#AHA21

RANDOMIZED TRIAL OF TARGETED TRANSENDOCARDIAL DELIVERY OF MESENCHYMAL PRECURSOR CELLS IN HIGH-RISK CHRONIC HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION – THE DREAM-HF TRIAL

Emerson C. Perin, MD, PhD
Medical Director

Texas Heart® Institute

American Heart Association.

DISCLOSURES

- Mesoblast – Consultant (minor)

DREAM-HF TRIAL

- **Multicenter, randomized, double-blind, sham-controlled, events-driven trial of MPCs in HFrEF**
- **Sponsor:** Mesoblast, Inc.
- **Study Steering Committee:**
  - Emerson C. Perin, Co-Chairman, Texas Heart Institute
  - Barry Greenberg, Co-Chairman, Univ. of California, San Diego
- **Clinical Endpoint Committee:**
  - Scott D. Solomon, Co-Chairman, Brigham & Women's Hospital
  - Hicham Skali, Co-Chairman, Brigham & Women's Hospital
- **Data Monitoring Committee:**
  - Jean Rouleau, Chair, Montreal Heart Institute
  - Henry Dargie, Western Infirmary, Glasgow
  - David DeMets, University of Wisconsin
  - Mandeep Mehra, Brigham & Women's Hospital

DREAM-HF INVESTIGATORS

	Heart Failure Investigator	Interventional Cardiologist	Location of Clinical Trial Site
1	Emerson Perin, MD, PhD	Jie Cheng, MD, R. David Fish, MD	Texas Heart Institute, St. Luke's Hospital, Houston, TX
2	David Chang, MD	Tim Henry, MD	Cedars-Sinai Medical Care Foundation, Los Angeles, CA
3	Alain Bouchard, MD, Thomas Cawthon, MD	Farrell Mendelsohn, MD	Cardiology, P.C., Birmingham, AL
4	Leslie Miller, MD	Parag Patel, MD	Morton Plant Hospital, Clearwater, FL
5	Elizabeth Swiggum, MD	Anthony Della Siega, MD	Victoria Heart Institute Foundation, Victoria, Canada
6	Eric Adler, MD	Ehtisham Mahmud, MD	University of California San Diego, Altman Clinical and Translational Research Institute, La Jolla, CA
7	Robert Scott, MD	David Fortuin, MD	Mayo Clinic, Phoenix, AZ
8	Eugene Chung, MD	Dean Kereiakes, MD	The Christ Hospital Lindner Research Center, Cincinnati, OH
9	(James) Tom Heywood, MD	Richard Schatz, MD	Scripps Clinic, La Jolla, CA
10	Carl Pepine, MD	R. David Anderson, MD	Shand's Hospital at University of Florida, Gainesville, FL
11	Barry Borlaug, MD	Amir Lerman, MD	Mayo Clinic, Rochester, MN
12	Mosi Bennett, MD	Jay Traverse, MD	Minneapolis Heart Institute, Minneapolis, MN
13	Amit Patel, MD , David Bull, MD , Craig Selzman, MD	Anwar Tandar, MD	University Hospital, Salt Lake City, UT
14	David Murray, MD	Amish Raval, MD	University of Wisconsin School of Medicine and Public Health, Madison, WI
15	Neal Lee Weintraub, MD	Adam Berman, MD	Georgia Regents University, Medical College of Georgia, Augusta, GA
16	Peter Fattal, MD	Safwan Kassas, MD	Michigan Cardiovascular Institute, Covenant Medical Center, Saginaw, MI
17	Rene Alvarez, MD , Eman Hamad, MD, Pravin Patil, MD	Vikas Aggarwal, MD	Temple University Hospital, Philadelphia, PA
18	Sandra Viviana Chaparro, MD , Roberto Miki, MD	Claudia Martinez, MD	University of Miami, Miller School of Medicine, Miami, FL
19	Nasir Sulemanjee, MD	Suhail Allaqaband, MD	Aurora Health Care Patient Centered Research Milwaukee, WI
20	Stephanie Dunlap, DO, Vladimir Cortalan, DO	Imran Arif, MD	University of Cincinnati Heart Failure Clinic, Cincinnati, OH
21	John Petersen II, MD	Paul Huang, MD	Heart & Vascular Research, Seattle, WA
22	Burhan Mohamedali, MD, Dinesh Karla, MD, Tisha Suboc, MD	Gary Schaer, MD	Rush University Medical Center, Chicago, IL
23	Guilherme Oliveira, MD	Marco Costa, MD	University Hospital, Case Medical Center, Cleveland, OH
24	Marc Simon, MD, MS	Catlin Toma, MD	University of Pittsburgh Heart and Vascular Institute, PA
25	Maryjane Farr, MD	Torsten Vahl, MD	Columbia University Medical Center, Center for Advanced Cardiac Care, New York, NY
26	Frank McGrew III, MD	Basil Paulus, MD	Stern Cardiovascular Foundation, Inc., Germantown, TN

DREAM-HF INVESTIGATORS

	Heart Failure Investigator	Interventional Cardiologist	Location of Clinical Trial Site
27	Kelly Tucker, MD	Ehtisham Mahmud, MD	Orange County Cardiology, Orange, CA
28	Anantharam Kalya, MD, Gautam Kedia, MD	Nabil Dib, MD	Mercy Gilbert Medical Center, Gilbert, AZ
29	Thomas Povsic, MD	W. Schuyler Jones, MD	Duke University Hospital, Durham, NC
30	Kimberly Parks, DO, Sunu Thomas, MD	Jagmeet Singh, MD	Massachusetts General Hospital, Boston, MA
31	Ahmed Abdel-Latif, MD, PhD	Dean Kereiakes, MD	University of Kentucky, Gill Heart Institute, Lexington, KY
32	Ronald Freudenberger, MD	Vikas Aggarwal, MD	Lehigh Valley Hospital, Allentown, PA
33	Andrew Kaplan, MD, Anantharam Kalya, MD	Nabil Dib, MD	Cardiovascular Associates of Mesa, Mesa, AZ
34	German Larrain, MD	Amish Raval, MD	Aspirus Research Institute, Wausau, WI
35	Shahab Ghafghazi, MD , Emma Birks, MD	Michael Flaherty, MD	University of Louisville, Louisville, KY
36	Ranjith Shetty, MD, Kwan Lee MD	Nabil Dib, MD	University of Arizona Medical Center, Tucson, AZ
37	Roger Gammon, MD	Jie Cheng, MD	Austin Heart, Austin, TX
38	Joseph Mishkin, MD	Glen Kowalchuck, MD	Carolinas Healthcare System, Sanger Heart and Vascular Institute, Charlotte, NC
39	David Markham, MD	Arshed A. Quyyumi, MD	Emory University School of Medicine, Atlanta, GA
40	Linda Cadaret, MD	Phillip Horwitz, MD	University of Iowa, Department of Internal Medicine, Iowa City, IA
41	Richard Rothschild, MD	Alejandro Garcia, MD	St. John's Regional Medical Center, Oxnard, CA
42	Brian Drachman, MD	Sameer Khandhar, MD	University of Pennsylvania, Penn Presbyterian Medical Center, Philadelphia, PA
43	Sumanth Prabhu MD	Brigitta Brott, MD	University of Alabama at Birmingham Hospital, Birmingham, AL
44	Saurabh Kapoor, MD	Mark Zucker, MD	Barnabas Heart Center, Newark, NJ
45	Mohammadreza Tabesh, MD	Charles Lambert, MD	University Community Hospital Inc., Tampa, FL
46	Christina Michael, MD	George Daniels, MD	Bethesda Heart Hospital, Boynton Beach, FL
47	Barry Trachtenberg, MD	Miguel Valderrabano, MD	Houston Methodist Hospital, Houston, TX
48	Cara East, MD	Carlos Velasco, MD	Baylor Soltero Cardiovascular Research, Dallas, TX
49	Philip Yang, MD	David Lee, MD	Stanford University Hospital, Stanford, CA
50	Anupam Basuray, MD	Carlos Sanchez, MD	The Ohio Health Research Institute, Columbus, OH
51	Richard, Shehane, MD	Ehtisham Mahmud, MD	University Medical Center of Southern Nevada, Las Vegas, NV

BACKGROUND

- Mesenchymal precursor cells (MPCs) are allogeneic STRO-1/STRO-3+ cells that are immunoselected from adult human bone marrow mononuclear cell populations.
- Preclinical studies suggest MPCs have anti-inflammatory, immunomodulatory, and proangiogenic effects in ischemic and non-ischemic cardiomyopathy models.[1,2]
- The first-in-human transendocardial injection of MPCs in ischemic cardiomyopathy was performed in 2006 in NSW, Australia.
- Results from a phase II dosing study suggest that MPCs may reduce HF-associated events and adverse ventricular remodeling in patients with persistent HFrEF.[3,4]

[1] Psaltis et al. JACC Cardiovasc Interv 2010;3:974-83.
[2] Kocher et al. Nat Med 2001;7:430-6.
[3] Perin et al. Circ Res 2015;117:576-84.
[4] Borow et al. Circ Res 2019;125:265-81.

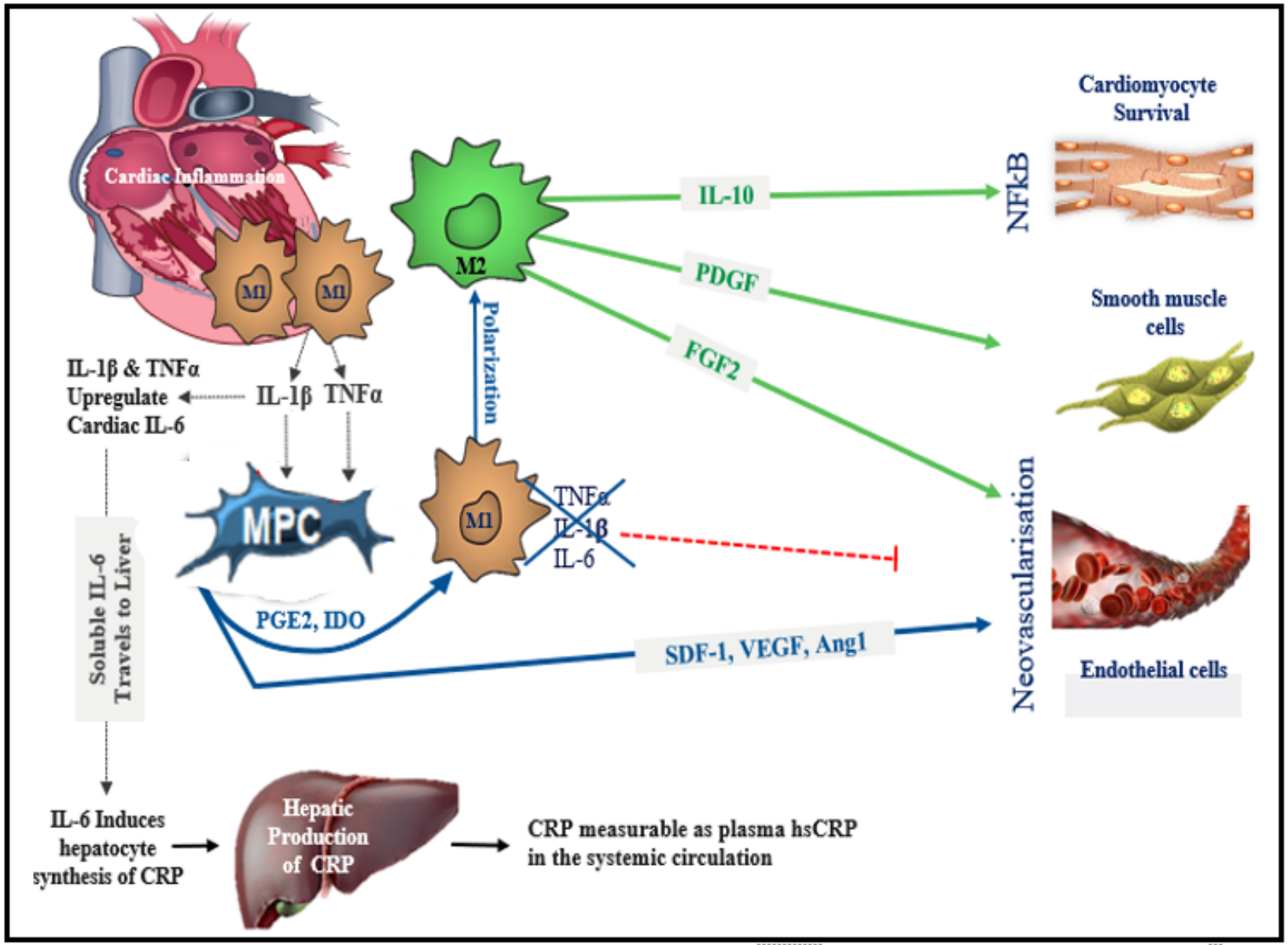
DREAM-HF

PROPOSED MECHANISMS OF ACTION OF INTRACARDIAC MPC ADMINISTRATION

MPCs are thought to beneficially impact the **heart** and the **systemic vasculature** in HFrEF:

- Decrease cardiac and systemic inflammation
- Reduce heart muscle death
- Induce microvascular network and capillaries within viable heart muscle
- Reverse endothelial dysfunction

Previous trials of targeted anti-cytokine therapy (TNFα) in HFrEF have failed.



DREAM-HF

Modified from Borow KM, Yaroshinsky A, Greenberg B, Perin E. Phase 3 DREAM HF-1 Trial of Mesenchymal Precursor Cells in Chronic Heart Failure: A Review of Biological Plausibility and Implementation of Flexible Clinical Trial Design. *Circ Res.* 2019;125:265-281

ELIGIBILITY

Key Inclusion Criteria

- 18 to ≤80 years of age
- Chronic ischemic or nonischemic heart failure with **NYHA class II or III** symptoms
- Be receiving **optimal medical therapies for heart failure** at stable and tolerated doses for at least 1 month before study intervention
- No option for percutaneous coronary intervention or coronary artery bypass graft surgery
- **LVEF ≤ 40%** by two-dimensional echocardiogram
- Enrichment criteria:
  - **At least 1 heart failure hospitalization** or **outpatient visit** requiring intravenous diuretic, vasodilator, and/or
  - positive inotropic therapy >1 month but ≤9 months or less before initiation of screening procedures and/or
  - plasma levels of **NT-pro-BNP** >1000 pg/mL (>1200 pg/mL for patients with atrial fibrillation)

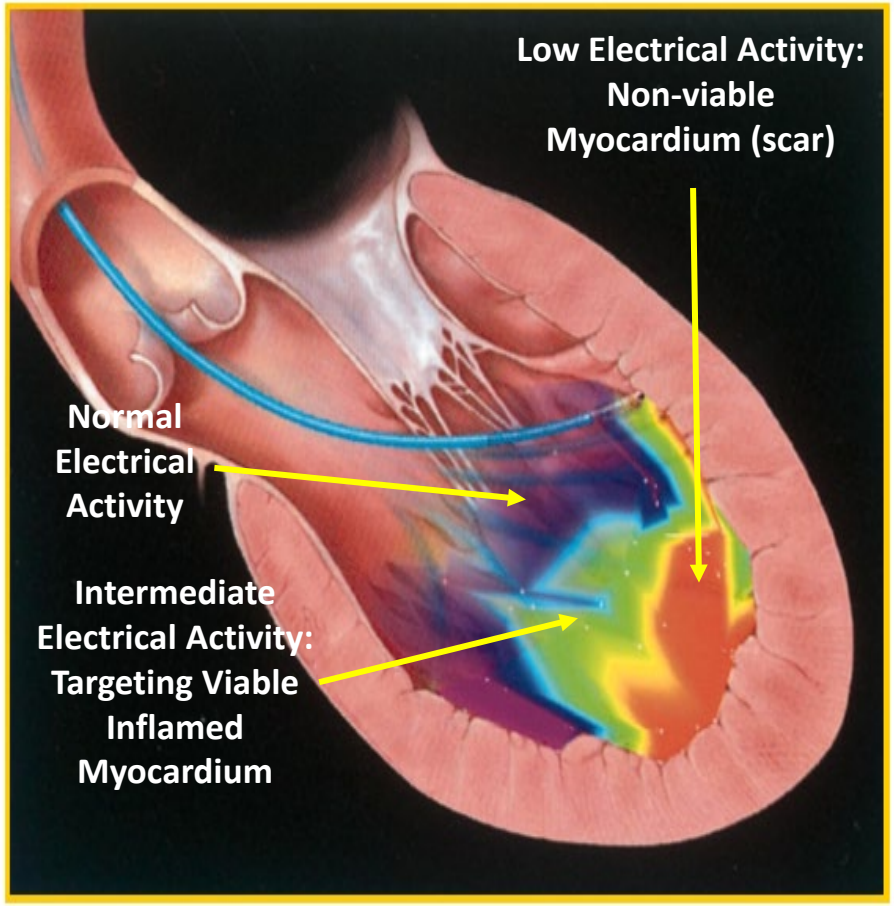
Key Exclusion Criteria

- NYHA functional class I or class IV symptoms
- Acute MI within 1 month of screening procedures
- Unstable angina pectoris within 1 month of screening
- Peripartum or postpartum cardiomyopathy
- Ischemic or hemorrhagic stroke within 3 months of study enrollment
- Coronary arterial or peripheral arterial revascularization procedure within 2 months screening procedures
- Intravenous therapy with diuretic, vasodilator, and/or positive inotropes or aquapheresis within 1 month of screening
- History of malignant ventricular arrhythmia or sustained ventricular tachycardia in the absence of an ICD
- Restrictive, obstructive, or infiltrative cardiomyopathy; pericardial constriction; amyloidosis; or uncorrected thyroid disease
- Moderate to severe aortic stenosis (valve area < 1.0 cm^2)
- Previous left ventricular reduction surgery, implanted LVAD, cardiac transplantation, or artificial heart placement
- Left ventricular thrombus

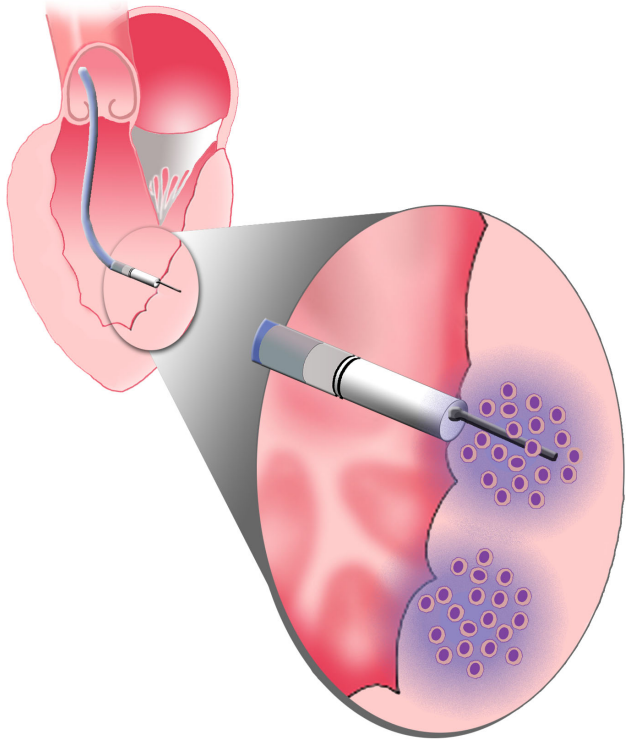
DREAM-HF

TARGETED DELIVERY OF MPCs TO THE MYOCARDIUM

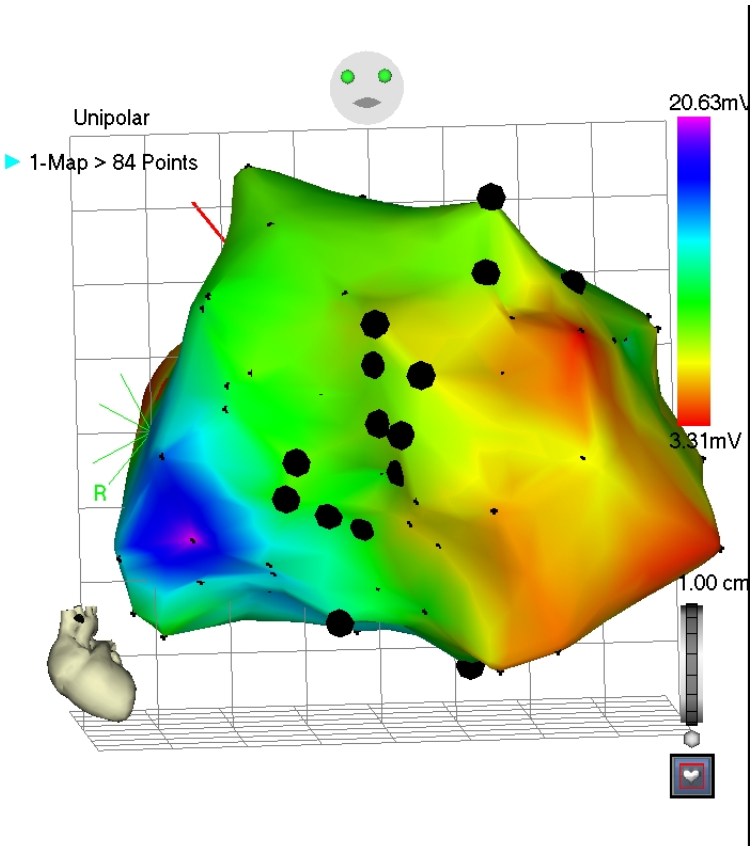
1. LV ELECTROMECHANICAL MAPPING SYSTEM (NOGA)



2. TRANSENDOCARDIAL INJECTION

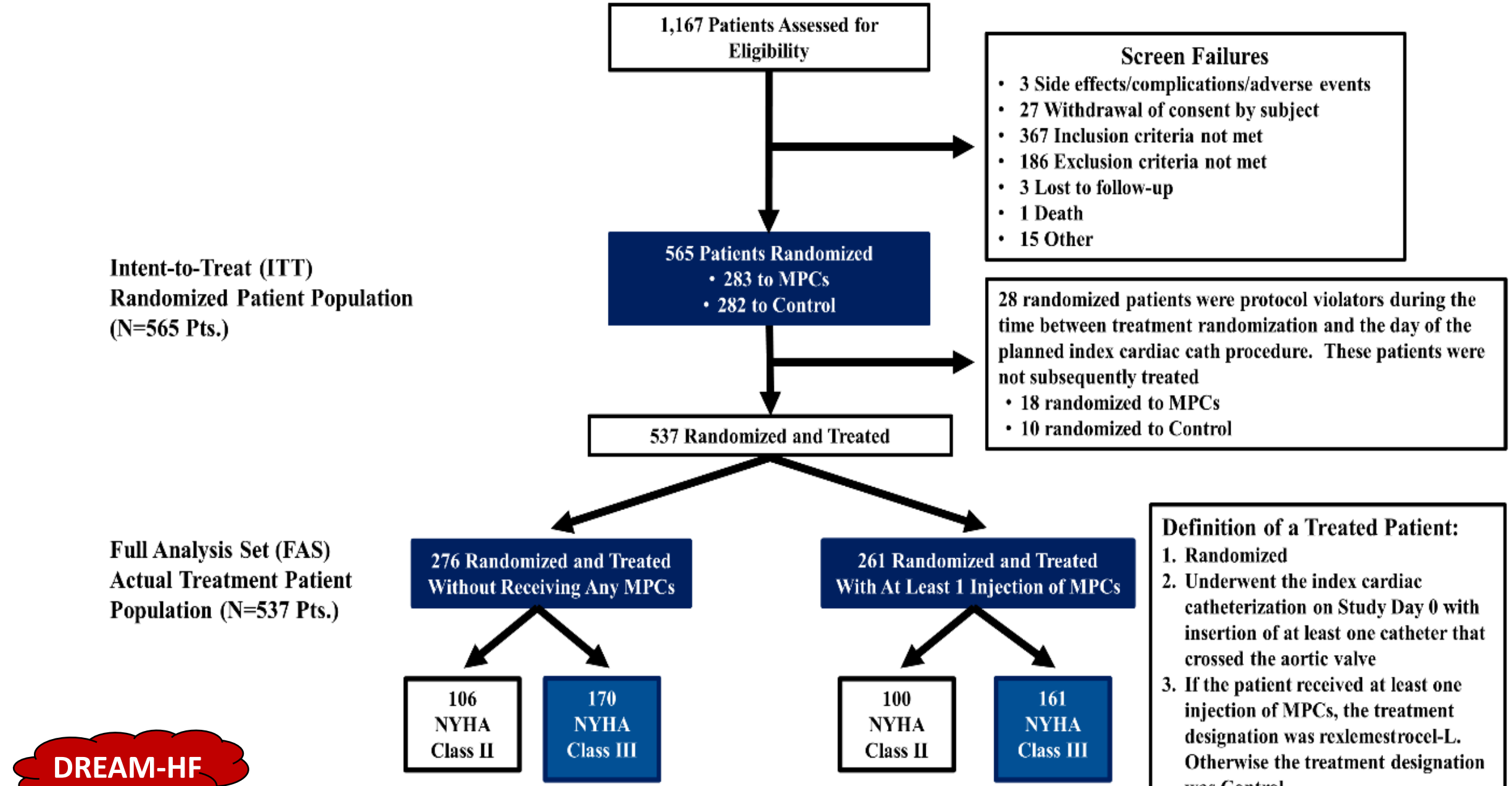


3. COMPLETED PROCEDURE



DREAM-HF

ENROLLMENT AND RANDOMIZATION



DREAM-HF

BASELINE CHARACTERISTICS AND DEMOGRAPHICS

Characteristic	MPCs (N=261)	Sham Control (N=276)
Male	207 (79.3)	221 (80.1)
Race		
White	198 (75.9)	216 (78.3)
Black	52 (19.9)	47 (17.0)
Other	11 (4.2)	13 (4.7)
Age (years): mean (SD)	62.7 (11.0)	62.8 (10.4)
Body mass index (kg/m^2): mean (SD)	30.5 (6.9)	29.8 (6.2)
SBP (mmHg): mean (SD)	121.7 (19.3)	120.7 (19.4)
DBP (mmHg): mean (SD)	73.6 (11.7)	72.2 (12.3)
Pulse rate (BPM): mean (SD)	71.1 (11.1)	72.5 (12.0)
Cardiomyopathy etiology		
Ischemic	150 (57.5)	153 (55.4)
Nonischemic	111 (42.5)	123 (44.6)
NHYA functional class		
Class II	100 (38.3)	106 (38.4)
Class III	161 (61.7)	170 (61.6)
History of hypertension	214 (82.0)	219 (79.3)
History of diabetes	115 (44.1)	116 (42.0)
History of atrial fibrillation	103 (39.5)	108 (39.1)
Previous MI	140 (53.6)	140 (50.7)
Previous stroke/CVA	30 (11.5)	18 (6.5)
Coronary revascularization (CABG/PCI)	154 (59.0)	156 (55.3)
Any defibrillator (AICD/CRT-D)	221 (84.7)	234 (84.8)

*Data are presented as n (%) unless otherwise noted.

DREAM-HF

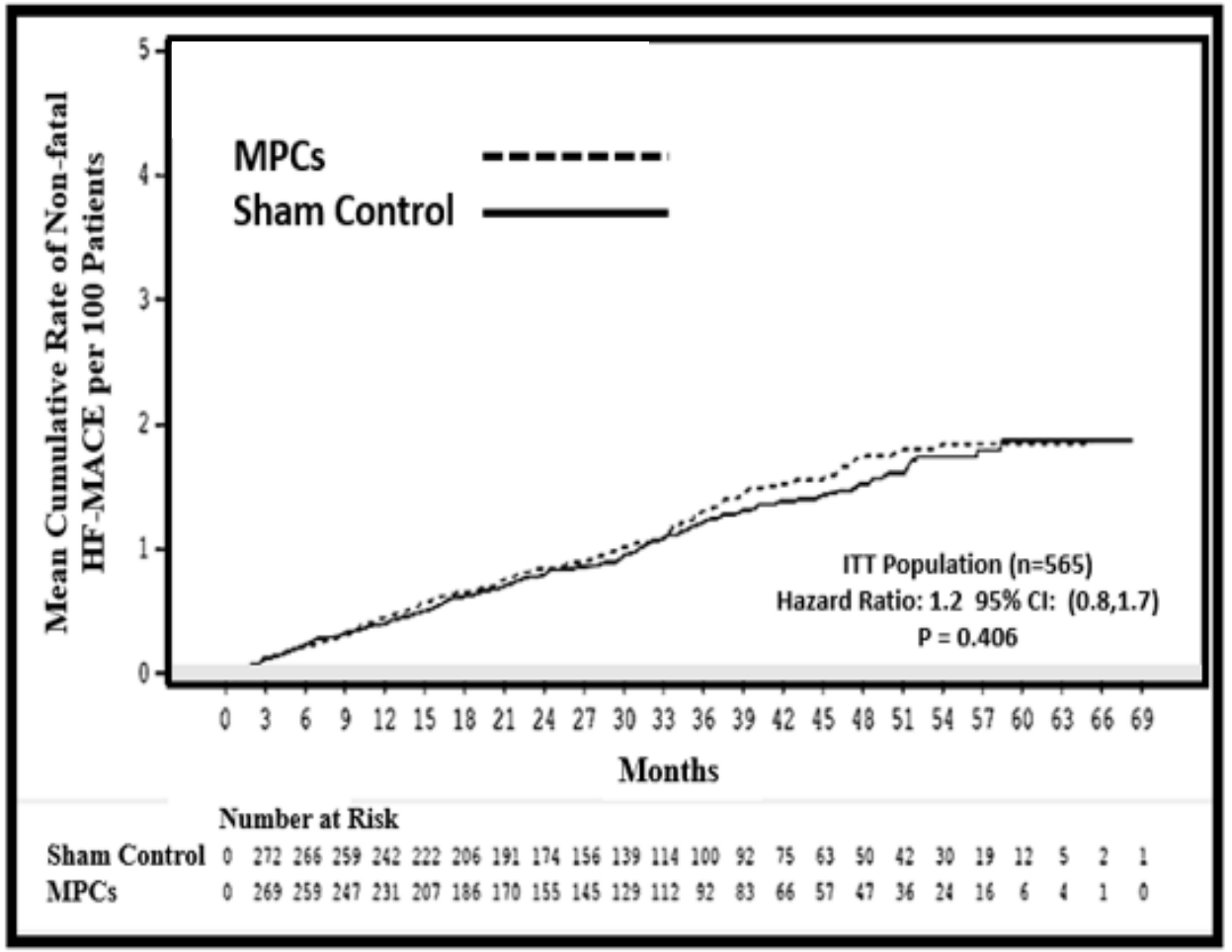
BASELINE CHARACTERISTICS AND DEMOGRAPHICS (cont.)

Characteristic	MPCs (n=261)	Sham Control (n=276)
Cardiovascular medications		
All RAAS medications	236 (90.4)	256 (92.8)
ACE Inhibitors	97 (37.2)	119 (43.1)
ARBs	55 (21.1)	56 (20.3)
ARNi	65 (24.9)	52 (18.8)
Mineralocorticoid receptor agonists	155 (59.4)	168 (60.9)
Diuretics	235 (90.0)	242 (87.7)
Beta blockers	249 (95.4)	267 (96.7)
Digitalis	78 (29.9)	63 (22.8)
Oral anticoagulants	95 (36.4)	88 (31.9)
Anti-platelet agents	226 (86.6)	224 (81.2)
SGLT-2 inhibitors	3 (1.1)	5 (1.8)
Statins	177 (67.8)	180 (65.2)
Echocardiography: mean (SD)		
LVEF (%)	28.7 (6.6)	28.6 (7.0)
LVESV (mL)	149 (58)	151 (67)
LVEDV (mL)	206 (67)	207 (78)
6MWT distance: mean (SD)	342 (80.3)	347 (90.3)
Biomarkers: mean (SD)		
NT-proBNP (ng/L)	2182 (2509)	2201 (2676)
hsCRP (mg/L)	4.7 (7.5)	5.9 (10.7)

*Data are presented as n (%) unless otherwise noted.

PRIMARY ENDPOINT:

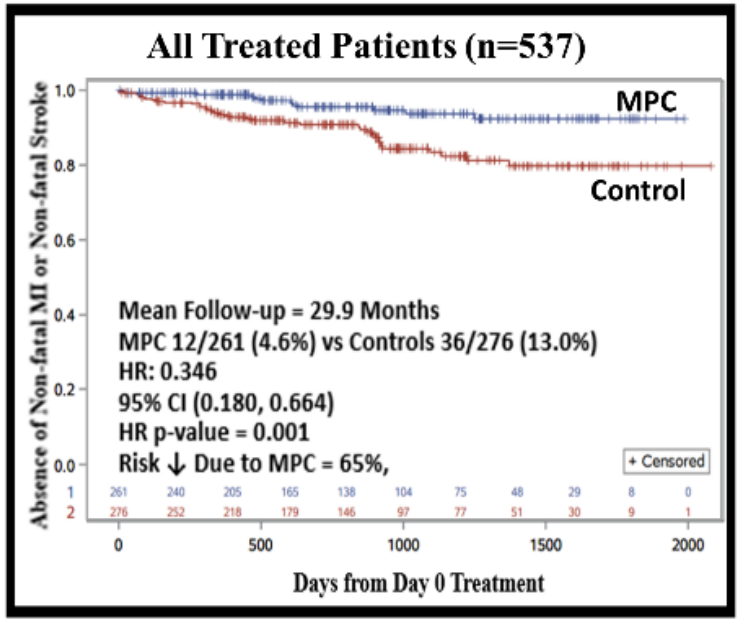
Mean Cumulative Rate of Recurrent Non-fatal Decompensated Heart Failure Events Per 100 Patients

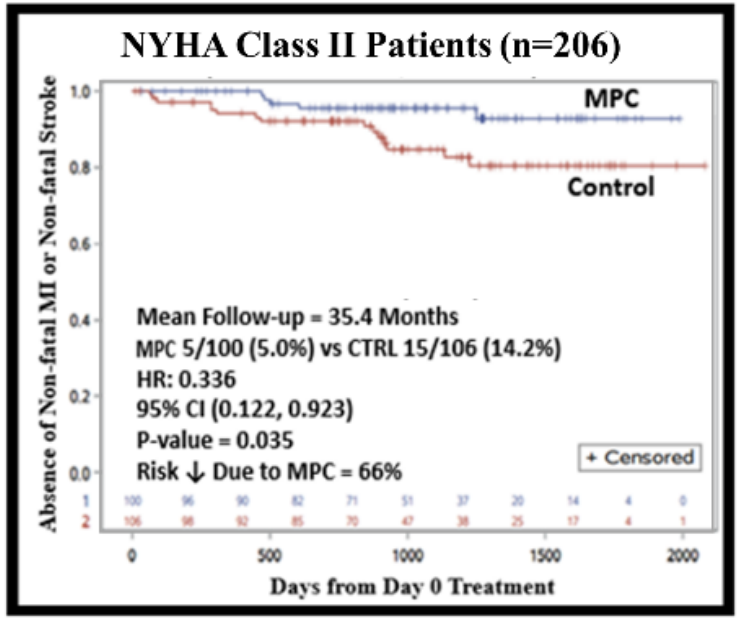


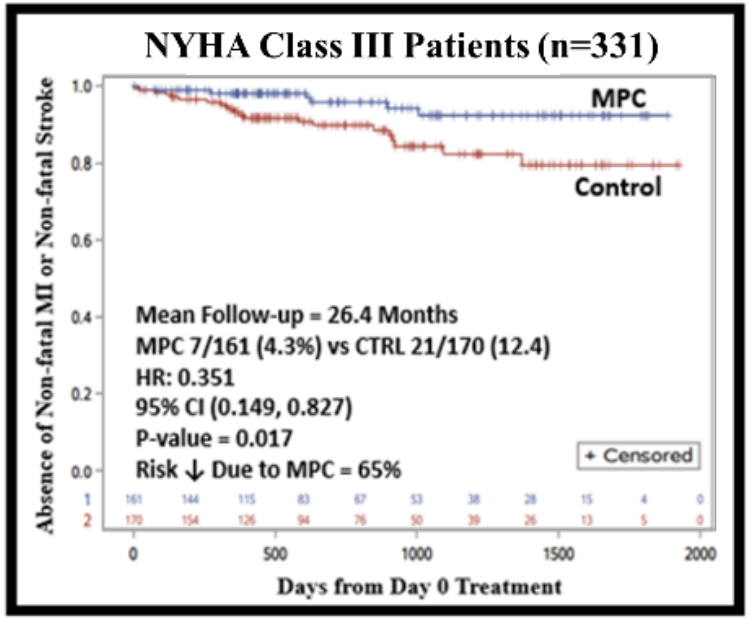
DREAM-HF

RISK OF NON-FATAL MI OR NON-FATAL STROKE

A







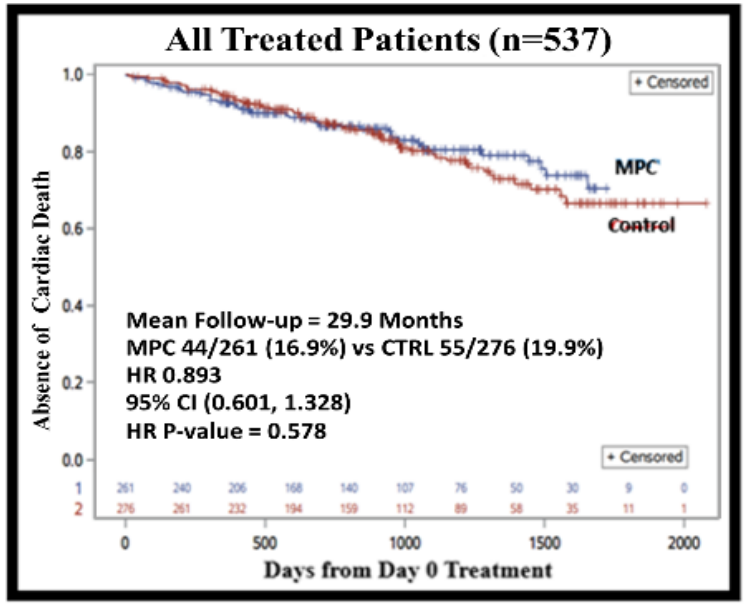
B

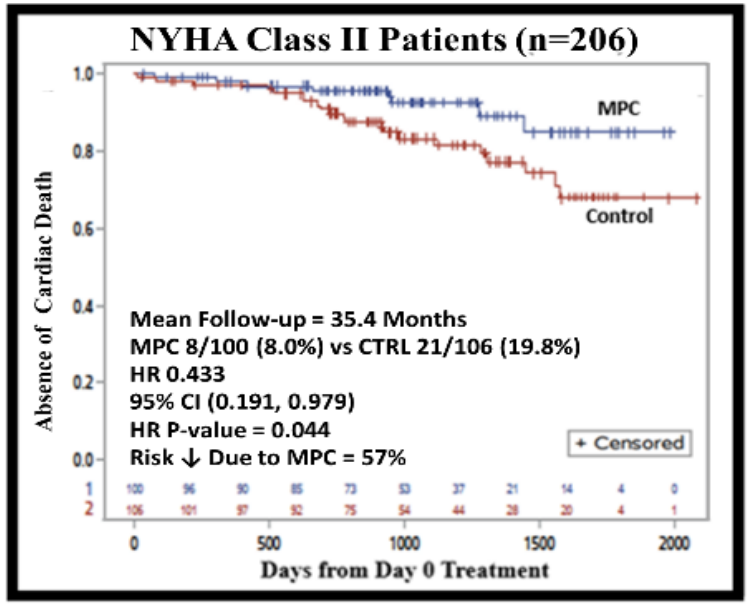
Patient Groups	Total # Pts.	MPC				CTRL				Forest Plots	Rate ↓ Due to MPCs	Rate Ratio	95% CI	P-Value
		# Pts.	# Events	Person Yrs f/u	Events Per 100 Yrs f/u	# Pts	# Events	Person Yrs f/u	Events Per 100 Yrs f/u					
All Treated Patients	537	261	12	632	1.900	276	44	709	6.208		69%	0.306	0.162, 0.579	<0.001
NYHA Class II	206	100	5	286	1.751	106	19	314	6.052		71%	0.289	0.108, 0.775	0.014
NYHA Class III	331	161	7	346	2.022	170	25	395	6.333		68%	0.319	0.138, 0.738	0.008

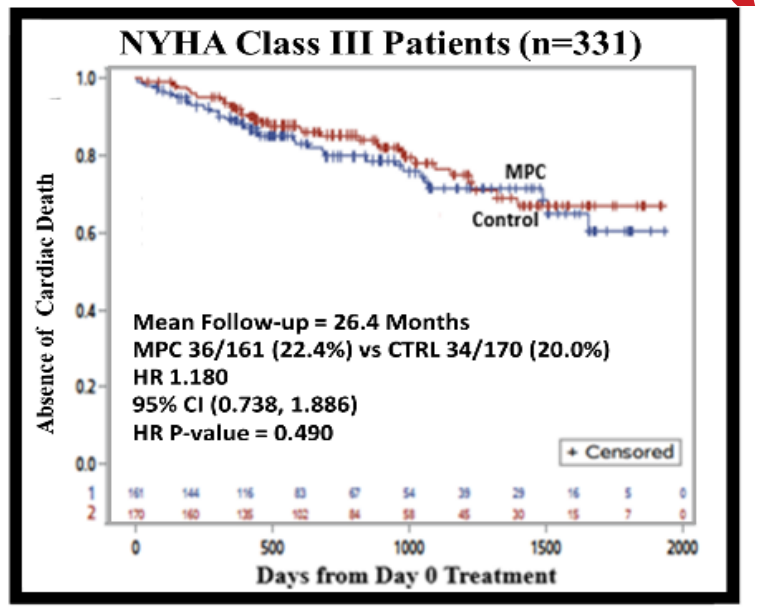
DREAM-HF

RISK OF CARDIAC DEATH

A

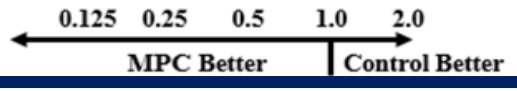






B

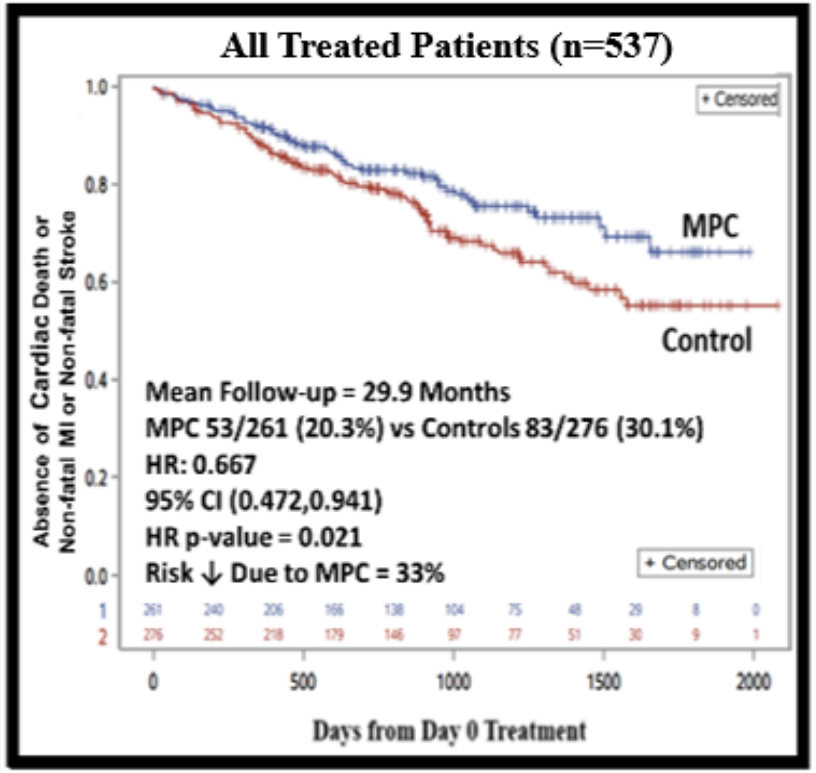
Patient Groups	Total # Pts,	MPC				CTRL				Forest Plots	Rate ↓ Due to MPCs	Rate Ratio	95% CI	P-Value
		# Pts.	# Events	Person Yrs f/u	Events Per 100 Yrs f/u	# Pts	# Events	Person Yrs f/u	Events Per 100 Yrs f/u					
All Treated Patients	537	261	44	632	6.966	276	55	709	7.760		NA	0.898	0.604, 1.334	0.593
NYHA Class II	206	100	8	286	2.802	106	21	314	6.689		58%	0.419	0.186, 0.946	0.036
NYHA Class III	331	161	36	346	10.401	170	34	395	8.613		NA	1.208	0.756, 1.930	0.430

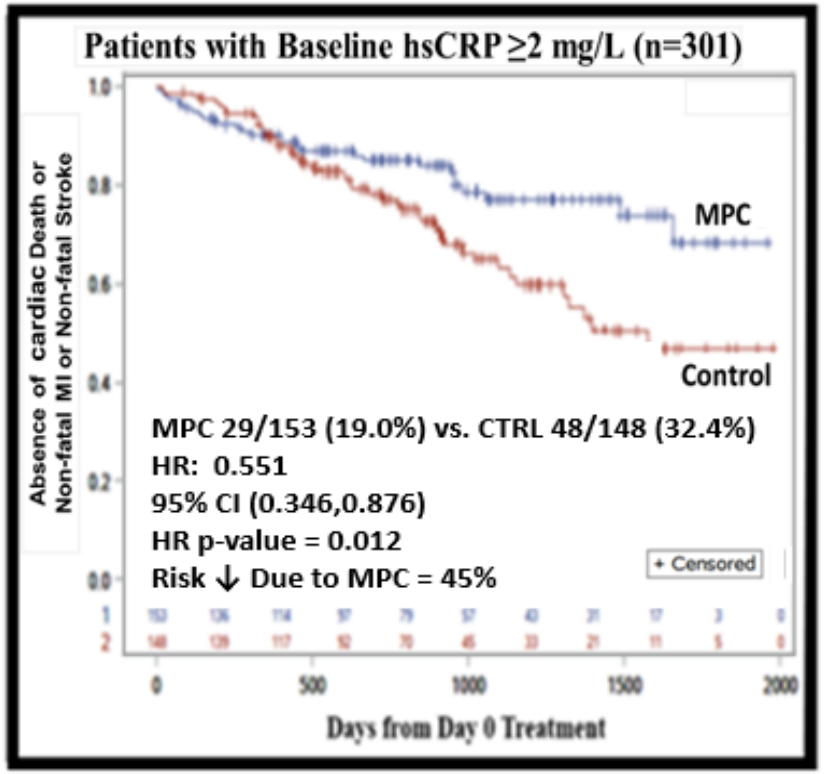


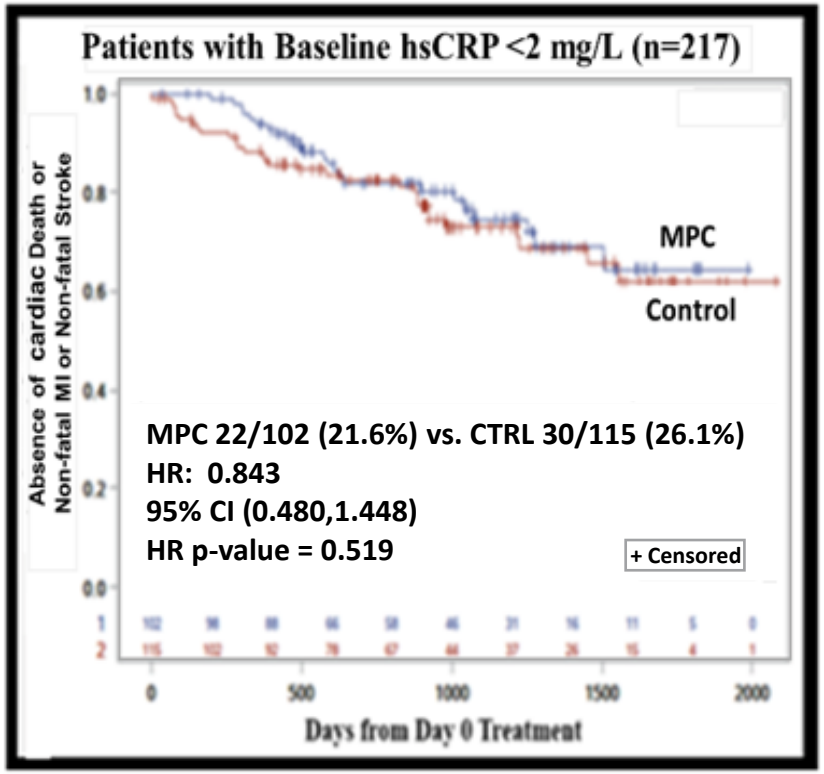
DREAM-HF

COMPOSITE MACE AND INFLAMMATION

Time-to-First-Event for Cardiac Death or Non-fatal MI or Non-fatal Stroke



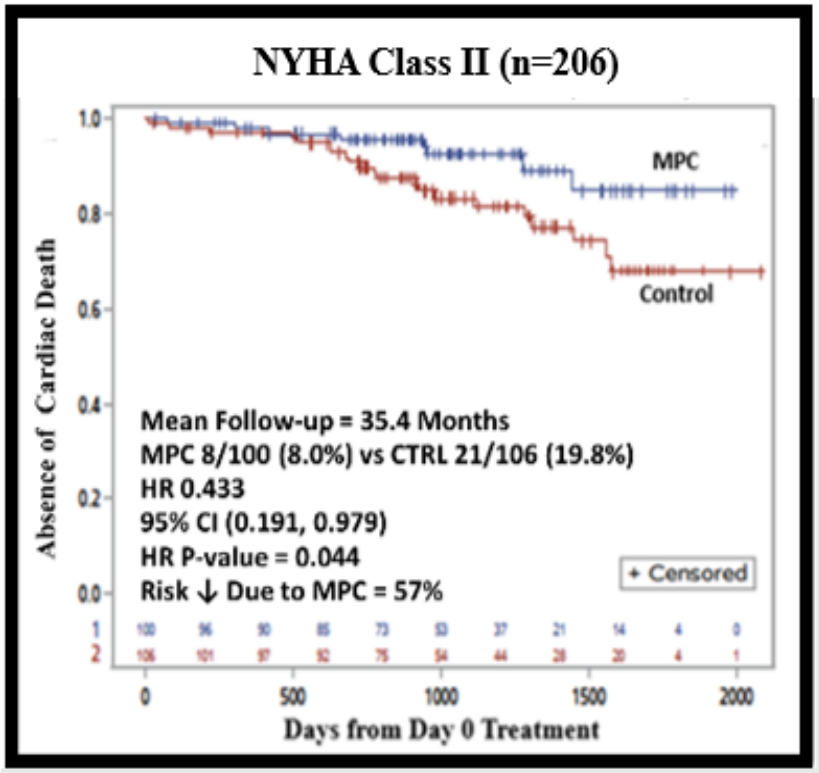


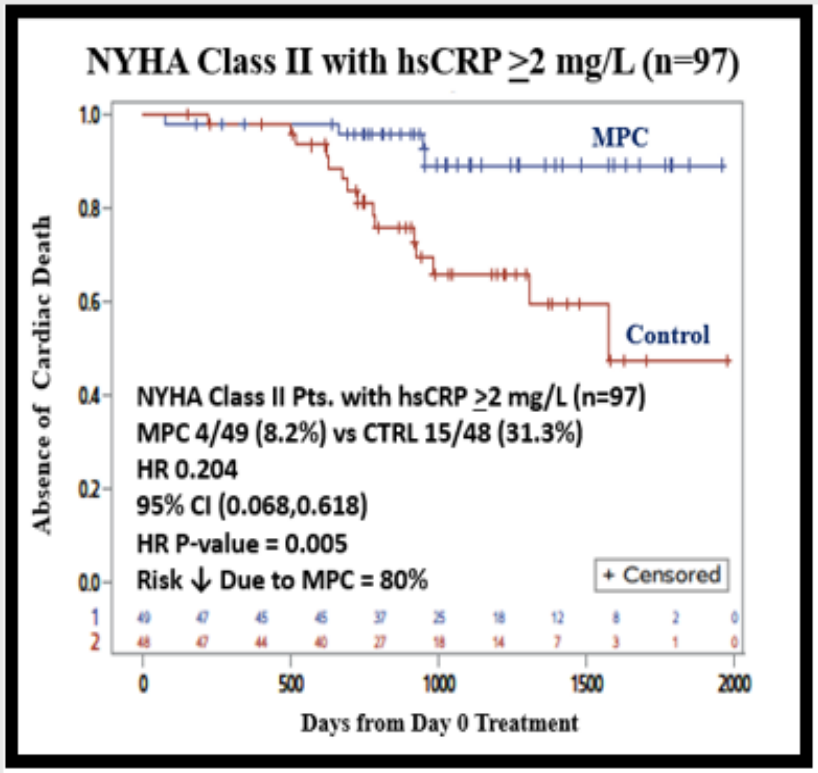


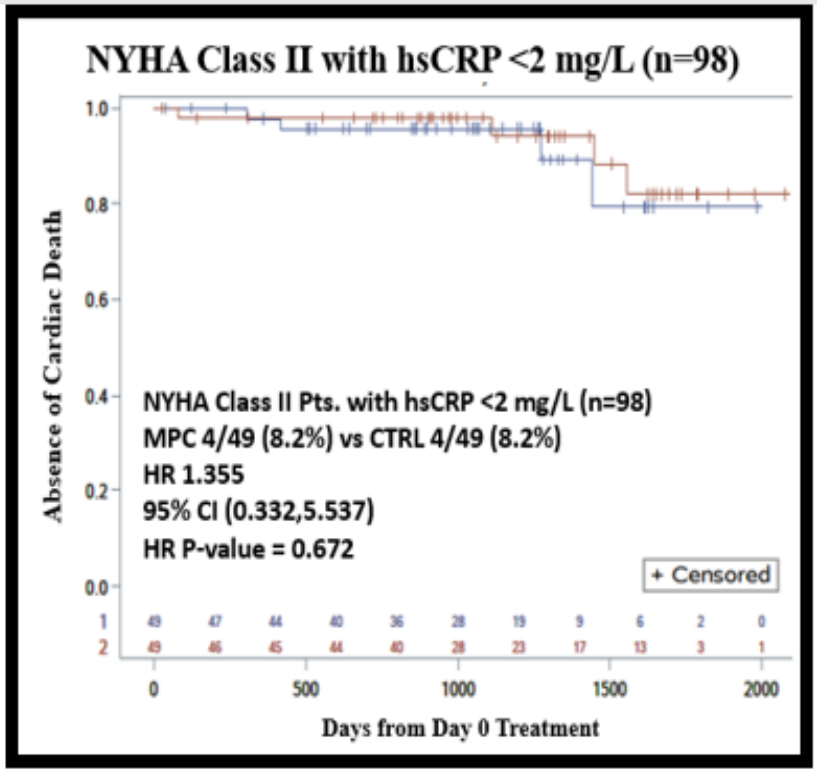
DREAM-HF

INFLAMMATION AND TIME-TO-CARDIAC DEATH

Time-to-Cardiac Death in NYHA Class II Patients







DREAM-HF

SAFETY

- Treatment-emergent adverse events and serious adverse events were similar in MPC-treated and control patients.
- MPC administration did not elicit clinically meaningful immune related responses in any patient. No important differences were seen in HLA responses against the allogeneic MPCs used in this trial.
- Transendocardial delivery of cells was safe. No complications were associated with LV angiography. One left ventricular perforation occurred during LV mapping (incidence of 0.4%).

CONCLUSIONS

- Transendocardial delivery of 150 million MPCs was safe and did not elicit any clinically meaningful immune-related responses.
- MPCs did not reduce cumulative recurrent non-fatal decompensated HF events in patients with persistent HFrEF.
- Over a mean follow-up of 30 months, a single MPC dosing procedure added to GDMT significantly reduced:
  - Non-fatal MI or non-fatal stroke
  - Cardiac death in NYHA class II but not class III patients
  - Composite of cardiac death or non-fatal MI or non-fatal stroke
- Benefits of MPC therapy were most evident in patients with baseline inflammation (plasma hsCRP ≥2 mg/L).

DREAM-HF

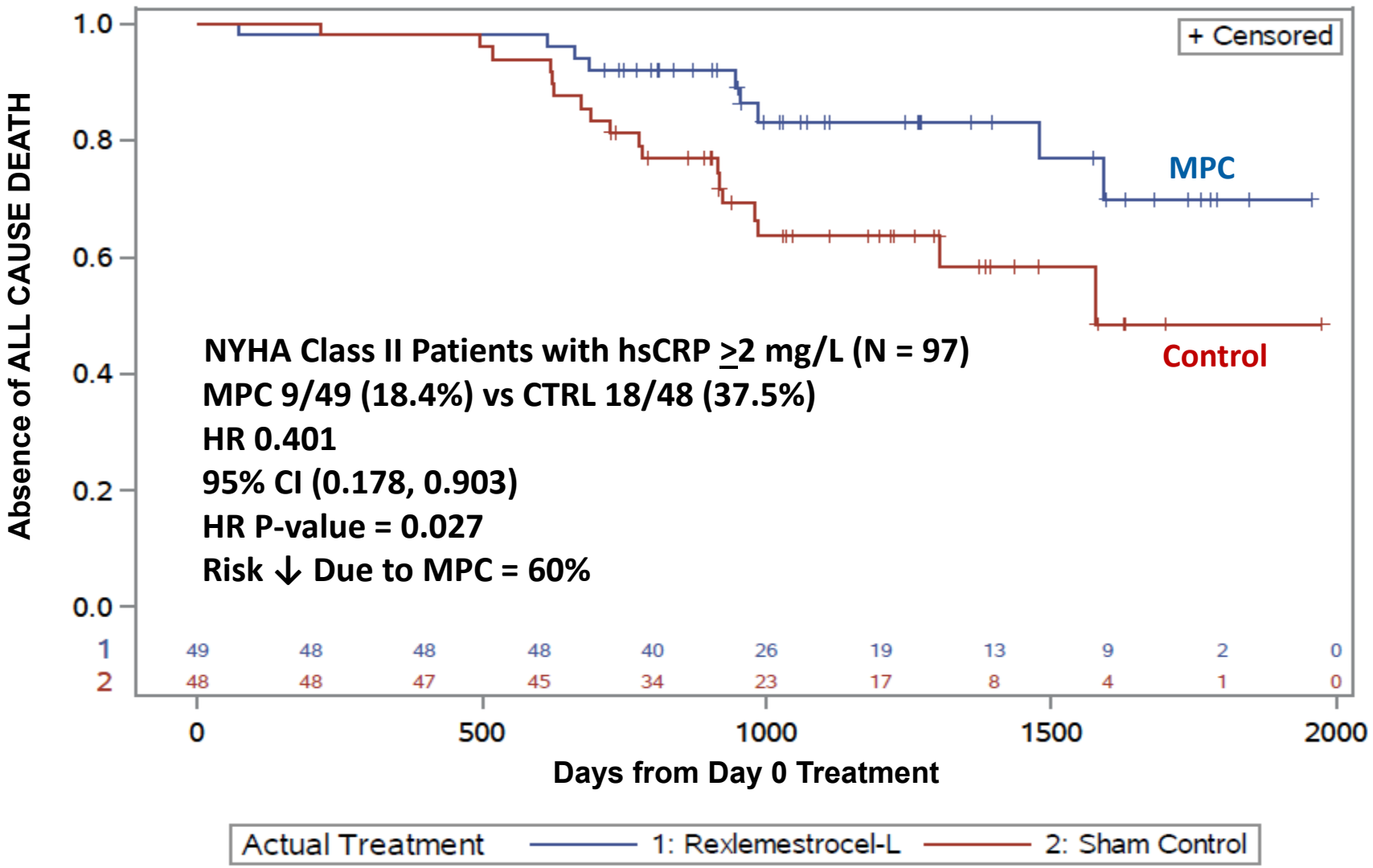
THANK YOU

American Heart Association®

Scientific Sessions

#AHA21

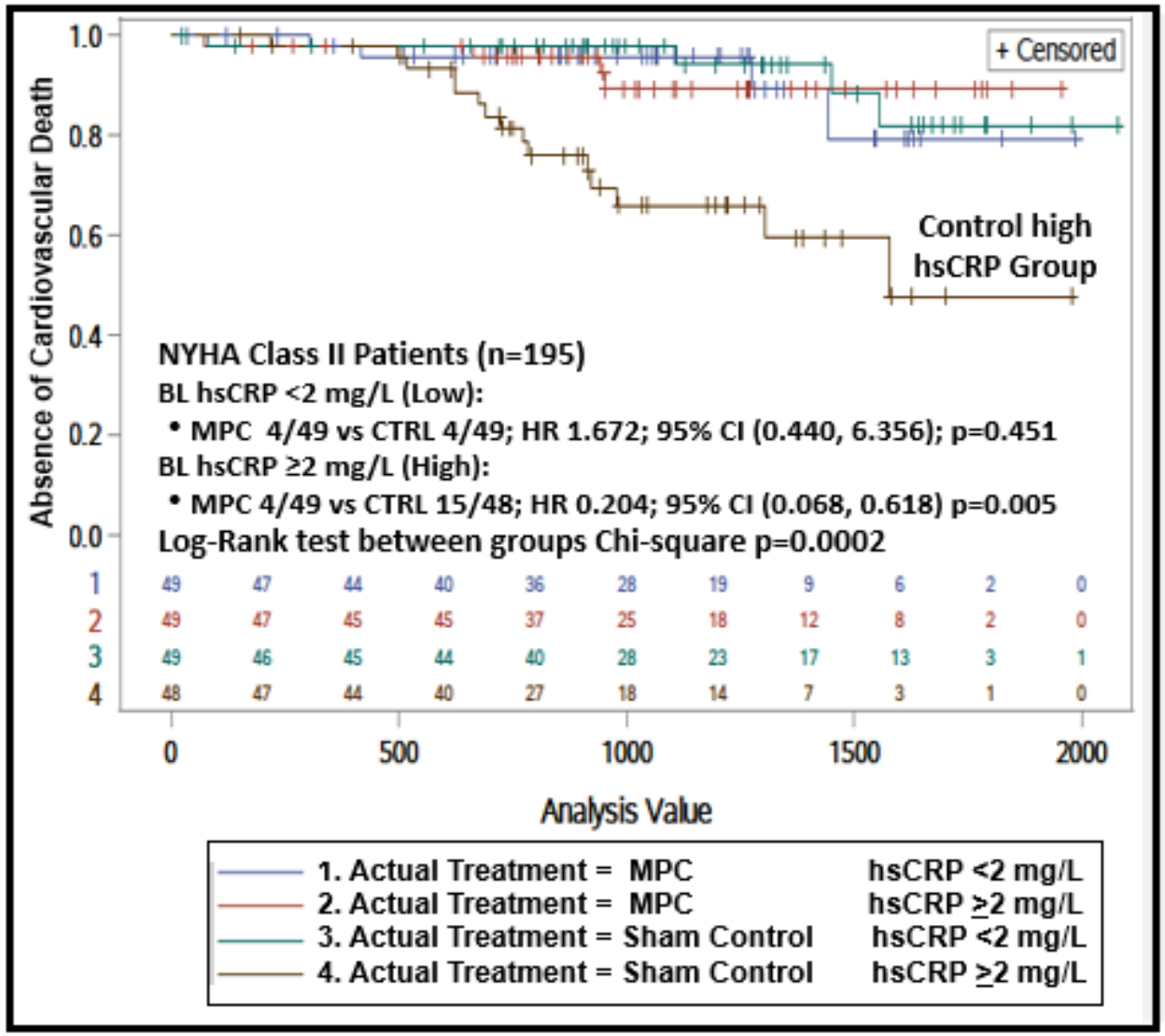
ALL CAUSE DEATH: NYHA Class II Patients (hsCRP ≥2 mg/L)



DREAM-HF

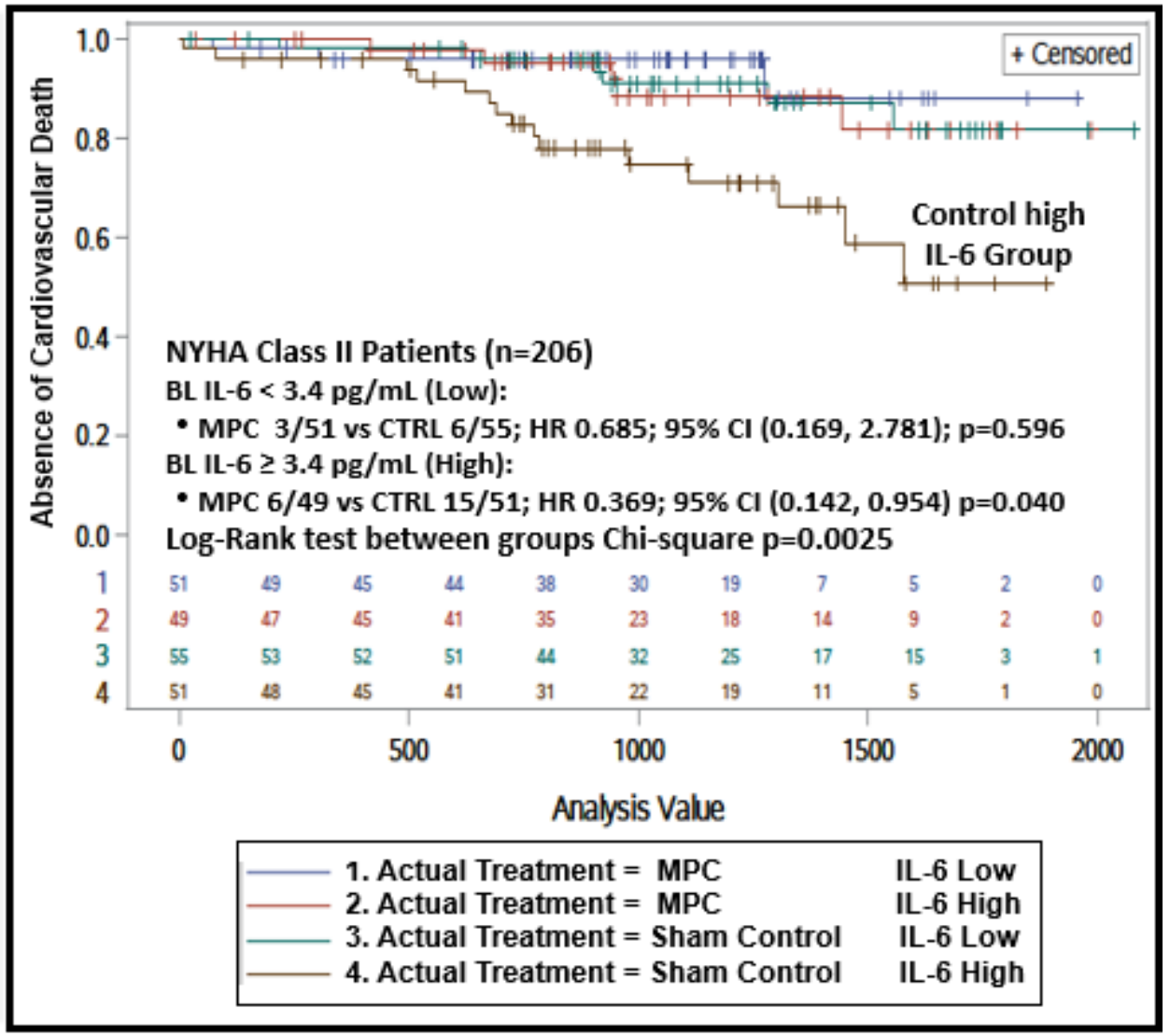
hs-CRP

Cardiovascular Death in NYHA Class II



IL-6

Cardiovascular Death in NYHA Class II



DREAM-HF

BASELINE CHARACTERISTICS IN NYHA CLASS II vs. CLASS III

Parameter	Statistic	NYHA Class II (N=206)	NYHA Class III (N=331)	p-value Class II vs. III
Past MI	n (%)	106 (51.5%)	174 (52.6%)	0.802
CABG or PCI	n (%)	119 (57.8%)	188 (56.8%)	0.825
AICD or CRT	n (%)	168 (81.6%)	283 (85.5%)	0.225
Baseline LVEF (%)	n	205	327	
	Mean (SD)	28.6 (7.2)	28.7 (6.5)	0.882
Baseline LVESV (mL)	n	205	327	
	Mean (SD)	155 (72)	146 (55)	0.106
Baseline LVEDV (mL)	n	205	327	
	Mean (SD)	213 (83)	203 (65)	0.099
Baseline 6 Minute Walk (m)	n	206	327	
	Mean (SD)	367 (81)	330 (85)	<0.001
Baseline NT-proBNP (ng/L)	n	203	326	
	Mean (SD)	1813 (1902)	2427 (2922)	0.008
Baseline hsCRP (mg/L)	n	195	323	
	Mean (SD)	3.6 (5.9)	6.4 (10.7)	<0.001
Baseline Creatinine (mcmol/L)	n	206	330	
	Mean (SD)	100 (29)	110 (33)	<0.001
Baseline Creatinine Clearance (mL/min/1.73m2)	n	206	330	
	Mean (SD)	70 (22)	64 (23)	0.002

Note: Percentages were based on the number of subjects in the NYHA Class.
Note: P-values indicate tests of differences of NYHA Class II vs. Class III and were two-sided.
Categorical responses were tested using a Chi-Square test.
Tests of differences in means were performed using an ANOVA.

DREAM-HF