A Phase II Dose-Escalation Study of Allogeneic Mesenchymal Precursor Cells in Patients With Ischemic and Nonischemic Heart Failure

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Texas Heart® Institute

Stem Cell Center

Study Site	PI	Enrollment
Minneapolis Heart Institute	Timothy Henry	20
Mercy Gilbert Medical Center	Nabil Dib	19
Texas Heart Institute	Emerson Perin	12
Univ. of California, San Diego	Anthony DeMaria	5
University of Pittsburgh	Oscar Marroquin	3
Swedish Medical Center	Paul Huang	1

Study Sponsor

mesoblast
the regenerative medicine company
www.mesoblast.com

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Background

1. Most clinical trials in cell therapy have used autologous adult stem cells in patients with chronic ischemic cardiomyopathy or refractory angina.

2. Autologous cell therapy may be limited by variability in cell quality due to host factors such as age and comorbidities.

3. Allogeneic cell therapy offers “off the shelf” logistics with
   a) defined product characterization;
   b) batch-to-batch consistency;
   c) immediate availability.

4. Immunoselected allogeneic Mesenchymal Precursor Cells (MPCs) are a homogeneous cell population, which has demonstrated efficacy in animal models of ischemic and non-ischemic heart disease.

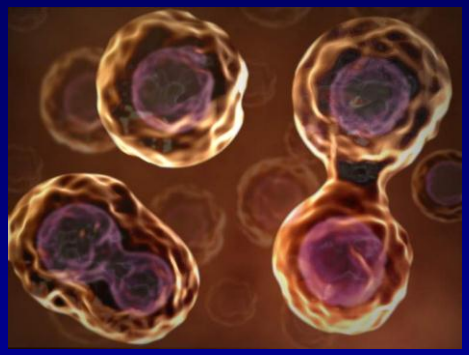
5. Allogeneic MPCs may be an attractive candidate for cardiac cell therapy.

Mesenchymal Precursor Cells (MPCs)

Bone marrow + STRO-3+ antibody

Magnetic beads

Isolated cells



MPC highly expandable

Culture-expanded cells

- Heart muscle
- Blood vessels

Cardiovascular disease therapies

- Pancreas
- Immune system
- Bone

Diabetes, immunologic/ inflammatory conditions

- Bone
- Cartilage

Orthopedic diseases

- Derived from young, healthy, unrelated donors
- Well-controlled, large-scale cell expansion
- FDA, EU, GMP, and ISO compliant manufacturing
- Centralized manufacturing

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Major Inclusion and Exclusion Criteria

Inclusion Criteria

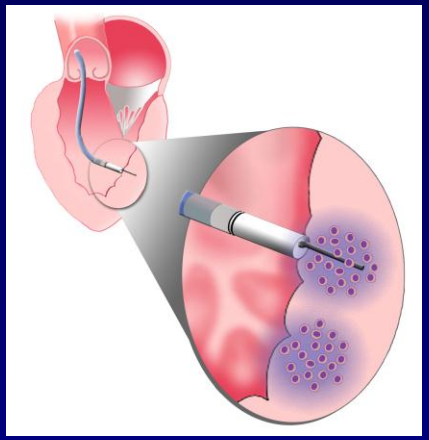
- NYHA II-IV
- Age between 20 and 80 years
- Cardiomyopathy of ischemic or non-ischemic etiology
- LVEF ≤ 40% (Echo)
- Not amenable to either CABG or PCI (CAD patients)
- Maximal medical therapy
- LV wall thickness ≥ 8 mm at target injection site (Echo)
- Signed informed consent

Major Inclusion and Exclusion Criteria

Exclusion Criteria

- Atrial fibrillation, LV thrombus, severe AS
- Stroke within 3 months of enrollment
- Presence of bleeding diathesis
- History of malignancy within 3 years
- MI within 30 days, ACS, cardiogenic shock
- ICD discharge within 28 days of procedure
- Sustained VT on screening ECG or 24h Holter
- PRA ≥20% and/or presence of specific antibodies to donor HLA antigens
- Known hypersensitivity to DMSO or murine and/or bovine products
- Abnormal selected laboratory values

Study Design



Eligible
n=151

Excluded (n=91)
- Did not meet inclusion criteria (n=63)
- Refused to participate (n=6)
- Other (n=22)

Enrollment
n=60

25M MPCs
n=20

Aug 2008 - Dec 2008

3:1

Treatment
n=15

Control
n=5

75M MPCs
n=20

May 2009 - Aug 2009

3:1

Treatment
n=15

Control
n=5

150M MPCs
n=20

Feb 2010 - Jun 2010

3:1

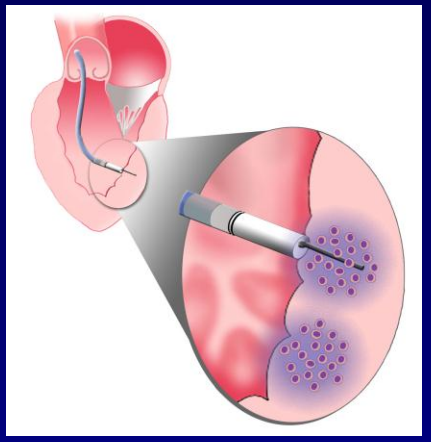
Treatment
n=15

Control
n=5

Safety F/U up to 3y

NYHA class,
Echocardiogram,
6 minute walk,
BNP,
Immunology
F/U at 3,6 and 12 mos.

Study Design



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- Other (n=22)

Enrollment
n=60

25M MPCs
n=20

Aug 2008 - Dec 2008

3:1

- Treatment n=15 — *Ischemic n=15*
- Control n=5 — *Ischemic n=2*

75M MPCs
n=20

May 2009 - Aug 2009

3:1

- Treatment n=15 — *Ischemic n=12*
- Control n=5 — *Ischemic n=3*

150M MPCs
n=20

Feb 2010 - Jun 2010

3:1

- Treatment n=15 — *Ischemic n=11*
- Control n=5 — *Ischemic n=3*

Safety F/U up to 3y

NYHA class,
Echocardiogram,
6 minute walk,
BNP,
Immunology
F/U at 3,6 and 12 mos.

SPECT 6 mos.
Ischemic only

Demographic and Baseline Characteristics

	Control (n=15)	Pooled MPC Treatment (n=45)	25M MPCs (n=15)	75M MPCs (n=15)	150M MPCs (n=15)
Age (years)	62.7 (11.2)	62.2 (10.3)	60.1 (8.8)	63.9 (11.5)	62.7 (10.8)
Female	4 (26.7)	1 (2.2) *	0	0	1 (6.7)
Previous PCI	10 (66.7)	33 (73.3)	12 (80.0)	13 (86.7)	8 (53.3)
Previous MI	9 (60.0)	38 (84.4)	14 (93.3)	13 (86.7)	11 (73.3)
Previous CABG	5 (33.3)	21 (46.7)	10 (66.7)	5 (33.3)	6 (40.0)
Diabetes	2 (13.3)	13 (28.9)	5 (33.3)	5 (33.3)	3 (20.0)
Hypertension	9 (60.0)	29 (64.4)	10 (66.7)	9 (60.0)	10 (66.7)
Dyslipidemia	11 (73.3)	37 (82.2)	15 (100.0)	12 (80.0)	10 (66.7)
Stroke	2 (13.3)	7 (15.6)	3 (20.0)	2 (13.3)	2 (13.3)
Tobacco use	9 (60.0)	32 (71.1)	10 (66.7)	11 (73.3)	11 (73.3)
LVEF (%)	33.5 (7.7)	31.6 (8.7)	29.1 (9.2)	31.1 (7.8)	34.4 (8.9)

All data are presented as n (%) unless otherwise noted.

*P=0.012 compared to control.

Immunologic Monitoring Methods

- HLA antigens of the MPC were identified by serologic methods.
- MPC HLA alloantigens could be immunogenic in recipients; therefore, we evaluated the antibody and cellular immune responsiveness of patients entered into the study.
- Antibody specificity was assessed when the PRA determined by flow cytometry was > 5% throughout the study.
- Donor-specific and non-donor-specific HLA antibodies were measured.

Immunologic Monitoring Results

Donor-Specific Anti-HLA Antibody Response

6 of 45 (13%) MPC-treated patients developed DSA.

Anti-HLA antibodies produced transiently (< 1 month):

- 4 of 45 (9%) total MPC-treated

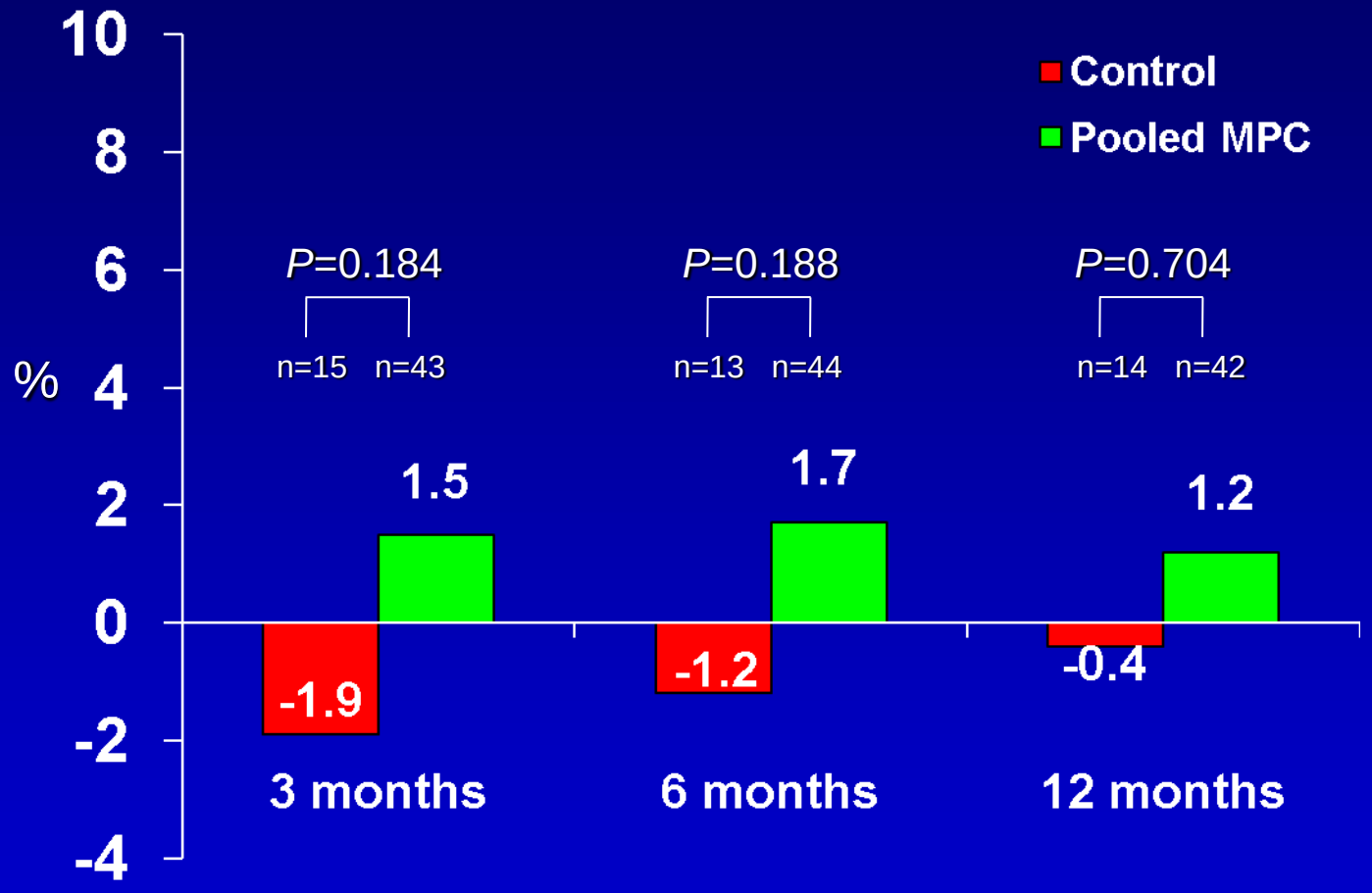
Anti-HLA antibodies persisting > 1 month:

- 2 of 45 (4%) total MPC-treated
  - 2 of 15 (13%) high-dose MPC (150M)
  - 0 of 30 (0%) low and mid-dose MPC (25M and 75M)

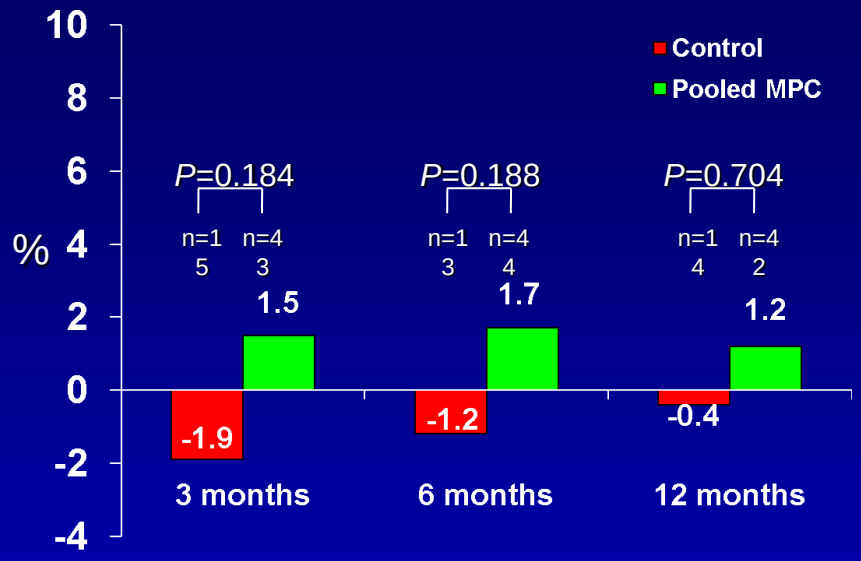
All anti-HLA antibodies were against donor HLA class I.

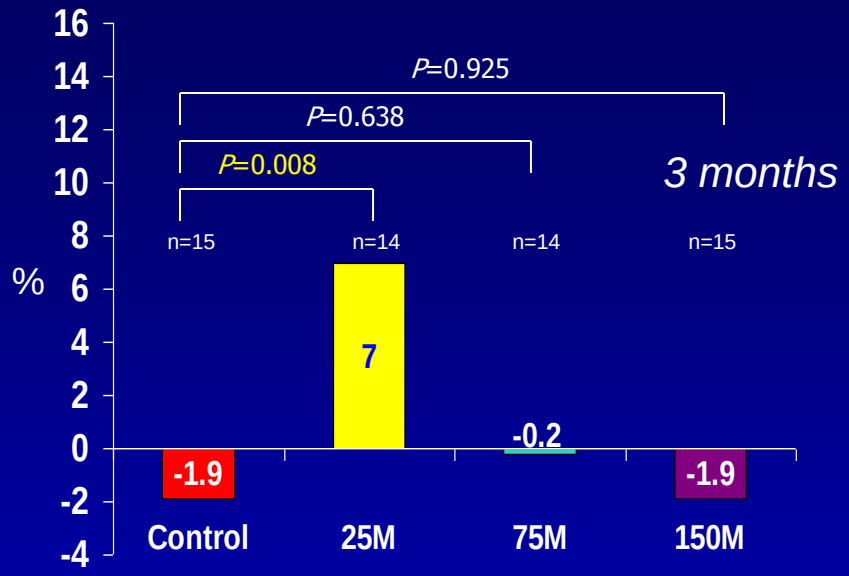
- No clinical symptoms/signs
- No effect on outcome

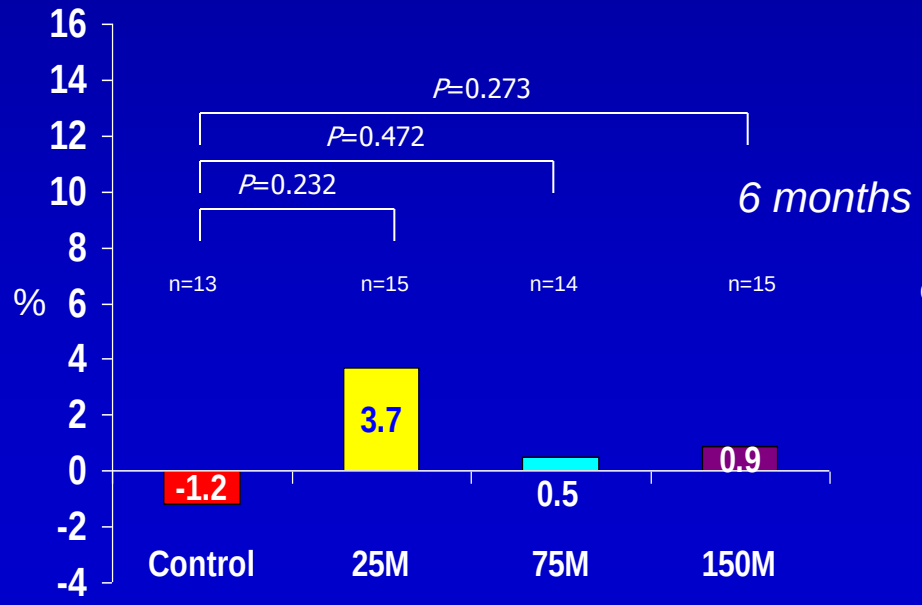
Changes in LV Ejection Fraction

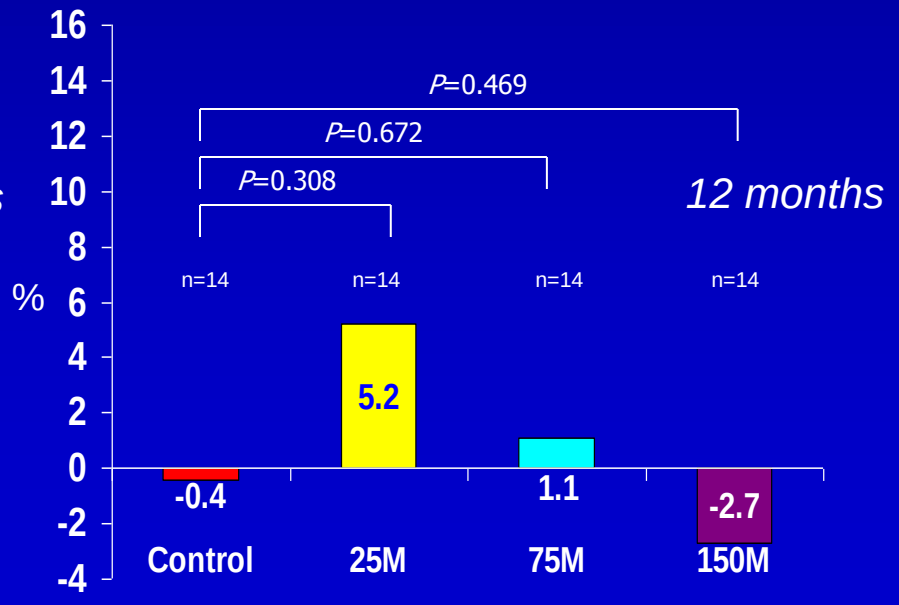


Changes in LV Ejection Fraction

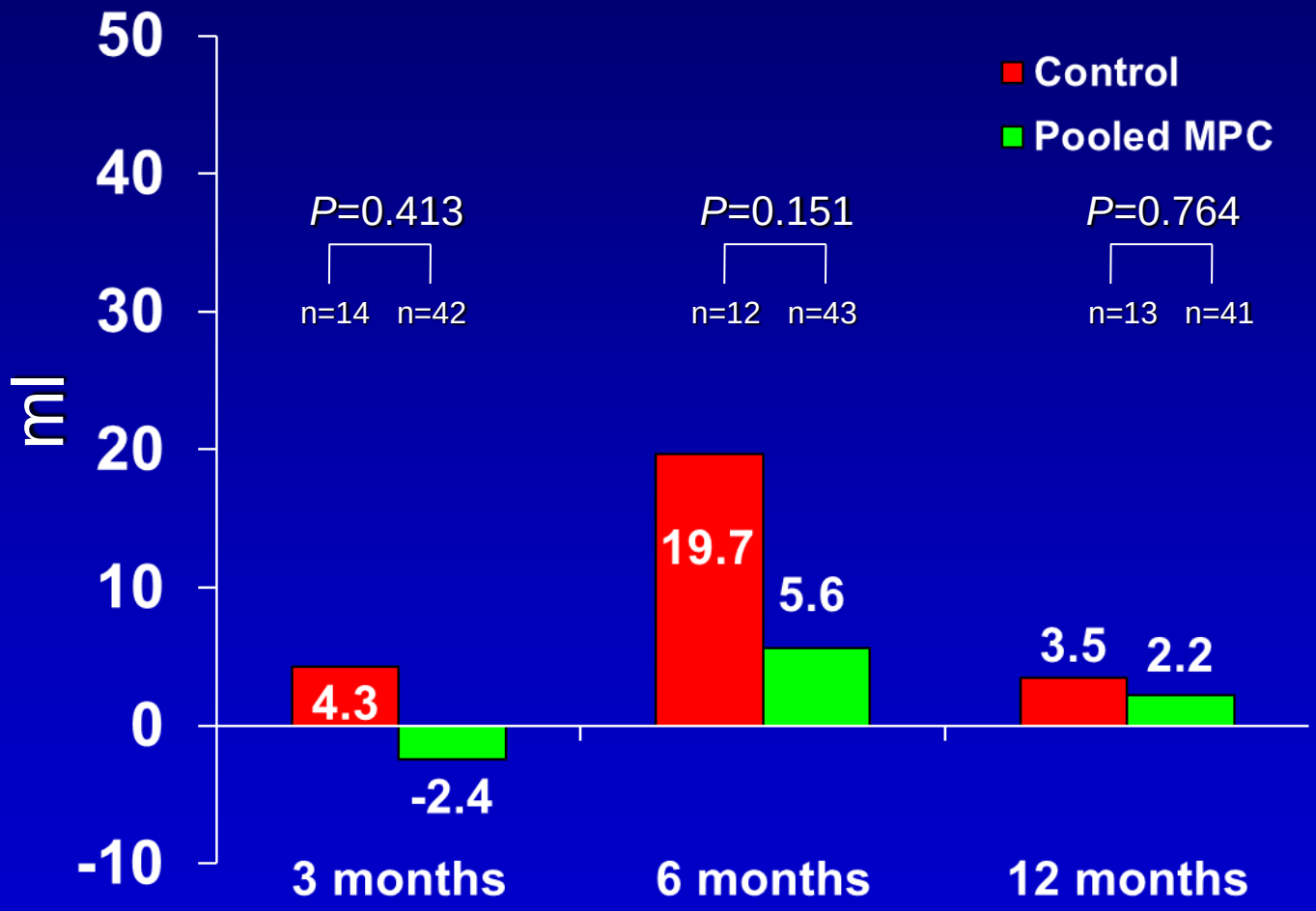




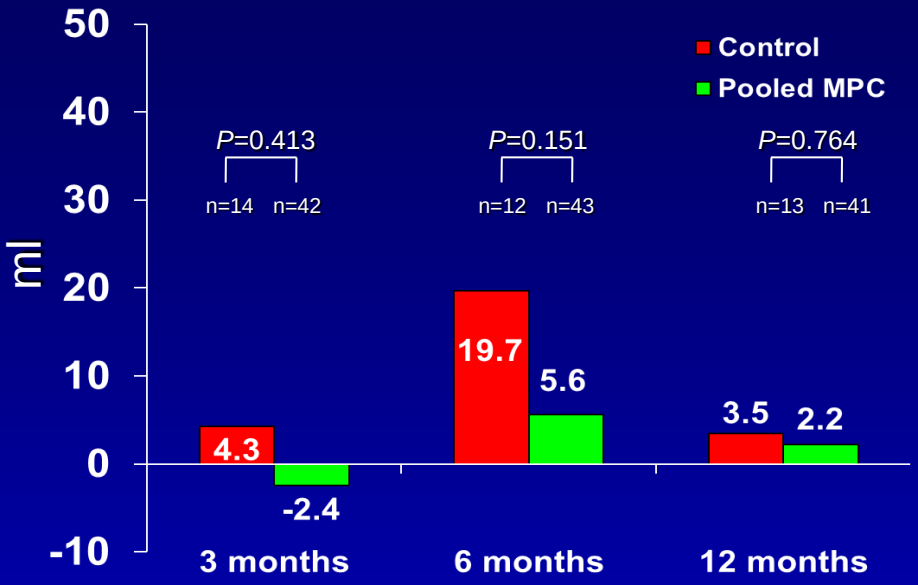


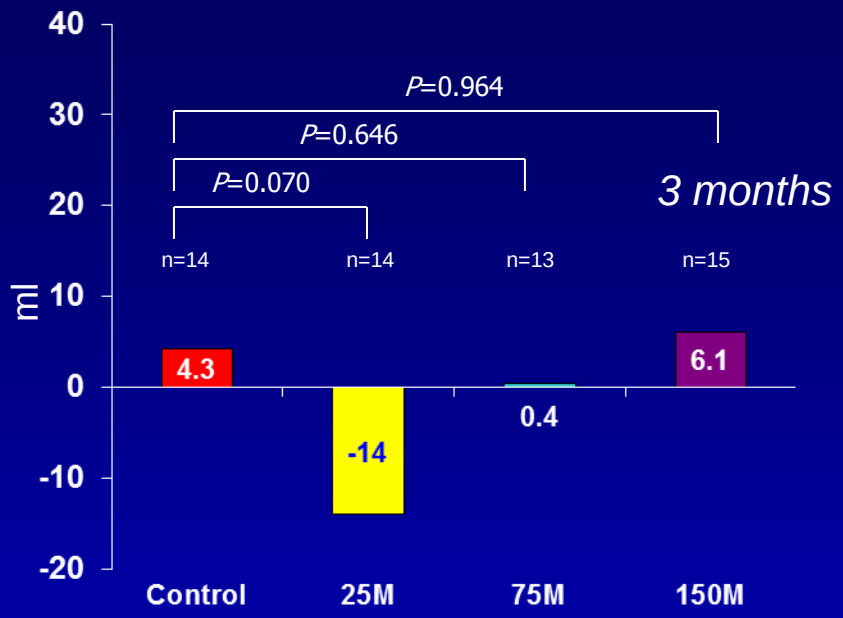


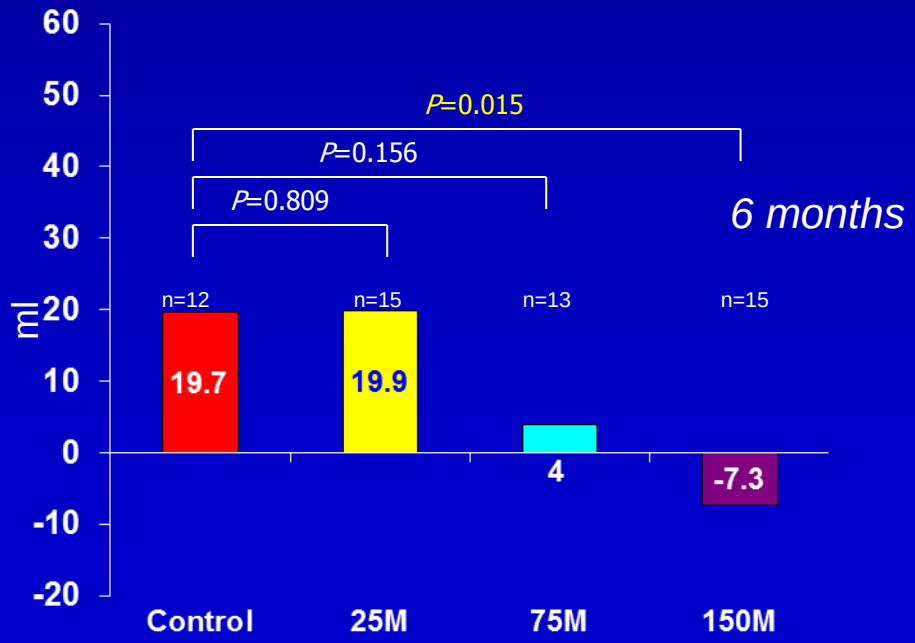
Changes in LV End Systolic Volume

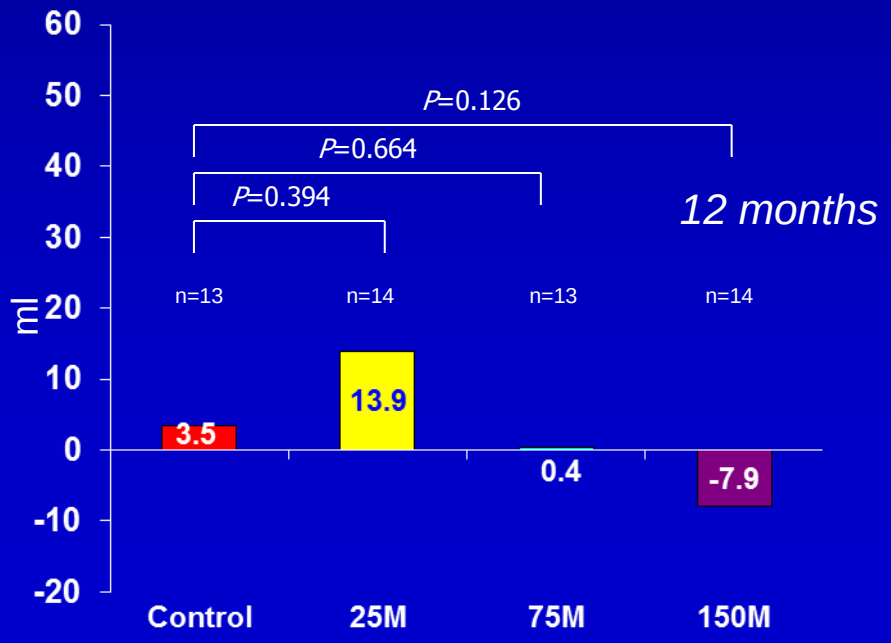


Changes in LV End Systolic Volume

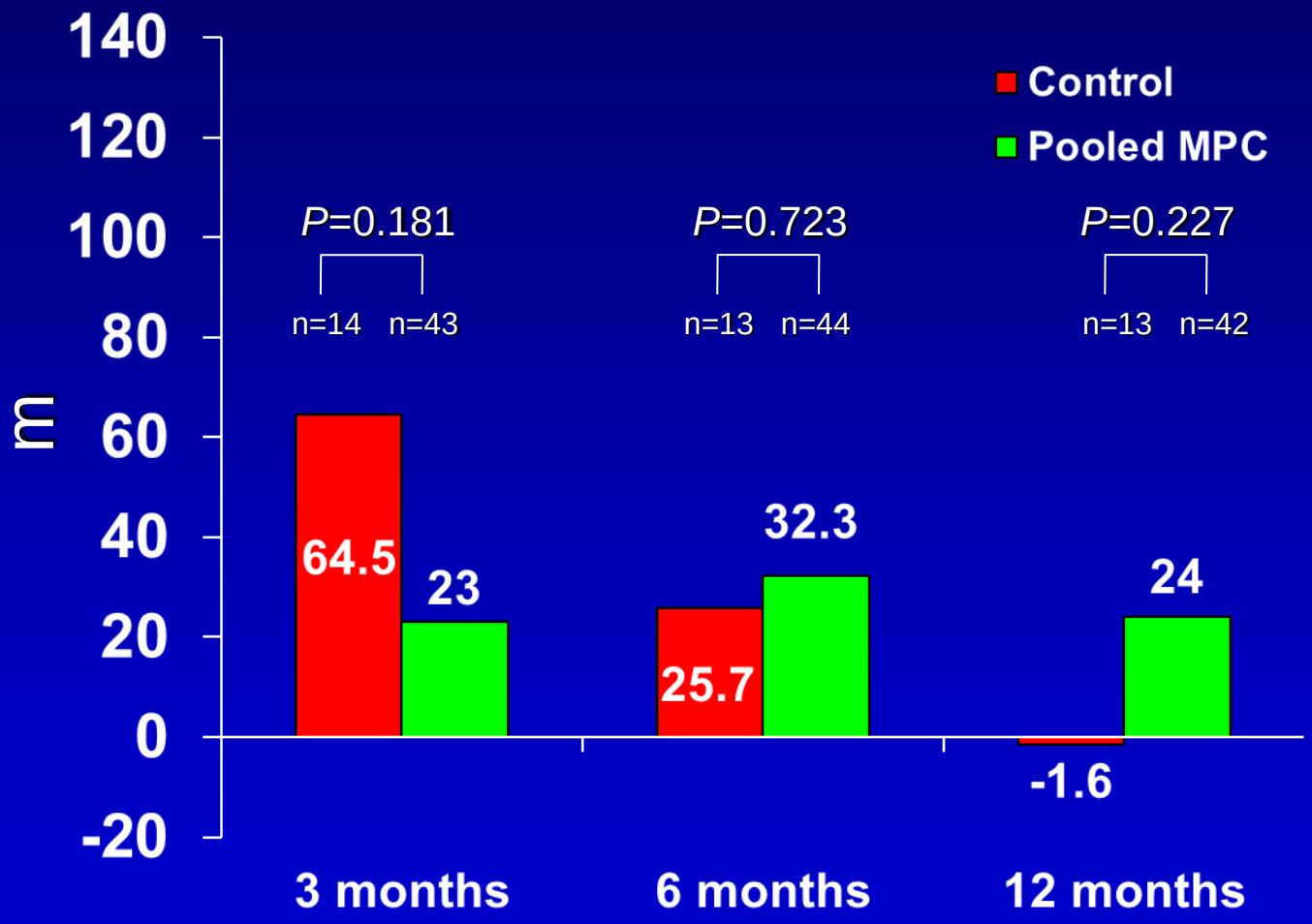








Delta 6-minute Walk



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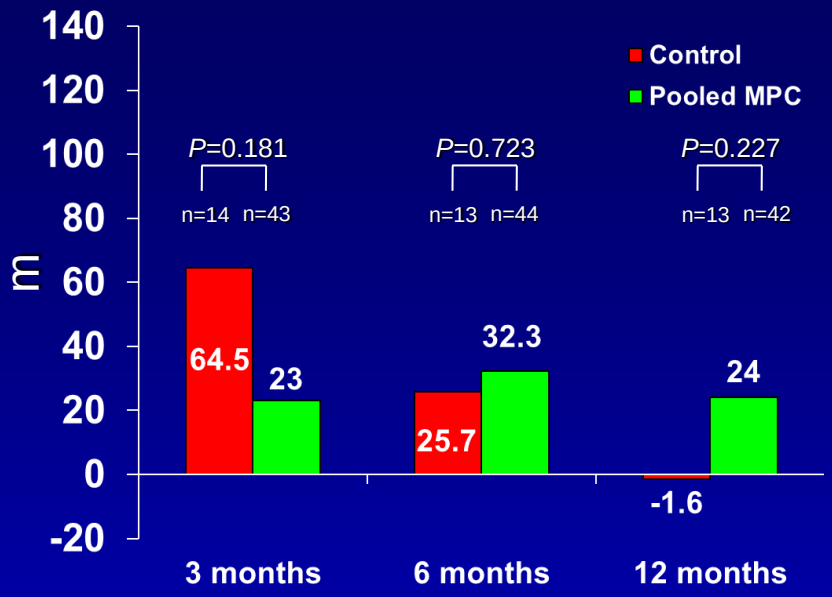
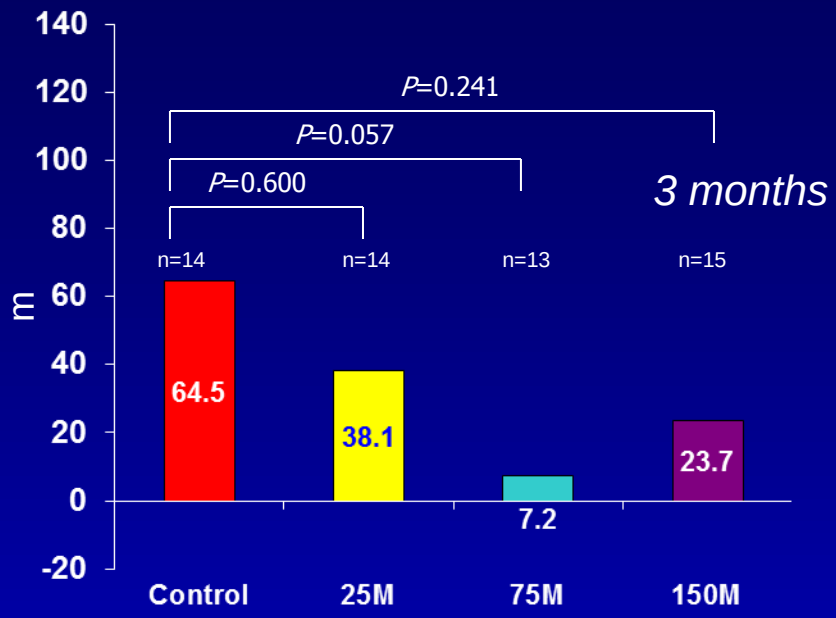
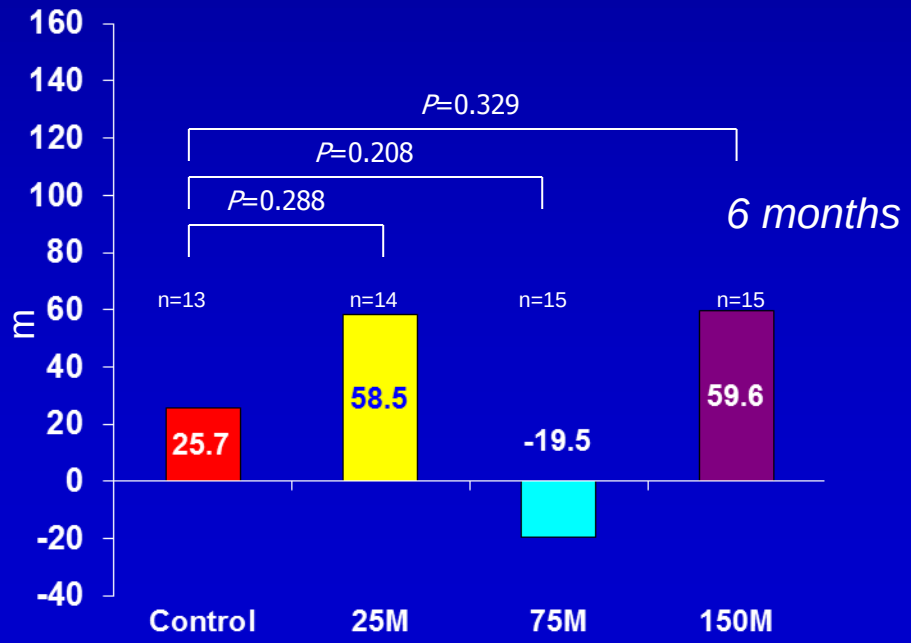
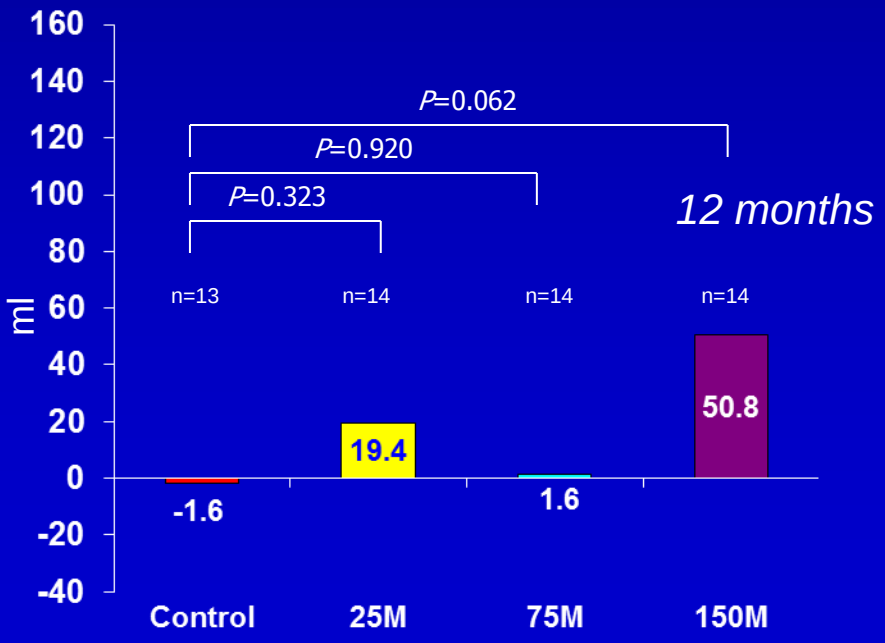
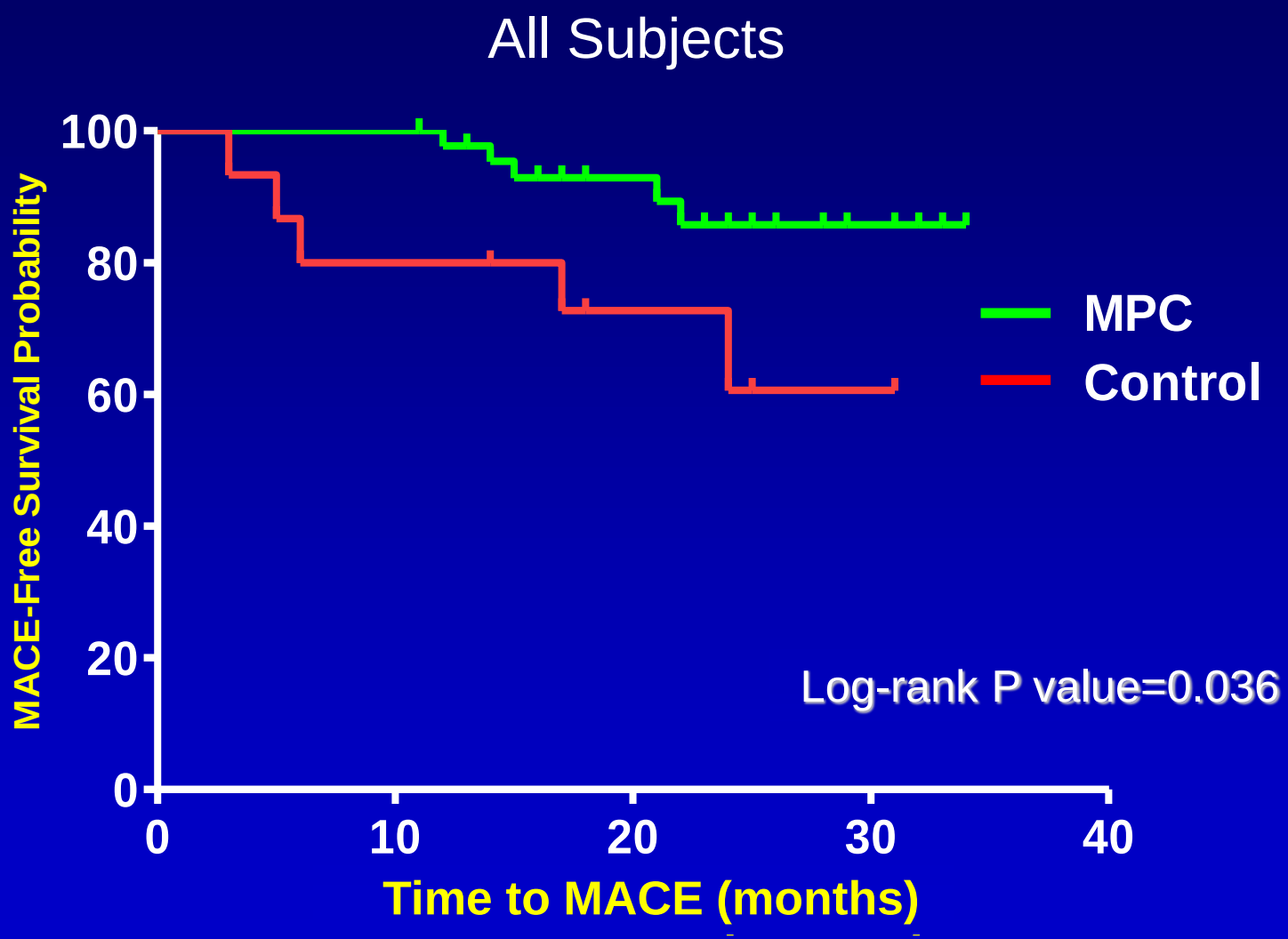








MACE Free Survival



MACE: Cardiac Death, Revascularization, MI

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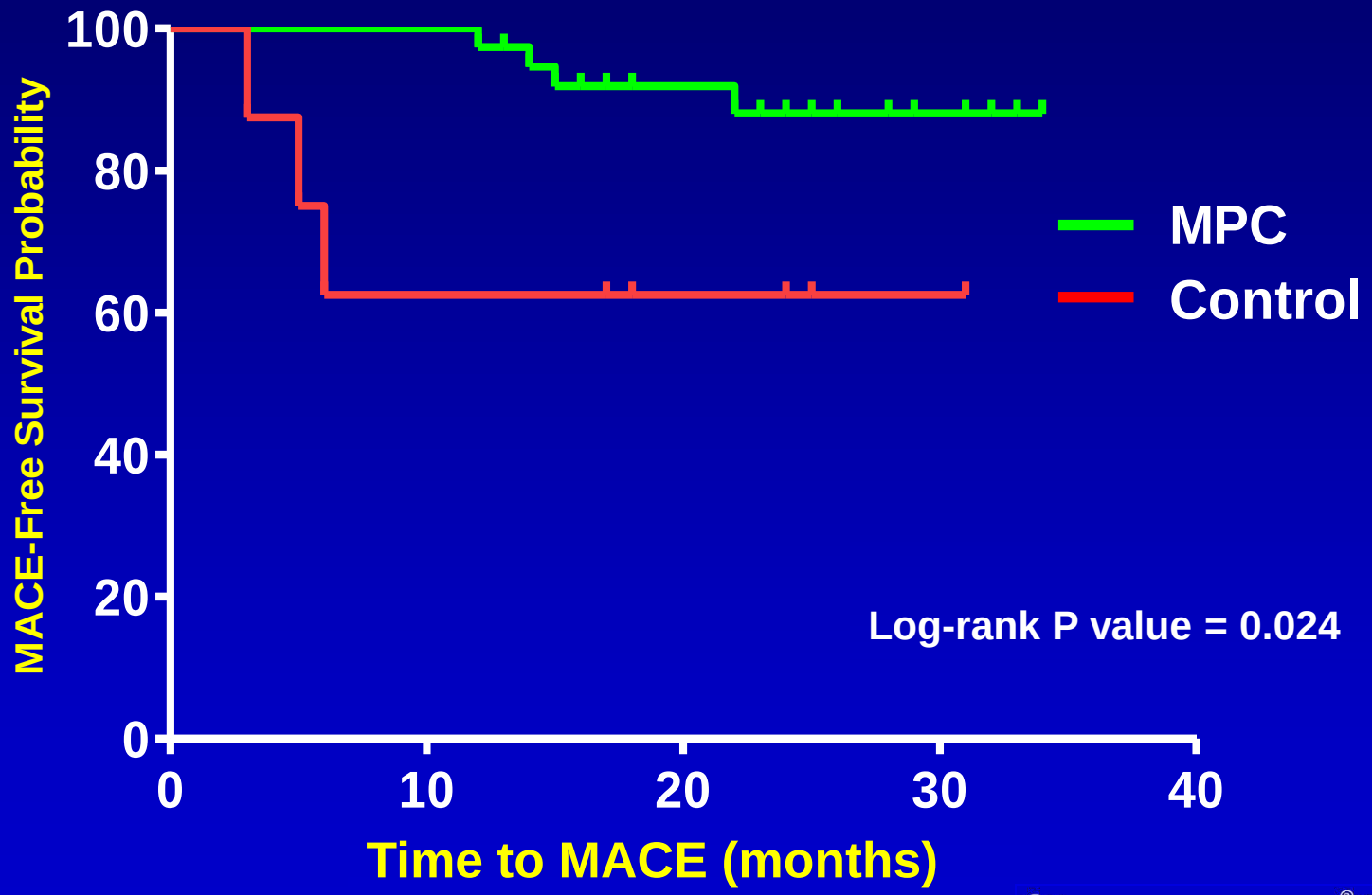
MACE Free Survival

Ischemic Subjects



MACE: Cardiac Death, Revascularization, MI

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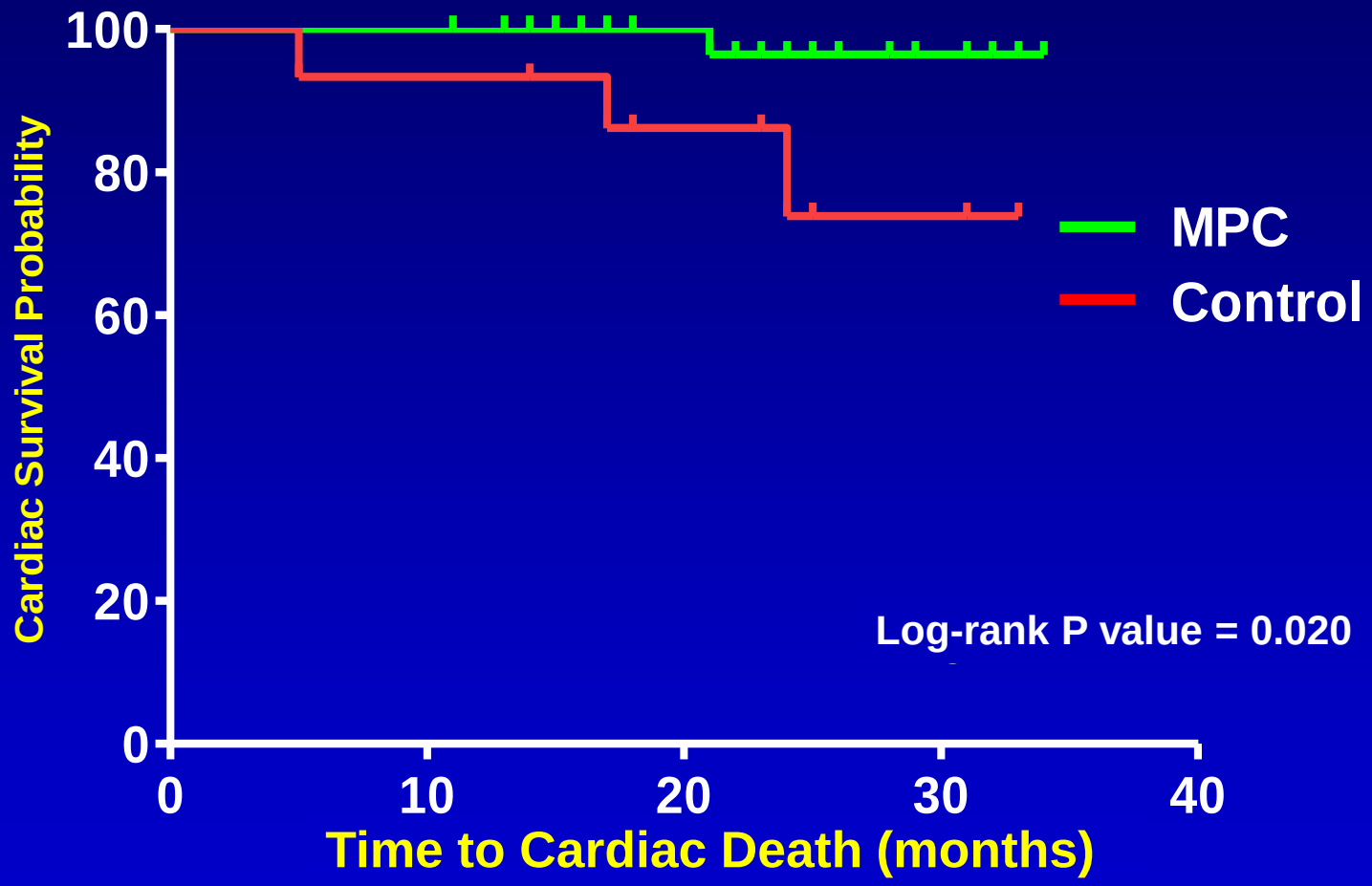
Cardiac Death Free Survival

All Subjects



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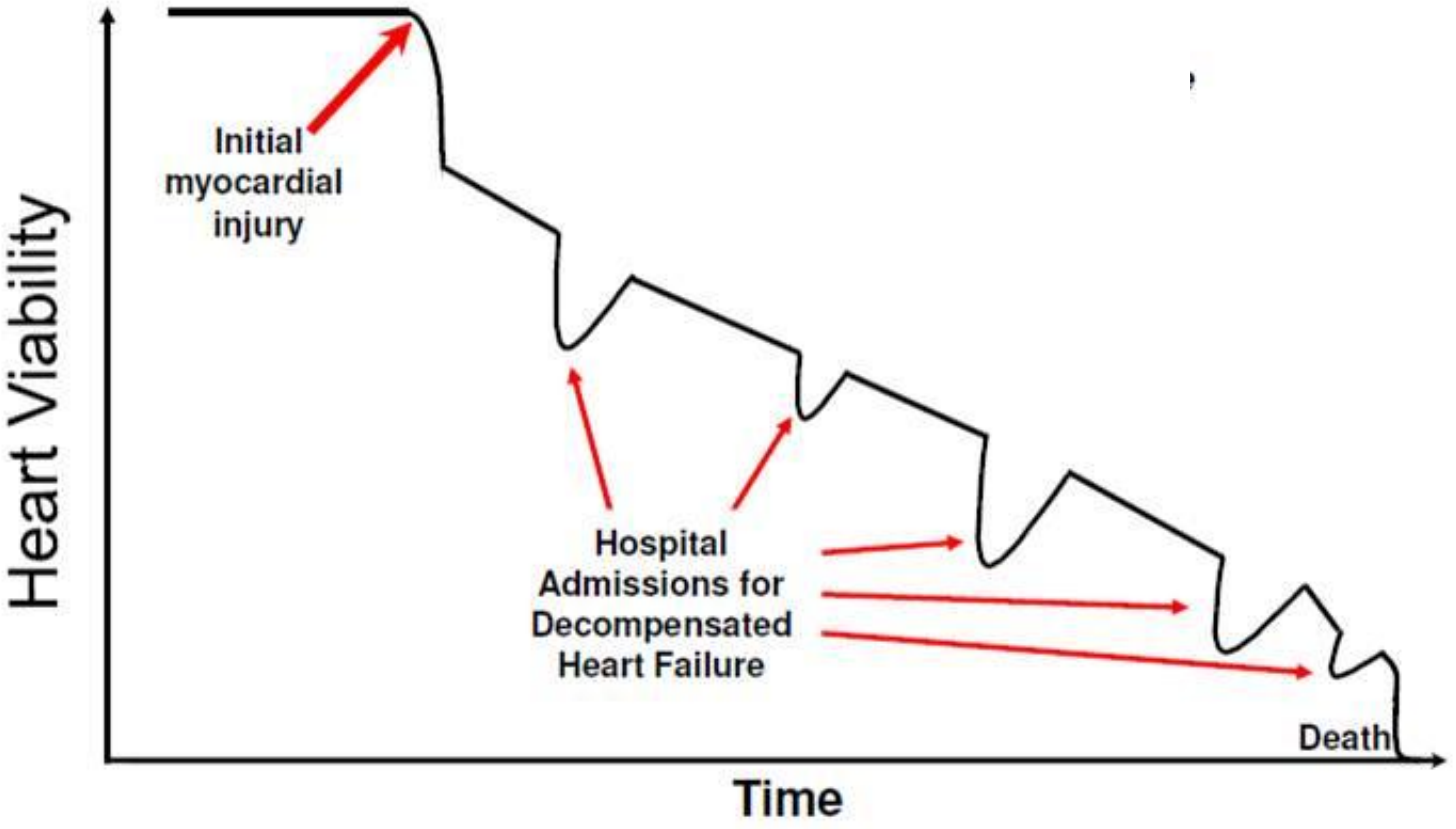
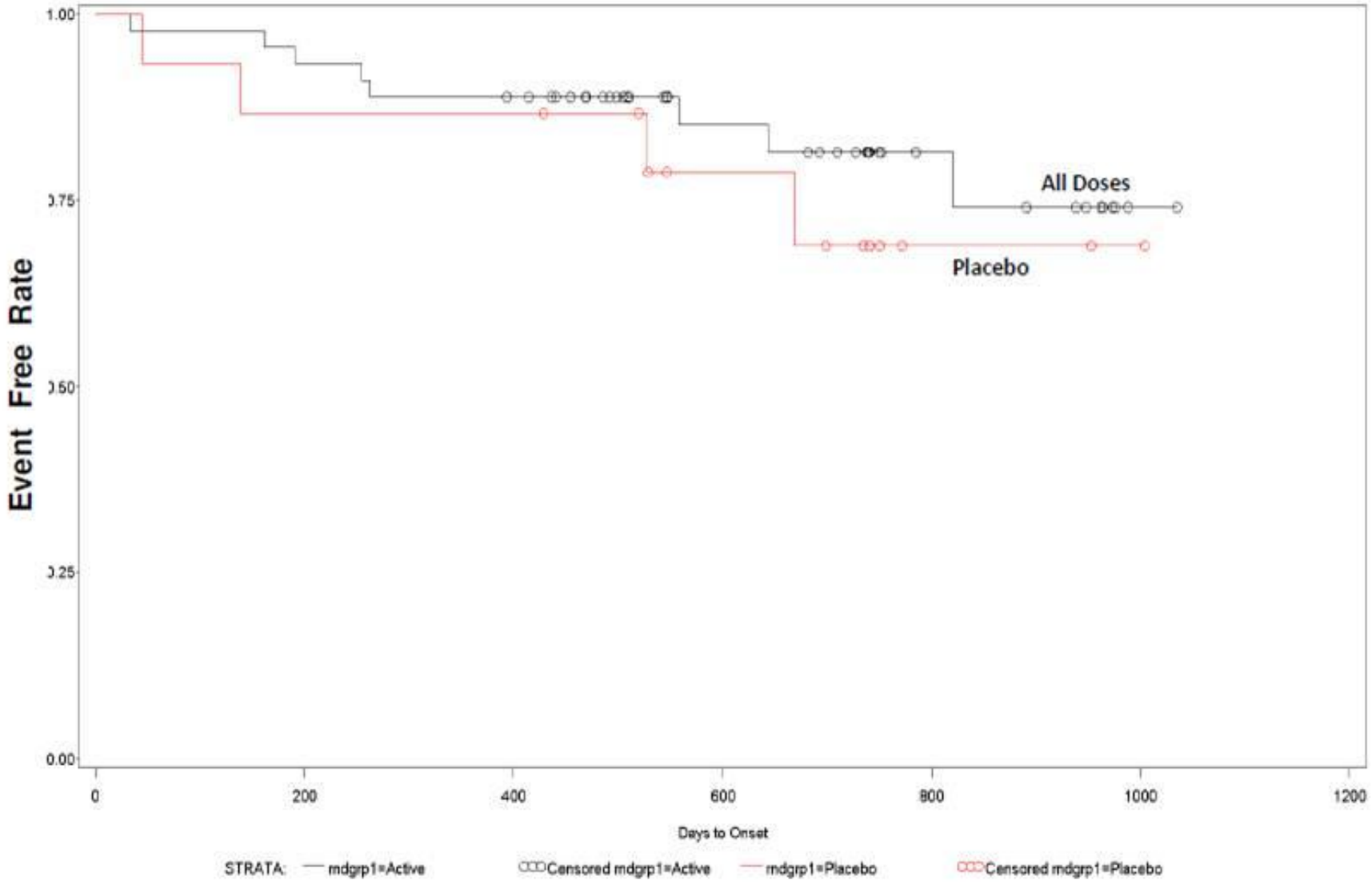
Natural History of the Chronic Heart Failure Patient

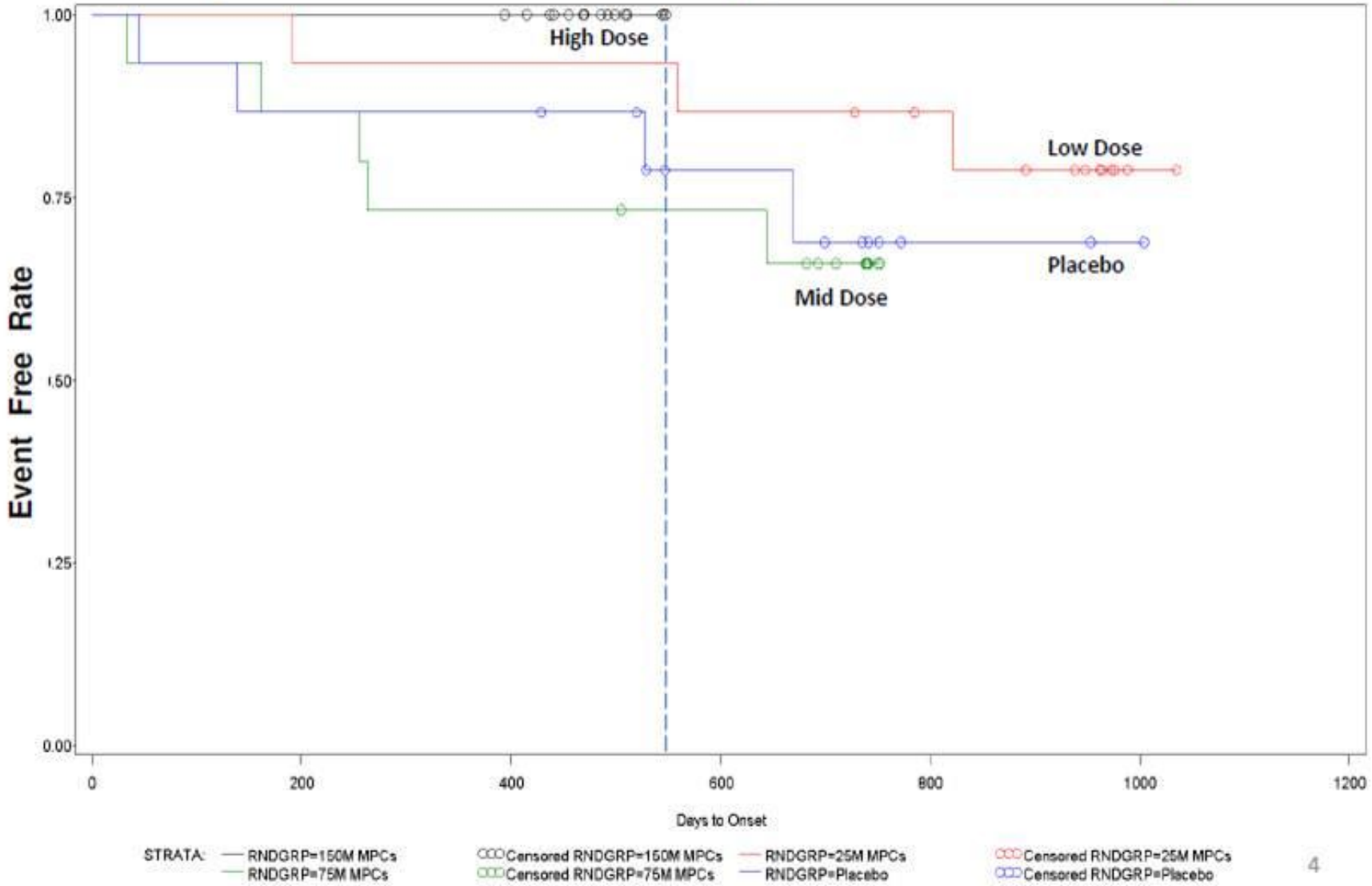
Normal Heart ⟶ Chronic Heart Failure ⟶ Death



Kaplan-Meier Plot of Time to First Event (Cardiac Death, HF Hosp, Resuscitated VFib)



Time to First Event By Treatment Group (Cardiac Death, HF Hosp, Resuscitated VFib)



Conclusions

1. Transendocardial injection of MPCs in patients with chronic heart failure was safe and feasible.

2. Treatment of patients in this study with allogeneic MPCs was not associated with a clinically significant immune response.

3. There was a significant early improvement in LVEF noted in the 25 million MPC dose group when compared to controls.

4. There was a significant later improvement in LVESV (remodeling) noted in the 150 million MPC dose group and a trend in 6 minute walk time (functional capacity) when compared to controls.

5. In a time-to-event analysis, the MACE event rate and cardiac mortality were significantly decreased for MPC-treated patients up to 3 year follow-up.