Effect of Transendocardial Delivery of Autologous Bone Marrow Mononuclear Cells on Functional Capacity, Left Ventricular Function, and Perfusion in Chronic Ischemic Heart Failure: The FOCUS-CCTRN Trial

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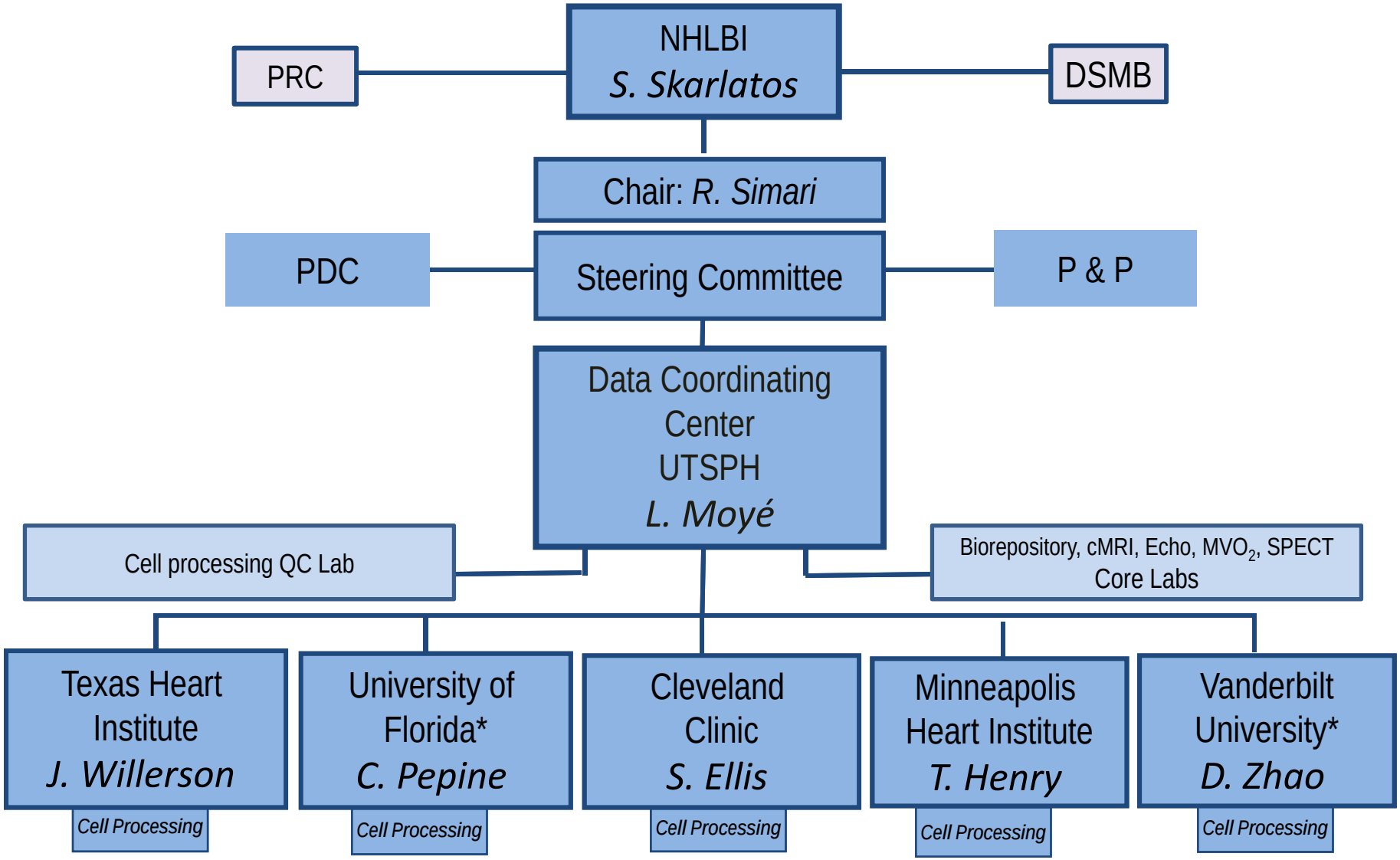
Cardiovascular Cell Therapy Research Network

Organizational Structure: NHLBI Cardiovascular Cell Therapy Research Network (CCTRN)



*Skills Development Core

Cell Therapy in Ischemic Heart Failure

Cell Types

Allogeneic Cells

- Mesenchymal stem cells (MSCs)
- Mesenchymal precursor cells (MPCs)

- Possible immunological Reaction
- Uniform cell quality and function (single/ limited numbers of healthy donors)
- Relatively pure cell population

Autologous Cells

- Bone marrow mononuclear cells (ABMMNCs)
- Selected bone marrow cells $ALDH^{br}$ cells

- No immunological Issues
- Variable cell quality and function due to host factors such as age and comorbidities
- Relatively mixed cell population

FOCUS CCTRN

- Double blinded, randomized, multicenter trial
- Transendocardial delivery of a dose of 100 million Autologous Bone Marrow Mononuclear Cells
- Patients with chronic ischemic heart disease and LV dysfunction with heart failure and/or angina
- Uniform local cell processing: Sepax
- Centralized Biorepository

CCTRN Biorepository

When a patient enters a clinical study

Blood drawn for PC and cytokine measurements

"Biorepository"

Center for Cardiovascular Repair

University of MN/Univ FL

Confidential and Privileged

Shipments Date Entered into Web Interface

Web Interface Sends an e-mail to Coordinator and Technician to expect shipped samples

Arrival Logged in Web Interface

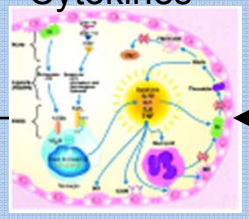
Samples are Prepared

FACS

Stem cells

Results Entered into Web Interface

Cytokines



Inflammation

Functional Measurements

Effect

Real time status and tracking
Report generation
Blinded data analysis
Easy data sharing
Regulatory compliance
Reduced work load

Inclusion Criteria

- Patients > 18 y old with significant coronary artery disease.
- LVEF ≤ 45% (by echocardiogram) and limiting angina (class II-IV) and/ or heart failure (NYHA class II-III).
- Patients should be on maximal medical therapy.
- Presence of reversibility by SPECT (adenosine stress) and/or viability as identified by NOGA.
- Coronary artery disease not well suited to any other revascularization procedure (percutaneous or surgical) in the target region of the left ventricle.
- Hemodynamic stability as defined by systolic BP ≥80mmHg without IV pressors or support devices.
- Women of childbearing age must be willing to use 2 forms of birth control for the duration of the study
- A signed consent form approved by the Institutional Review Board.

Exclusion Criteria (1)

1. Atrial fibrillation, atrial flutter, and /or significant uncontrolled arrhythmias.
2. ICD shock within 30 days of baseline screening.
3. Unstable Angina.
4. High-risk ACS or a myocardial infarction in the month before evaluation.
5. LV thrombus, as documented by echocardiography or LV angiography.
6. Vascular anatomy that precludes cardiac catheterization.
7. Severe valvular disease or mechanical aortic valve that would preclude safe entry of the catheter into the left ventricle.
8. Platelet count <100K/mm^3.
9. WBC <2K/mm^3.
10. Revascularization within 30 days of study enrollment.
11. TIA or stroke within 60 days of study enrollment.
12. Bleeding diathesis defined as an INR ≥2.0 in the absence of warfarin therapy.

Exclusion Criteria (2)

13. History of non-basal cell carcinoma malignancy in the last 5 years.
14. Infectious-disease test result positive for HIV, hepatitis B, or hepatitis C.
15. Any previous transplant requiring immunosuppressive medication.
16. LV wall thickness of < 8 mm (by echocardiogram) at the target site for cell injection.
17. Inability to walk on a treadmill, except for class IV angina patients who will be evaluated separately.
18. Enrollment in an investigational device or drug study within the previous 30 days.
19. Hepatic dysfunction as defined by AST and ALT levels.
20. Chronic renal insufficiency.
21. Pregnancy as determined by a positive pregnancy test at baseline.
22. Any other contraindication to enrollment or follow-up.

Study Endpoints
6 Months

Primary Endpoints

- Change in maximum oxygen consumption (MVO2)
- Change in LVESV as assessed by echocardiography
- Change in ischemic (reversible) defect size as assessed by SPECT

Secondary Endpoints

- Wall motion by echocardiography
- Change in LVEDV as assessed by echocardiography
- Change in total and fixed defect size as assessed by SPECT
- Change in functional class (NYHA,CCS) and serum BNP levels

Exploratory Analyses

- LVEF by echocardiography
- Phenotypic and bone marrow function analyses with relevant endpoints
- Relationship of Age and relevant endpoints

FOCUS CCTRN Study Flow

2:1 Randomization
2 BMC:1 Cell-Free

Informed Consent

Meets Inclusion/ Exclusion Criteria

Baseline Echo MVO_2 SPECT

6 Month Echo MVO_2 SPECT

Yearly Safety Follow-up up to 4 Years

BMCs (n=61)

Screening period w/in 60 days (N=92)

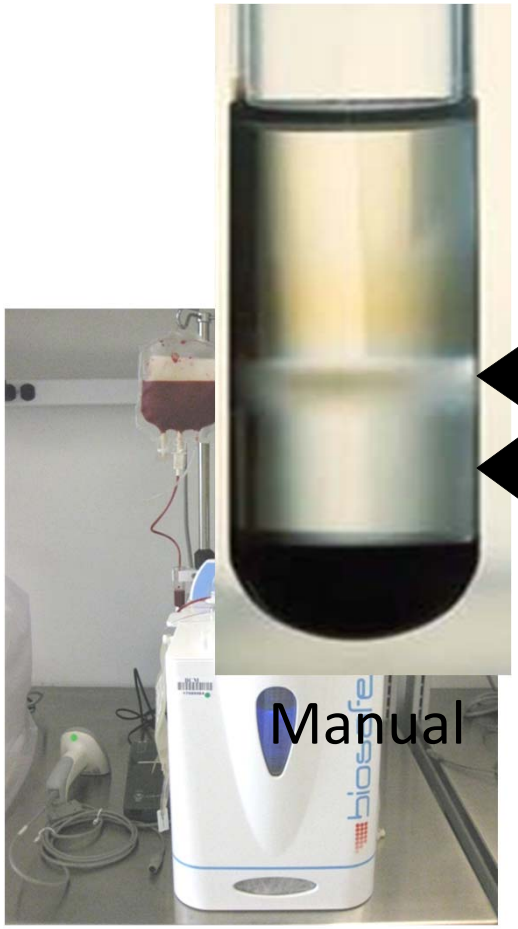
Cell Free Placebo (n=31)

BM Aspiration/ Cell Processing*

Coronary angiography, LV Mapping and Transendocardial Injections

**CP-Quality Control - Biorepository - Cell Function Core*

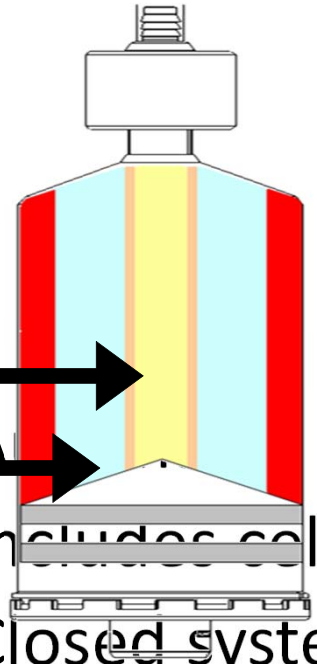
Cell Processing



BMC

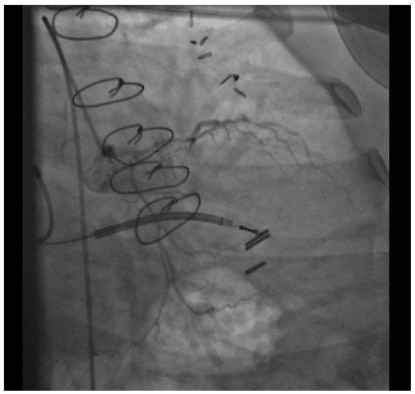
Ficoll

Sepax

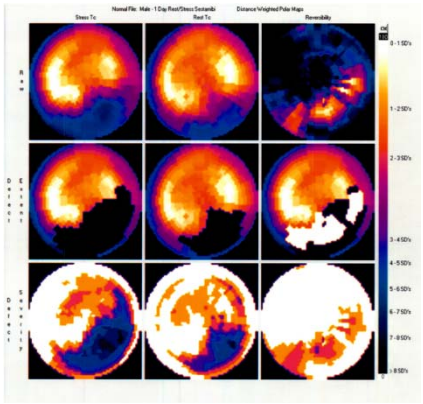


- ✓ A[illegible] processing
- ✓ In[illegible]ll washing
- ✓ Closed system
- ✓ Sterile disposable set
- ✓ Local processing

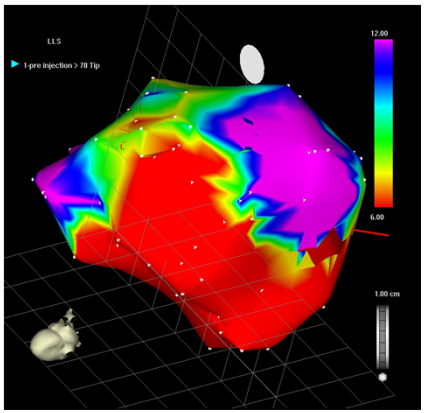
Targeting of Stem Cell Injections



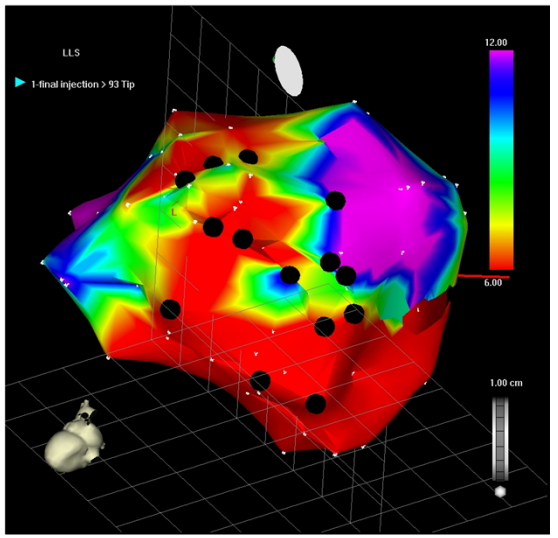
Anatomical
(angiogram)



Perfusion
(SPECT)

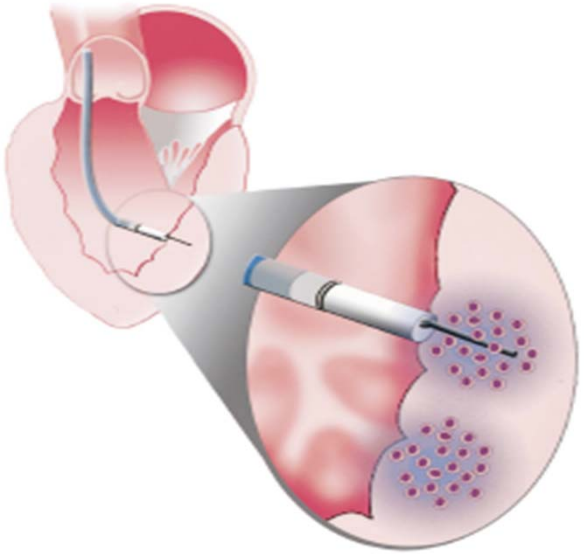


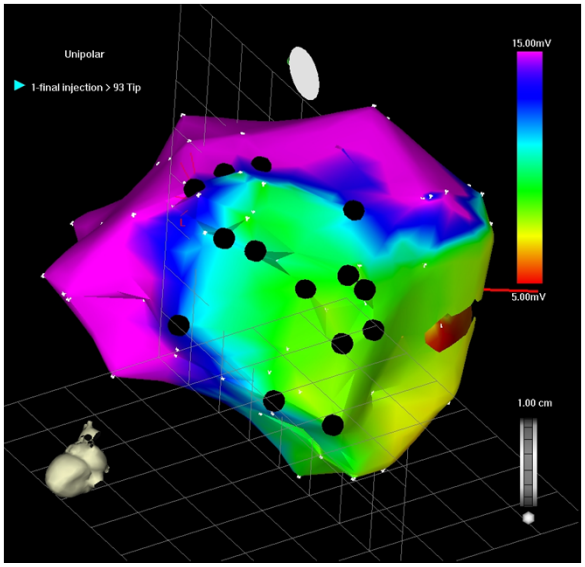
Viability/
hibernation
(EMM)



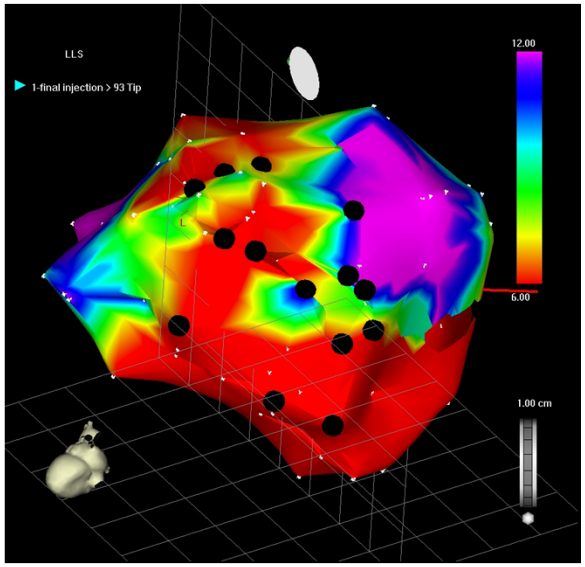
Transendocardial Injections

- Total of 15 injections
- Volume of 0.2 cc
- Targeted to ischemic myocardium
- Injection Criteria:
  - Unipolar voltage ≥6.9mV
  - Loop Stability ≤4
  - PVC upon needle insertion

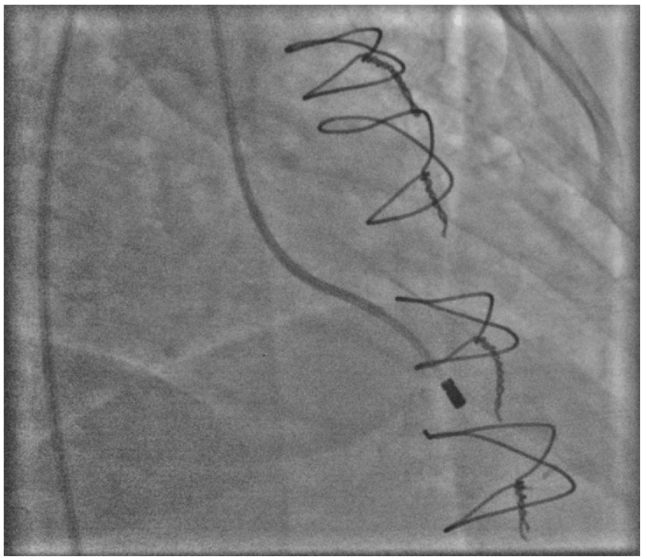




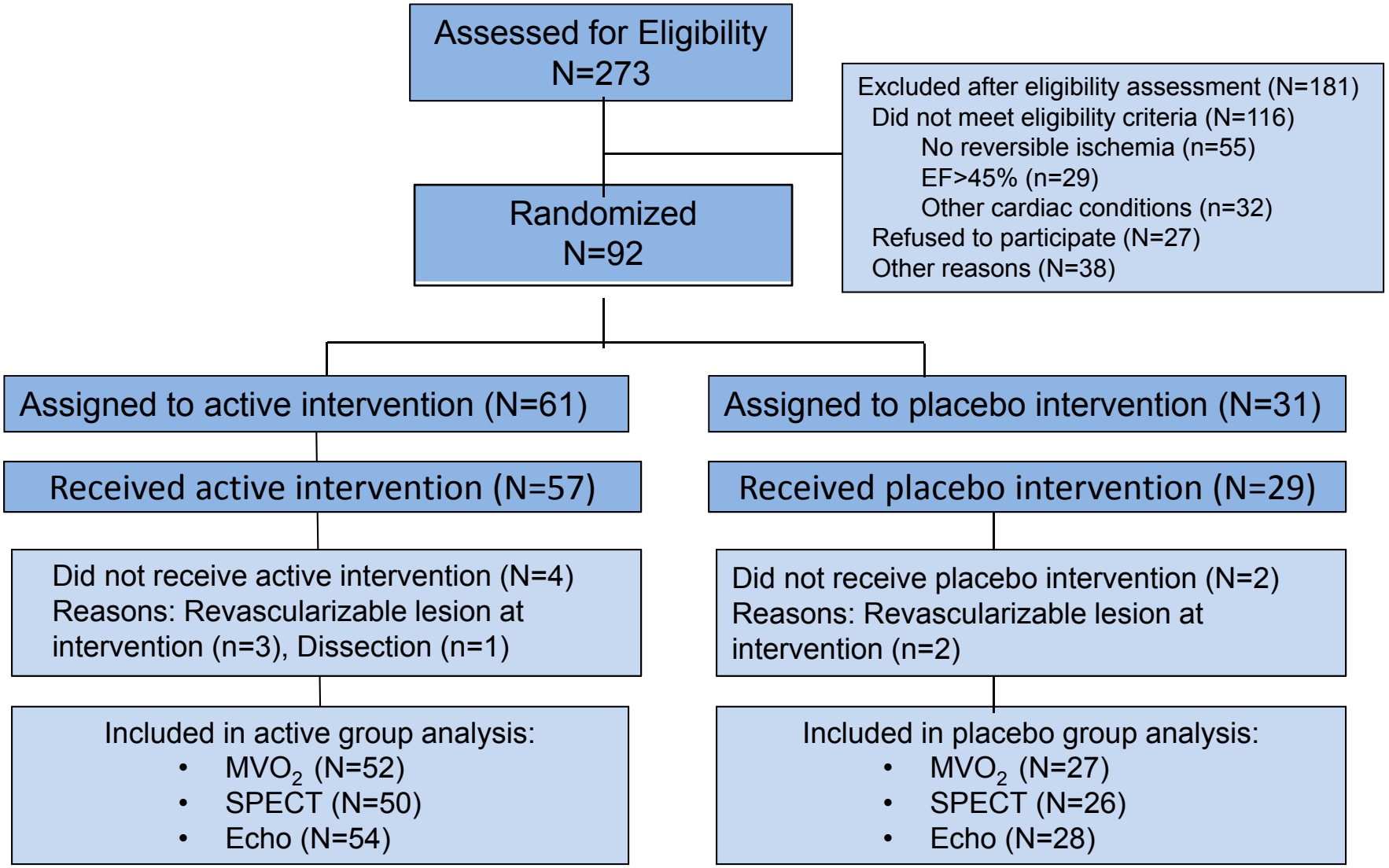
UniV



LLS



Results: Patient Flow



Baseline Characteristics

N (%) unless otherwise specified	BMC N=61	Placebo N=31	P-value
Patient Characteristics:			
Age in years, mean (SD)	63.95(10.90)	62.32(8.25)	0.47
Female	8(13.11)	2(6.45)	0.49
White	58(95.08)	30(96.77)	1.00
Hispanic	3(4.92)	1(3.23)	1.00
BMI, mean (SD)	30.10(6.14)	31.80(6.60)	0.23
NYHA Classification:			
Class I	6(9.84)	2(6.45)	
Class II	32(52.46)	14(45.16)	
Class III	23(37.70)	15(48.39)	0.59
Class IV	0 (0.00)	0 (0.00)	
CCS Classification: (BMC=54, Placebo=25)			
Class I	13(24.07)	10(40.00)	
Class II	24(44.44)	10(40.00)	
Class III	16(29.63)	5(20.00)	
Class IV	1(1.85)	0(0.00)	0.45
BP in mmHg, mean (SD):			
Systolic	120.59(19.69)	122.13(15.78)	0.71
Diastolic	70.95(11.18)	74.77(10.35)	0.12
Qualifying LVEF (echo), mean (SD) (BMC=60)	32.43(9.23)	30.19(7.76)	0.25
Aspiration to Injection Time (hours), mean (SD) (BMC=58, Placebo=29)	8.95(1.18)	8.56(2.22)	0.28

Baseline Characteristics

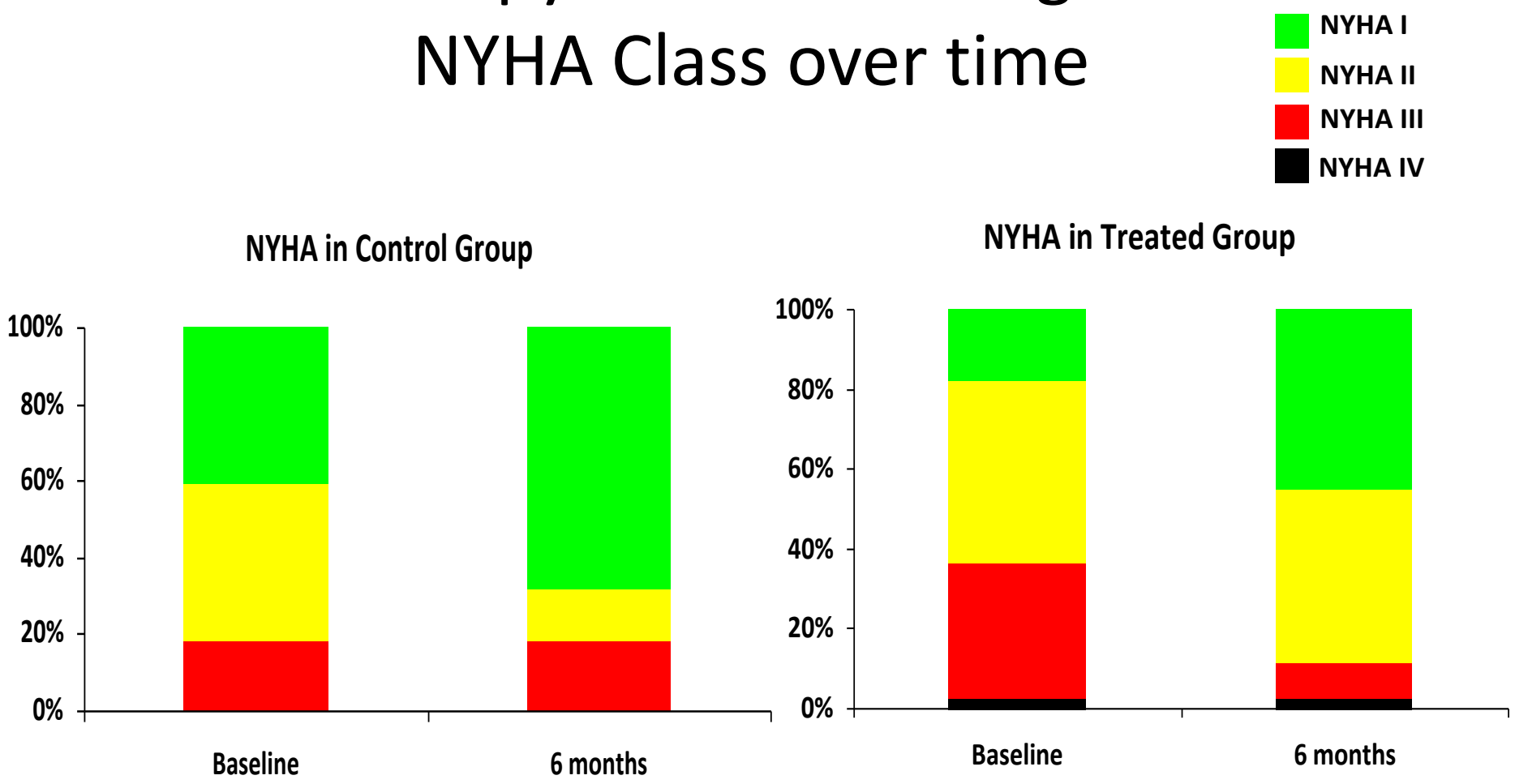
N (%) unless otherwise specified	BMC N=61	Placebo N=31	P-value
Medical History:			
Diabetes	21(34.43)	16(51.61)	0.12
Hypertension	49(80.33)	24(77.42)	0.79
History of MI (BMC=57)	53(92.98)	29(93.55)	1.00
Prior Revascularization	51(83.61)	26(83.87)	1.00
Prior CABG	47(77.05)	25(80.65)	0.79
Number CABG Operations:			
1	33(70.21)	21(84.00)	
2	13(27.66)	4(16.00)	
3	1(2.13)	0(0.00)	0.39
Medications at Time of Randomization:			
ACEi/ARB	37(60.66)	22(70.97)	0.37
Diuretics	41(67.21)	23(74.19)	0.63
Statins	44(72.13)	21(67.74)	0.81
Ranolazine	21(34.43)	3(9.68)	0.01
Laboratory Evaluations:			
GFR in ml/min/1.73m^2, median (range) (BMC=58, Placebo=29)	71.2 (29.6-155.4)	70.1 (30.5-107.3)	0.96
BNP in pg/ml, median (range) (BMC=46, Placebo=23)	132.0 (16.0-545.0)	105.0 (26.0-140.0)	0.68
ProBNP in pg/ml, median (range) (BMC=15, Placebo=8)	833.0 (50.0-9793.0)	828.0 (103.0-5778.0)	0.95

Cell Characteristics and Function

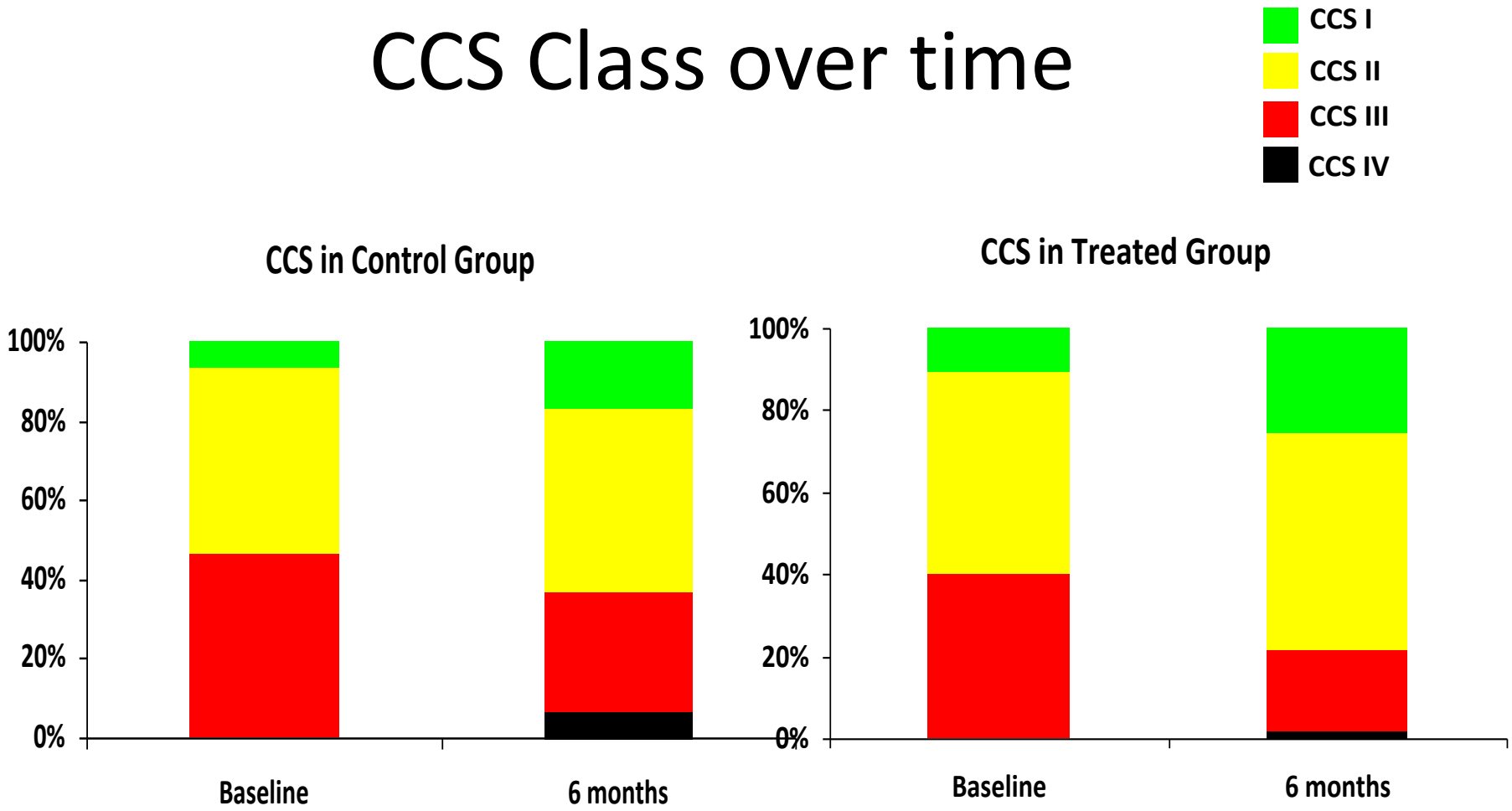
N (%) unless otherwise specified	BMC N=61	Placebo N=31	P-value
Total Nucleated Cells/Product (x10^6), mean (SD)	99.03(5.58)	100.03(0.18)	0.322
%Viability/product by Trypan blue exclusion, mean (SD)	98.56(1.11)	98.70(0.89)	0.523
%CD34 cells/product, mean (SD)* (BMC=57, Placebo=30)	2.71(1.19)	2.60(0.93)	0.673
%CD133 cells/product, mean (SD)* (BMC=57, Placebo=30)	1.21(0.62)	1.14(0.48)	0.588
Colony Forming Units-Hill/product, mean (SD)* (BMC=55, Placebo=30)	109.41(206.29)	151.33(244.20)	0.404
Endothelial Colony Forming Cells/product, mean (SD)* (BMC=49, Placebo=28)	131.84(164.62)	156.44(240.12)	0.596

* Four patients either declined participation or had insufficient product for the Biorepository.

Therapy Effect on change in NYHA Class over time

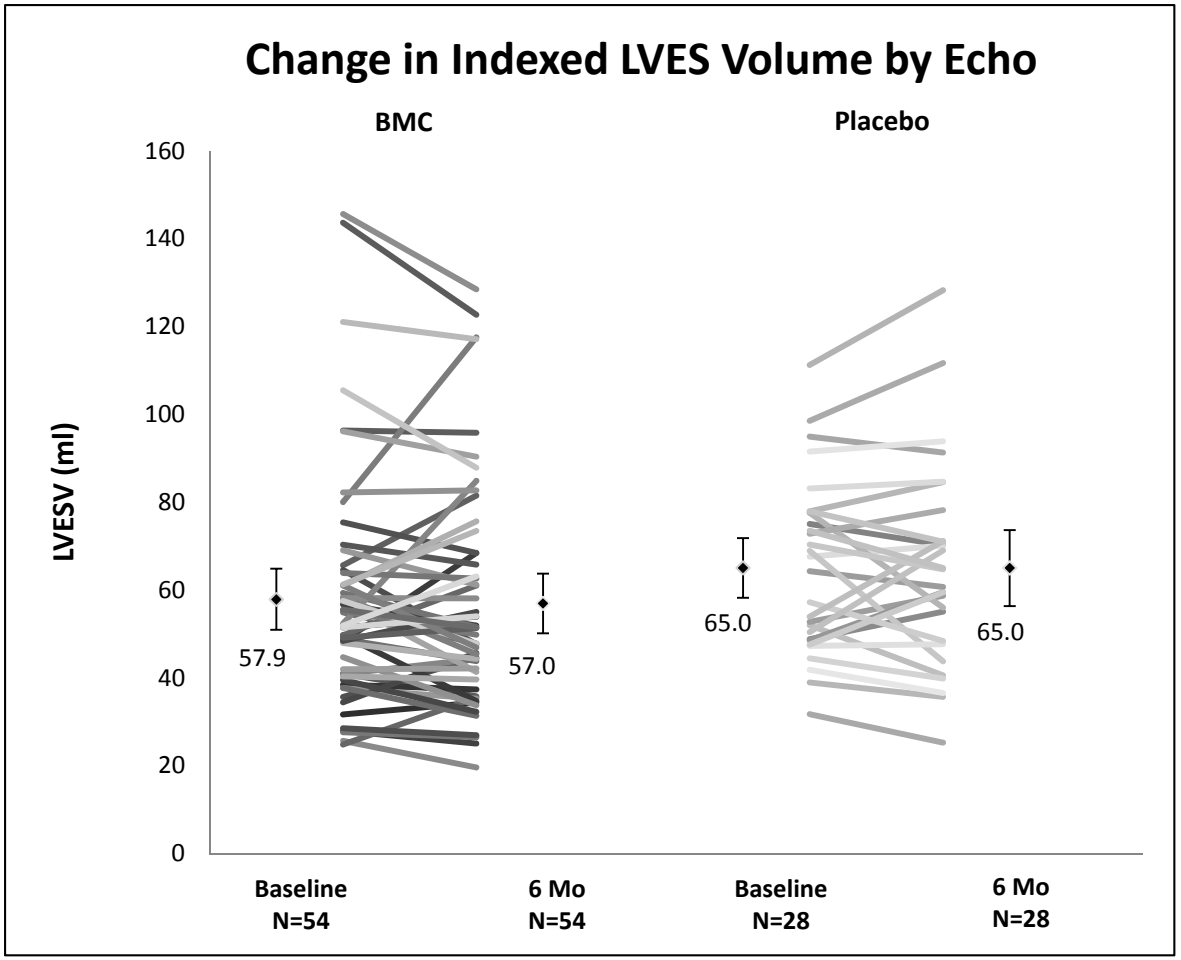


Therapy Effect on change in CCS Class over time



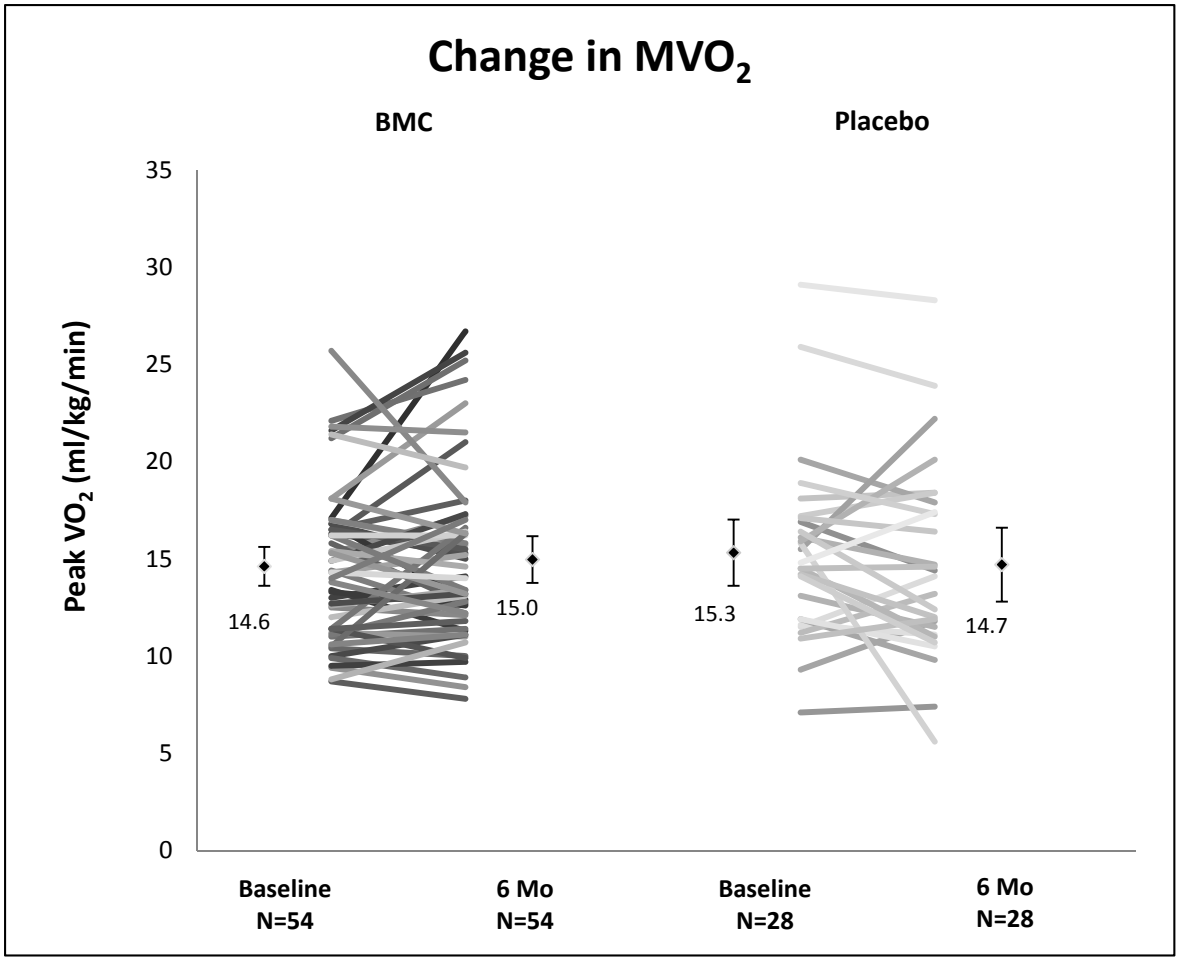
Primary Endpoint: LVESV

No difference in the change in indexed LVESV by Echo between BMC and Placebo groups from baseline to 6 months



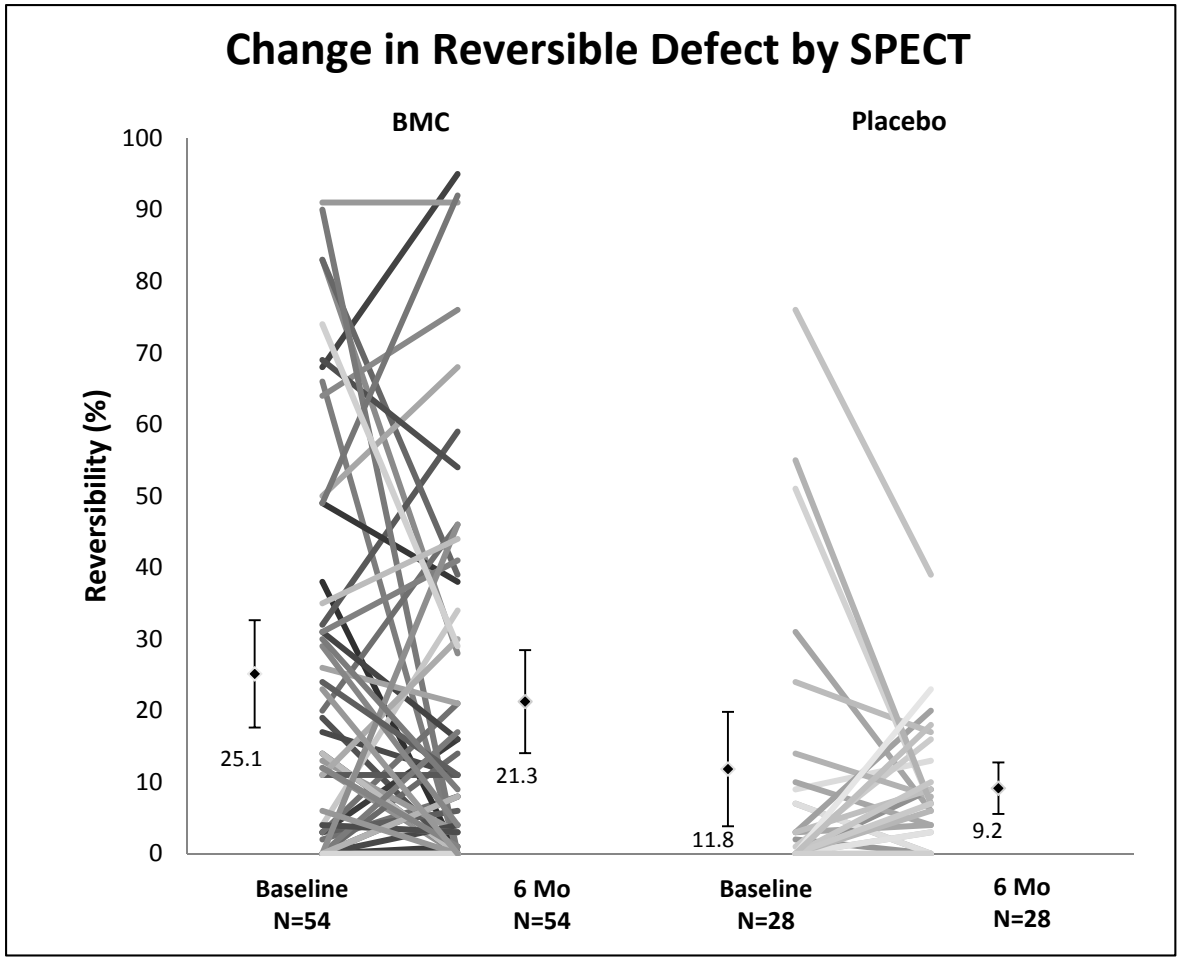
Primary Endpoint: MVO_2

No difference in the change in MVO_2 between BMC and Placebo groups from baseline to 6 months



Primary Endpoint: Reversible Defect

No difference in the change in reversible defect by SPECT between BMC and Placebo groups from baseline to 6 months

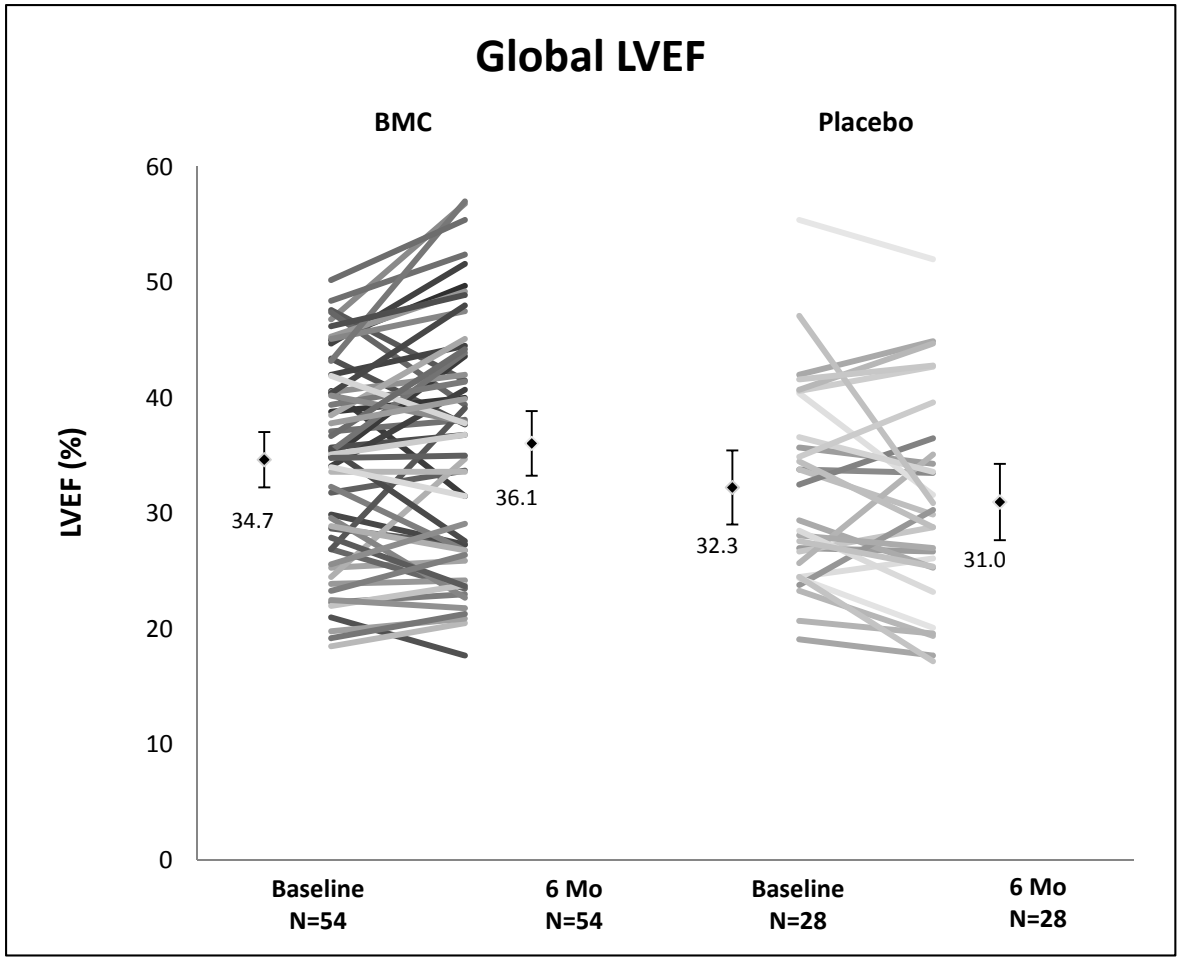


Clinical Outcomes within 6-month Endpoint Window

	BMC (n=61)	Placebo (n=31)
Death	1	0
New MI	1	0
Rehospitalization for PCI	0	0
Rehospitalization for ACS	1	0
Rehospitalization for CHF	3	5
New AICD implantation	0	0
Heart Transplant	0	1
LVAD	1	1
Total Outcomes	**7**	**7**
Patients	**4 (7%)**	**4 (13%)**
Crude Incidence Rate	0.066	0.129

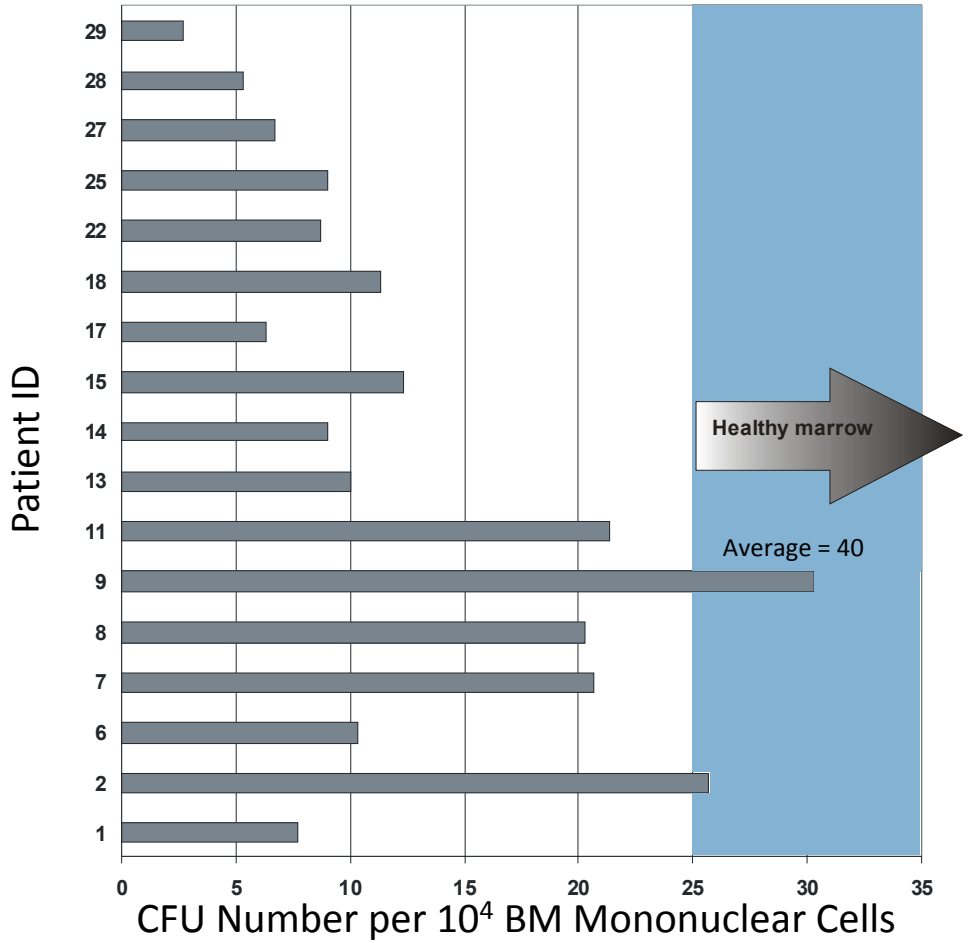
Exploratory Analysis: LVEF

Significant difference in the change in LVEF between BMC and Placebo groups from baseline to 6 months (1.4 vs -1.3, p=0.030)



Bone Marrow Sample Analysis in Focus HF: *CFU-GM*

Only 2 patients had CFU in the “normal” range.

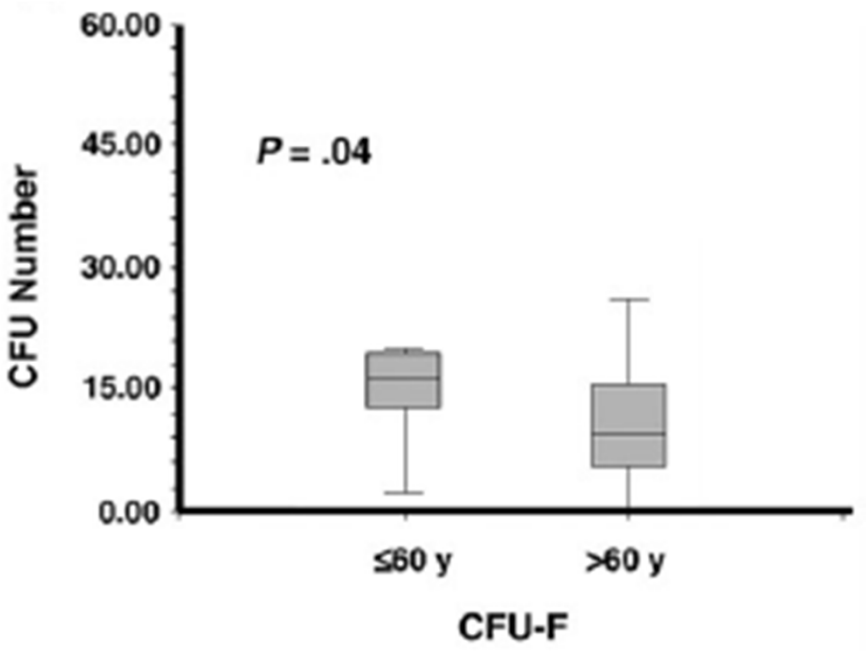


Am Heart J 2011;161:1078-1087

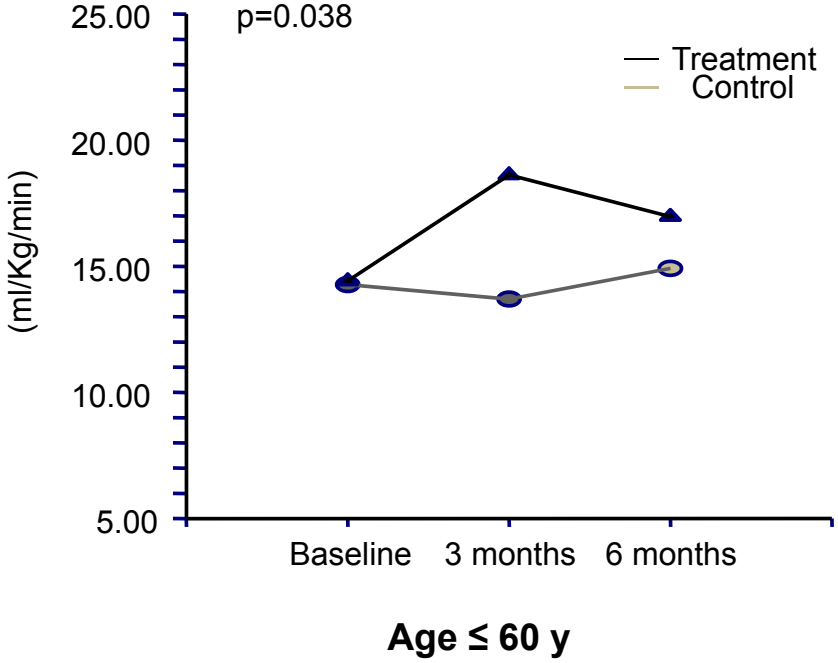
Focus HF

Bone Marrow Sample Analysis

Age and CFU



Age and MVO_2



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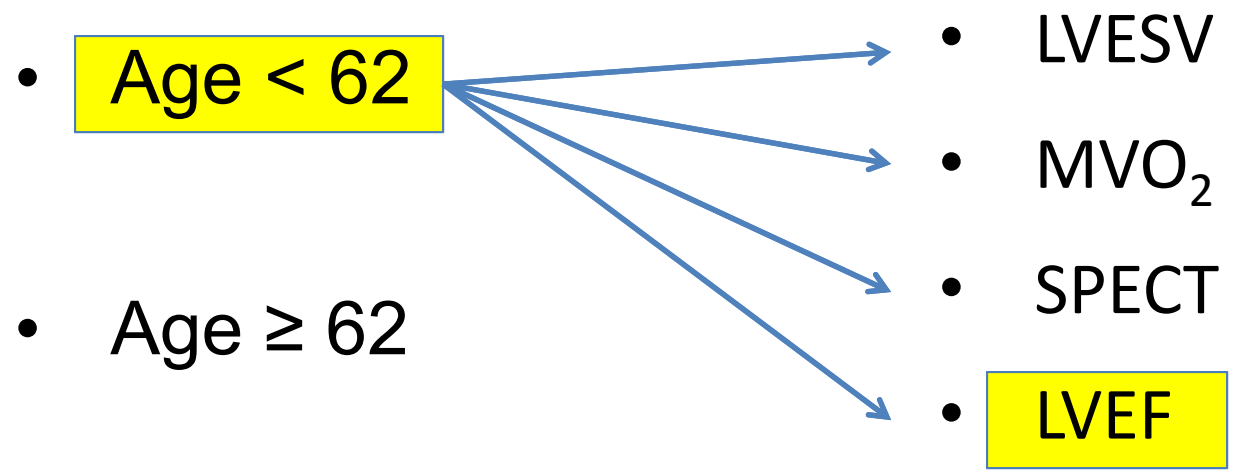
Pre-Specified Analysis

Relationship of Age with Endpoints

Age (median 62y)	Primary and Exploratory Endpoints



Delta LVEF and Age

LVEF- Treatment: Age < 62

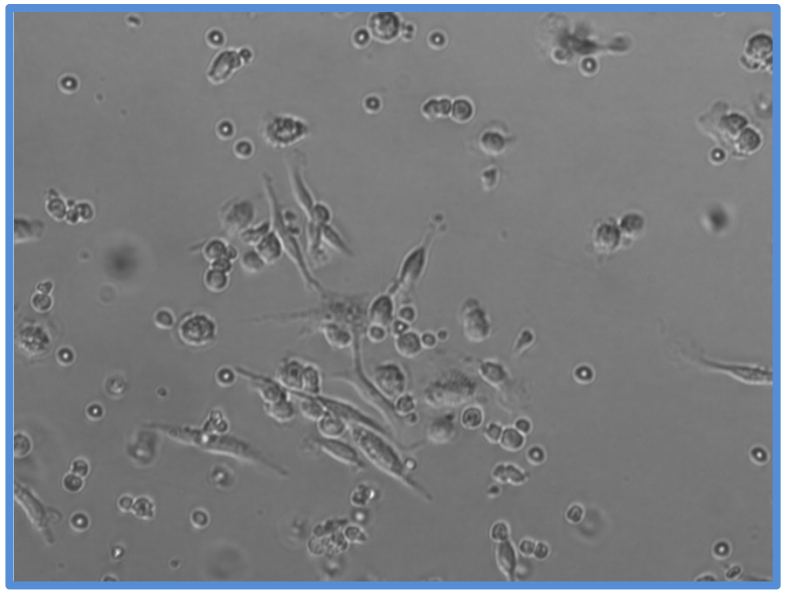
	BMC			Placebo								
LVEF (Echo Core)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**						
Baseline	**27**	**35.1**	**9.0**	**15**	**32.0**	**8.0**						
Followup	**27**	**38.2**	**11.8**	**15**	**30.4**	**7.8**	**Change**	**SD**	**Test Statistic**	**95% Confidence Interval P-value**	**LB**	**UB**
Change	**27**	**3.1**	**5.2**	**15**	**-1.6**	**6.6**	**4.7**	**5.7**	**2.55**	**0.015**	**0.97**	**8.37**

LVEF- Treatment: Age ≥ 62

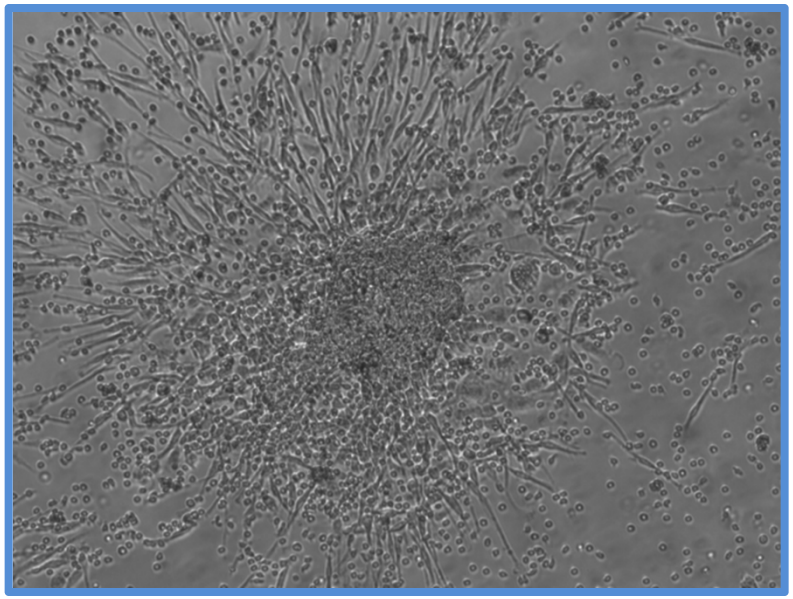
	BMC			Placebo								
LVEF (Echo Core)	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**						
Baseline	**27**	**34.2**	**8.8**	**13**	**32.5**	**9.6**						
Followup	**27**	**33.9**	**8.9**	**13**	**31.6**	**10.5**	**Change**	**SD**	**Test Statistic**	**95% Confidence Interval P-value**	**LB**	**UB**
Change	**27**	**-0.3**	**4.7**	**13**	**-0.9**	**3.0**	**0.6**	**4.2**	**0.43**	**0.668**	**-2.28**	**3.52**

Cell Function Heterogeneity

Age and Comorbidities



Low ECFC capacity

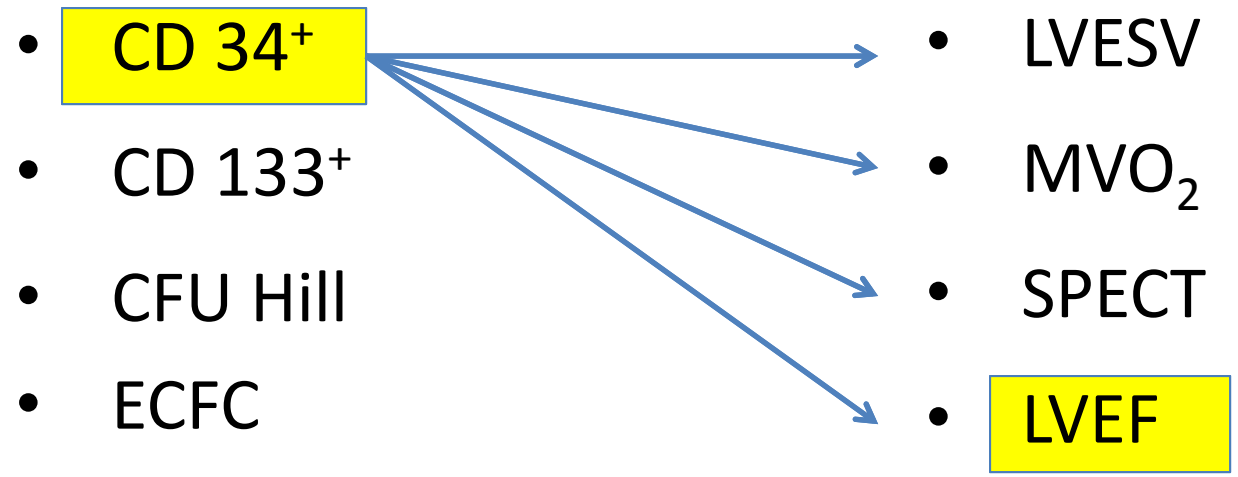


High ECFC capacity

Pre-Specified Bone Marrow Analysis

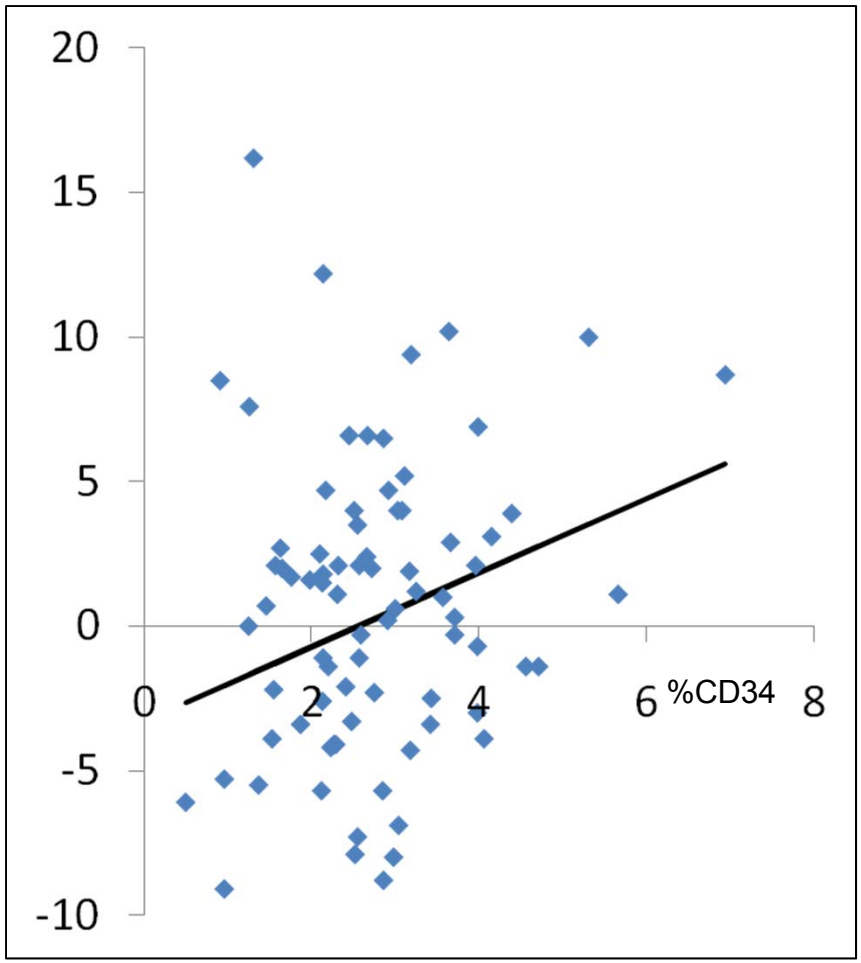
Relationship with Endpoints

Preliminary Bone Marrow Functional and Phenotypic Analyses	Primary and Exploratory Endpoints



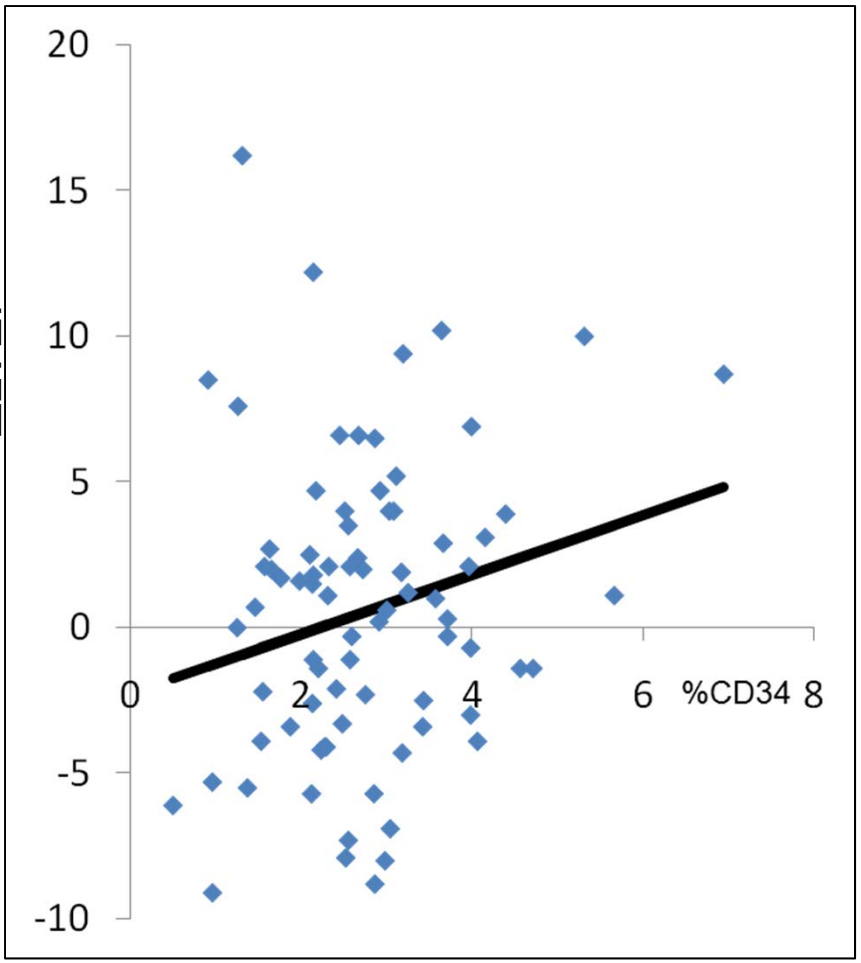
Correlation between ΔLVEF and %CD34

Unadjusted



R^2= 8%
P = 0.012

Adjusted for Age and Therapy

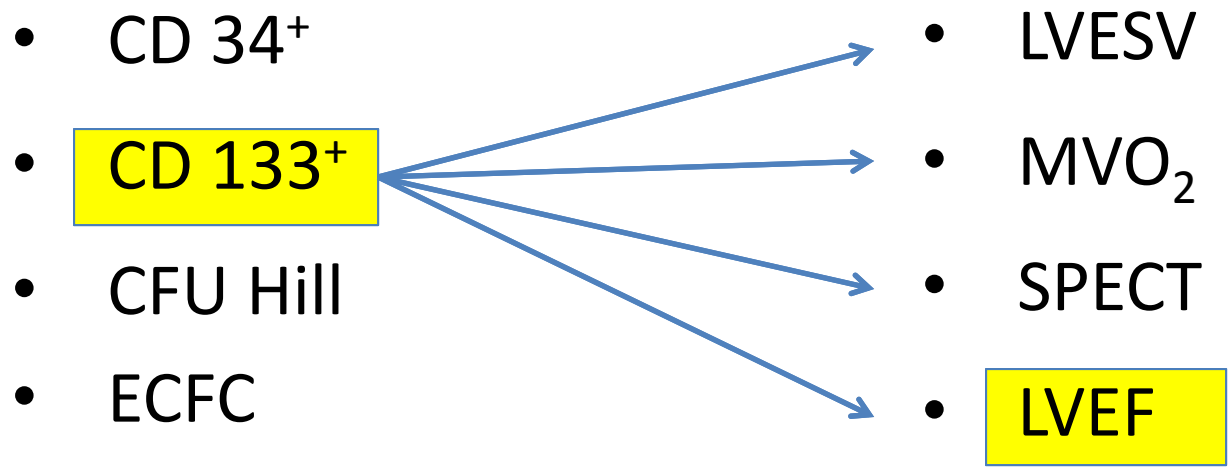


R^2= 16%
P=0.043

Pre-Specified Bone Marrow Analysis

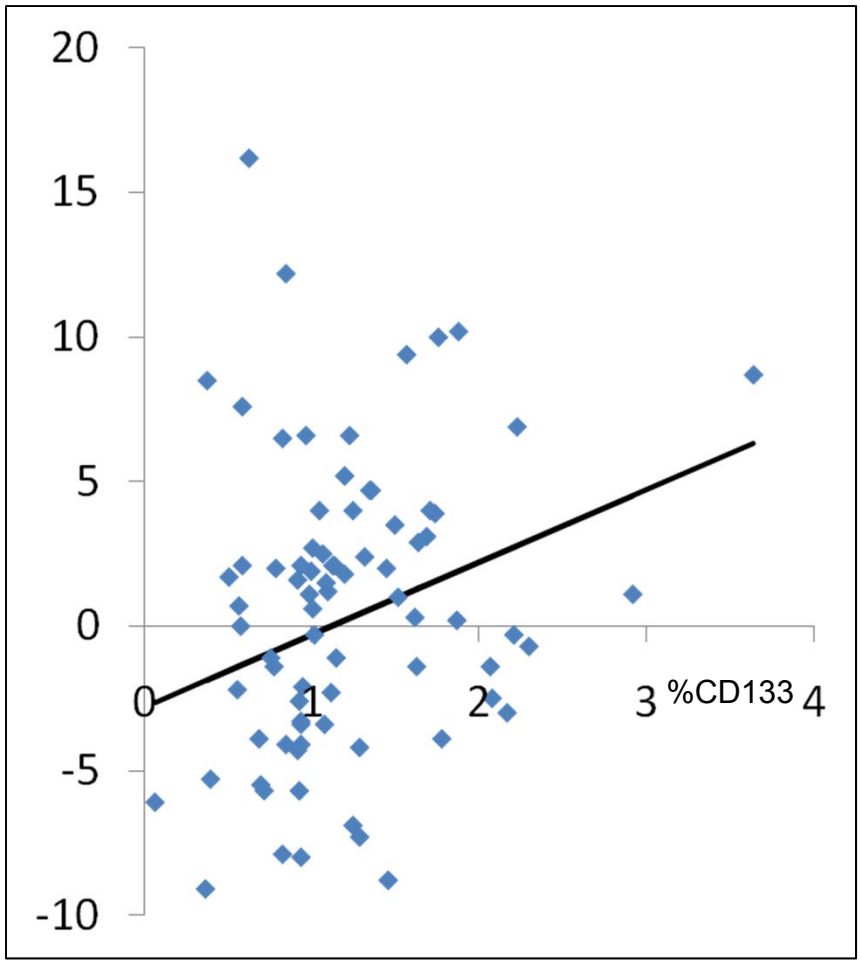
Relationship with Endpoints

Preliminary Bone Marrow Functional and Phenotypic Analyses	Primary and Exploratory Endpoints



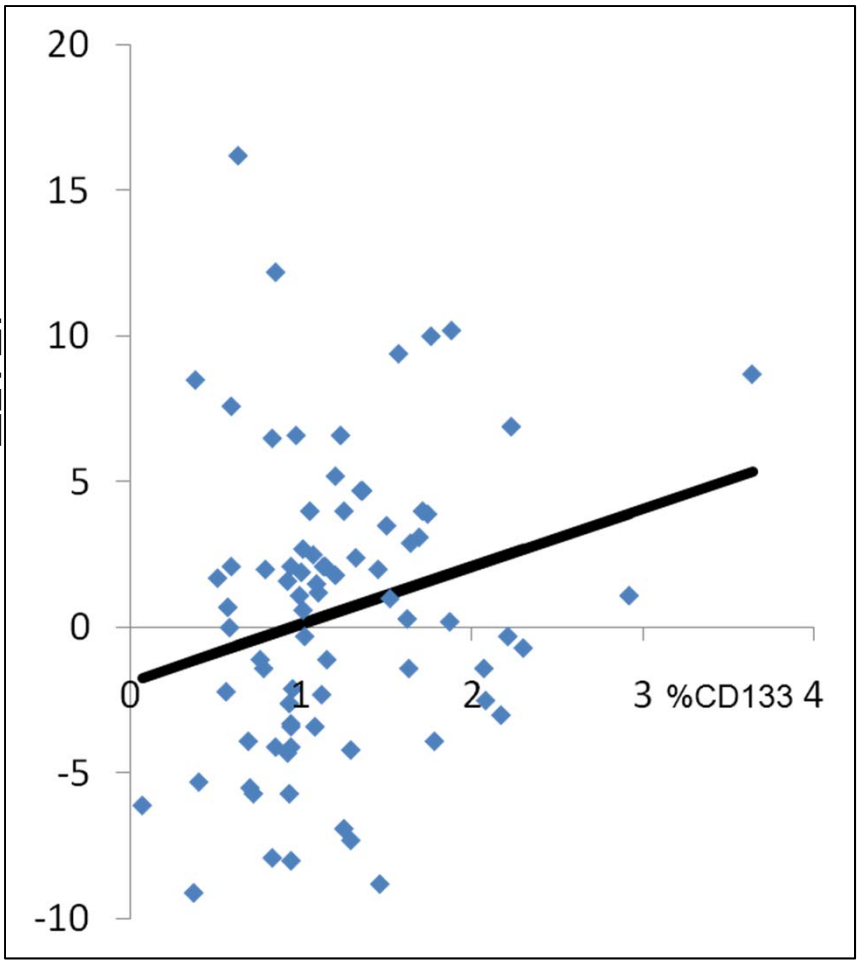
Correlation between ΔLVEF and %CD133

Unadjusted



R^2= 8%
P = 0.010

Adjusted for Age and Therapy

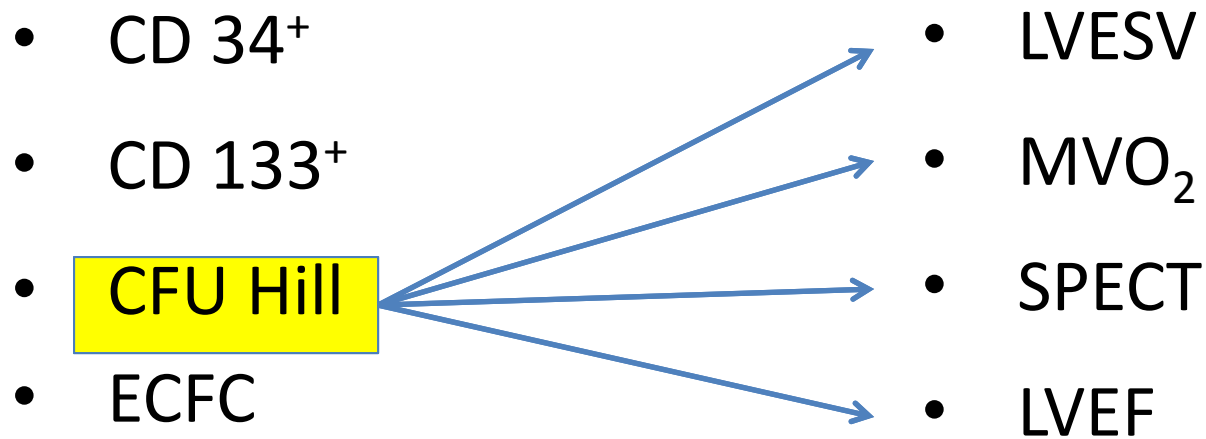


R^2= 16%
P=0.041

Pre-Specified Bone Marrow Analysis

Relationship with Endpoints

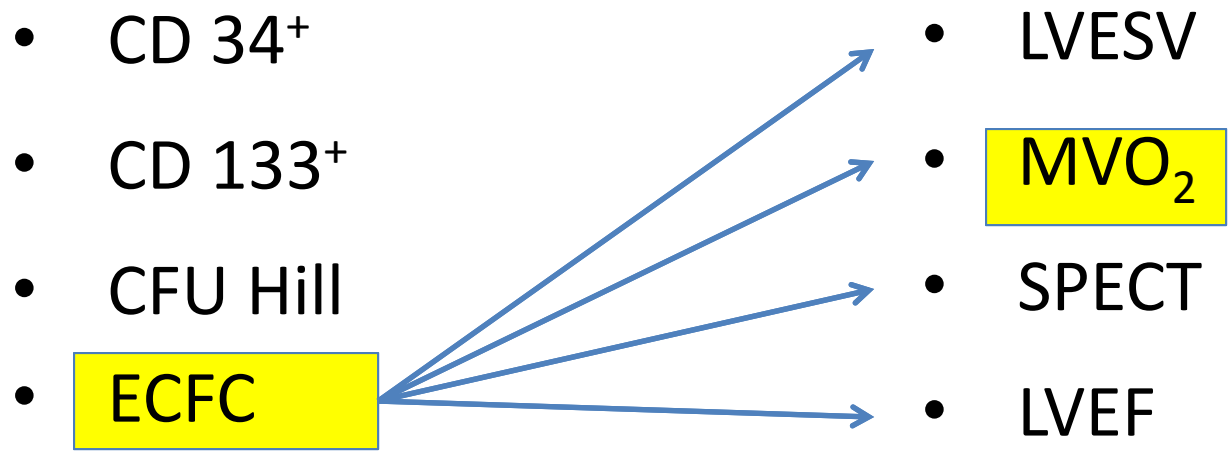
Preliminary Bone Marrow Functional and Phenotypic Analyses	Primary and Exploratory Endpoints



Pre-Specified Bone Marrow Analysis

Relationship with Endpoints

Preliminary Bone Marrow Functional and Phenotypic Analyses	Primary and Exploratory Endpoints



Exploratory Endpoint Analysis ECFCs > 80 (median)

	BMC			Placebo		
Peak VO2 ml/kg/min	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Baseline	**20**	**14.6**	**3.3**	**11**	**15.2**	**3.1**
Followup	**20**	**15.3**	**4.8**	**11**	**13.4**	**3.7**
Change	**20**	**0.7**	**2.9**	**11**	**-1.8**	**3.4**

Change	SD	Test Statistic	95% Confidence Interval		
			P-value	LB	UB
2.5	**3.1**	**2.18**	**0.037**	**0.16**	**4.88**

Conclusions

- In patients with chronic ischemic heart disease and LV dysfunction with heart failure and/or angina there were no significant differences in a priori selected primary endpoints of LVESV, Reversibility by SPECT and MVO_2 between subjects treated with 100 million autologous bone marrow mononuclear cells and placebo at 6 month follow-up.

- In this phase II study, exploratory analyses revealed that LVEF improved in the BMC group compared with the placebo group.

- LVEF improvement was significant in patients younger than the median study population age and correlated with the percentage of $CD34^+$ and $CD133^+$ cells in BM samples.

Conclusions cont'd

- A pre-specified analysis of cell function (ECFC) showed significant improvement in MVO2 in those study patients with higher than median ECFC values.
- Evaluating inherent variability in the cell product may provide mechanistic insights and help select patients that are likely to benefit from autologous cell therapy.
- Additional analyses of cell function will be forthcoming from the CCTRN biorepository and should help guide the design of future clinical trials in patients with ischemic heart disease and LV dysfunction.

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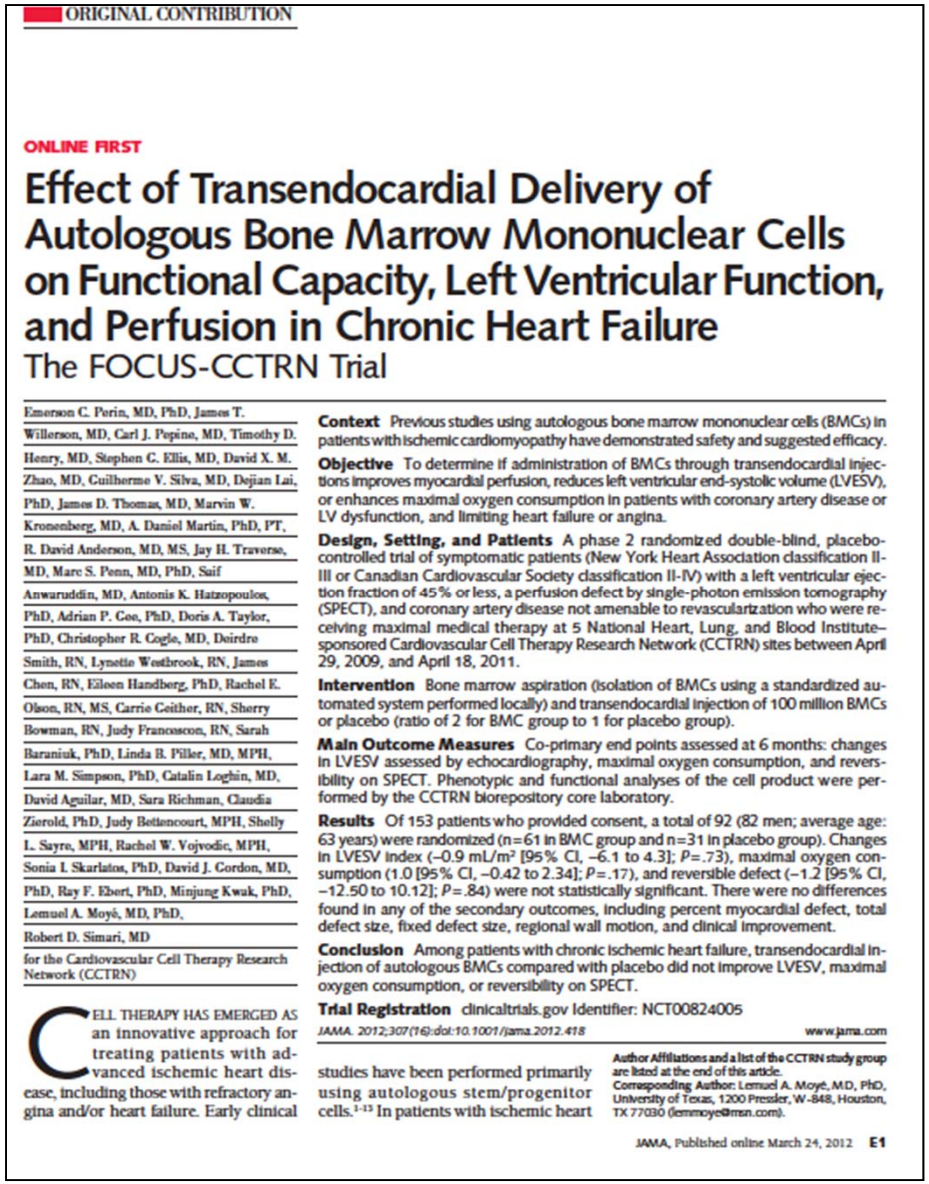
- Center for Cell & Gene Therapy, Baylor College of Medicine
- The University of Florida MVO2 Exercise Laboratory, Cleveland Clinic Echo Core Labs, and Vanderbilt University SPECT Core Lab
- The University of Minnesota and University of Florida Biorepositories



ORIGINAL CONTRIBUTION

ONLINE FIRST

Effect of Transendocardial Delivery of Autologous Bone Marrow Mononuclear Cells on Functional Capacity, Left Ventricular Function, and Perfusion in Chronic Heart Failure

The FOCUS-CCTRN Trial

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for the Cardiovascular Cell Therapy Research Network (CCTRN)

Context Previous studies using autologous bone marrow mononuclear cells (BMCs) in patients with ischemic cardiomyopathy have demonstrated safety and suggested efficacy.

Objective To determine if administration of BMCs through transendocardial injections improves myocardial perfusion, reduces left ventricular end-systolic volume (LVESV), or enhances maximal oxygen consumption in patients with coronary artery disease or LV dysfunction, and limiting heart failure or angina.

Design, Setting, and Patients A phase 2 randomized double-blind, placebo-controlled trial of symptomatic patients (New York Heart Association classification II-III or Canadian Cardiovascular Society classification II-IV) with a left ventricular ejection fraction of 45% or less, a perfusion defect by single-photon emission tomography (SPECT), and coronary artery disease not amenable to revascularization who were receiving maximal medical therapy at 5 National Heart, Lung, and Blood Institute–sponsored Cardiovascular Cell Therapy Research Network (CCTRN) sites between April 29, 2009, and April 18, 2011.

Intervention Bone marrow aspiration (isolation of BMCs using a standardized automated system performed locally) and transendocardial injection of 100 million BMCs or placebo (ratio of 2 for BMC group to 1 for placebo group).

Main Outcome Measures Co-primary end points assessed at 6 months: changes in LVESV assessed by echocardiography, maximal oxygen consumption, and reversibility on SPECT. Phenotypic and functional analyses of the cell product were performed by the CCTRN biorepository core laboratory.

Results Of 153 patients who provided consent, a total of 92 (82 men; average age: 63 years) were randomized (n=61 in BMC group and n=31 in placebo group). Changes in LVESV index (−0.9 mL/m² [95% CI, −6.1 to 4.3]; $P=.73$), maximal oxygen consumption (1.0 [95% CI, −0.42 to 2.34]; $P=.17$), and reversible defect (−1.2 [95% CI, −12.50 to 10.12]; $P=.84$) were not statistically significant. There were no differences found in any of the secondary outcomes, including percent myocardial defect, total defect size, fixed defect size, regional wall motion, and clinical improvement.

Conclusion Among patients with chronic ischemic heart failure, transendocardial injection of autologous BMCs compared with placebo did not improve LVESV, maximal oxygen consumption, or reversibility on SPECT.

Trial Registration clinicaltrials.gov Identifier: NCT00824005

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CELL THERAPY HAS EMERGED AS an innovative approach for treating patients with advanced ischemic heart disease, including those with refractory angina and/or heart failure. Early clinical studies have been performed primarily using autologous stem/progenitor cells.[1-13] In patients with ischemic heart

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