Effects of A Fully Magnetically Levitated Centrifugal-Flow or Axial-Flow Left Ventricular Assist Device on Von Willebrand Factor

A Prospective Multicenter Clinical Trial

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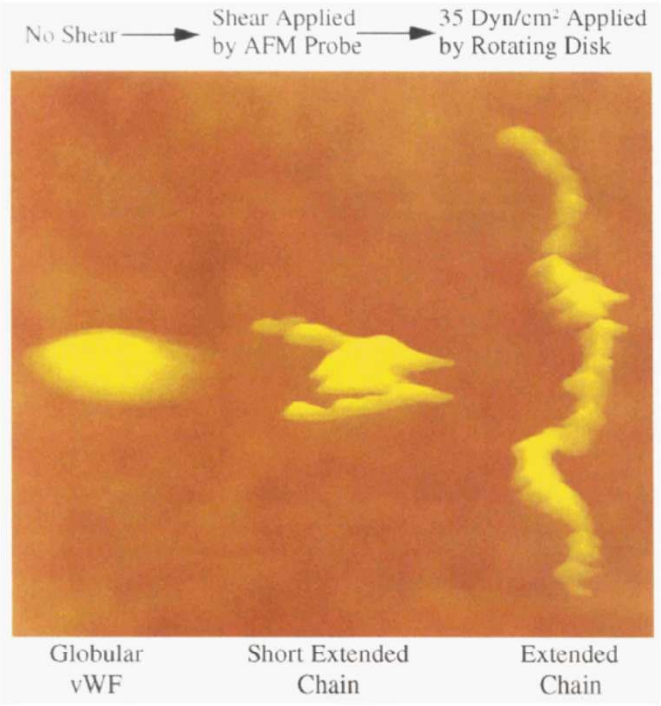
MOMENTUM 3

Financial Disclosures

- Consultant and recipient of research grants from Abbott and TandemLife

von Willebrand Factor (vWF)

- Multimeric protein that binds collagen on vascular sub-endothelium and platelets
- High molecular weight multimers (HMWM) of vWF are more active in mediating platelet adhesion and aggregation
- Protein responds to shear stress by exposing binding and cleavage domains for ADAMTS13 to cleave to form smaller multimers
- Acquired von Willebrand Syndrome (AvWS) is a disorder of vWF characterized by decreased HMWM
  - Congenital von Willebrand Disease results in decreased vWF antigen, function, or both[1]



Siedlecki CA, Lestini BJ, et al. Blood. 1996 Oct; 88(8):2939-50

[1]SChen D, Tange JI, Meyers BJ, et al. *J Thrombosis and Haemostasis*. 2011 Oct;9(10)

LVADs and vWF HMWM

- Loss of vWF HMWM is attributed to shear damage (force and time of exposure) in LVADs

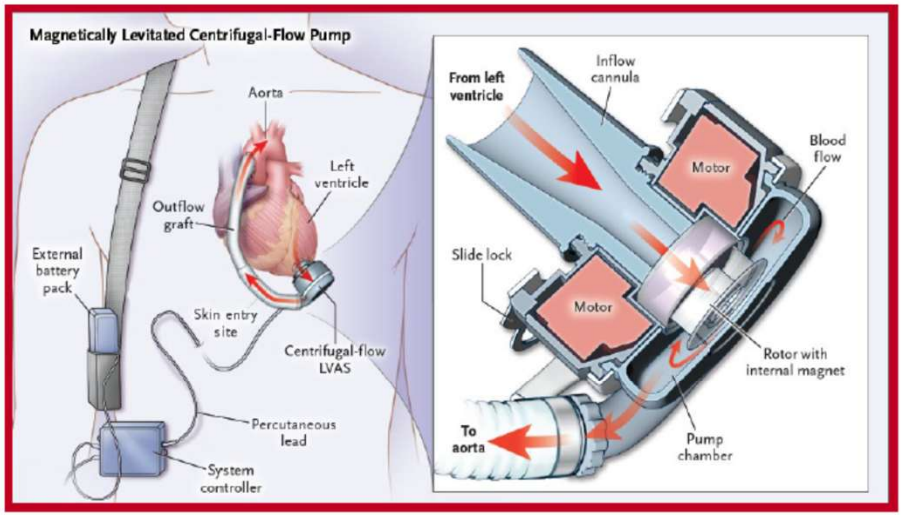
- Association of GI Bleeding noted with loss of vWF HMWM

- Axial flow LVADs (HM II) and Centrifugal Flow LVADs (HVAD) both associated with similar effects on vWF HMWM[1]

[1]Proudfood AG, Davidson SJ, Strueber M. *J Heart Lung Transplant*. 2017;36:1155-1163

The HM3 LVAD and vWF HMWM

- Single-center experiences evaluating vWF HMWM suggested greater preservation with HM3 compared with other devices[1,2]
  - *Studies not designed to evaluate clinical outcomes from bleeding*



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

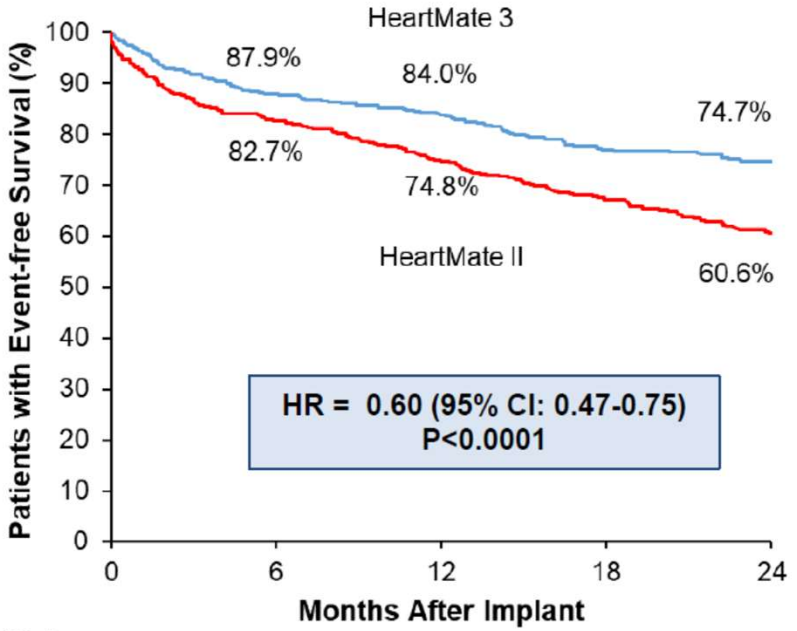
Mehra MR et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* 2017;376(5):440-50

[1]Netuka I, Kvasnicka T, Kvascnicka J, et al. *J Heart Lung Transplant*. 2016;35-860-7

[2]Klaeska K, Dieterlen MT, Scholz U, et al. *Eur J Cardiothorac Surg*. 2019 Feb

MOMENTUM 3 TRIAL: Final Results (n=1028)

Primary Endpoint: Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device



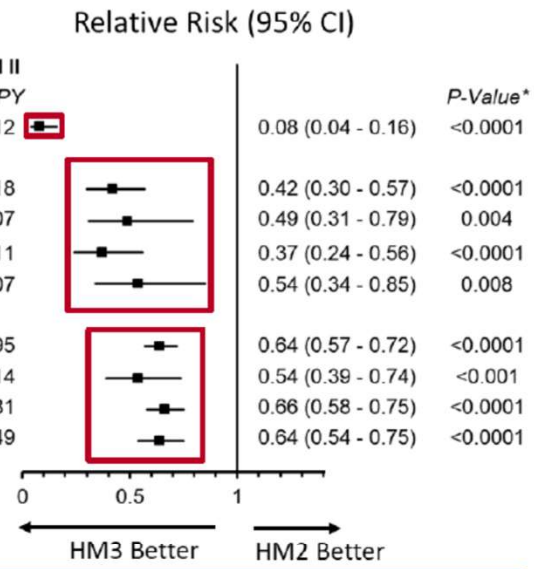
HR = 0.60 (95% CI: 0.47-0.75)
P<0.0001

No. at Risk:

HeartMate 3	516	438	373	313	280
HeartMate II	512	401	321	264	223

Principal Hemocompatibility Related Adverse Events (HRAEs) at 2 years

Adverse Event	HM3 n (%)	HM II n (%)	HM3 EPPY	HM II EPPY	P-Value*
Suspected pump thrombosis	7 (1.4)	70 (13.9)	0.01	0.12	0.08 (0.04 - 0.16) <0.0001
Any stroke	51 (9.9)	98 (19.4)	0.08	0.18	0.42 (0.30 - 0.57) <0.0001
Hemorrhagic stroke	25 (4.9)	43 (8.5)	0.03	0.07	0.49 (0.31 - 0.79) 0.004
Ischemic stroke	29 (5.6)	65 (12.9)	0.04	0.11	0.37 (0.24 - 0.56) <0.0001
Disabling stroke	26 (5.0)	38 (7.5)	0.04	0.07	0.54 (0.34 - 0.85) 0.008
Any bleeding	225 (43.7)	278 (55.0)	0.61	0.95	0.64 (0.57 - 0.72) <0.0001
Requiring surgery	50 (9.7)	89 (17.6)	0.08	0.14	0.54 (0.39 - 0.74) <0.001
Not requiring surgery	197 (38.3)	251 (49.7)	0.53	0.81	0.66 (0.58 - 0.75) <0.0001
Gastrointestinal bleeding	126 (24.5)	156 (30.9)	0.31	0.49	0.64 (0.54 - 0.75) <0.0001



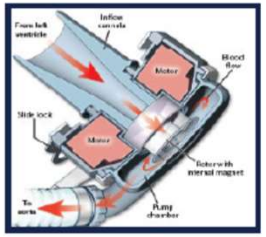
HM3 superior to HMII with reduction in *pump thrombosis*, *strokes* of any type and severity, *all bleeding* including *GI bleeding*, *cardiac arrhythmias* and *hospital readmissions*

Mehra, et al. NEJM 2019; DOI: 10.1056/NEJMoa1900486

Study Objectives

- Evaluate the preservation of vWF HMWM between HM3 and HMII
- Assess vWF functional characteristics
  - vWF Antigen, vWF Activity, vWF Activity to Antigen Ratio, and ADAMTS13
- Correlate clinical characteristics with changes in vWF HMWM and their associations with outcomes related to bleeding complications in HM3
- **Primary endpoint**
  - Comparison of vWF HMWM 90 days post-implant

Consort Diagram



Patients enrolled in MOMENTUM 3 CAP Substudy (HeartMate 3) N = 60

Baseline
N = 56/60

Sample clotted (N=2)
Inadvertently cancelled (N=1)
Lost sample (N=1)

Expired

N=1 – POD 19 – Right Heart Failure

N=1 – POD 46 – Hemorrhagic Stroke

90 Day Post-Implant
N = 53/58

Visit not conducted (N=4)
Sample not collected (N=1)

Evaluable Population with vWF HMWM data at Baseline and 90-Day Post-Implant N=51

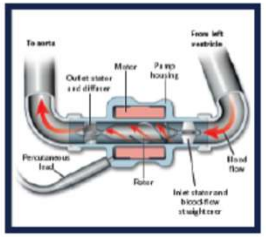
PREVENT Study (HeartMate II) N = 30

Baseline
N = 29/30

Sample Clotted (N=1)

90 Day Post-Implant
N = 30/30

Evaluable Population with vWF HMWM data at Baseline and 90-Day Post-Implant N=29



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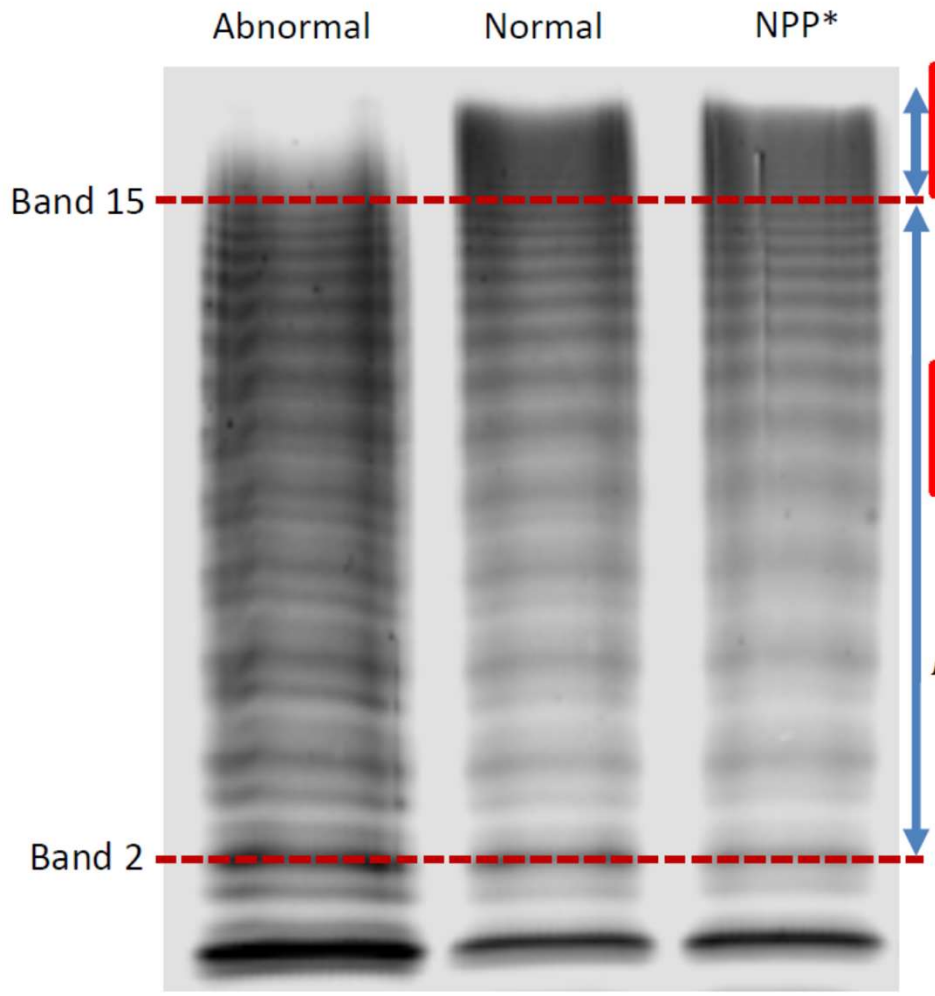
Multimer Quantification Technique



High Molecular Weight Multimers

Low and Intermediate Molecular Weight Multimers

$$vWF\ HMWM\ Ratio = \frac{Fluorescent\ Intensity\ vWF\ HMWM}{Fluorescent\ Intensity\ Low\ and\ Intermediate\ \ MWM}$$

$$Normalized\ vWF\ HMWM\ Ratio = \frac{vWF\ HMWM\ Ratio_{Patient}}{vWF\ HMWM\ Ratio_{NPP}}$$

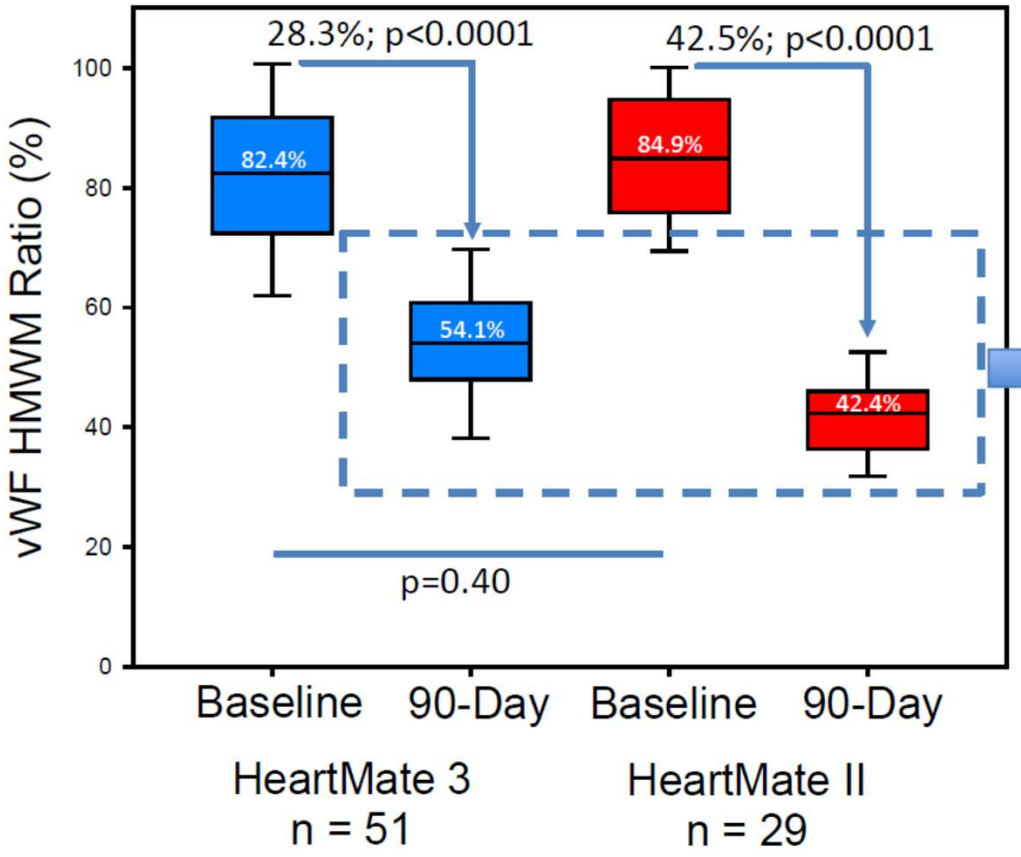
*NPP: Normal Pooled Plasma

Baseline Characteristics

	HM3 (n=51)	HMII (n=29)	P-value*
Age (Years)	60.5 ± 11.9	57.2 ± 15.9	0.55
Male Gender – % (no.)	80.4% (41/51)	100.0% (29/29)	0.01
INTERMACS Profile – % (no.)			
INTERMACS - Profile 1-2 (Severe Heart Failure)	43.1% (22/51)	24.1% (7/29)	
INTERMACS - Profile 3-4 (Less Severe Heart Failure)	56.9% (29/51)	75.9% (22/29)	0.09
Body Surface Area – m^2	2.04 ± 0.24	2.20 ± 0.24	0.006
Diabetes – % (no.)	35.3% (18/51)	55.2% (16/29)	0.08
Arterial Blood Pressure – mm Hg			
Systolic	111.8 ± 15.1	108.8 ± 16.3	0.42
Diastolic	68.0 ± 10.5	63.7 ± 9.1	0.06
Mean Arterial Pressure	83.48 ± 10.55	82.77 ± 9.45	0.76
BUN (mg/dL)	26.18 ± 11.08	33.79 ± 16.59	0.06
Creatinine (mg/dL)	1.36 ± 0.31	1.47 ± 0.51	0.62
eGFR (mL/min/1.73 m^2)	57.8 ± 19.3	60.1 ± 22.1	0.64
ALT (U/L)	41.5 ± 73.6	68.6 ± 175.3	0.43
AST (U/L)	31.7 ± 30.8	52.1 ± 97.9	0.29

*Data were/was compared between groups using t-test, Wilcoxon Rank Sum test, or Fisher's exact test/Chi-square test, as appropriate

vWF HMWM Analysis



Primary Endpoint
p<0.0001

Graph represents Normalized vWF HMWM Ratio of Patient to Normal Pooled Plasma

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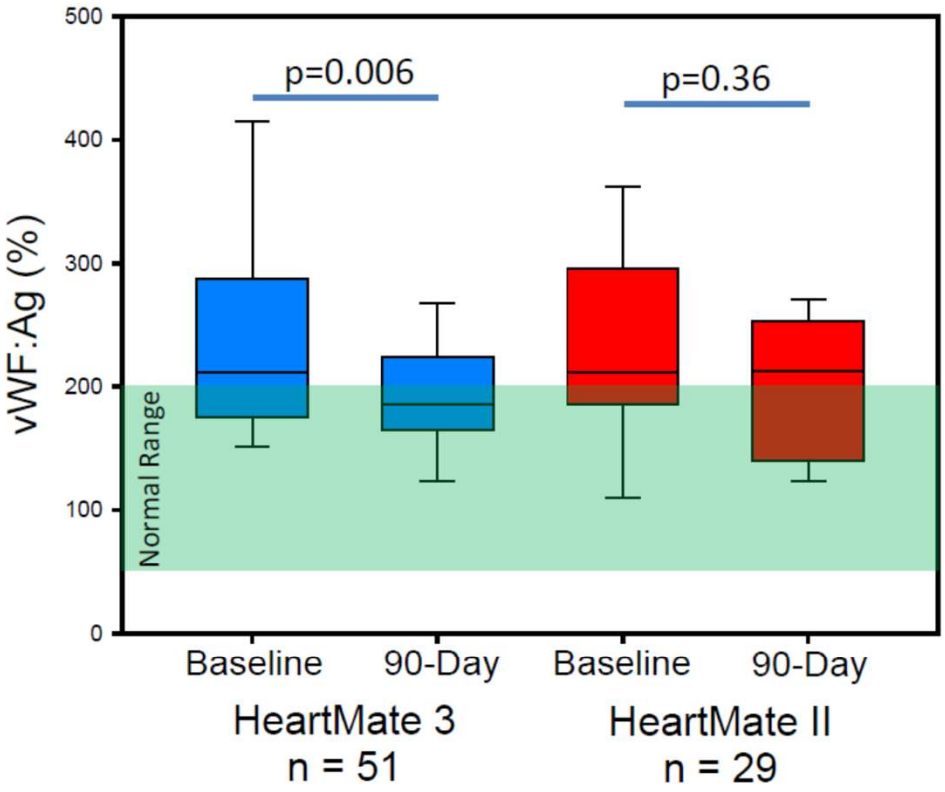
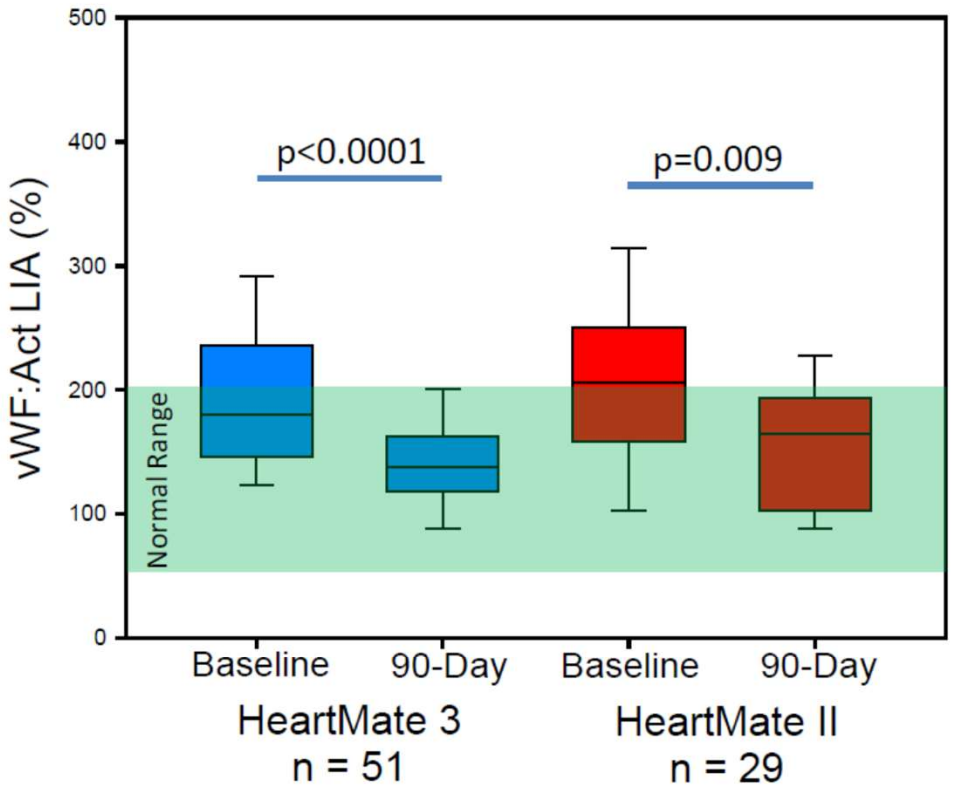
Multivariable Model Analysis

	vWF HMWM	P-Value
Pre-Implant Baseline		
Severity of Heart Failure (INTERMACS Profile: 1-2 vs 3-4)	↓	0.04
Not Significant Variables: Age, MAP, eGFR, Platelets		
90-Day Post-Implant		
Pump (HM3 vs HMII)	↑ (Preserves)	0.001
Not Significant Variables: Age, AST, Creatinine, BUN, Diastolic Pressure, Body Surface Area, Diabetes		

vWF Antigen, vWF Activity and Activity to Antigen Ratio





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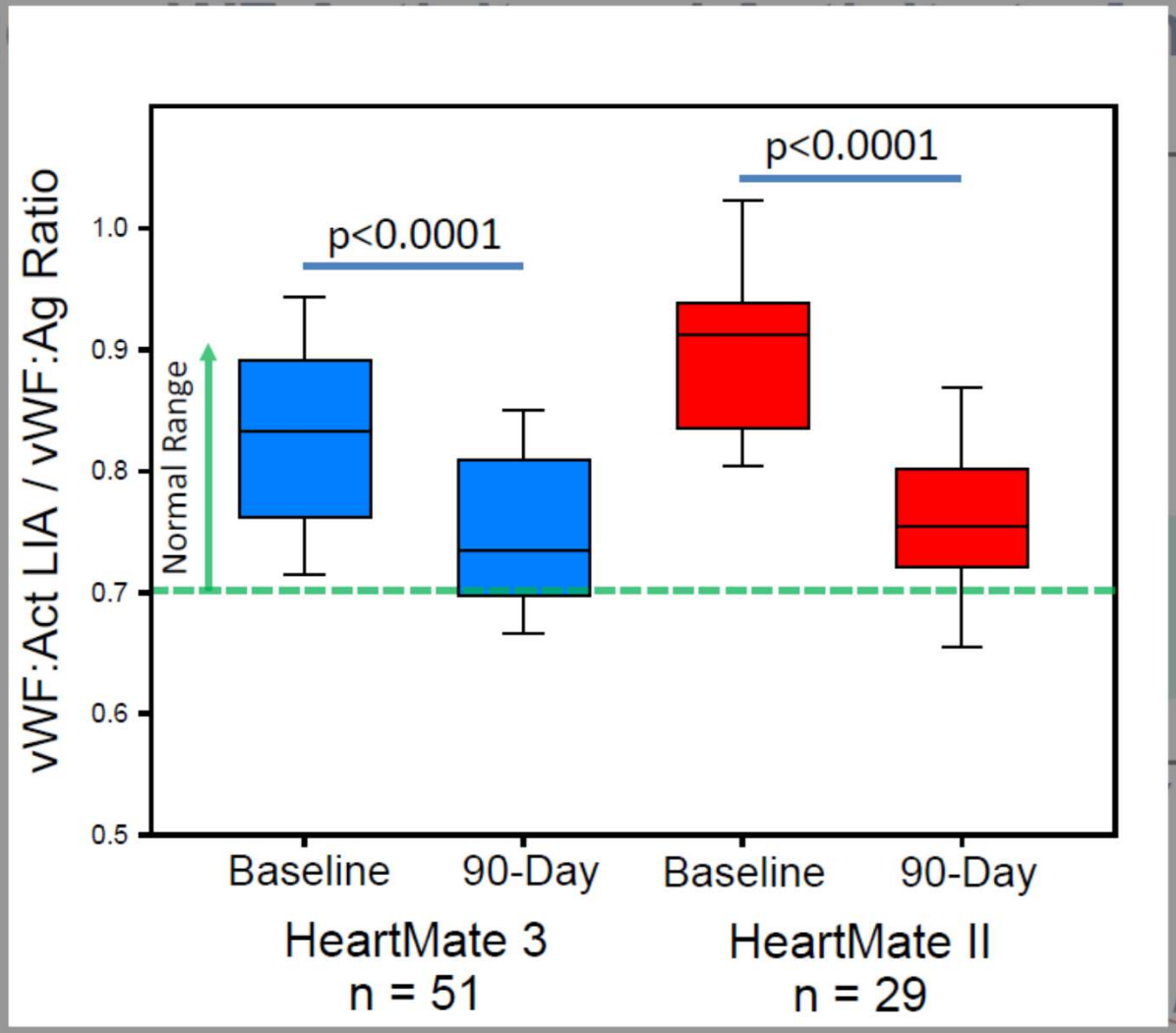
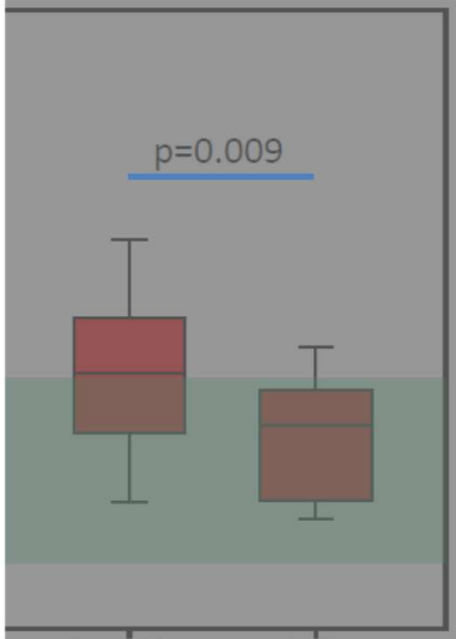
vWF Antig ntigen Ratio





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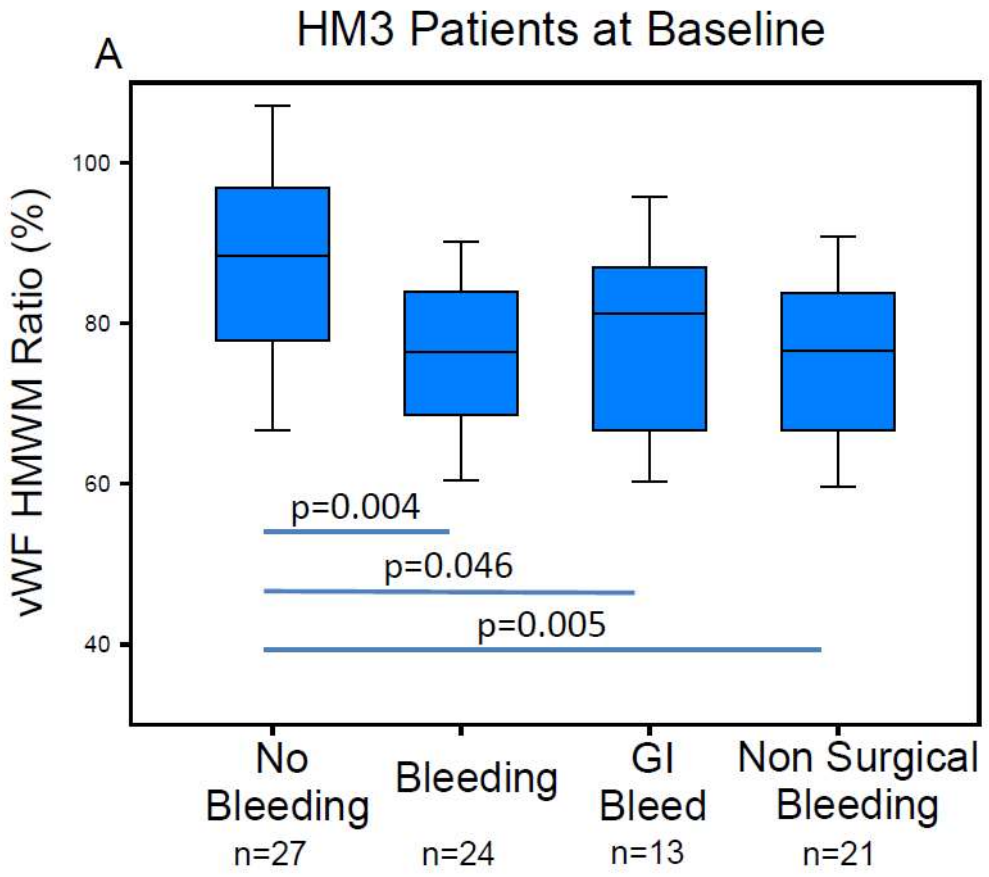
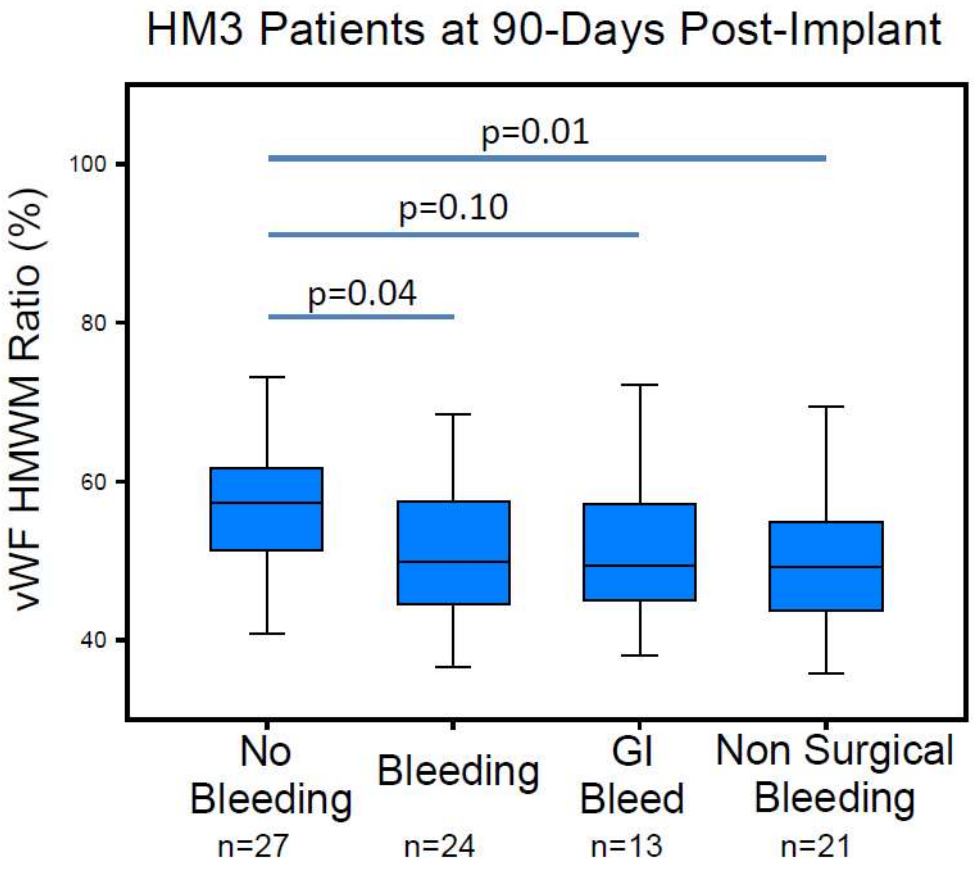
ADAMTS13 Activity

	Baseline	90 Days	
Proportion of Patients with Normal ADAMTS13 Activity (≥70)			
HeartMate 3	82.4% (42/51)	96.1% (49/51)	p=0.05
HeartMate II	72.4% (21/29)	93.1% (27/29)	p=0.08
ADAMTS13 Activity (%) in Patients With Low ADAMTS13 Activity (<70)			
HeartMate 3	59 [41-69]*	53, 50	
HeartMate II	58.5 [43-69]*	68, 44	

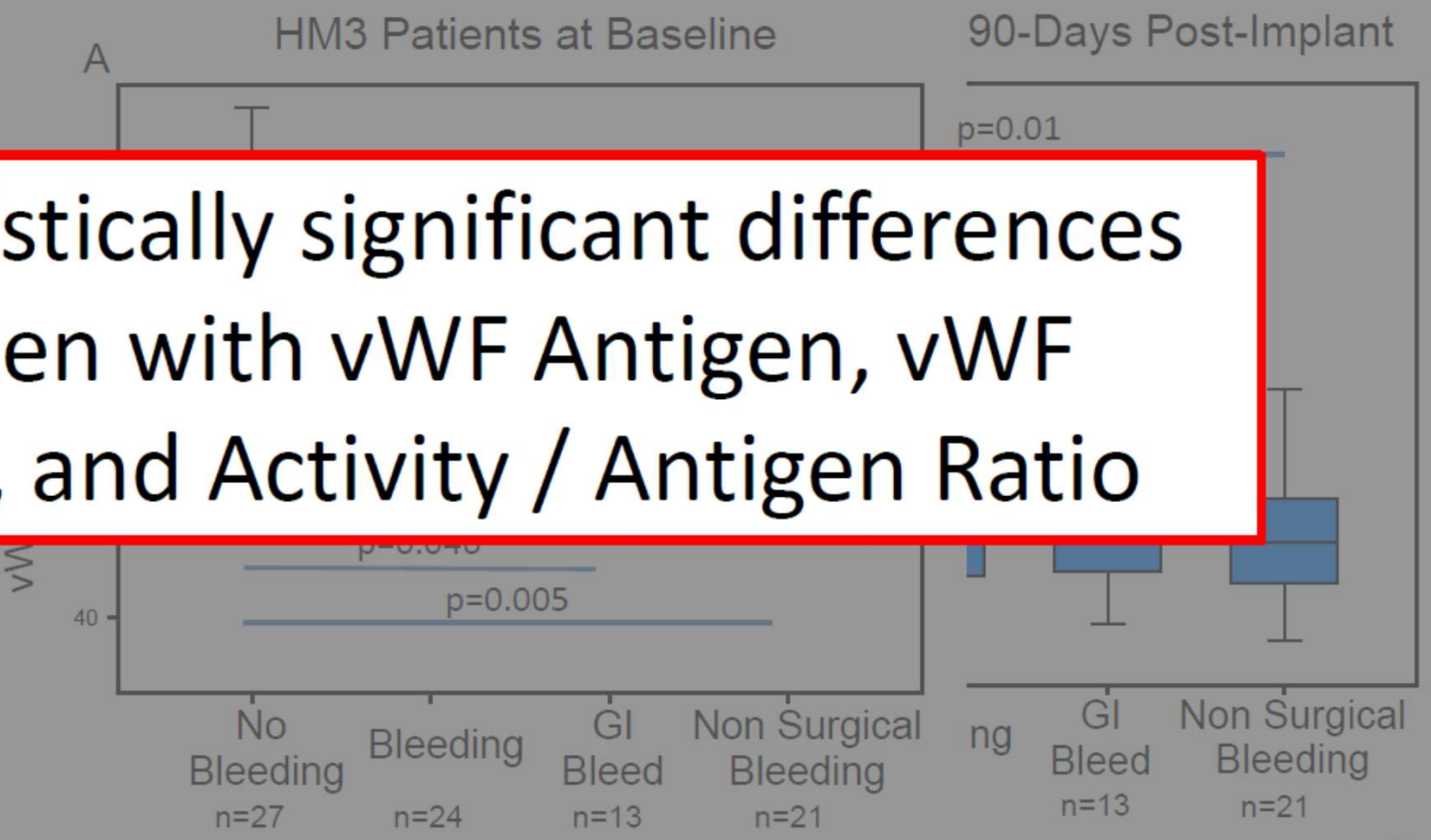
*Values represented as Median [Range]

HM3 Association of Bleeding and vWF HMWM Degradation





HM3 Association of Bleeding and vWF HMWM Degradation



No statistically significant differences were seen with vWF Antigen, vWF Activity, and Activity / Antigen Ratio

Conclusions

- Degradation of vWF HMWM was seen in both pumps
  - Significantly greater preservation of vWF HMWM seen with HM3 compared to the HMII
- Functional attributes of vWF (antigen and activity) are within normal range post-LVAD (although “normal” values post-LVAD may need to be defined)
- vWF HMWM alterations (but not functional changes) are closely correlated with episodes of bleeding and non-surgical bleeding in HM3

Summary

- Advanced heart failure patients pre-implant exhibit vWF HMWM degradation
  - Greater severity of HF at pre-implant is associated with greater loss of vWF HMWM even at the pre-implant measurement
- The degree of loss of vWF HMWM *at pre-implant* correlates with bleeding tendency *post LVAD implant* in HM3
- **Loss of vWF HMWM appears to be a sensitive biomarker for post-LVAD circulation related bleeding complications**

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ORIGINAL CLINICAL SCIENCE

Effects of a fully magnetically levitated centrifugal-flow or axial-flow left ventricular assist device on von Willebrand factor: A prospective multicenter clinical trial

Aditya Bansal, MD,[a] Nir Uriel, MD,[b] Paolo C. Colombo, MD,[c] Keerthy Narisetty, MD,[d] James W. Long, MD, PhD,[e] Arvind Bhimaraj, MD,[f] Joseph C. Cleveland, MD,[g] Daniel J. Goldstein, MD,[h] John Stulak, MD,[i] Samer S. Najjar, MD,[j] David E. Lanfear, MD,[k] Eric D. Adler, MD,[l] Walter Dembitsky, MD,[m] Sami I. Somo, PhD,[n] Daniel L. Crandall, PhD,[n] Dong Chen, MD, PhD,[i] Jean Marie Connors, MD,[o] and Mandeep R. Mehra, MD[o]

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Cardiovascular.Abbott/HeartMate3

Rx Only
Brief Summary: Prior to using these devices, please review the Instructions for Use for a complete listing of indications, contraindications, warnings, precautions, potential adverse events and directions for use.

HeartMate 3™ LVAS Indications: The HeartMate 3™ Left Ventricular Assist System is indicated for providing short- and long-term mechanical circulatory support (e.g., as bridge to transplant or myocardial recovery, or destination therapy) in adult and pediatric patients with advanced refractory left ventricular heart failure and with an appropriate body surface area.

HeartMate 3™ LVAS Contraindications: The HeartMate 3 Left Ventricular Assist System is contraindicated for patients who cannot tolerate, or who are allergic to, anticoagulation therapy.

HeartMate 3™ LVAS Adverse Events: Adverse events that may be associated with the use of the HeartMate 3 Left Ventricular Assist System are: death, bleeding, cardiac arrhythmia, localized infection, right heart failure, respiratory failure, device malfunctions, driveline infection, renal dysfunction, sepsis, stroke, other neurological event (not stroke-related), hepatic dysfunction, psychiatric episode, venous thromboembolism, hypertension, arterial non-central nervous system (CNS) thromboembolism, pericardial fluid collection, pump pocket or pseudo pocket infection, myocardial infarction, wound dehiscence, hemolysis (not associated with suspected device thrombosis) or pump thrombosis.

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