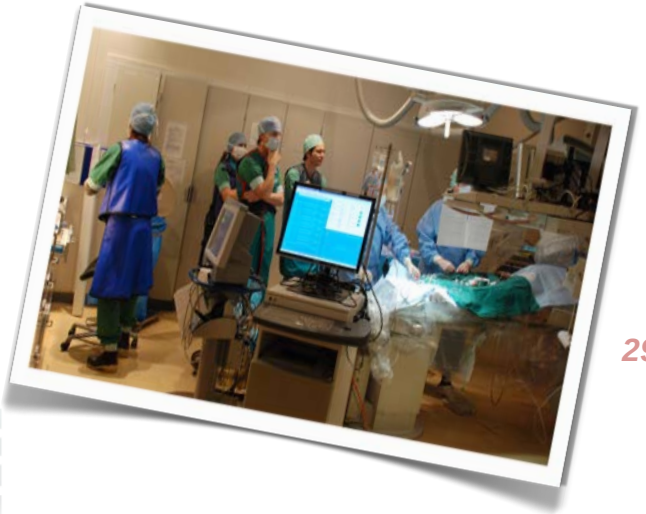
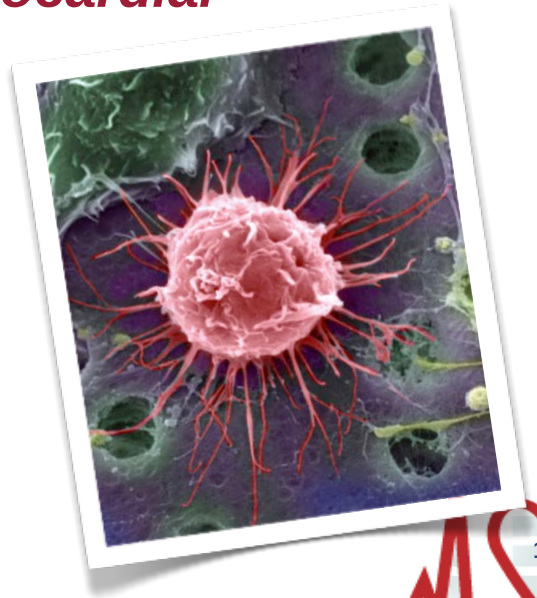
Stem Cells:
Theories and Current CV Cell Therapy Program

Autologous Bone Marrow Mononuclear Cells Therapy in Patients with Post Myocardial Infarction Heart Failure





Eric Duckers

29th Annual Spring Update in Cardiology:

New Paradigms in CV Therapy

Oklahoma Heart Institute

10:00-10:45, Tulsa, May 4th, 2018

BioCardia

Disclosures

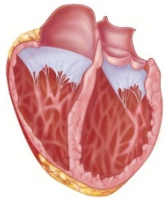
- ***BioCardia:*** *CMO, shareholder*

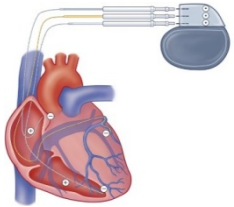
- *Advisory Board (current/previous)*
  - *AngioBlast/MesoBlast*
  - *TEVA*
  - *OrbusNeich*
  - *Cytori*
  - *Celyad*
  - *NHS*
  - *NeuroPhyxia (DSMB)*

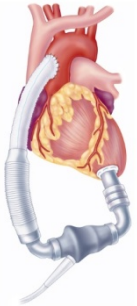
Images from Cleveland Clinic

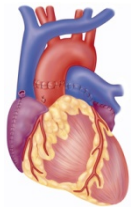
CURRENT THERAPEUTIC OPTIONS

Class I, II, & III → Class III → Class IV









Medications
- ACE inhibitors/ARBs
- Beta-blockers
- Aldosterone antagonists
- Diuretics and nitrates
- Ivabradine (AMGEN)
- Entresto (Novartis)

Devices
- Bi-V pacemakers + defibrillators (CRT-D)

Hemodynamic Support
- IV inotropes
- LVAD

Transplantation
- Immuno-suppression

LVADs and heart transplants used in late-stage HF patients can cost $150,000 per procedure

Regenerative therapy is advocated as a new avenue in the treatment\ of NYHA HF class II-IV Heart Failure

Images from Cleveland Clinic


ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Home Search Study Topics Glossary
Search
List Results
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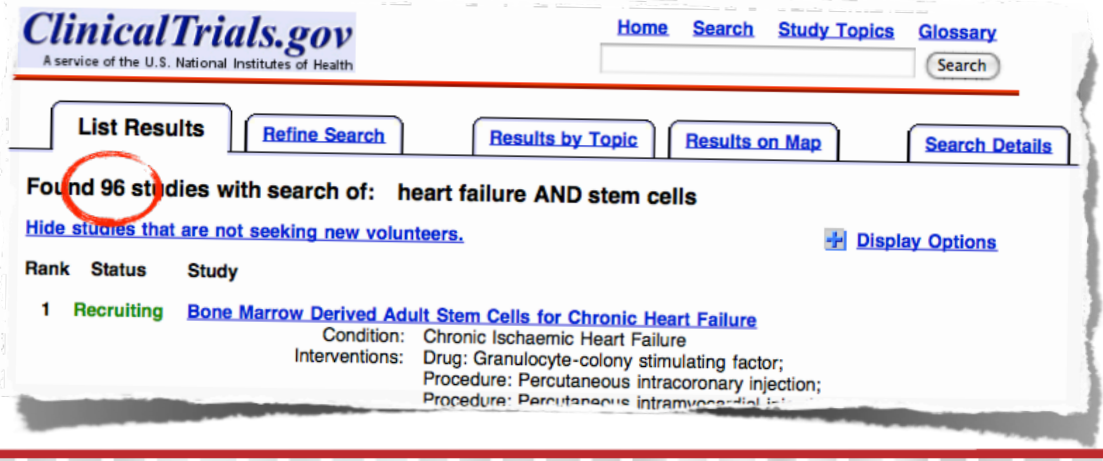
Results by Topic
Results on Map
Search Details
Found 954 studies with search of: cardiac cell therapy
Hide studies that are not seeking new volunteers.
Display Options
Rank Status Study
1 Terminated Stem Cell Therapy as Adjunct to Revascularization
Conditions: Coronary Arteriosclerosis; Coronary Artery Bypass Graft; Myocardial Revascularization
Interventions: Procedure: Autologous stem cell therapy; Procedure: CABG; Procedure: CMRI


ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Home Search Study Topics Glossary
Search
List Results
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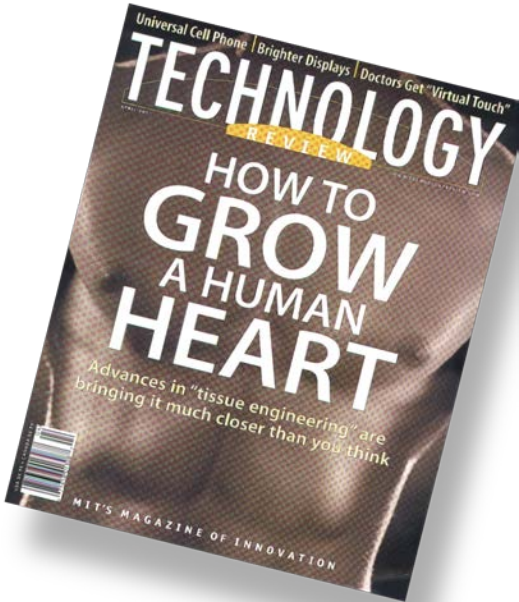
Results by Topic
Results on Map
Search Details
Found 96 studies with search of: heart failure AND stem cells
Hide studies that are not seeking new volunteers.
Display Options
Rank Status Study
1 Recruiting Bone Marrow Derived Adult Stem Cells for Chronic Heart Failure
Condition: Chronic Ischaemic Heart Failure
Interventions: Drug: Granulocyte-colony stimulating factor; Procedure: Percutaneous intracoronary injection;

The Promise of CardioVascular Stem Cell Therapy

Use of stem cells for myocardial and/or vascular regeneration

- NeoAngiogenesis (new vessel formation)
- NeoMyogenesis (new cardiac muscle formation)
- Myocardial ‘salvage’ (only significant in Acute Myocardial Infarction)
  - *reduction of ischemia/ hypoxic damage*
  - *reduction of inflammation*
  - *reduction of oxidative stress (reperfusion injury)*
  - *resident cells more resistant to cell death (pAkt/ Bax/ Bad)*
- Reduced adverse cardiac remodeling on long term
  - *potentially secondary to former beneficial effects*

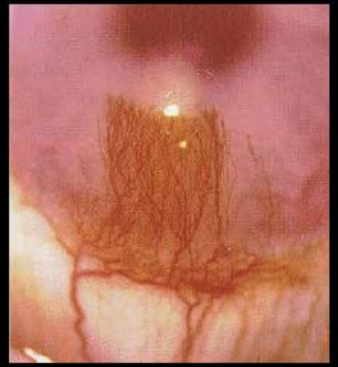


The Promise of CardioVascular Stem Cell Therapy

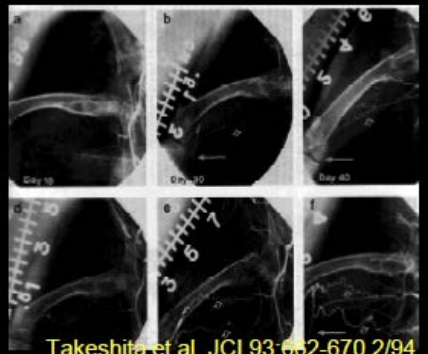
Neoangiogenesis has been demonstrated in numerous in vitro and in vivo models

Chick Allantoic Membrane

Rabbit Cornea

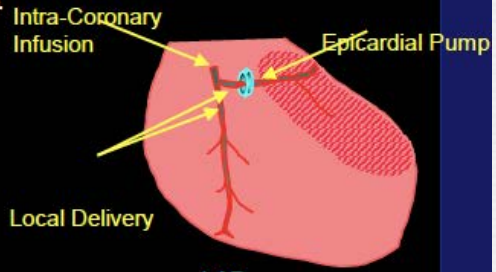


Rabbit Hindlimb



Takeshita et al. JCI 93:662-670 2/94

Ameroid Pig Heart



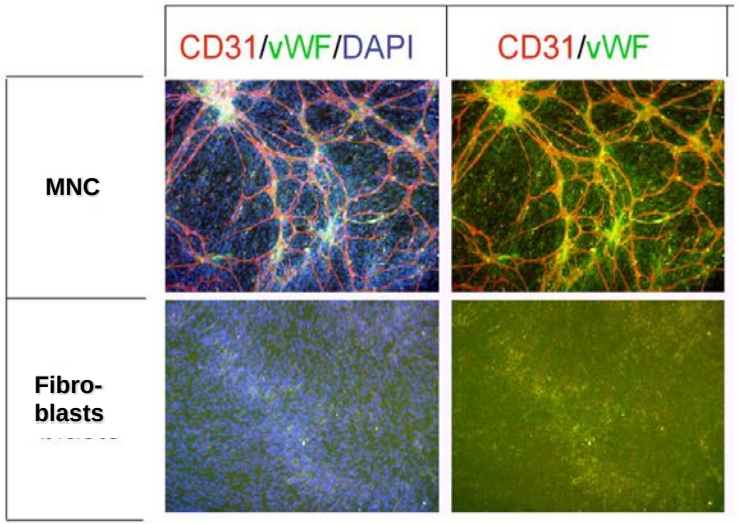
Plasticity of human bone marrow stem cells

differentiation into endothelial cells in vitro and *in vivo*

in vitro

(2D MatriGel)

Formation of neo vessels in culture dish



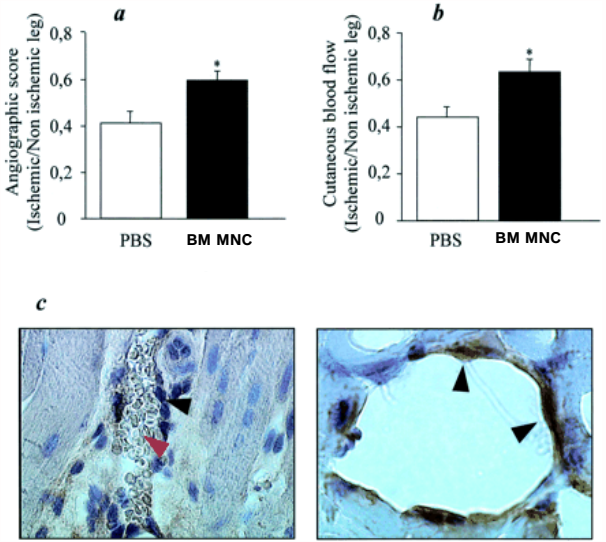
BM MNC (top row) in a tube formation assay
fibroblasts (bottom row) were used as a control.

Rutenberg et al.

in vivo

(mouse hind limb ischemia model)

Formation of new vessels in ischemic limb

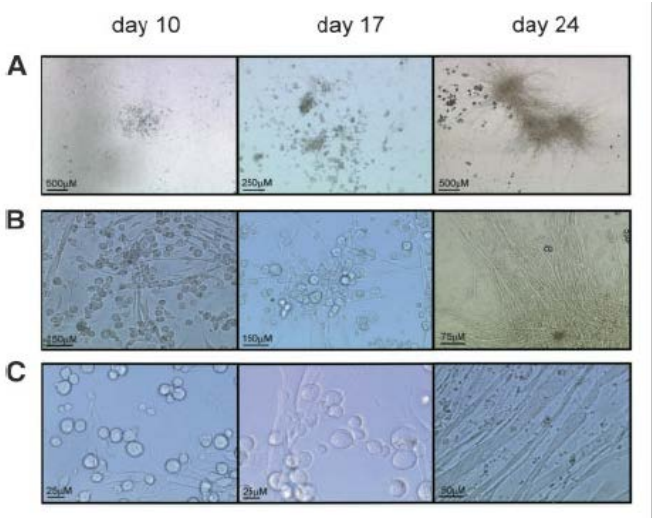


Incorporation of (beta Gal ~ purple) stem cells
in newly formed vessels in the mouse limb

Planat-Benard et al., Circulation (2004)

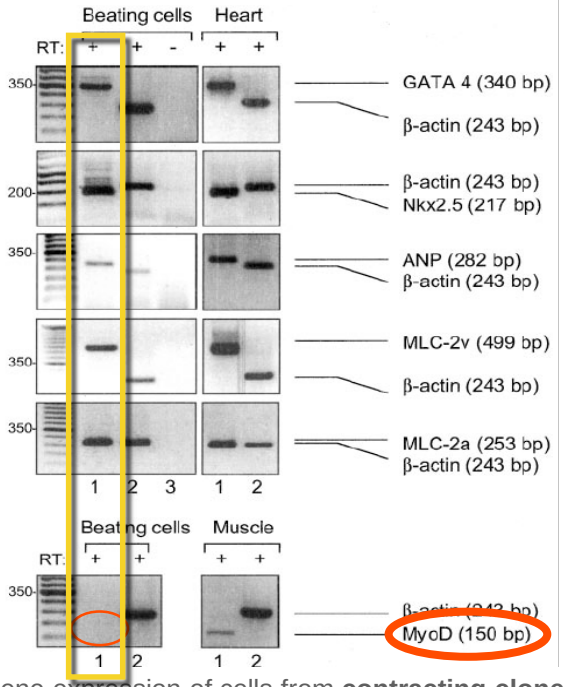
Plasticity of human bone marrow stem cells

differentiation into cardiomyocytes in vitro



Phased-contrast microscopy of contracting clones
Isolated BM MNC plated into methylcellulose
Rounded cells becomes elongated and finally aligned and branched myofibrils are seen.

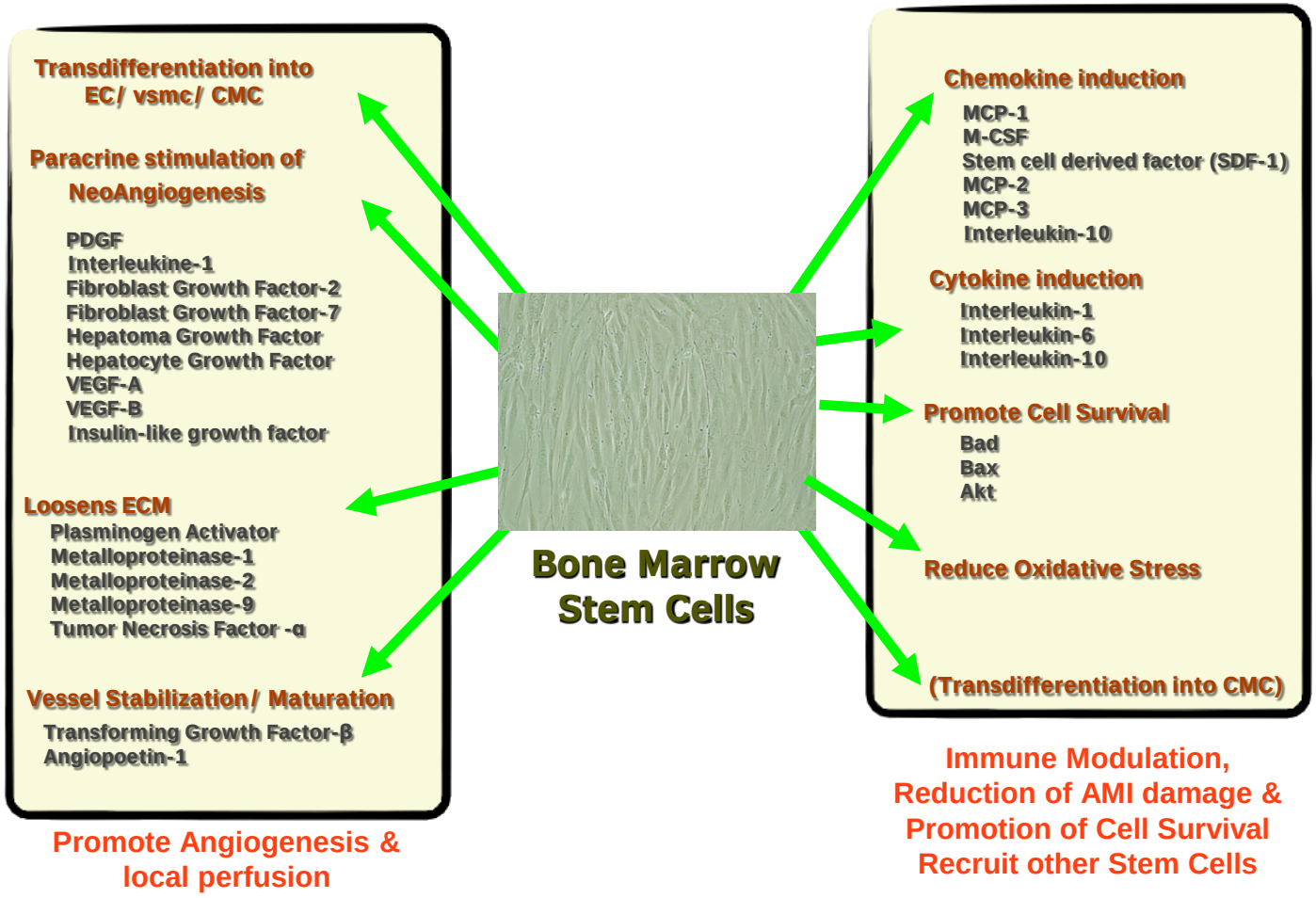
Reverse transcription polymerase chain reaction analysis



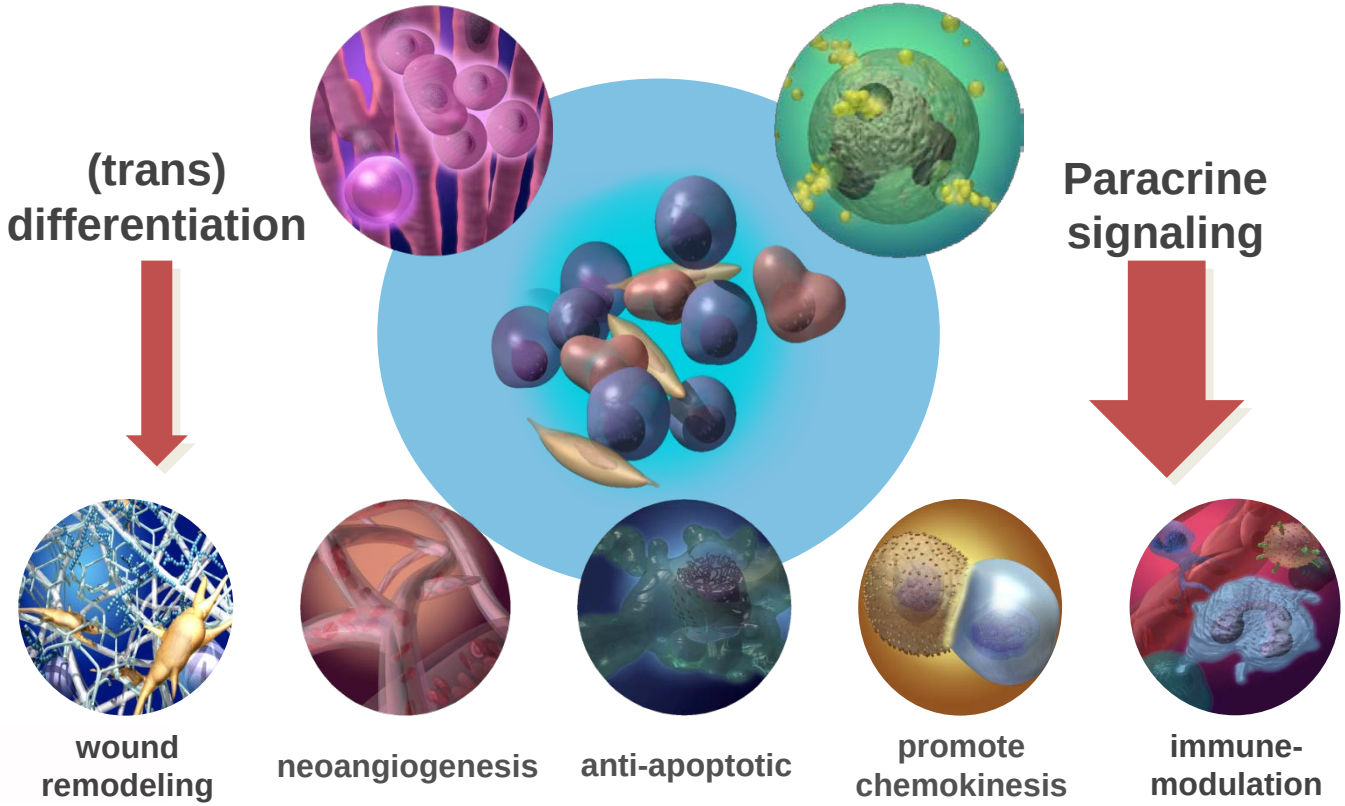
Gene expression of cells from **contracting clones** was compared with control cells from **mouse heart muscle**. Absence of MyoD demonstrate BM MNC are **not skeletal muscle** cells.

Planat-Benard V. Circ. Res. 2004;94;223-229
Léobon et al, Cardiovasc Res. 2009 Sep 1;83(4)

Bone marrow stem cells are cytokine factories



Mechanisms of Cell Regeneration by Bone Marrow Stem Cells



Study acronym studies > 15 pts recruitment < 5 yrs		Delivery	pts	indication	start	SetUp		Primary End Point	Sec End Point	Phase	PI
TOPCARE-CHD	autol. BM (214 Mill)	intracoronary	96	AMI > 3 mo	Jan-2002	Registry	MonoCenter - -	NT-proBNP NT-proANP MACCE	LVEF (LV Angio)	I	A. Zeiger, Frankfurt
TAC HFT	placebo (PBS/Alb) autol. BM 100/200 Mill autol. MSC 100/200 Mill	EndoCard BioCardia Helical cath	60	EF 20-50%	aug 1, 2008	RCT	MonoCenter Double-Blind Core Lab ?	SAE	cMRI 6/12 mo TTE 6/12 mo VO2 max/ 6 MWT	I/II	J Hare, Miami
CELLWAVE	placebo (PBS/Alb) autol. BM w extracorp shockwave (<24 hr)	intracoronary	100	EF < 50%	May-2006	RCT	Single Center Double-Blind -	LVEF (LV Angio)	TTE 4/12 mo NT BNP MACCE	I/II	A Zelher, Frankfurt
Rostock	CABG CABG/ autol.immun.sel. CD						MonoCenter -	LVEF (TTE)	SPECT SPECT	I	G Steinhoff, Rostock
PERFECT	CABG/ placebo (PBS/Se CABG/ autol.immun.sel. CD133+ (1-10 Mill)	epicard. inj.	142	25%< EF < 35%	Jul-2009	RCT	Double-Blind	LVEF	cMRI 6 mo		Rostock
FOCUS-CCTRN	placebo (PBS/Alb) autol. BM (100 Mill)						Multi-Center -	VO2 max QoL			
ESCAPE	placebo (optimal med.Tx) autol. BM (150 Mill)	intracoronary	250	EF < 35% w ischemia	Febr-2007	RCT	Multi-Center single blind	MACCE		III	P Evgeniy, Novosobirsk
Herrera										II	IC Herrera/ Murcia
de Carvalho	placebo (PBS/Alb) autol. BM	intracoronary	300	idiop. DCM EF<50%	Jan-2006	RCT	Multi-Center -	LVEF	MACCE VO2 max QoL	III	Carvalho/ Rio de Janeiro
PROGENITOR	placebo (?) autol.CD133	EndoCard ?	30	NYHA II-IV w ischemia	mei 1, 2008	RCT	MonoCenter Double-Blind Core Lab ?		cMRI SPECT	I	PJ Quevedo/ Madrid M Sabate
Baxter-CD34	autol. immune-sel CD34	EndoCard	10 > 30	EF < 40%	Mar-2008	NRT	MonoCenter Open label -			I	D Losordo, Chicago
Kastrup	placebo (PBS) autol.BM-MSC (20-30 Mill)	EndoCard NOGA	60 (pend)	EF < 40%	Sept-2008	RCT	MonoCenter - -	LEVF		I/II	J Kastrup, Kopenhagen
C-Cure	placebo BM-MSC -									II/III	J Bartunek, Aalst A Terzec, Rochester
Revascor-CHF	placebo (transp.medium) allogenic immunsel. MPC 3 doses (25, 75, 150 Mill)	EndoCard NOGA	60	EF < 40%	Aug-2008	RCT	Multi-Center Double-Blind Central core lab	MACCE			
Revascor-LVAD	placebo (transp.medium) allogenic immunsel. MPC 2 doses (25 and 75 Mill)	EndoCard			Au		Central core lab	SAE			w York York
PRECISE	placebo (Ring.Lact) ADRC/ MSC-like 3 doses (0.4-0.8-1.2 Mill/kg)	EndoCard NOGA	27	EF < 45% w ischemia	Jan-2007 closed	RCT	Multi-Center Double-Blind Central core lab	MACCE	cMRI 6/12 mo TTE 6/12 mo SPECT	I	Fern-Aviles, Madrid E Perin, Houston
SCIPIO	placebo (PBS/Alb) CSC (from RAA)						Multi-Center	MACCE/ SAE			
MAGIC	CABG/ placebo (Medium) CABG/ autol.SKM (400/ 800 Mill)	Epicard. inj.	97	EF < 35%	Nov-2002	RCT	Multi-Center Double-Blind central core lab	LVEF (TTE) TTE wms		II	P Menasche, Paris
MYOHEART	autol.SKM (25/75/225/675 Mill)	EndoCard MyoCath	20	20%<EF< 40%	Febr-2003	NRT	Multi-Center Open label Central core lab	SAE	LVEF (TTE)	I	W. Sherman, New York
CAUSMIC	placebo (no inj) autol.SKM (30/100/300/600 Mill)	EndoCard NOGA	23	EF < 40%		RCT	Multi-Center Double-Blind Central core lab	SAE			Diego
SEISMIC	placebo (transp.medium) autol. SKM (600 Mill)	Endo Myo					Center abel Central core lab	LVEF (MU SAE			Rotterdam
PERCUTANEO	placebo (Medium) SKM (single dose)	EndoCard	50	EF < 40%	mrt 1, 2008	RCT	MonoCenter Double-Blind Core Lab ?	LVEF (TTE TTE wms			Navarra
MARVEL	placebo (transp.medium) autol.SKM (400/800 Mill)	EndoCard NOGA	180	EF < 35%	Sept-2007	RCT	Multi-Center Double-Blind Central core lab	6 MW QoL	readmissions	II/III	W. Sherman, New York
REGEN	placebo (transp.medium) autol. SKM/ SDF1	EndoCard NOGA	15	EF < 35%		NRT	MonoCenter - -	-	-	I	-

hematopoietic stem cells and endothelial progenitors

mesenchymal(-like) stem cells

resident stem cells

myoblasts

Current (stem) cell therapy studies in cardiovascular disease:

- ***heart failure** (ischemic, non-ischemic)*
- ***myocardial infarction***
- ***arrhythmia** (pacemaker cells, VT)*

Lessons from clinical cell therapy studies

Table 3 Summary of clinical outcomes

Outcome	No. of trials	Time point measure[a]	Relative risk (95% CI)	P-value
Mortality	5	1–12 months	0.62 (0.22, 1.76)	0.37
Morbidity				
Re-infarction	7[b]	<30 days (1)	0.33 (0.01, 7.81)	0.49
		1–4 months (4)	0.61 (0.12, 2.96)	0.54
		12 months (1)	0.08 (0.00, 1.37)	0.08
Arrhythmias	1	Not known	0.57 (0.21, 1.53)	NA
Restenosis	7[b]	6 months (5)	1.10 (0.68, 1.80)	0.69
		12 months (1)	0.34 (0.01, 8.13)	0.51
Re-admission	4[b]	1–6 months (2)	0.61 (0.25, 1.52)	0.29
		12 months (1)	0.15 (0.01, 2.78)	0.2
Revascularization	6[b]	1–6 months (2)	0.55 (0.19, 1.62)	0.28
		12 months (1)	0.71 (0.42, 1.20)	0.2
Adverse events	5[c]	Not reported in all studies	NA	NA
Quality of life	2	21 day–6 months	Not measured	NA
Re-operation	1	12 months	0.61 (0.39, 0.95)	NA

NA, not applicable.
[a]Number of trials that measured the outcome at each time point is in brackets.
[b]One study did not report the time point at which the outcome was measured.
[c]Adverse events not always reported in full details to allow statistical analysis.

Meta analysis of 14 RCT with BM MNC in AMI (n=811 pts)

improvement of clinical end points is suggested:
- re-AMI
- re-admission due to CHF
- revascularization
- no effect on mortality/ morbidity

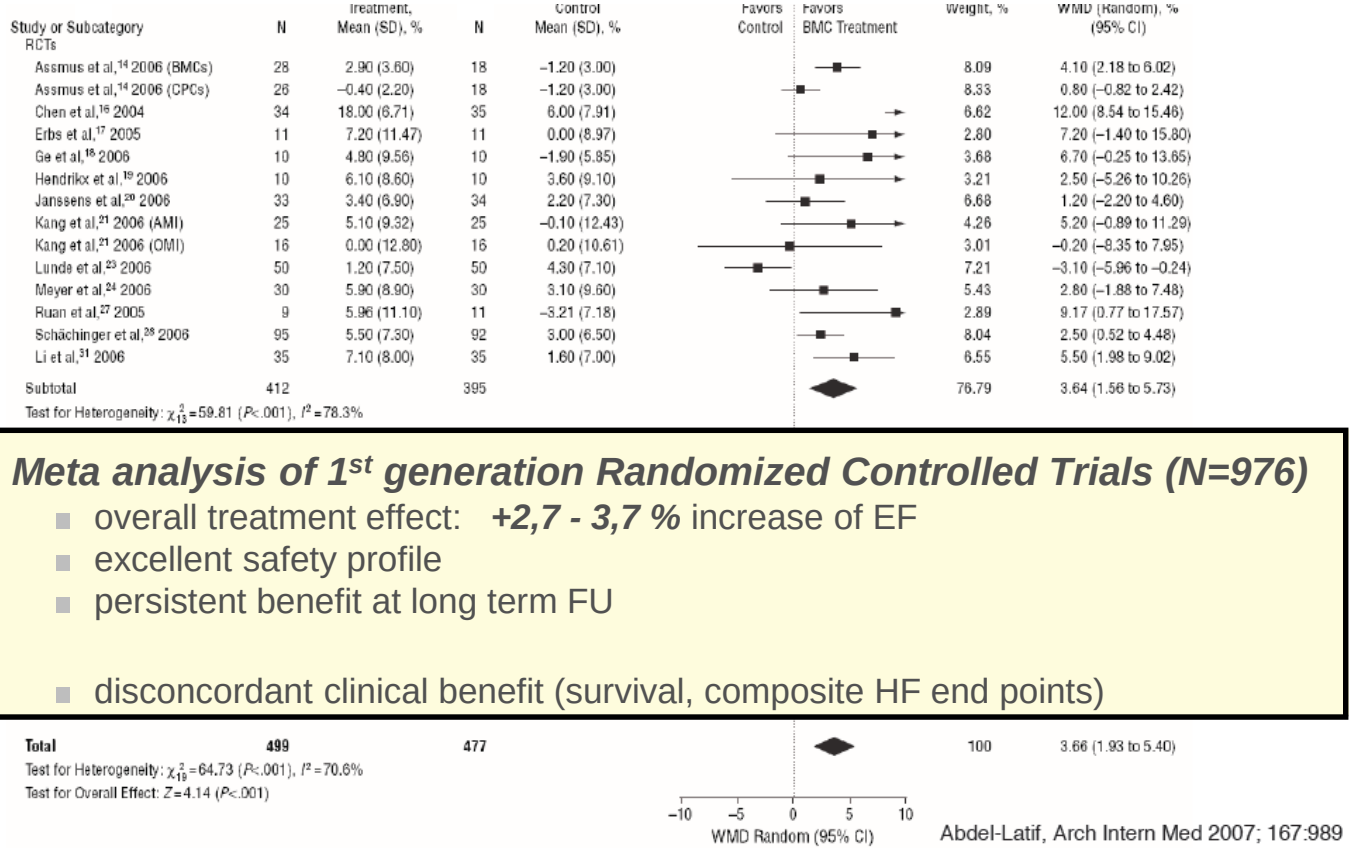
- Dose-dependent relationship is suggested between BMSC and effect on LVEF
- Suggestion of improvement of diastolic (dys)function as well

- increase of ~3% LVEF
- reduction of ventricular volumes
- reduction of infarct size of 3.5-5.6%
- improved regional function

Martin-Rendon, E. et al. Eur Heart J 2008, 29

Lipinsky et al, JACC 2007, 50(18)

End point: Left Ventricular Ejection Fraction



Study or Subcategory	N	Treatment, Mean (SD), %	N	Control Mean (SD), %	Weight, %	WMD (Random), % (95% CI)
RCTs						
Assmus et al,[14] 2006 (BMCs)	28	2.90 (3.60)	18	−1.20 (3.00)	8.09	4.10 (2.18 to 6.02)
Assmus et al,[14] 2006 (CPCs)	26	−0.40 (2.20)	18	−1.20 (3.00)	8.33	0.80 (−0.82 to 2.42)
Chen et al,[16] 2004	34	18.00 (6.71)	35	6.00 (7.91)	6.62	12.00 (8.54 to 15.46)
Erbs et al,[17] 2005	11	7.20 (11.47)	11	0.00 (8.97)	2.80	7.20 (−1.40 to 15.80)
Ge et al,[18] 2006	10	4.80 (9.56)	10	−1.90 (5.85)	3.68	6.70 (−0.25 to 13.65)
Hendrikx et al,[19] 2006	10	6.10 (8.60)	10	3.60 (9.10)	3.21	2.50 (−5.26 to 10.26)
Janssens et al,[20] 2006	33	3.40 (6.90)	34	2.20 (7.30)	6.68	1.20 (−2.20 to 4.60)
Kang et al,[21] 2006 (AMI)	25	5.10 (9.32)	25	−0.10 (12.43)	4.26	5.20 (−0.89 to 11.29)
Kang et al,[21] 2006 (OMI)	16	0.00 (12.80)	16	0.20 (10.61)	3.01	−0.20 (−8.35 to 7.95)
Lunde et al,[23] 2006	50	1.20 (7.50)	50	4.30 (7.10)	7.21	−3.10 (−5.96 to −0.24)
Meyer et al,[24] 2006	30	5.90 (8.90)	30	3.10 (9.60)	5.43	2.80 (−1.88 to 7.48)
Ruan et al,[27] 2005	9	5.96 (11.10)	11	−3.21 (7.18)	2.89	9.17 (0.77 to 17.57)
Schächinger et al,[28] 2006	95	5.50 (7.30)	92	3.00 (6.50)	8.04	2.50 (0.52 to 4.48)
Li et al,[31] 2006	35	7.10 (8.00)	35	1.60 (7.00)	6.55	5.50 (1.98 to 9.02)
Subtotal	412		395		76.79	3.64 (1.56 to 5.73)
Test for Heterogeneity: $\chi^2_{13}=59.81$ ($P<.001$), $I^2=78.3\%$						
Total	**499**		**477**		100	3.66 (1.93 to 5.40)
Test for Heterogeneity: $\chi^2_{15}=64.73$ ($P<.001$), $I^2=70.6\%$						
Test for Overall Effect: $Z=4.14$ ($P<.001$)						

Favors Control | Favors BMC Treatment

−10 −5 0 5 10

WMD Random (95% CI)

Abdel-Latif, Arch Intern Med 2007; 167:989

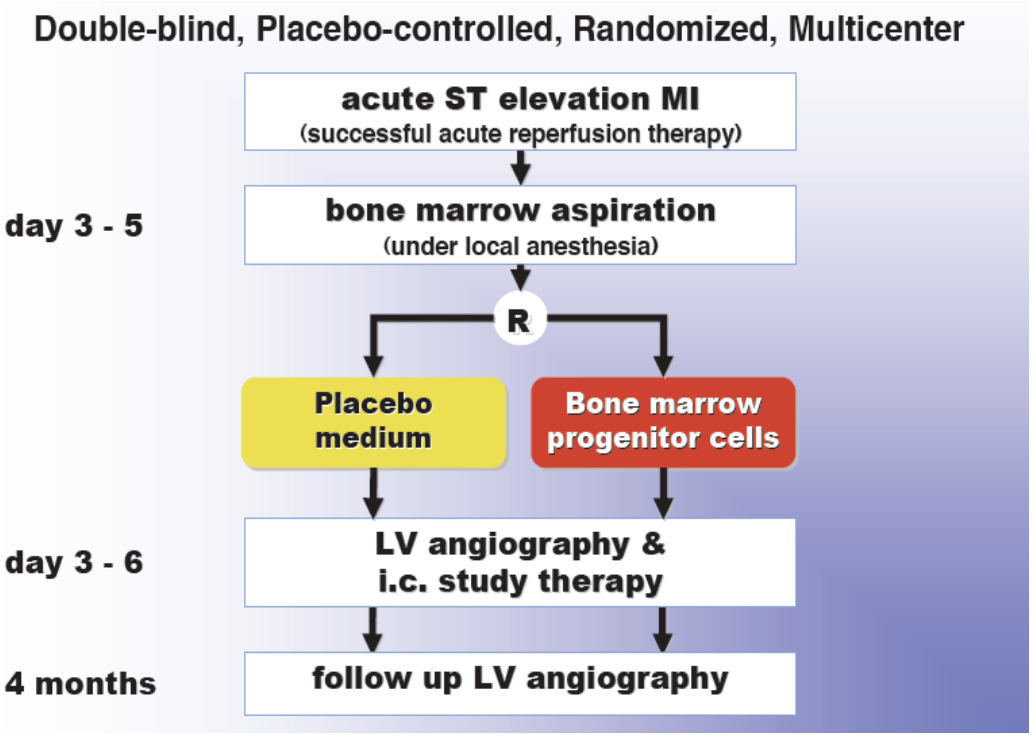
Meta analysis of 1st generation Randomized Controlled Trials (N=976)

- overall treatment effect: ***+2,7 - 3,7 %*** increase of EF
- excellent safety profile
- persistent benefit at long term FU
- disconcordant clinical benefit (survival, composite HF end points)

compare to effect of current standard of care of AMI, the primary PCI procedure

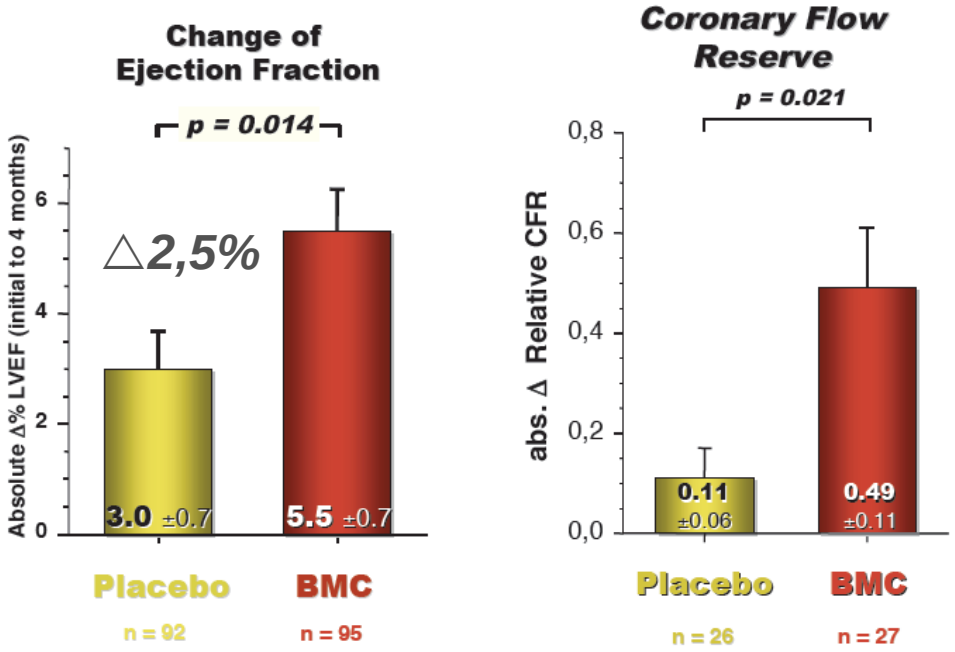
4% improvement of LV ejection fraction

Study design of REPAIR-AMI



Schachinger et al, NEJM 2006

Bone marrow cell therapy enhances cardiac contractile recovery and abrogates heart failure in the REPAIR-AMI



(Schächinger et al. NEJM 2006)

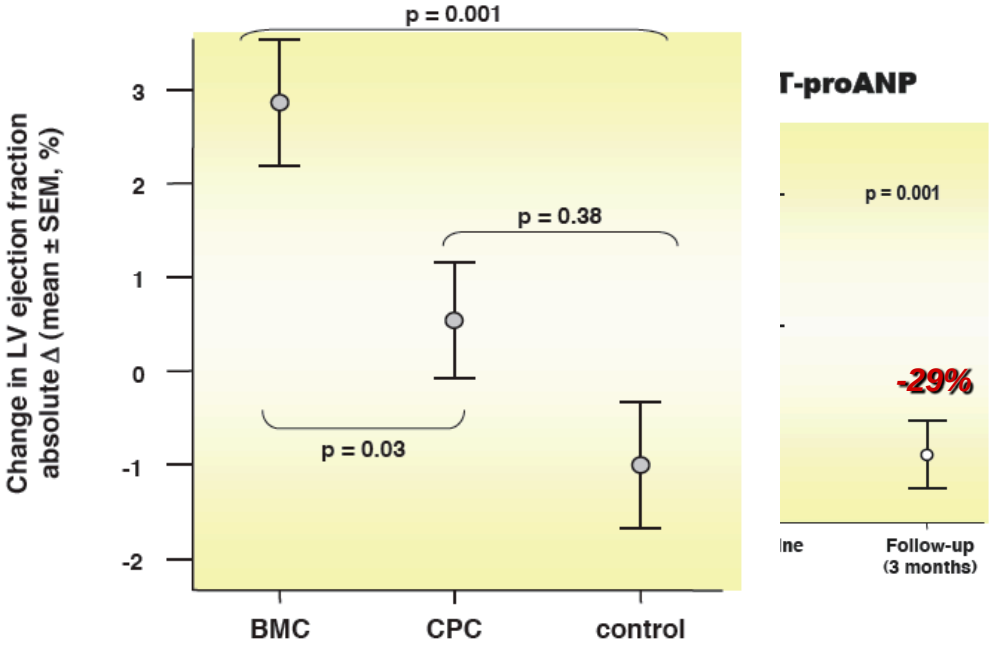
2 year clinical follow up of the BMC therapy in AMI

REPAIR-AMI

Per patient analysis	Placebo n = 103	BMC n = 101	p value
	number of patients		
Death (n)	8	3	0.13
- **Cardiac** (n) (AMI, myocard. rupture, sudden death, heart failure)	5	3	
- **Cardiovascular** (n) (stroke)	1		
- **Non-cardiovascular** (n) (cancer, suicide)	2		
Myocardial reinfarction (n)	7	0	**0.014**
Rehospitalization for heart failure (n)	5	1	0.21
Revascularization (n)	38	25	0.061
- **Target vessel revascularization** (n)	27	17	0.13
- - Stent thrombosis (n)	3	1	0.62
- **Non-target revascularization** (n)	16	9	0.15

Moderate Improved LV EF after BMC therapy in patients with chronic heart failure

TOPCARE-CHD



MRI subanalysis of 35 pts demonstrated

- improvement of regional LV contractile function (number hypocontractile segments)
- no change in infarct size

n=28 pts n=24 pts n=23 pts

n=97 pts

Assmus et al, NEJM 2006; 355
Assmus et al, Circ Res 2007; 100

The small number of patients without contraindications for MRI (n=17) precluded performing an informative analysis on the MRI data. There were no significant differences in the change between the 2 groups in regional wall motion (–0.1 [95% CI, –0.30 to 0.14]; *P*=.47) and LV end-diastolic volume index (2.5 [95% CI, –4.4 to 9.3]; *P*=.48).

Forty percent of patients in the BMC group and 47% of patients in the placebo group were NYHA class III at baseline. The decrease over time in the percentage of patients in the BMC group who were NYHA class III was statistically significant (40% vs 20%; for difference: 95% CI, 3% to 37%; *P*=.02); there was no significant difference in the analogous change for the placebo group. However, when the between-group analysis was applied, this finding was not statistically significant. Similarly, there were no significant differences in the change in CCS class (difference in the percent change: 0.18 [95% CI, –0.07 to 0.43];

Findings for stroke volume were similar, with a mean (SD) increase of 2.7 (12.9) mL in the BMC group and a decrease of –5.8 (15.2) mL in the placebo group; this difference was significant (8.4 [95% CI, 2.1 to 14.8]; *P*=.01).

In an exploratory analysis, BMC therapy was associated with an improvement in maximal oxygen consumption for patients with number of endothelial colony-forming cells greater than the median value of 80 (change: 2.5 [95% CI, 0.16 to 4.88]). However the interaction test for this assessment was not significant (interaction effect size: 2.61 [95% CI, –0.30 to 5.51]; *P*=.08).

A regression analysis showed that higher CD34 cell or CD133 cell counts were associated with greater absolute unit increase in LVEF. The range of CD34 was 0.5% to 6.9% (SD, 1.2%). Assuming that differences of 1.96 for SD or 2.4% are more likely due to biological variability, the effect of differences in CD34 cell level beyond that expected due to natural variability was examined, using a 3% level to be conservative. Every 3% higher level of CD34 cells was associated with on average a 3.0% greater absolute unit increase in LVEF in a multiple variable model that included age and treatment as predictor variables (3.06 [95% CI, 0.14-5.98]; *P*=.04). An analogous computation for CD133 cells (range, 0.1%-3.6%; SD=0.62) revealed that every 3% higher level of CD133 cells was associated with on average a 5.9% greater absolute unit increase in LVEF (5.94% [95% CI, 0.35%-7.57%]; *P*=.04).

Table 1. Patient Baseline Characteristics

	BMC Group (n = 61)	Placebo Group (n = 31)	*P* Value
Mean (SD) Age, y	63.95 (10.90)	62.32 (8.25)	.47

With a low dose of BM MNC

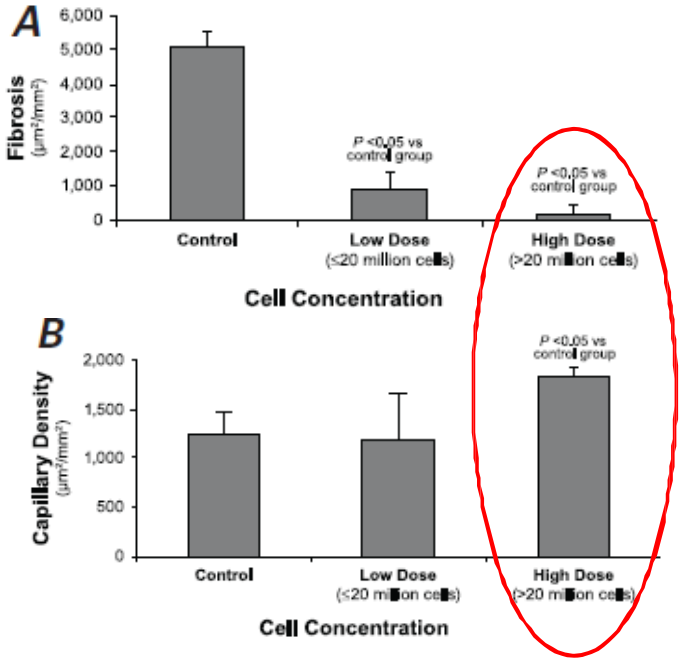
(NOGA delivery catheter - 100 Mill BM MNC)

BIOCARDIA

Perin, EC *et al. JAMA 2012, 307(16), pg 418*

Bone marrow Cells – Preclinical Experience (Pig)

Dose Dependence: Higher dose of MNC led to less fibrosis and increased microvessel formation in infarcted pig myocardium 60 days after treatment



Reduced Fibrosis

>100 Million BMC resulted in less fibrosis

Increased Capillary Density

200 Million BMC (>20 Million BMC/segment) resulted in highest capillary density and least fibrosis

BioCardia

Silva, GV. *et al.* (2011) Tex Heart Inst J. 38(3):219-24

Do these improvements of surrogate markers in stem cell trials also improve hard clinical endpoints ?

Cochrane Library 2014

Cochrane Database of Systematic Reviews

Stem cell therapy for chronic ischaemic heart disease and congestive heart failure (Review)

Fisher SA, Brunskill SJ, Doree C, Mathur A, Taggart DP, Martin-Rendon E

Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD007888.

Main results

We include 23 RCTs involving 1255 participants in this review. Risk of bias was generally low, with the majority of studies reporting appropriate methods of randomisation and blinding, Autologous bone marrow stem cell treatment reduced the incidence of mortality

At >12 month follow-up

- ✓ Reduced Mortality (P=0,0001)
- ✓ Reduced hospitalization due to Heart Failure (P=0,04; MACE-HF)
- ✓ Reduction in Left Ventricular Systolic Volume (P<0,00001)
- ✓ Improvement of Left Ventricular Ejection Fraction (P=0,02)
- ✓ Improvement Stroke Volume Index (P=0,01)
- ✓ Improvement of NYHA functional Heart Failure Class (P=0,0002) and CCS score (P=0,03)
- ✓ Trends were also seen at short term follow-up (4-6 months)
- ✓ Only 4 Adverse Events in 19 RCT of the meta analysis

BMSC were administered following acute myocardial infarction (AMI), we found some evidence for a potential beneficial clinical effect in terms of mortality and performance status in the long term (after at least one year) in people who suffer from chronic IHD and heart

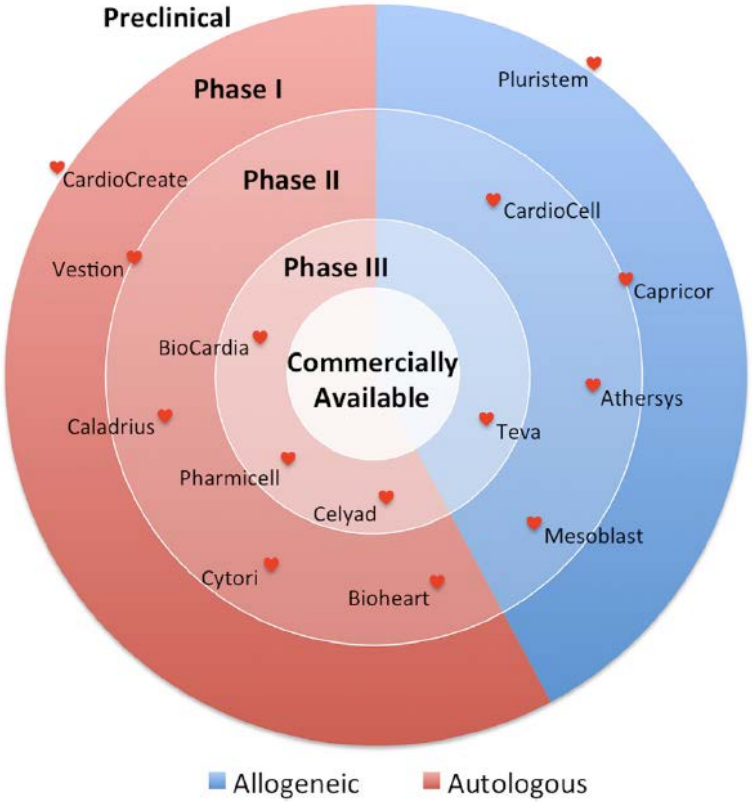
Fischer *et al., Cochrane Database of Systematic Reviews* 2014, Issue 4.

Initial Experience with Stem Cell Therapy in Heart Failure Patients

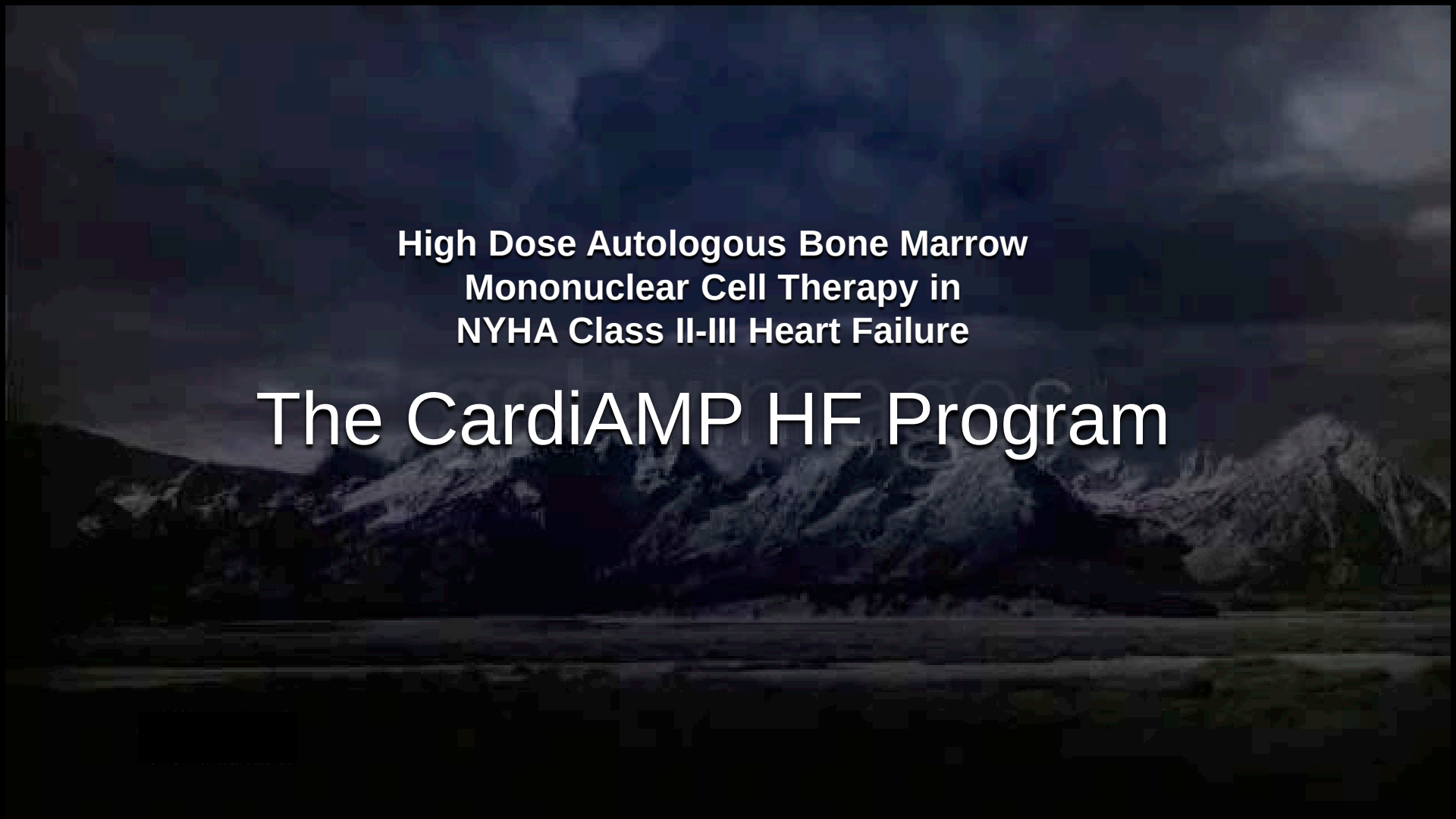
- improvement in LVEF
- reduction of adverse remodeling
- Reduced NYHA and CCS HF class
- reduced MACE HF events (rehospitalizations, HTx, LVAD)
- improved survival

- excellent safety profile
- no arrhythmias or other cell-related mortality/ morbidity

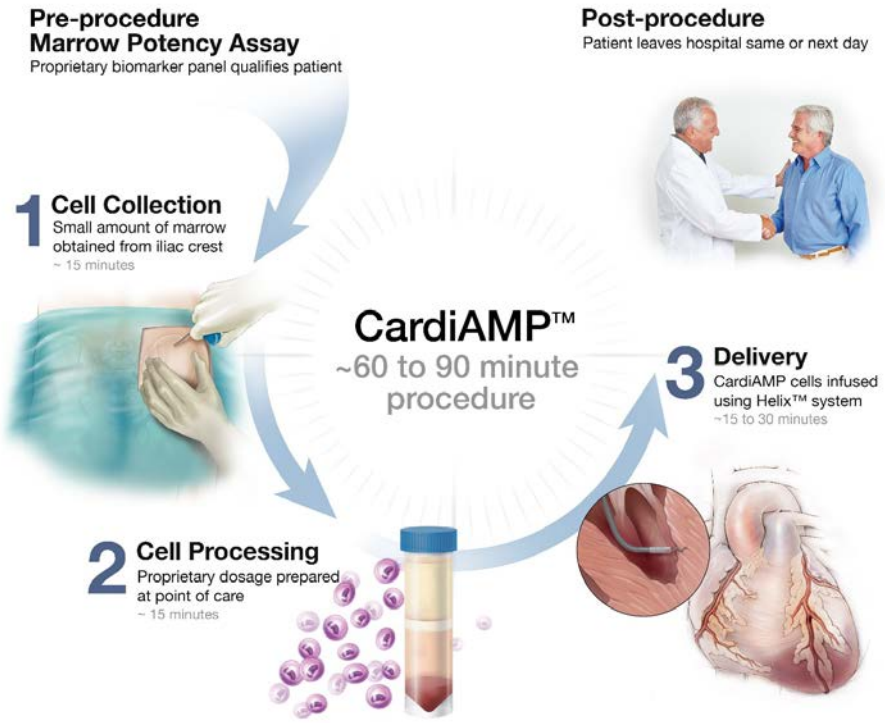
Current Programs in Cardiovascular Cell Therapy



Broughton KM1, Sussman MA*; "Empowering Adult Stem Cells for Myocardial Regeneration V2.0: Success in Small Steps."* ***Circulation Research. 2016 Mar 4***;118(5): pg 867-80.


High Dose Autologous Bone Marrow
Mononuclear Cell Therapy in
NYHA Class II-III Heart Failure
The CardiAMP HF Program

CardiAMP: Novel and Rapid Treatment Paradigm

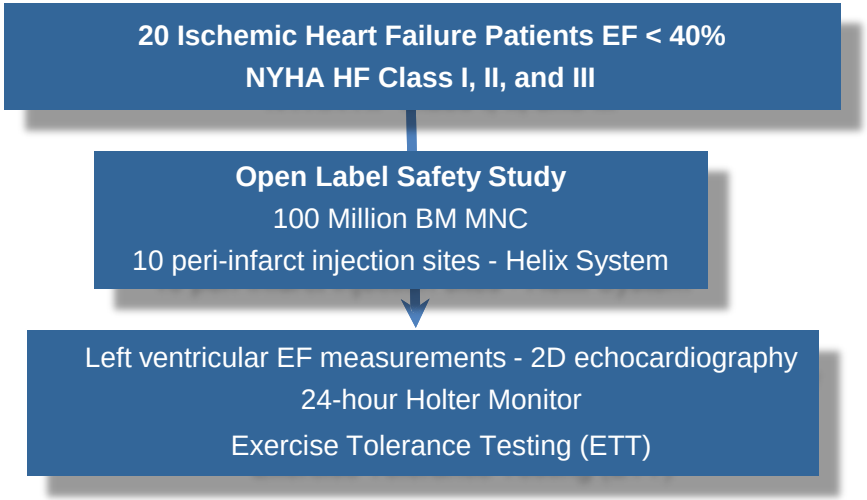


CardiAmp as a Phase III pivotal trial, anticipate to be deliver final results in 2020

BIOCARDIA

CardiAMP: Phase I Trial

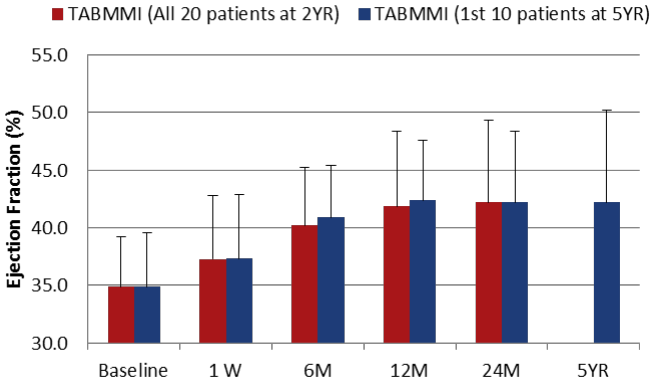
Transendocardial Autologous Bone Marrow MNC in Myocardial Infarction (TABMMI, 2003 – 2007)



- **Bone marrow aspirate harvested from iliac crest.**
- **Isolated Bone Marrow Mononuclear Cells (BM MNC) were injected using Helix Transendocardial Delivery System.**

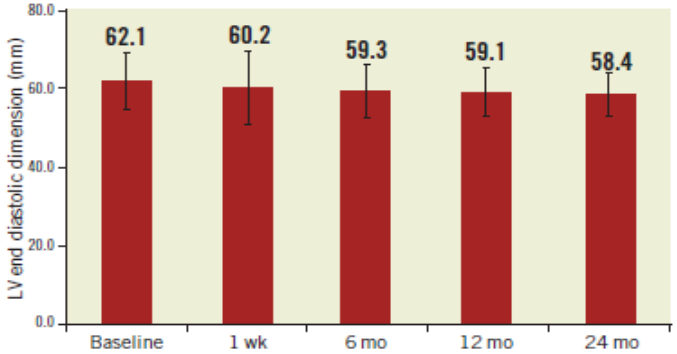
CardiAMP: Phase I TABMMI Trial

Improved Cardiac Function



LV Ejection Fraction at 2 and 5 yr FU

Persistent improvement at 24 & 60M of +7.1 %, (p<0.0001, p<0.0001)



LV End Diastolic Dimensions

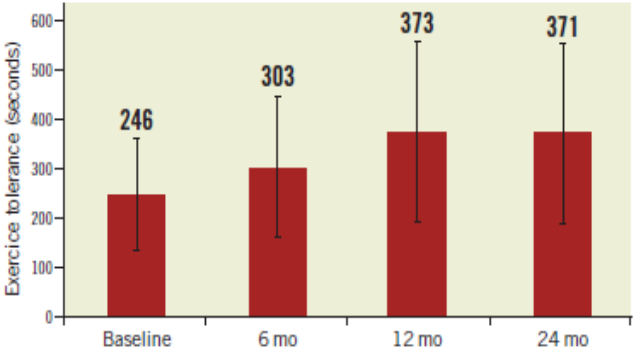
Improvement at 12 & 24 months by -3.5 mm (NS; n=20)

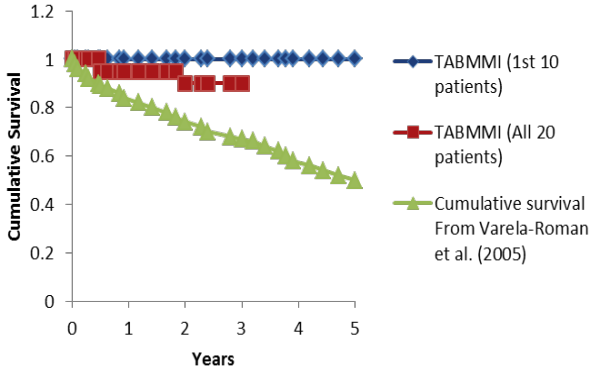
BIOCARDIA

De la Fuente LM, et al. EuroIntervention 2011, 7: 805-812; .

CardiAMP: Phase I TABMMI Trial

Long term improved cardiac function & prognosis





Exercise Tolerance Time

Improvement at 12 & 24 months

by +125 sec (±181 sd)

(+52% & +51%, p ≤ 0.006, n=20)

Survival at 5 year FU

First 10 patients (5 yr FU) – No death

All 20 patients (3 yr FU) – 2 deaths

- **D177 Elective heart transplant**
- **D695 Unknown causes**

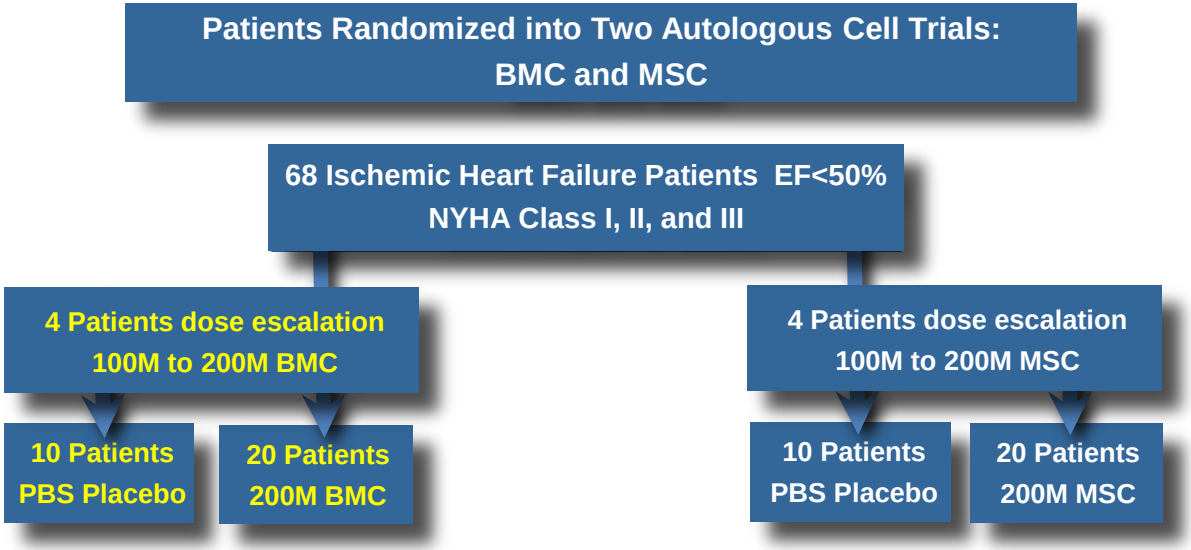
Compare to mortality of 54,7% at 5 yr follow-up in comparative HF population

BIOCARDIA

De la Fuente LM, *et al.* Catheterization & Cardiovascular Interventions 2011, Vol 77(S1), pg S34
Varela-Roman A, *et al.* Heart 2005, 91(4), pg 489

CardiAMP: Phase II Trial Design

Transendocardial Autologous BMC and MSC in Heart Failure Trial (TAC-HFT RCT, 2007 – 2013)



Higher dose BM MNC, and superior retention:

Effective dose is estimated to be ± 6-fold higher

**BMC: bone marrow mononuclear cells*
***MSC: mesenchymal stem cells*

BIOCARDIA

Heldman AW et al, JAMA 2014, 311(1), pg 62-73

CardiAMP: Phase II Trial Design

Transendocardial Autologous Cells in Heart Failure Trial
(TAC-HFT, 2007 – 2013)

Primary Endpoints

- **Incidence of any treatment emergent serious adverse events at 30 days FU**
  - Death, non-fatal MI, stroke, hospitalization due to worsening HF, perforation, tamponade

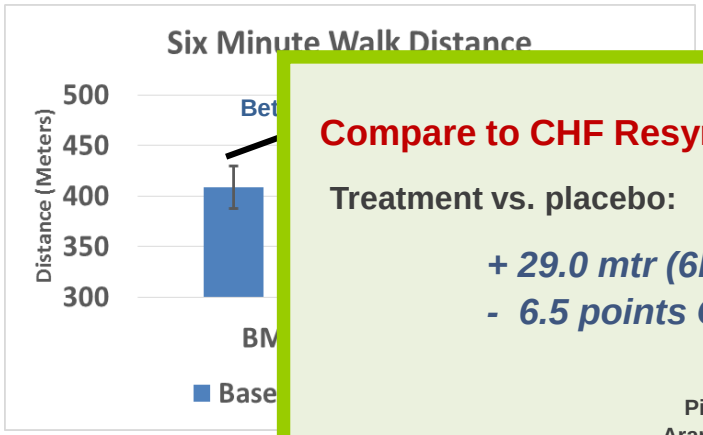
Secondary Efficacy Endpoints at 6 and 12 months FU

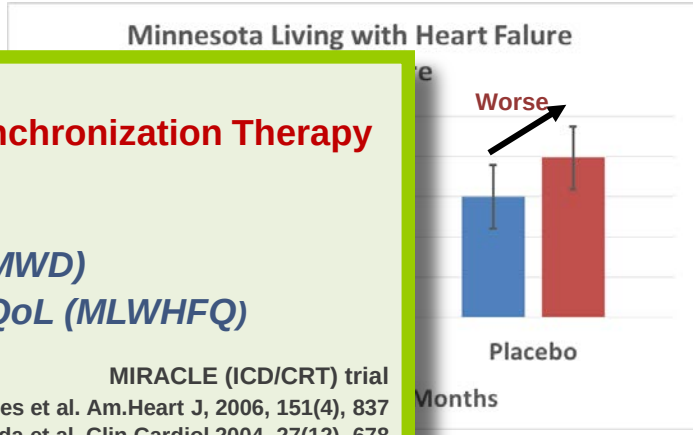
- New York Heart Association (NYHA) heart failure class
- Minnesota Living with Heart Failure quality-of-life questionnaire
- Peak oxygen consumption (VO_2max)
- Six minute walking distance
- Cardiac imaging endpoints (CMR, MSCT, 2D TTE)
  - Infarct Size
  - Regional wall motion at injection sites
  - Global LV size and function

    Using cardiac magnetic resonance imaging, MSCT, 2D transthoracic echocardiography

Phase II TAC-HFT - BMC

- **Primary safety endpoint:** No treatment emergent SAE at 30 days FU
- **Secondary efficacy endpoints:**





Compare to CHF Resynchronization Therapy

Treatment vs. placebo:

+ 29.0 mtr (6MWD)

- 6.5 points QoL (MLWHFQ)

MIRACLE (ICD/CRT) trial
Pires et al. Am.Heart J, 2006, 151(4), 837
Aranda et al, Clin.Cardiol 2004, 27(12), 678
Young et al, JAMA 2003, 289(20), 2685

Improved ality of Life

Treatment vs. placebo: +56.3 m,
(p=0.049, at 12 mo FU)

Treatment vs. placebo: -17.4 pts,
(p=0.038, at 12 mo FU)

BIOCARDIA

Heldman AW et al, JAMA 2014, 311(1), pg 62-73

CardiAMP: Phase II Results

- All other remaining secondary endpoints favor therapy

Secondary Efficacy Endpoints	Active (Mean)	Placebo (Mean)	Treat. Difference	Favors CardiAMP	P-value
6 minute walk (meters)	+14.3	-42.0	+56.3	✓	**0.049**
Minnesota living with HF questionnaire	-7.7	+9.7	-17.4	✓	**0.038**
Maximum Oxygen Use (mL/kg·min)	+0.16	-0.870	+1.03	✓	0.321
NY Heart Association Class	-0.42	-0.25	-0.17	✓	0.638
LV End Systolic Volume (ml)	+3.2	+47.2	-44	✓	0.129
LV End Diastolic Volume (ml)	+4.5	+51.2	-46.7	✓	0.149
LV Ejection Fraction (%)	+0.97	-2.38	+3.35	✓	0.252

Wong Po Foo et al 2015.

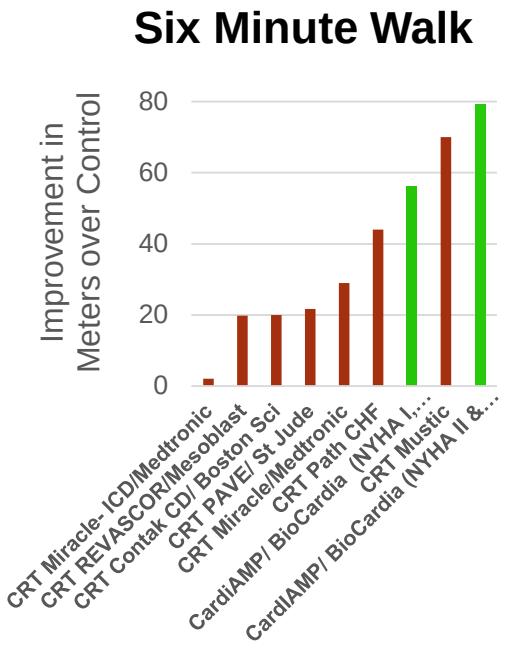
CardiAMP

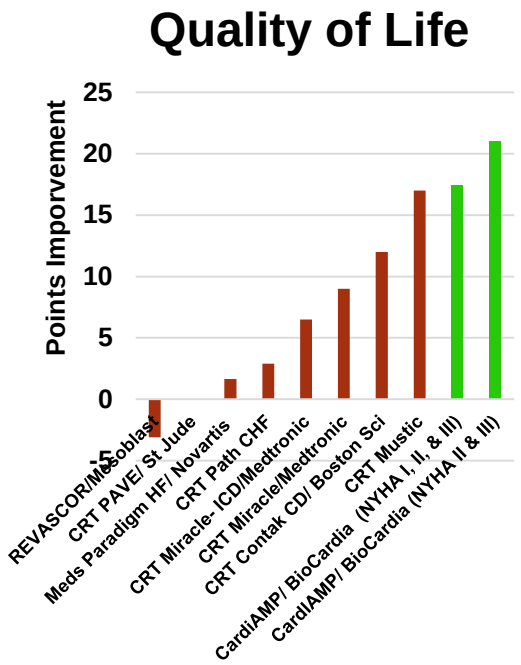
Phase II study Results for NYHA class II and III

TAC-HFT BMC NYHA II & III Only	Changes at Six Months					Changes at Twelve Months				
	BMC (N-15)	Placebo (N=7)	Change	T Test P Value	Favors	BMC (N=15)	Placebo (N=7)	Change	T Test P Value	Favors
Study Efficacy Endpoints No, Mean [SEM]										
Six Minute Walk, M	n=13, -6.2 [18.1]	n=7, -13.2 [27.5]	7	0.41	CardiAMP	n=13, 22.4 [18.1]	n=7, -56.9 [36.8]	79.3	0.021	CardiAMP
MLHF, points	n=14, -5.7 [6.5]	n=7, +8.7 [5.8]	-14.4	0.296	CardiAMP	n=15, -9.2[5.5]	n=7, +11.8 (9.6)	-21	0.027	CardiAMP
NYHA Class	n=14, -0.57 [0.20]	n=6, -0.16 [0.47]	-0.41	0.18	CardiAMP	n=14, -0.71 [.16]	n=6, -0.33 [-.49]	-0.38	0.17	CardiAMP
Peak VO2, mL/Kg/min	n=11, +0.33[0.50]	n=7, -0.91 [1.07]	1.24	0.12	CardiAMP	n=11, +0.16[0.47]	n=7, -0.58 [0.81]	0.74	0.2	CardiAMP
FEV1, %	n=14, 1.9 [2.75]	n=7, -12 [10.3]	13.9	0.043	CardiAMP	n=14, -0.71 [3.6]	n=7, -16 [11.3]	15.29	0.053	CardiAMP
Cardiac Imaging (MRI/CT_ Parameters, No, Mean (SD)										
LVEF, %	n=13, 0.47 ([1.38]	n=6, -3.35 [3.71]	3.82	0.12	CardiAMP	n=13, .31[1.98]	n=6, -4.5 [3.47]	4.81	0.1	CardiAMP
EDV, mL	n=13, -8.3 [3.1]	n=6, 74.2 [61.3]	-82.5	0.029	CardiAMP	n=13, 5.0 [8.6]	n=6, 74.3 [61.3]	-69.4	0.059	CardiAMP
ESV, mL	n=13, -5.1 [3.4]	n=6, 67 [55]	-72.1	0.024	CardiAMP	n=13, +5.4 [7.8]	n=6, 71 [54]	-65.6	0.049	CardiAMP
Scar mass, g	n=12, -0.56 [0.31]	n=6, 9.0 [9.8]	-9.56	0.088	CardiAMP	n=12, -3.34 [1.34]	n=6, 7.2 [10.5]	-10.54	0.089	CardiAMP
Scar size as % of LV, %	n=12, -0.31 [0.37]	n=6, 1.75 [2.6]	-2.06	0.13	CardiAMP	n=12, -0.85 [0.77]	n=6, 3.0 [2.7]	-3.85	0.03	CardiAMP
Viable tissue mass, g	n=12, -0.6 [1.1]	n=6, 4.26 [3.75]	-4.86	0.085	CardiAMP	n=12, 4.26 [3.75]	n=6, -33.34 [25.7]	37.6	0.028	CardiAMP
Notes:										
(1) This eliminates NYHA Class I patients (15, 29, 31, 54, and 67 in the CardiAMP cell therapy group 5/19, and 22, 28, and 63 in placebo group 3/10).										
(2) Note: patient 31 is lost to followup on much of previous analysis as only BL values available. Thus, seven patients excluded in this analysis w/ NYHA Class I.										
(3) Placebo patient 53 Imputation of worst observation carried forward due to stroke before 6 months, has a more significant effect in this analysis due to smaller N.										
(4) T Tests are one tailed, two sample, with assumed hemoscedastic distribution										

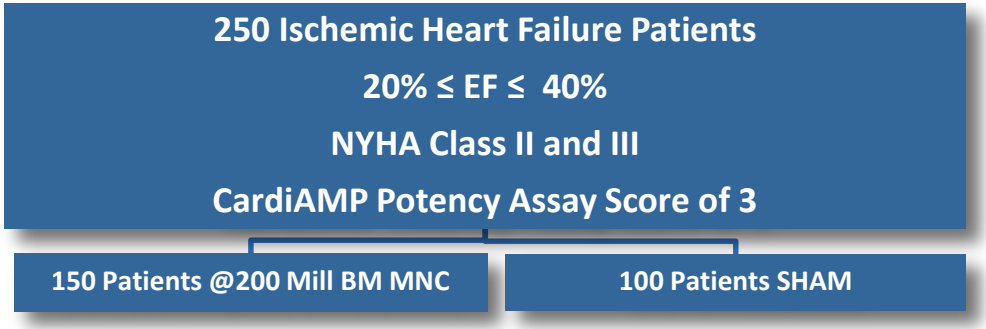
CardiAMP Data Relative to Peers (NYHA class II-III)

- Superior six minute Walk (6MW) and Quality of Life (QOL) as compared to CRT
- Superior 6MW and QOL to Mesoblast Revascor Phase II, with more consistent
- Superior QOL to that of Novartis Entresto, which does not report out 6MW





Phase III CardiAMP HF clinical Trial



- **Changes from Phase II:**
  - ☑ NYHA Class I patients are not included
  - ☑ potency assay is implemented to enhance response to therapy
- **Primary endpoint:**
  - Superiority with respect to functional capacity as measured by six minute walk test at one-year post-procedure (efficacy) ; achieved in Phase II
- **Secondary hierarchical endpoints:**
  - Non-inferiority with respect to survival (safety)
  - Non-inferiority with respect to MACE (safety)
  - Superiority with regard to quality of life as measured by the MLHFQ
  - Time to first heart failure (HF)-related major adverse cardiac events (efficacy)
  - Superiority with respect to survival (efficacy)

Achieved in Phase II

CardiAMP HF Trial Study Design

Study Design

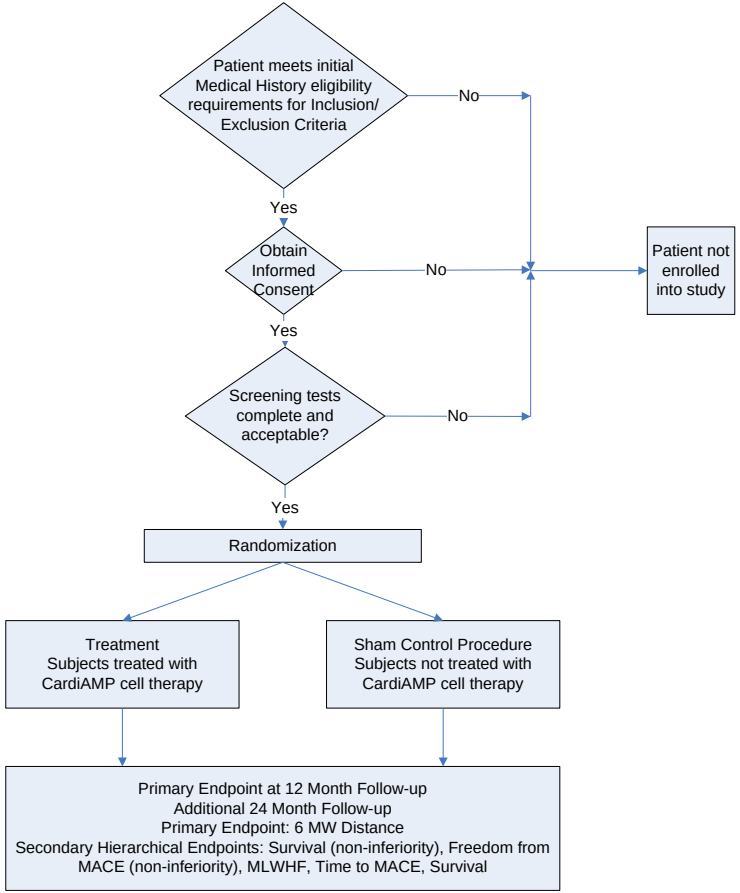
Prospective, multi-centered, 3:2 randomized, controlled, double-blinded phase III clinical trial to assess CardiAMP cell therapy in 260 patients with post-infarction heart failure.

Treatment Group: 160 Subjects treated with autologous BM MNC using the CardiAMP cell therapy and optimal medical therapy

Sham Control Group: 100 Subjects treated with optimal medical therapy

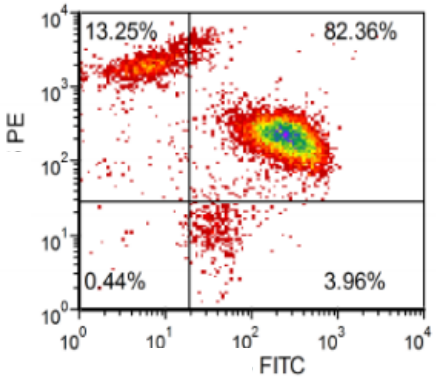
Roll-in Phase: Maximum of 10 subjects

Total Number of Patients: 260 subjects

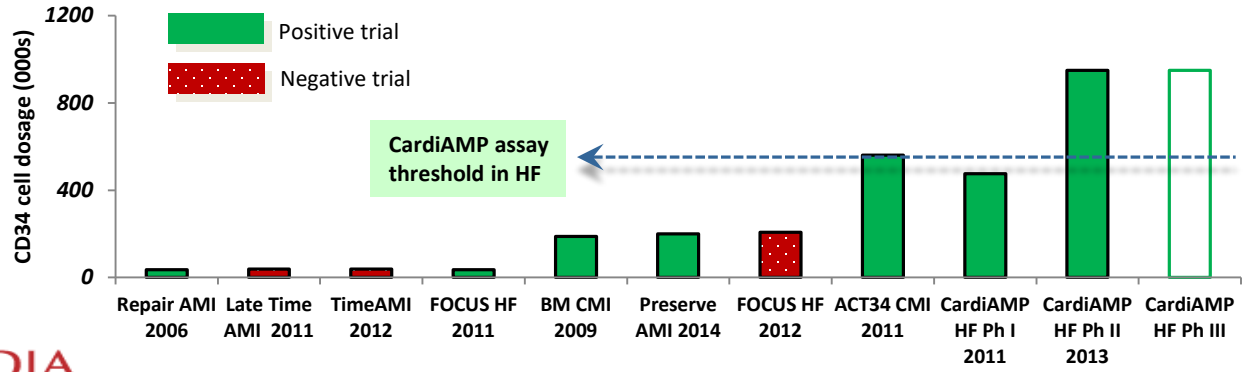


CardiAMP HF: Pre-procedure Marrow Potency Assay

- Biomarkers identified in previous BioCardia trials and the literature shown to correlate independently with efficacy of CV cell therapy
- Bone marrow sample 1-2 weeks before planned treatment. Proprietary Biomarker Analysis at Central Core Lab to assess presence of bone marrow characteristics associated with myocardial repair (flow cytometry and cell biology)
- Potency Assay ensures appropriate function and (sufficient high) titer of BM cells
- One of the markers is the CD34+ cell titer in the bone marrow



Estimated effective CD34+ cell dosage from leading trials

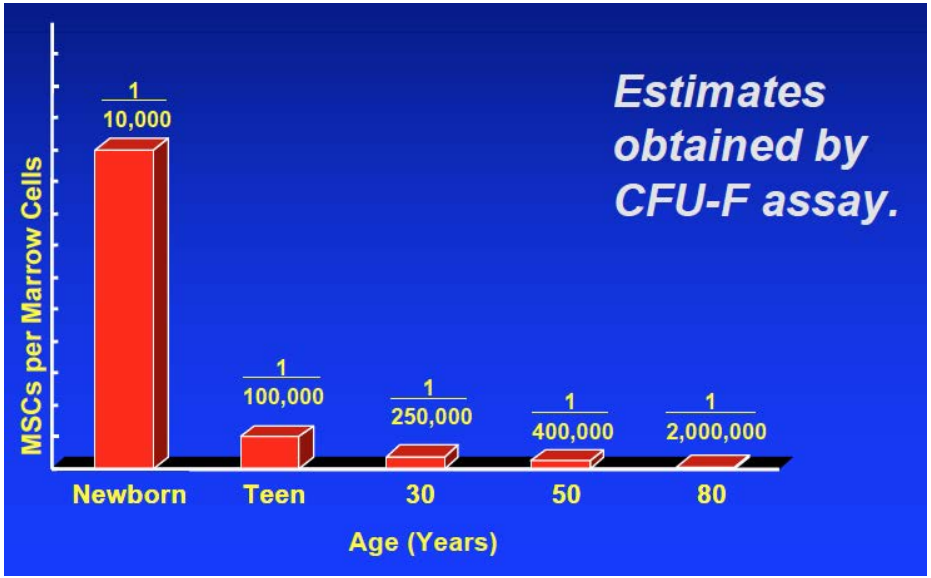


BIOCARDIA

Modified from Wong et al : International Conference on Cell Therapy for Cardiovascular Disease 2014

Autologous Stem Cell Therapy

- **naturally occurring variability in cell functionality between patients (biovariability)**
- **functionality of BM MNC, EPCs and MSCs is impaired in patients with ischemic CMP and diabetes (but also aging, hypertension, hypercholesterolaemia) ~ “depleted or damaged”**



BM Stem Cells number and function reduced (CFU)

- **aging**
- **hypertension**
- **smoking**
- **hypercholesterolemia**
- **diabetes**
- **(ACE inhibition)**
- **(heparin)**

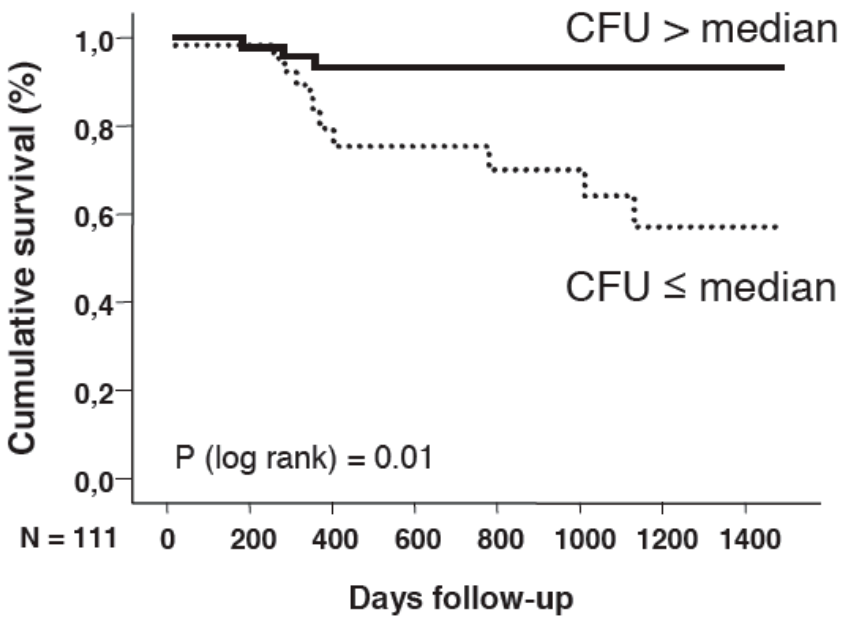
Appropriate action to promote graft efficacy ?

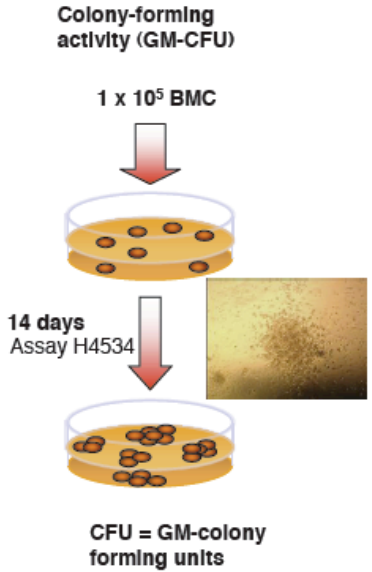
- **subculture cells**
- **pharmacotherapy**
- **selection of cells**
- **rejection of patient**

BIOCARDIA®

Predictor of survival after BMC therapy in chronic heart failure

functional capacity of progenitor cells predicts mortality after infusion of BM stem cells in congestive heart failure





Assmus et al., Circ Res 2007

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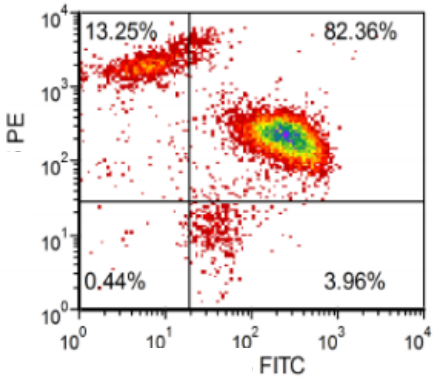
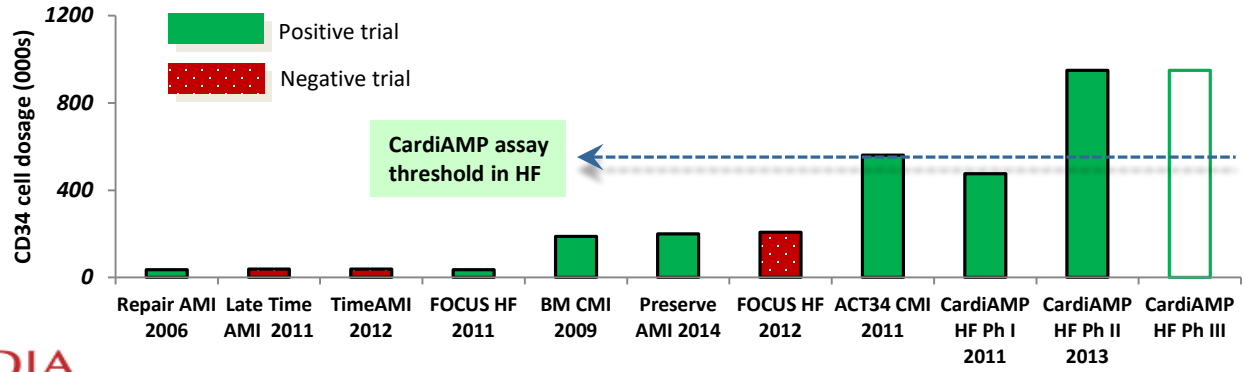


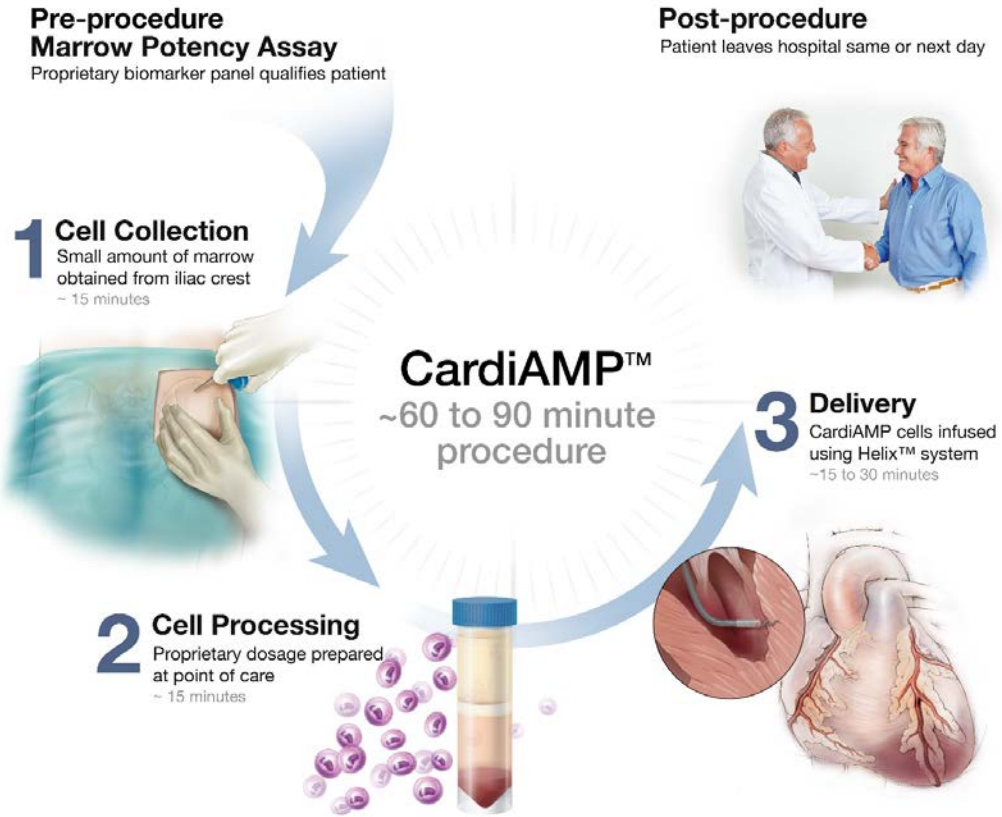
Estimated effective CD34+ cell dosage from leading trials



BIOCARDIA

Modified from Wong et al : International Conference on Cell Therapy for Cardiovascular Disease 2014

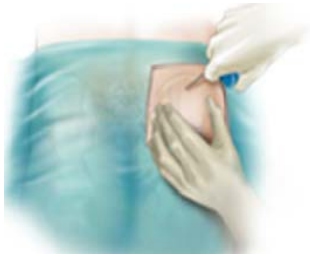
CardiAMP Step 2. The Stem Cell Harvest and Intramyocardial Delivery

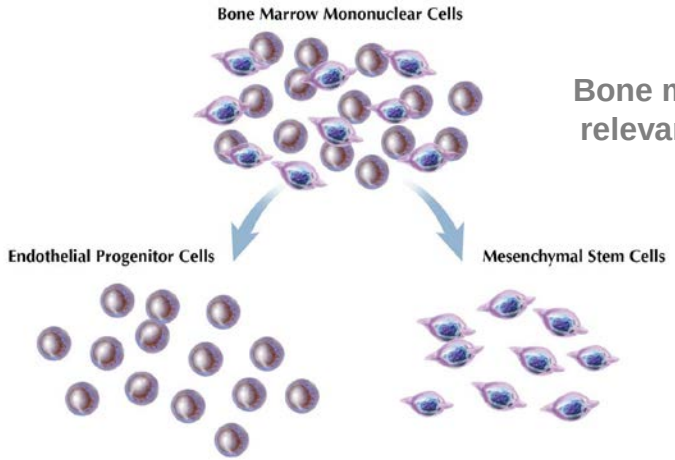


BIOCARDIA

CardiAMP Procedure Step 1: Cell Collection

- **The clinician draws 60 cc of bone marrow from the iliac crest**
- **The procedure is performed under local anesthesia and conscious sedation and takes approximately 15 minutes**





Bone marrow contains several relevant stem cell populations

The Helix/Morph delivery device results in superior retention with a higher dose of delivered BM MNC

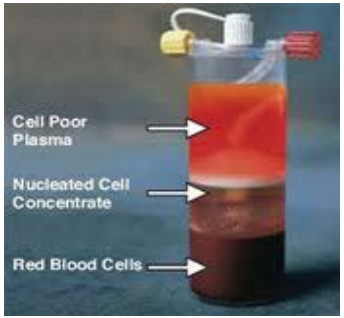
In CardiAMP HF trial patients receive 200 Mill MNC and 8-10 Mill CD34 cells (so dosing each of these functional sub populations at a therapeutic dose)

BIOCARDIA

Loffredo FS et al Stem Cell. 2011;8:389-98.

CardiAMP Procedure Step 2: Cell Processing

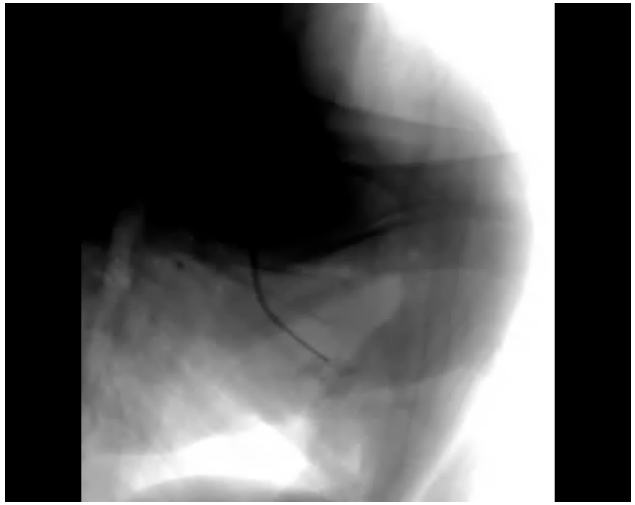
- The CardiAMP cell processing platform prepares the cell graft from the bone marrow sample using a proprietary point-of-care method
- The system includes a single-use, sterile, disposable separation tube that includes a density-tuned dual buoy separation system, designed for the isolation of BM nucleated cells
- Cells processing, while the patient is prepared for cell delivery, takes approximately 20 minutes

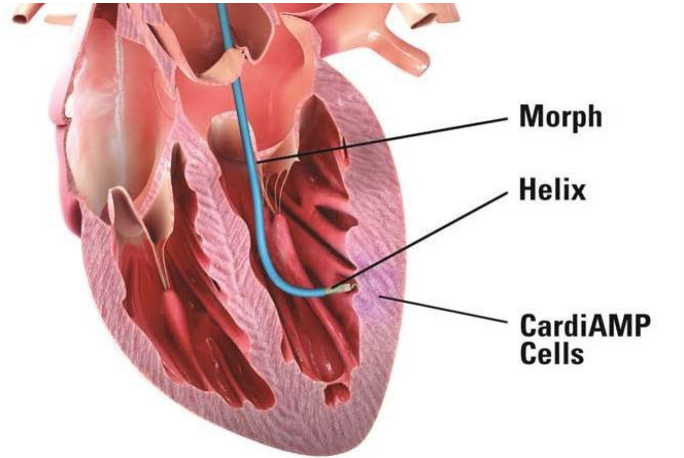


CardiAMP Procedure Step 3: Intramyocardial cell delivery

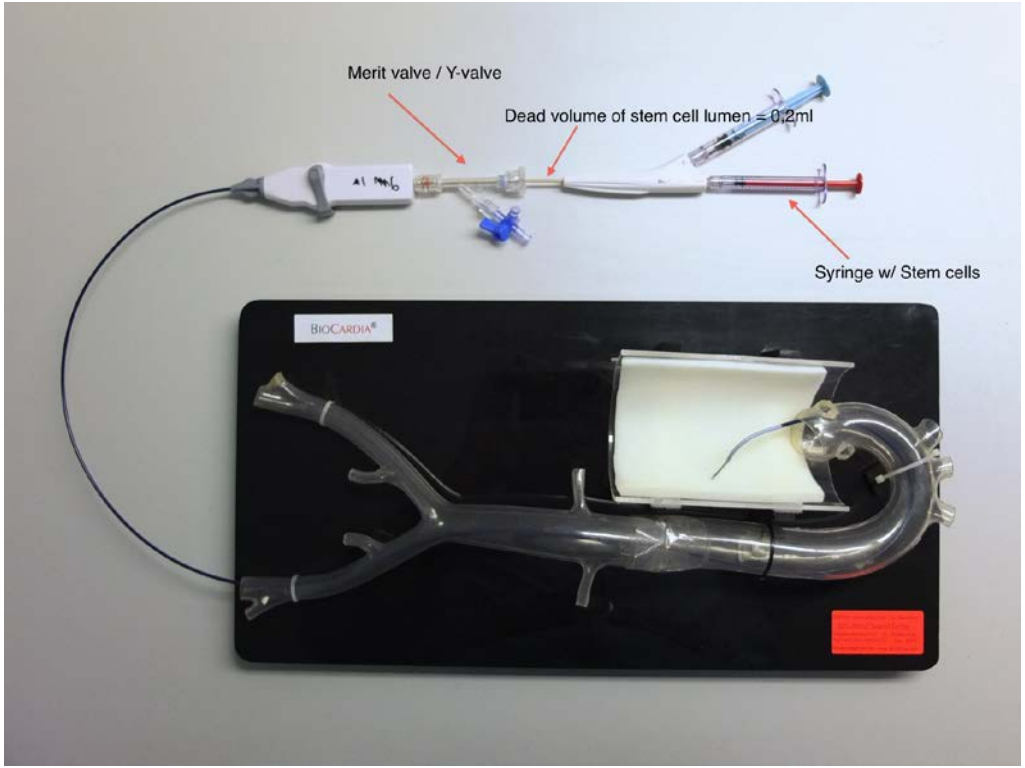
Intramyocardial injection of CardiAmp cell graft using the Helix system

- The CardiAMP cells are intramyocardially injected using the proprietary Helix percutaneous delivery system (10 injections of 0,5 cc)

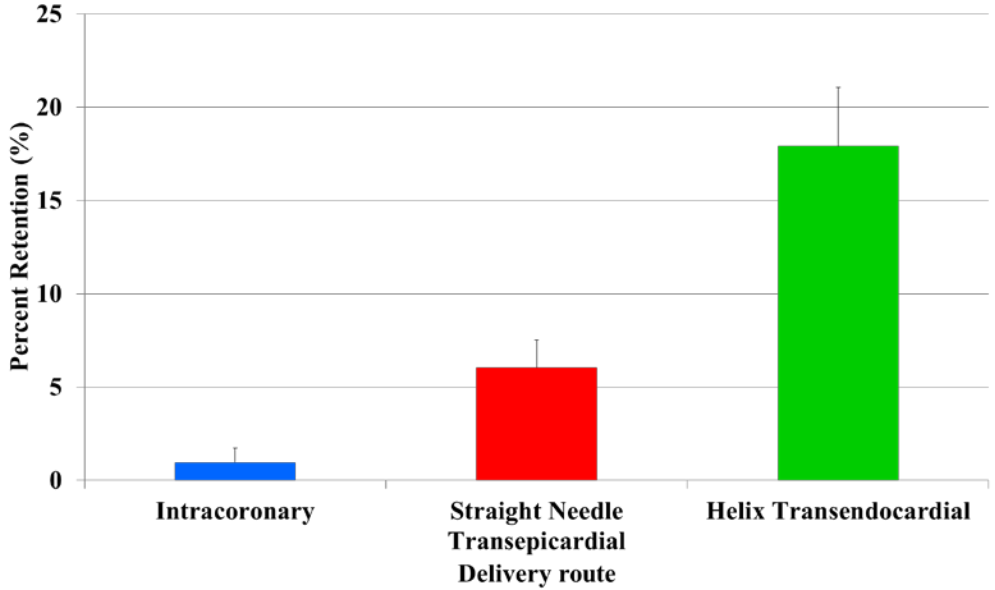




CardiAMP Procedure Step 3: Intramyocardial cell delivery



Increased efficiency of delivery increases effective dosage



Helical shaped needle in Helix/Morph delivery device results in superior myocardial retention and a higher effective dose of delivered BM MNC

In CardiAMP HF trial patients receive 200 Mill MNC and 8-10 Mill CD34 cells

Wong Po Foo, IC3D 2013.

CardiAMP Heart Failure Trial Study Design

Study Design

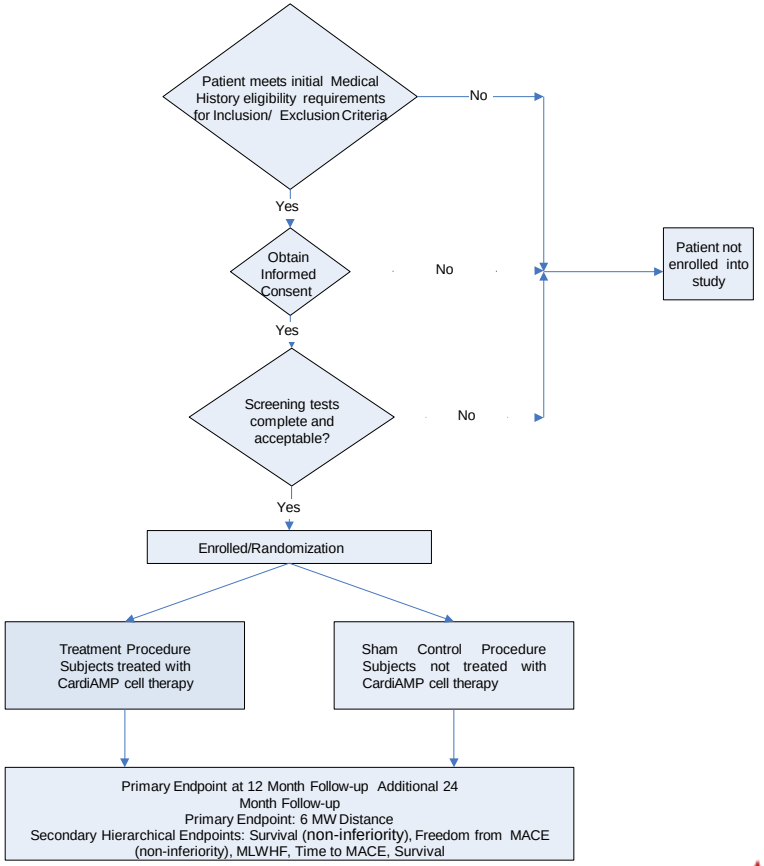
Prospective, multi-centered, 3:2 randomized, controlled, double-blinded phase III clinical trial to assess CardiAMP cell therapy in 260 patients with post-infarction heart failure.

Treatment Group: 160 Subjects treated with autologous BM MNC using the CardiAMP cell therapy and optimal medical therapy

Sham Control Group: 100 Subjects treated with optimal medical therapy

Roll-in Phase: Max of 10 subjects (completed)

Total Number of Patients: 260 subjects



Phase III CardiAMP committees

- **Executive Steering Committee/ ESC**
  - Carl Pepine – University of Florida (PI)
  - Amish Raval – University of Wisconsin (PI)
  - William Abraham - Ohio State University
  - Peter Johnston – Johns Hopkins Hospital
  - Jay Traverse – Minneapolis Heart Institute
  - Peter Altman – BioCardia
- **Data safety monitoring board/ DMSB**
  - 3 members (Int.card./ HF/ BioStat), undisclosed
- **Data adjudication committee/ CEC**
  - 3 members (Int.card./ HF), undisclosed
- **Core Laboratories**
  - Echocardiography — Yale Cardiovascular Research, New Haven (Lissa Sugeng)
  - Cell Analysis Lab — Center for Cell & Gene Therapy, Baylor Univ, Houston (Adrian Gee)

CardiAMP Heart Failure Trial

Inclusion Criteria

- New York Heart Association (NYHA) Class II or III
- Diagnosis of chronic left ventricular dysfunction, due to previous myocardial infarction (TTE)
- Left ventricular ejection fraction of 20 - 40% as determined by 2D/3D echocardiogram, and not in the setting of a recent ischemic event
- No recent MI within last 6 months
- Previous treatment with thrombolytic therapy, coronary artery bypass surgery, or percutaneous coronary revascularization
- On stable evidence-based medical and device therapy for heart failure, per the 2013 ACC/AHA Heart Failure guidelines, for at least 3M prior to randomization
  - Optimal pharmacotherapy (BB, ARB/ACE-I, diuretics, aldosteron.inh.)
  - Cardiac resynchronization therapy (CRT/ CRT-D) if appropriate
    - CRT or CRT-D implanted at least 3M prior to randomization
    - Eligible or anticipated to be eligible for CRT or CRT-D > 6M
- Cell Potency Assay Score of 3, as determined by the Cell Analysis Core Lab

CardiAMP Heart Failure Trial

Key Exclusion Criteria

- bronchospastic lung disease, orthopedic, muscular, or neurologic conditions that could limit the ability to perform the 6MWD Test
- Need for coronary artery revascularization. (PCI/CABG should occur at least 3 months prior to randomization)

- Severe mitral, tricuspid or aortic regurgitation (≥3+) ,
- Presence of aortic stenosis ((≥3+, AVA < 1.5 cm^2)

- mechanical aortic valve or heart constrictive device
- a life-threatening arrhythmia
- complete heart block or QTc interval >550 ms
- AICD firing in the past 60 days prior to the procedure

- peripheral artery disease involving the aorta or iliofemoral system that impacts the feasibility or safety of the study intervention.

CardiAMP Heart Failure Trial

Primary Endpoint at 12-months follow-up

- Change in 6-minute walking distance (6MWD)

Secondary Hierarchical Endpoints at 12-months follow-up

- Overall survival (non-inferiority outcome)
- Freedom from MACE (non-inferiority outcome)
- Change in Quality of Life as measured by Minnesota Living with Heart Failure (*superiority* outcome)
- Time to first MACE (*superiority* outcome)
- Overall survival (*superiority* outcome)

Additional Secondary Endpoints at 12-months follow-up

- Heart failure death
- Hospitalization due to exacerbation of heart failure
- All-cause hospitalization
- Days alive out-of-hospital
- Freedom from Serious Adverse Events
- NYHA Functional Class for Heart Failure
- Treatment-emergent Serious Adverse Events at 30-days follow-up
- Survival, at 24-months follow-up
- 6MWD repeated measure analysis
- Technical success, defined as successful percutaneous delivery of BM-MNC
- change in left ventricular ejection fraction, end systolic and end diastolic dimensions, and mitral regurgitation as analyzed by echocardiography (TTE)

Recruitment of Medical Centers

Site #	Site Name, Location, Phone	Physician IC/HF	Activated	State
1	John Hopkins Medical Center	Peter Johnston/ IC	Oct-17	Activated
	Baltimore MD	Gary Gerstenblith/ HF		
2	University of Florida MC - Shands	David Anderson/ IC	Oct-17	Activated
	Gainesville FL	Carl Pepine/ HF		
3	University of Wisconsin MC	Amish Patel/ IC	Oct-17	Activated
	Madison WI	Peter Rahko/ HF		
4	Virginia CommonWealth Universit	Keyur Shah/ HF	Oct-17	Activated
	Richmond VA	Zavhary Gertz/ IC		
5	Suburban Medical	Kumkumian/Lieberman	Dec-17	Activated
	Baltimore MD	Tony Dao/ HF		
6	Trinity Health Michigan Heart	Marlo Leonen/ IC	Oct-17	Activated
	Ypsilanti, MI	Zakir Sahul/ HF		
7	Stanford Medical	David Lee/ IC	Dec-17	Activated
	Stanford, CA	Philip Yang/ HF		
8	Morton Plant Mease Hospital	Les Miller/ HF	Dec-17	Activated
	Clearwater FL	Parag Patel/ IC		
9	University of Minnesota	Ganesh Raveendran/ IC	Mar-18	Activated
	Minneapolis MN	Emil Missov/ HF		
10	Atlantic Health DBA, Morristown M	Robert Kipperman/ IC	Mar-18	Activated
	Morristown NJ	Marc Goldschmidt/ HF		
11	St.Joseph Hospital, BayView Heal	Sadanandan/ IC	Apr-18	Close
	Tampa FL	Agoeha/ HF		
12	Henry Ford Hospital	Gerald Kooing/ IC	Apr-18	Activated

March
10 centers activate

April
12 centers activate

May
15 centers activated

Up to 40 US centers

BIOCARDIA®

CardiAMP HF stem cell therapy in Heart Failure

High Dose Autologous BM MNC Therapy by intramyocardial injection

Over the past decade, cell therapy has emerged as a new treatment of a variety of cardiac diseases, including chronic heart failure, refractory angina and AMI.

CardiAMP HF Therapy provides

- Harvest, isolation and delivery of autologous stem cells at point of care within 60-90 min
- Delivery of high dose BM MNC therapy at a target dose of 200 Million (8-10 Mill CD34 stem cells)
- Selection of suitable patients using a Cell Potency Assay (to verify potency of autologous BM cells)

The first results suggest

- Functional benefit of ~9 mtr (TAC HBT)
- Improvement of Quality of Life -21 pts (TAC HFT)
- Reduced NYHA HF classification
- Results of first 10 CardiAMP patients will be published in Circ.Res. (Johnston et al)
- CardiAMP HF Program will be initiated in next few weeks at Oklahoma Heart Institute

BIOCARDIA

ESC European Society of Cardiology

European Heart Journal (2018) 0, 1–9
doi:10.1093/eurheartj/ehx764

META-ANALYSIS

Autologous CD34$^+$ cell therapy improves exercise capacity, angina frequency and reduces mortality in no-option refractory angina: a patient-level pooled analysis of randomized double-blinded trials

Timothy D. Henry[1]*, Douglas W. Losordo[2], Jay H. Traverse[3], Richard A. Schatz[4], E. Marc Jolicoeur[5], Gary L. Schaer[6], Robert Clare[7], Karen Chiswell[7], Christopher J. White[8], F. David Fortuin[9], Dean J. Kereiakes[10], Andreas M. Zeiher[11], Warren Sherman[12], Andrea S. Hunt[13], and Thomas J. Povsic[7]

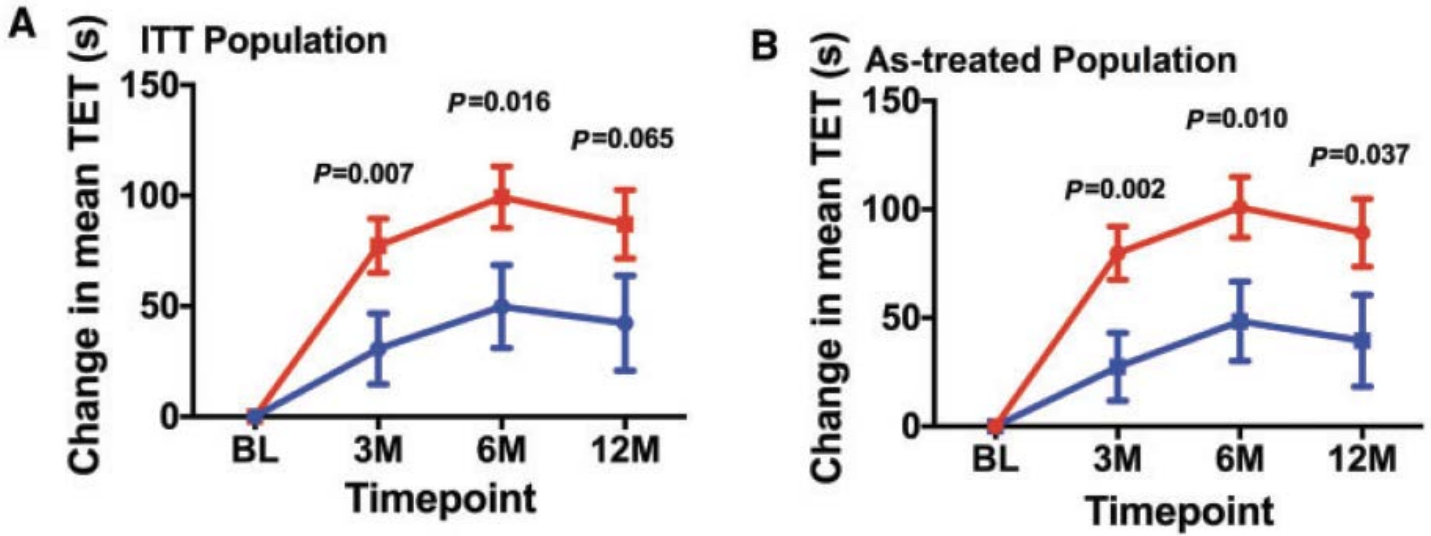
[1]Cedars-Sinai Heart Institute, Los Angeles, CA, USA; [2]Caladrius Biosciences, Inc., New York, NY, USA; [3]Minneapolis Heart Institute Foundation, Abbott Northwestern Hospital, Minneapolis, MN, USA; [4]Scripps Clinic Torrey Pines, La Jolla, CA, USA; [5]Montreal Heart Institute, Université de Montréal, Montréal, Quebec, Canada; [6]Rush University Medical Center, Chicago, IL, USA; [7]Duke University School of Medicine, Duke Clinical Research Institute, Durham, NC, USA; [8]Ochsner Clinical School, Ochsner Medical Center, New Orleans, LA, USA; [9]Mayo Clinic Hospital, Phoenix, AZ, USA; [10]The Christ Hospital Heart and Vascular Center, Lindner Research Center, Cincinnati, OH, USA; [11]University of Frankfurt, Frankfurt, Germany; [12]LoneStar Heart Inc., Irvine, CA, USA; and [13]Shire US, Lexington, MA, USA

Received 14 July 2017; revised 31 August 2017; editorial decision 27 October 2017; accepted 13 December 2017

n=304; Henry et al, EHJ, 2018

Meta Analysis of Cell Therapy in Chronic Myocardial Ischemia/ Refractory Angina

Treadmill Exercise Performance up to 12 months



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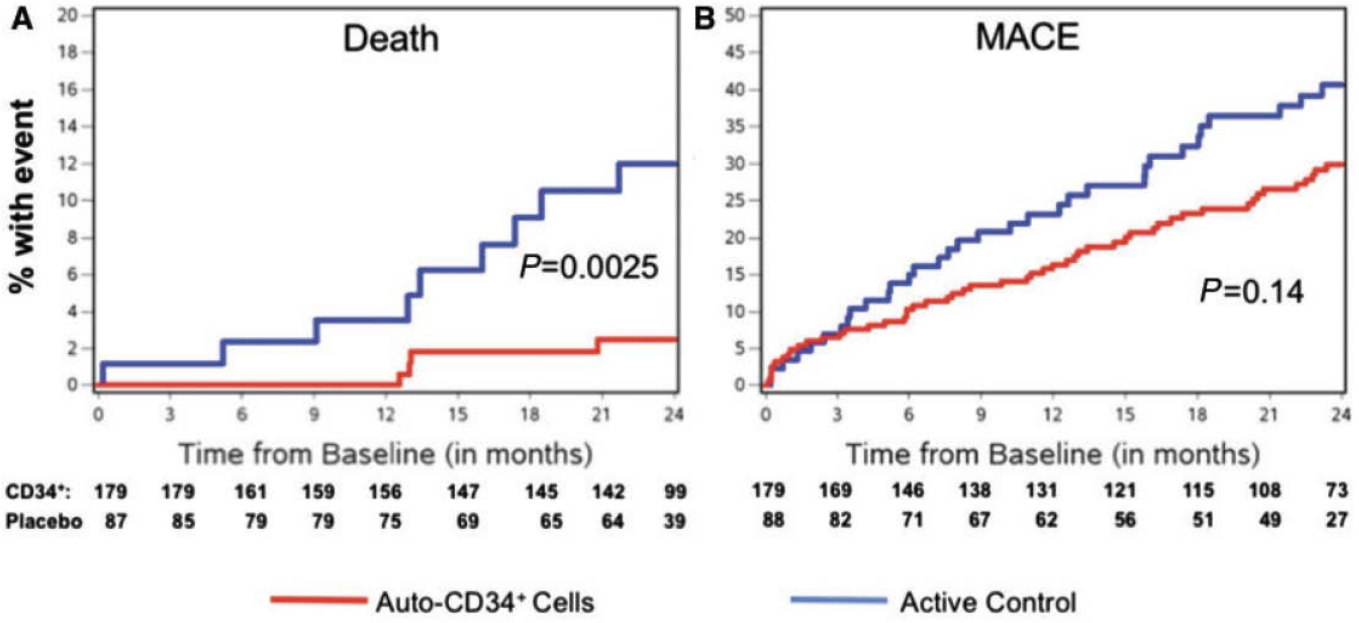
n=304; Henry et al, EHJ, 2018

Meta Analysis of Cell Therapy in Chronic Myocardial Ischemia/ Refractory Angina

MACE and all cause Mortality at 24 months

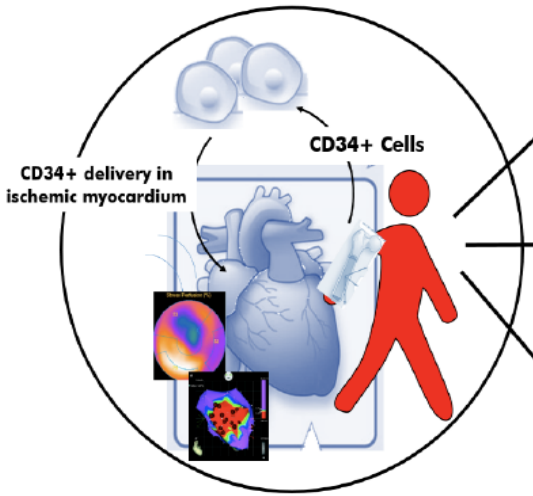


BioCardia

n=304; Henry et al, EHJ, 2018

CD34+ Cell Therapy for Patients with Refractory Angina

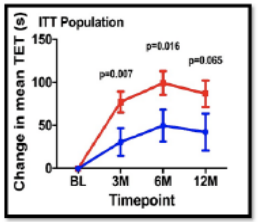
Improvement in exercise time, angina, and mortality compared to placebo

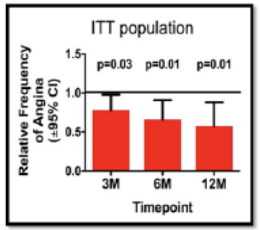


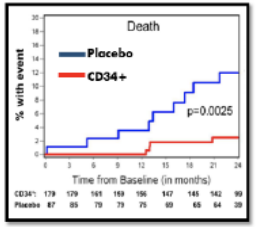
Improved total exercice time throughout the 3-12 month period on treadmill stress test

Lower relative frequency of angina throughout the 3-12 month period

Significant decrease in all-cause mortality at 24 months







RENEW protocol required 4 days of iv GCSF treatment, plasmapheresis and immune isolation (in a clean room facility) to generate a dose of 8 Mill CD34+ MNC Technology at hand allows one to generate this dose within 20-30 min in the Cath Lab

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n=304; Henry et al, EHJ, 2018

CardiAMP Chronic Myocardial Ischemia Trial Design

CardiAMP-CMI

Study Design

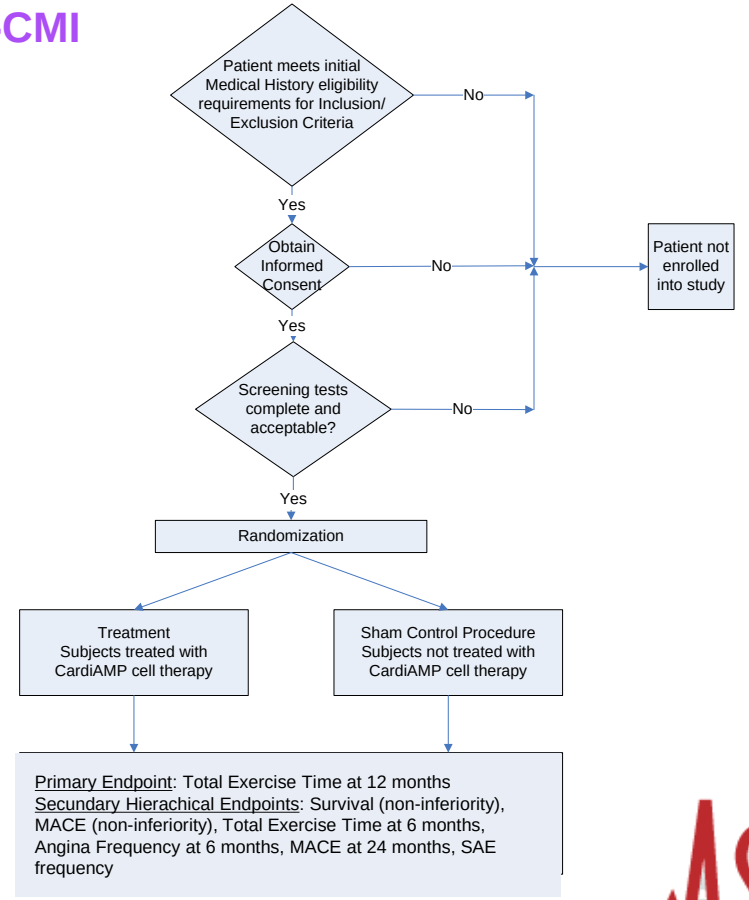
Prospective, multi-centered, 2:1 randomized, controlled, double-blinded phase III clinical trial to assess the effect of CardiAMP cell therapy in 343 patients with chronic myocardial ischemia/ refractory angina (CCS III-IV chronic refractory angina).

Treatment Group: 222 Subjects treated with autologous BM MNC using the CardiAMP cell therapy and optimal medical therapy

Sham Control Group: 111 Subjects treated with optimal medical therapy

Roll-in Phase: Maximum of 10 subjects

Total Number of Patients: 343 subjects



Thank you for your kind attention !

Eric Duckers

educkers@biocardia.com
BioCardia San Carlos, CA