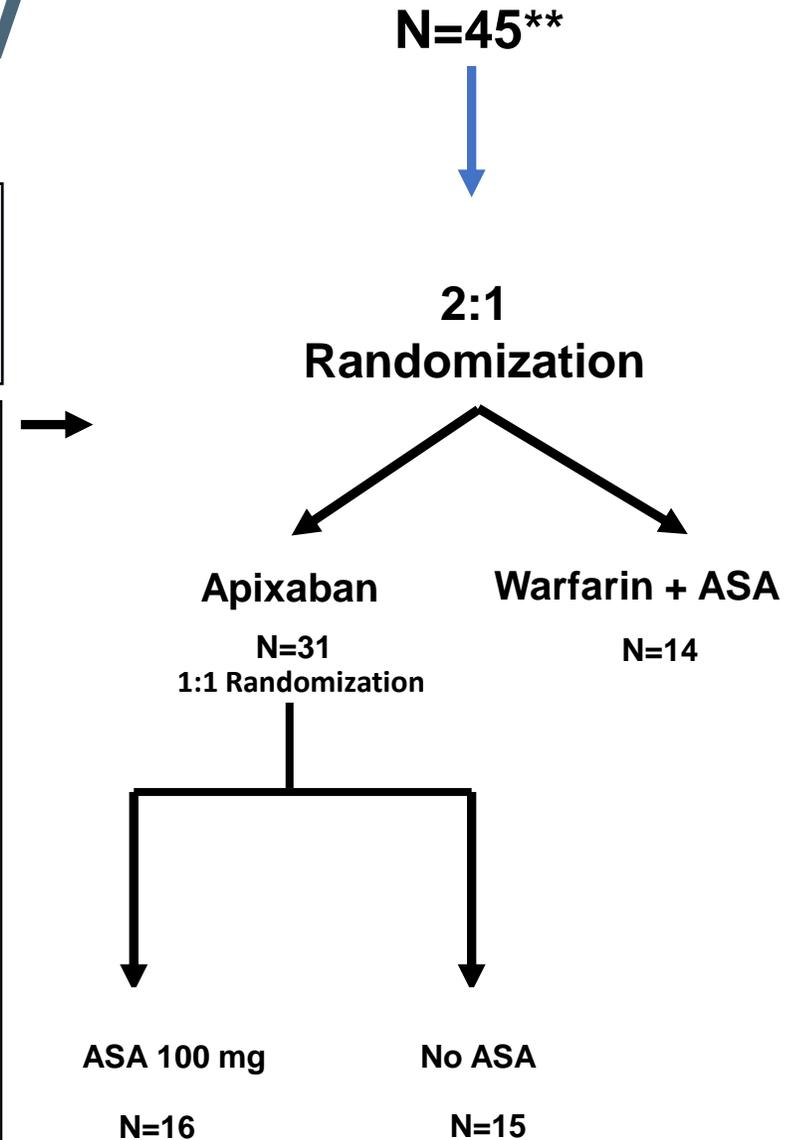
- Minimum 3 months post HeartMate 3 implant
- Stable, ambulatory and home discharged
- Consent provided

Key Exclusion Criteria

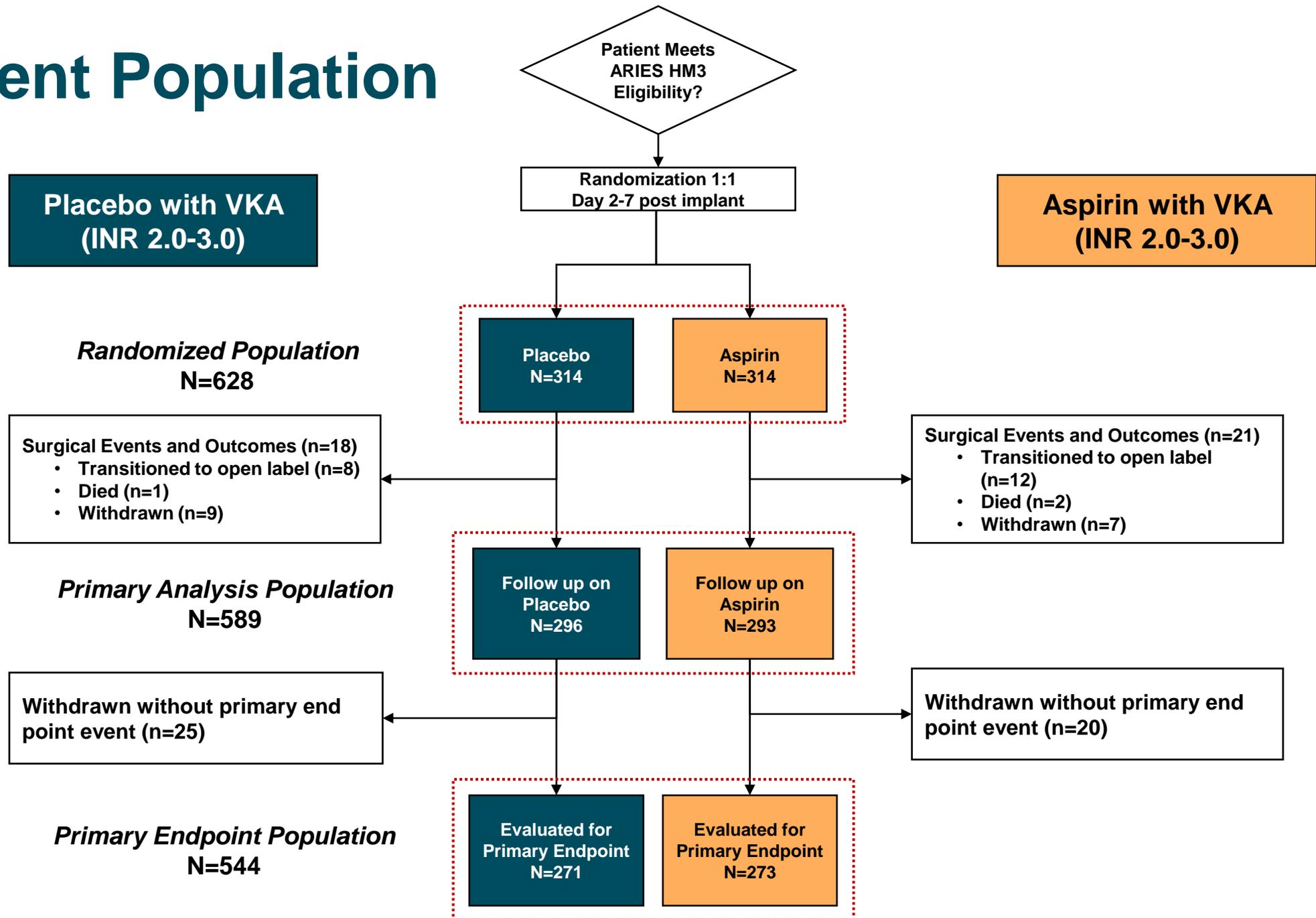
- Any Thromboembolism or Major Bleeding after implant
- Weight \leq 60 kgs. or age \geq 80 years
- Poor kidney function with serum creatinine \geq 221 μ mol/L or creatinine clearance $<$ 0.042 mL/s
- Mechanical valve or ancillary MCS
- Hemodynamically significant carotid stenosis
- Need for antiplatelet therapy for reasons other than LVAD therapy
- History of hyper-/hypo- coagulable disorder
- Aspirin or Apixaban hypersensitivity

*ARIES trial results unknown at inception of trial

**No study power assigned in this exploratory study and ITT principles used in describing outcomes

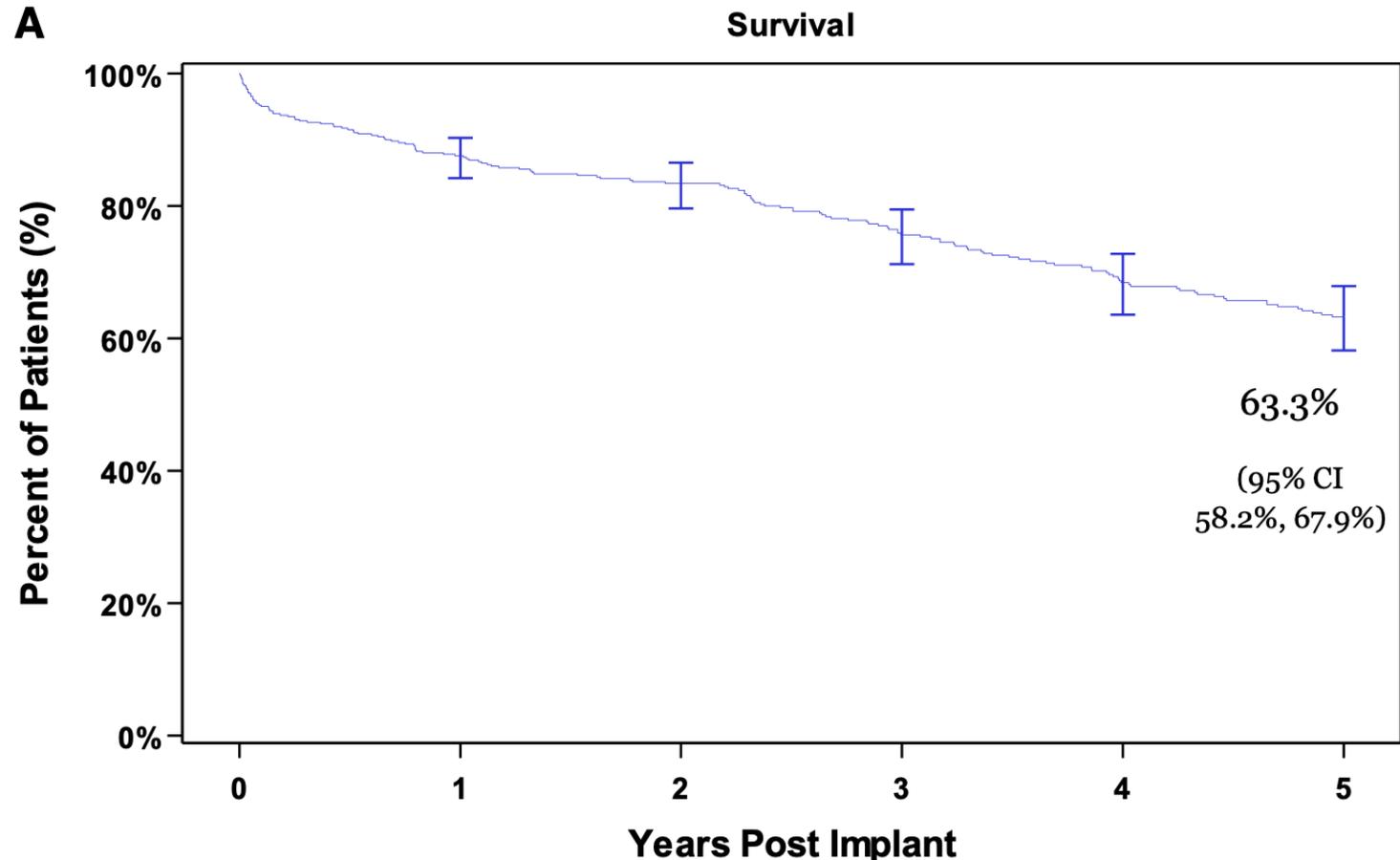


Patient Population

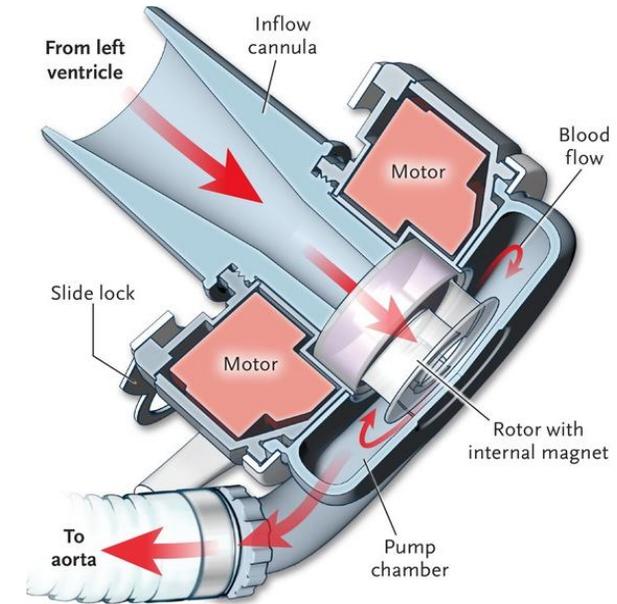
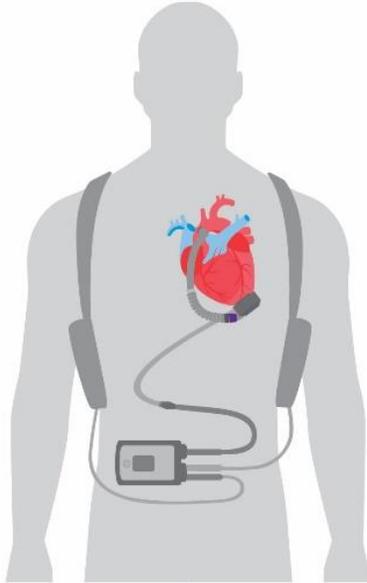


Fully magnetically centrifugal left ventricular assist device and long-term outcomes: the ELEVATE registry

Jan D. Schmitto^{1*†}, Steven Shaw^{2†}, Jens Garbade³, Finn Gustafsson⁴, Michiel Morshuis⁵, Daniel Zimpfer⁶, Jacob Lavee⁷, Yuriy Pya⁸, Michael Berchtold-Herz⁹, Aijia Wang¹⁰, Carlo Gazzola¹⁰, Evgenij Potapov^{11†}, and Diyar Saeed^{12†}; on behalf of the ELEVATE Registry Investigators



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

DOT HM3 Study Results – 3 + 6 months

Study group	Warfarin+ASA	Apixaban	Apixaban+ASA
Randomized	14	16	15
3M follow up completed	13	15	13
Withdrawn	1	1	2
Reason	palliative care (85 days in the study)	Tx (55 days)	Tx (14 days) GI bleeding (20 days)
HRAEs in the first 3M	2 episodes of metrorrhagia in 1 patient (21 and 54 days in the study) epistaxis (2 days in the study)	0	GI bleeding (20 days)
Mortality in the first 3M	0	0	0

Study group	Warfarin+ASA	Apixaban	Apixaban+ASA
6M follow up completed	12	13	9
Withdrawn between 3 and 6 months	1	2	4
Reason	Tx (90 days)	Tx (107 days) Mediastinitis (161 days)	Non-compliance (98 days) Tx (168 days) Tx (161 days) Tx (125 days)
HRAEs between 3 and 6 months	0	0	0
Mortality between 3 and 6 months	0	0	0