Stem Cell Treatment
Testimony of Buddhadeb Dawn, M.D.

Before the Joint Committee on Senate Public Health and Welfare and House Health and Human Services
February 7, 2013

Chairman Pilcher-Cook, Chairman Crum, and members of the Committee, thank you for the opportunity to testify on this important topic.

I am the Maureen and Marvin Dunn Professor and Director of the Division of Cardiovascular Diseases at the University of Kansas Medical Center. I am also the Director of the Cardiovascular Research Institute and Vice Chairman for research in the Department of Medicine at KUMC. I am a clinician-scientist with research interests focused primarily on heart repair by adult stem cells. The research conducted in my laboratory has been funded by the National Institutes of Health and the American Heart Association. I have authored more than 100 original scientific papers, review articles, editorials, and book chapters, including many focused on adult stem cell research and therapy. I am a Fellow of the American Heart Association, the American College of Cardiology, and the American College of Physicians. I serve on various scientific committees, grant review panels, and editorial boards of several prominent cardiovascular journals.

Over the past decade, adult stem cell transplantation has emerged as an effective therapeutic option for organ repair. The evidence from numerous scientific reports, both from animal models and human studies, supports the notion that adult stem cells are able to heal damaged tissues and restore function. Although repair of many organ systems have been tested in this regard, repair of the heart has been studied perhaps in the greatest detail. A paper published in 2001 reported the ability of adult bone marrow stem cells to repair the heart in mice after a heart attack [1]. These researchers injected Lin-/c-kit+ bone marrow cells into the periphery of dead myocardium, and reported improvement in heart function and structure with such therapy. Since then, numerous papers have reported variable degrees of benefit concerning heart structure and function with transplantation of various types of adult stem cells derived from the bone marrow as well as other adult tissues.

This therapeutic promise from animal models was quickly translated in humans in a study conducted in Germany in 2002, in which patient's own bone marrow cells were injected into the coronary artery [2]. Such therapy improved heart function and blood supply to heart muscle in patients with acute heart attack. Since this report, numerous clinical trials have been conducted in patients with both heart attacks and heart failure using several different types of adult stem cells [3]. These include bone marrow mononuclear cells, bone marrow mesenchymal stem cells, circulating progenitor cells, cardiac stem cells, adipose stem cells, and skeletal myoblasts, to name a few. However, the results from these relatively smaller clinical trials that used different types of adult stem cells in highly variable numbers at different time-points after heart attacks have been quite variable.

There are many gaps in our knowledge about how adult stem cells repair the heart - or any other organ for that matter. After a heart attack, a portion of the heart muscle is lost and replaced by scar tissue that cannot pump blood. This leads to dilation of the heart and eventual development of heart failure. When adult stem cells are injected into and around the damaged area, they are thought to facilitate the healing process with various biological substances, form new blood vessels, preserve the remaining heart muscle, and even form new heart muscle cells [4, 5]. However, there is clearly a tremendous

unmet need to study the mechanisms underlying the benefits conferred by the adult stem cells. This knowledge will help shape adult stem cell therapy into more effective regimens.

Besides unraveling the exact mechanisms, from a therapeutic standpoint, it is equally important to critically examine the outcomes of such treatment. In this regard, several parameters of heart function and structure were studied in many clinical trials. However, results from these smaller trials were often discordant, and therefore, we synthesized the current evidence by performing the first comprehensive meta-analysis of pooled data in 2007 [6]. Our analysis showed that therapy with adult bone marrow cells improve heart function, reduce the extent of damaged myocardium, and improve heart structure. These results were further upheld and extended in our subsequent meta-analysis of data from a much larger number of patients that was published in 2012 [7].

Importantly, our results also showed that adult bone marrow cell transplantation reduces all-cause mortality, cardiac mortality, recurrent heart attacks, and stent thrombosis during follow-up [7]. No significant adverse effect of adult bone marrow cell therapy was noted. Moreover, such therapy benefited patients with fresh heart attacks as well as those who developed heart failure due to prior heart attacks. The improvement in outcomes was greater in patients with worse heart function at baseline. Furthermore, there was no difference in most of the parameters based on timing of cell injection, suggesting that adult stem cell therapy may be effective over a rather long period of time after a heart attack. Collectively, these results indicate that bone marrow cell therapy may potentially benefit a large number of patients.

Although the above facts are highly encouraging, even more innovative therapy is being formulated in numerous laboratories and clinics around the world. These novel approaches include: deriving induced pluripotent stem cells from patient's own cells; using genes and biological molecules to make more potent adult stem cells; adding adult stem cells to biomaterials and patches; and expanding the use of adult stem cells to various other health problems. Implementing these endeavors in our region would need a systematic mechanism.

As an individual faculty member with expertise in this area, I think an adult stem cell therapy center may serve to greatly facilitate the delivery of adult stem cell therapy not only in Kansas, but also in a vast geographical territory in the Midwest. Such a center will engage in the production and modification of adult stem cells from various sources in a clinically acceptable clean facility following the Good Manufacturing Practice (GMP) guidelines. A stem cell therapy center will also bring cutting edge adult stem cell clinical trials to Kansas, and promote awareness about the availability of such therapy locally and regionally.

The scope of adult stem cell therapy is certainly not limited to the heart. Indeed, numerous diseases may potentially be treated with adult stem cells. These include: critical ischemia of legs, stroke, spinal cord injury, bone marrow diseases, joint diseases, to name a few from an ever-growing list. Further, adult stem cell therapy may also prove to be cost effective over the long term by curing diseases without significant side-effects.

In conclusion, adult stem cell therapy can potentially cure numerous diseases that pose substantial burden on health care in the US and worldwide. The creation of a systematic mechanism to facilitate adult stem cell therapy in Kansas will benefit patients in a large geographical territory. Such a facility will be instrumental in producing adult stem cells for use in clinical trials, and also in modifying adult stem

cells to make them more potent. Finally, research conducted in such a center will greatly advance our knowledge about adult stem cells and their therapeutic use.

Thank you very much for this opportunity to testify.

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Adult Stem Cell Therapy:
The Future Is Now

Joint Committee on Senate Public Health and Welfare
And House Health and Human Services
Topeka, Kansas
February 7, 2013

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Heart Repair with Adult Bone Marrow Cells

letters to nature

Bone marrow cells regenerate infarcted myocardium

Donald Orlic†, Jan Kajstura*, Stefano Chimenti*, Igor Jakoniuk*, Stacie M. Anderson†, Baosheng Li*, James Pickel‡, Ronald McKay‡, Bernardo Nadal-Ginard*, David M. Bodine†, Annarosa Leri* & Piero Anversa*

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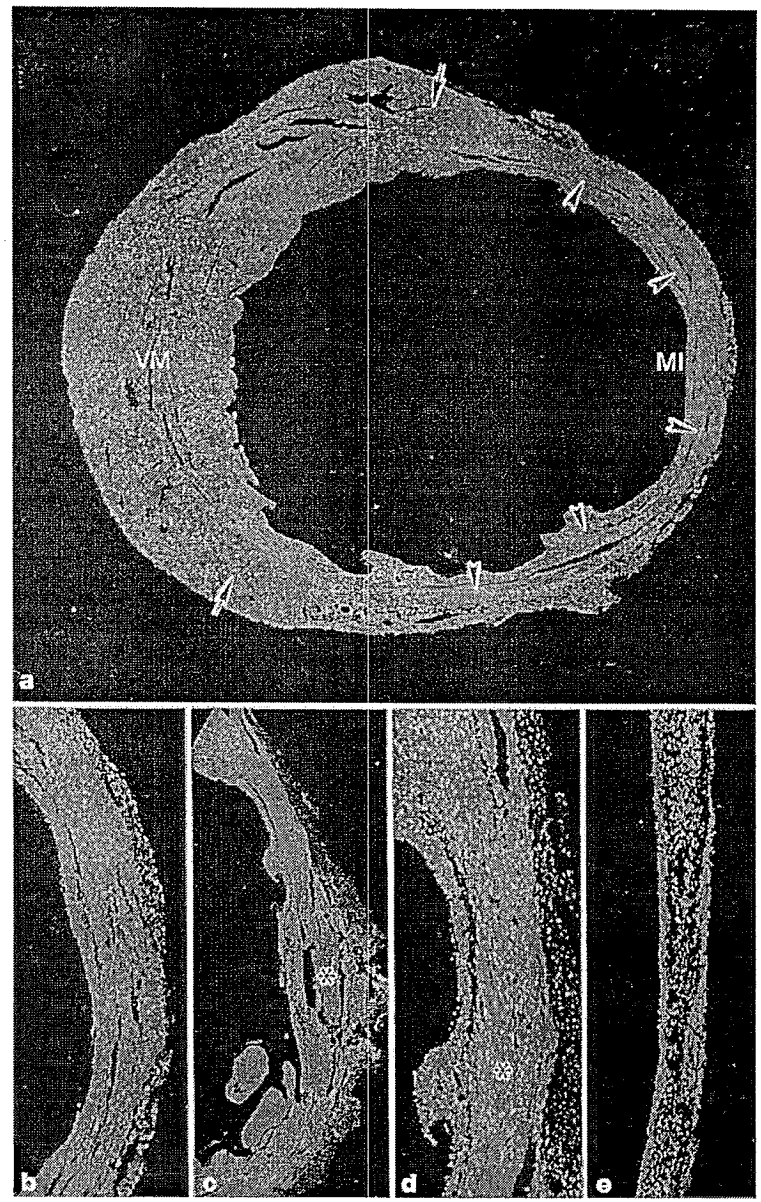


Nature. 2001 Apr 5;410(6829):701-5.

Lin-/c-kit+ BMCs

Repair of Infarcted Myocardium by Autologous Intracoronary Mononuclear Bone Marrow Cell Transplantation in Humans

Bodo E. Strauer, MD; Michael Brehm, MD; Tobias Zeus, MD; Matthias Köstering, MD; Anna Hernandez, PhD; Rüdiger V. Sorg, PhD; Gesine Kögler, PhD; Peter Wernet, MD

Background—Experimental data suggest that bone marrow–derived cells may contribute to the healing of myocardial infarction (MI). For this reason, we analyzed 10 patients who were treated by intracoronary transplantation of autologous, mononuclear bone marrow cells (BMCs) in addition to standard therapy after MI.

Methods and Results—After standard therapy for acute MI, 10 patients were transplanted with autologous mononuclear BMCs via a balloon catheter placed into the infarct-related artery during balloon dilatation (percutaneous transluminal coronary angioplasty). Another 10 patients with acute MI were treated by standard therapy alone. After 3 months of follow-up, the infarct region (determined by left ventriculography) had decreased significantly within the cell therapy group (from 30±13 to 12±7%, $P=0.005$) and was also significantly smaller compared with the standard therapy group ($P=0.04$). Likewise, infarction wall movement velocity increased significantly only in the cell therapy group (from 2.0±1.1 to 4.0±2.6 cm/s, $P=0.028$). Further cardiac examinations (dobutamine stress echocardiography, radionuclide ventriculography, and catheterization of the right heart) were performed for the cell therapy group and showed significant improvement in stroke volume index, left ventricular end-systolic volume and contractility (ratio of systolic pressure and end-systolic volume), and myocardial perfusion of the infarct region.

Conclusions—These results demonstrate for the first time that selective intracoronary transplantation of autologous, mononuclear BMCs is safe and seems to be effective under clinical conditions. The marked therapeutic effect may be attributed to BMC-associated myocardial regeneration and neovascularization. **(*Circulation*. 2002;106:1913-1918.)**

Adult Stem Cells for Heart Repair

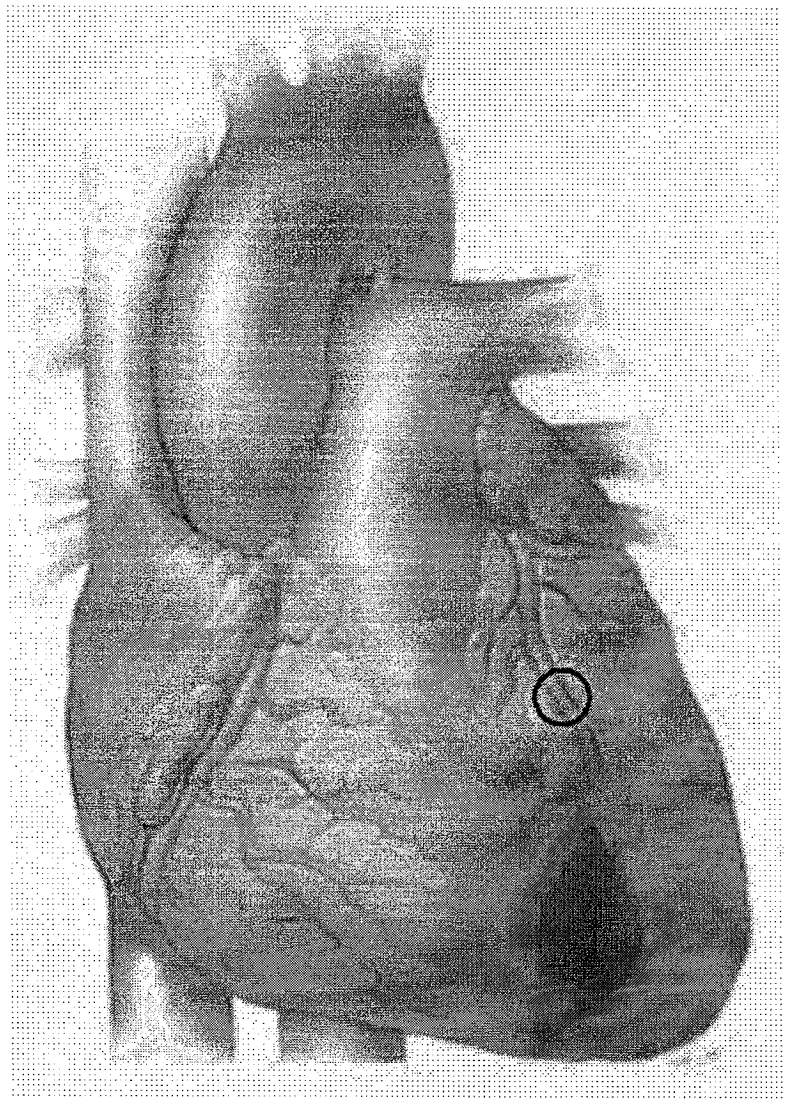
- Bone marrow mononuclear cells
- BM Mesenchymal stem cells (MSCs)
- Circulating progenitor cells (CPCs)

} Numerous clinical trials - completed and ongoing

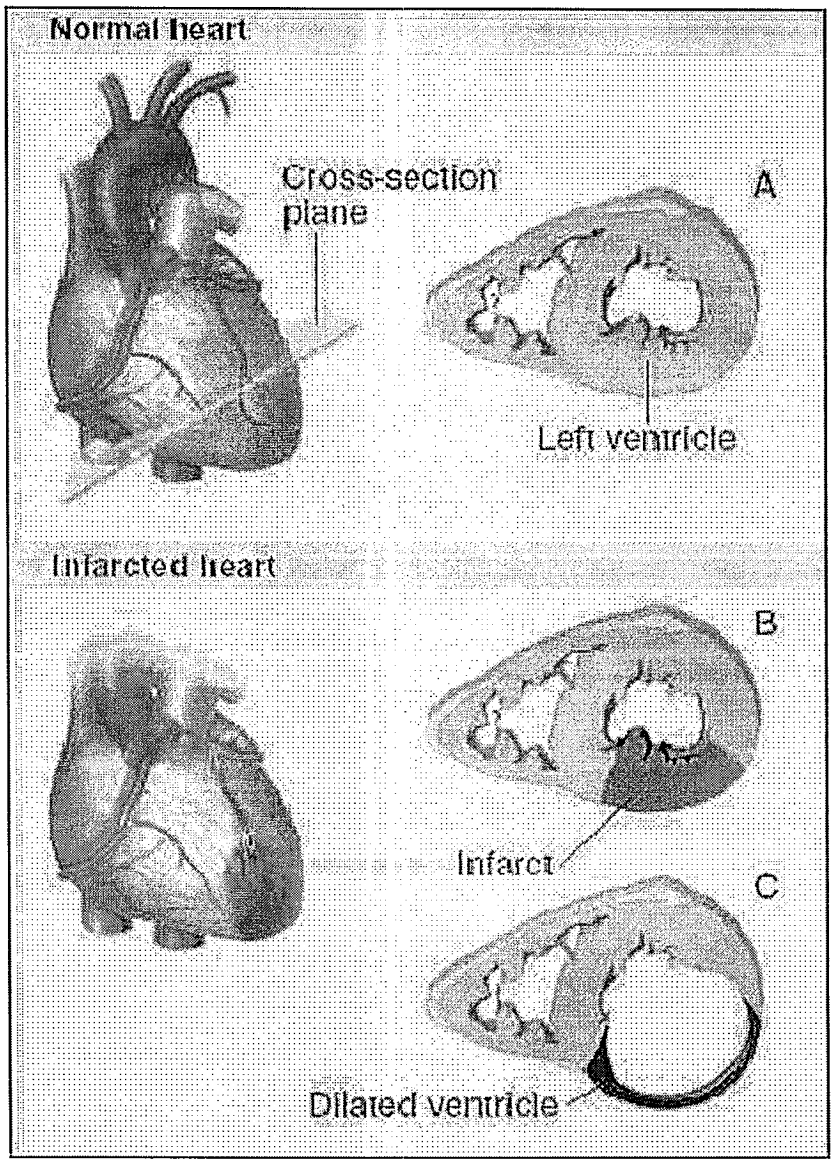
- Cardiac stem cells — 2 clinical trials
- Adipose stem cells — 2 clinical trials
- Skeletal myoblasts — Several clinical trials completed
- Cord blood cells

Individual studies have yielded variable results

Infarcted Heart – Target for Adult Stem Cell Therapy



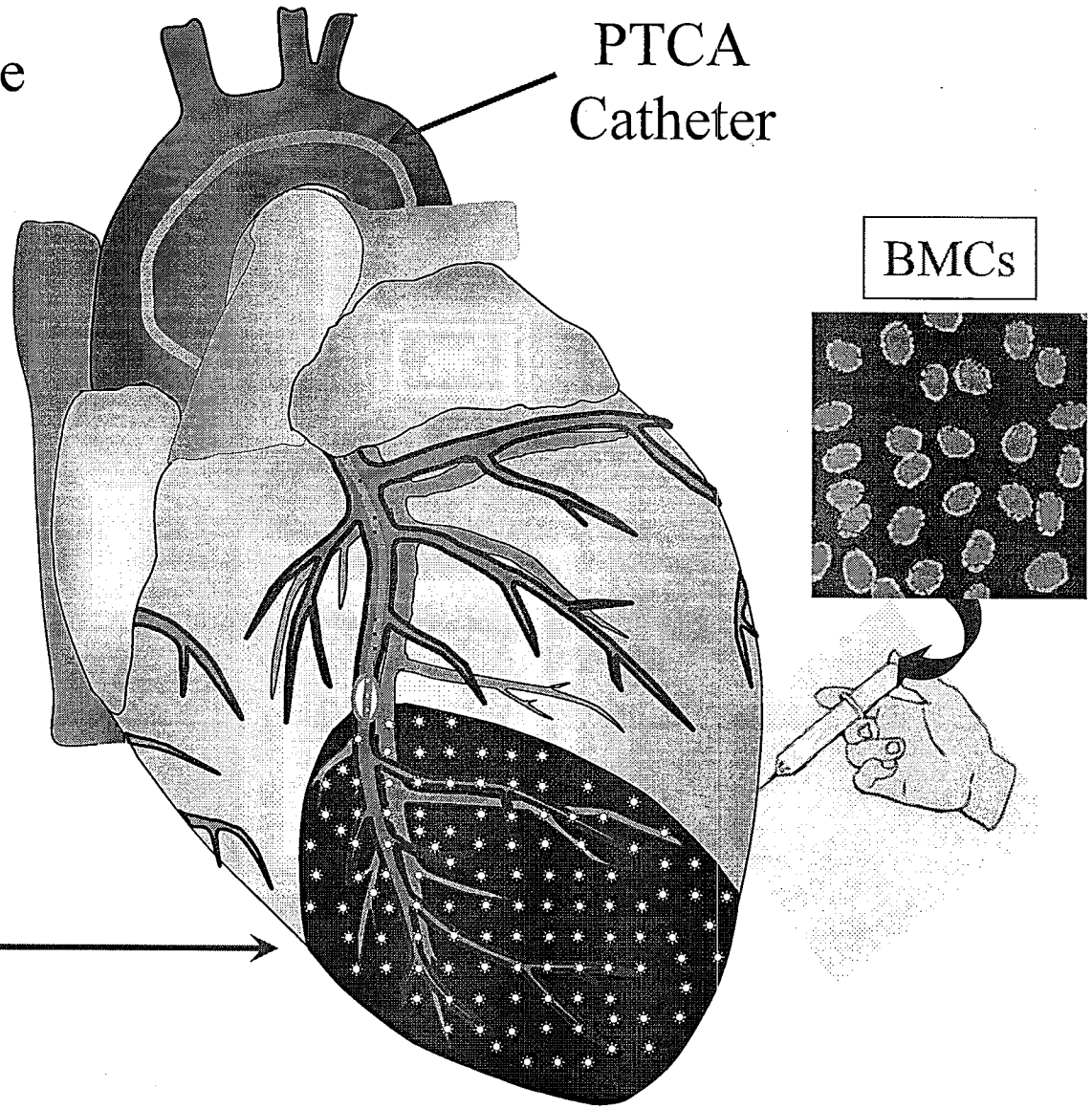
Thygesen *et al.* J Am Coll Cardiol 2012;60:1581-98.



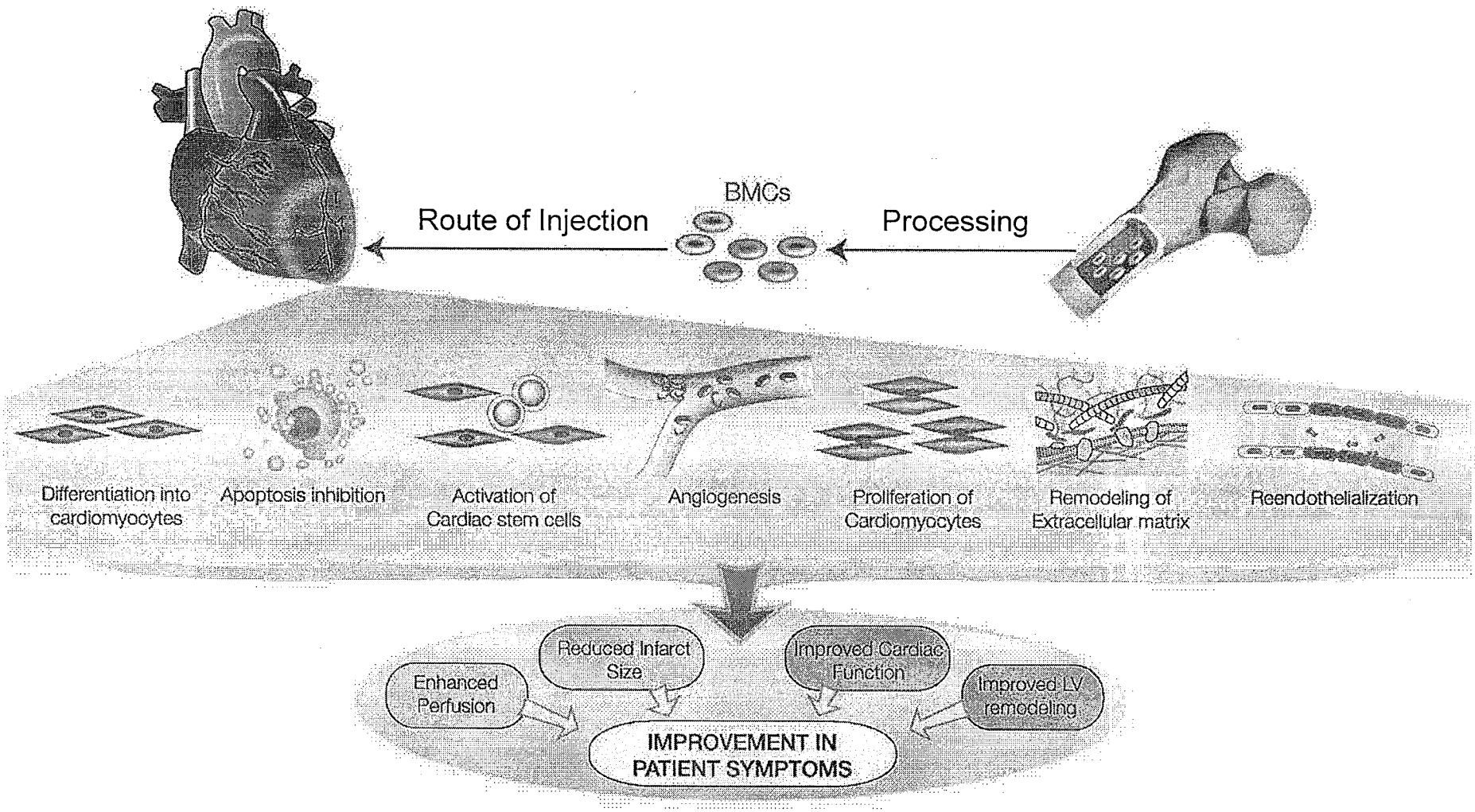
Source: http://www.health-pic.com/complications-of-myocardial-infarction/

Injection of BMCs for Heart Repair in Humans

More than 50 studies have been completed and published



Mechanisms of Heart Repair with Adult Bone Marrow Cells



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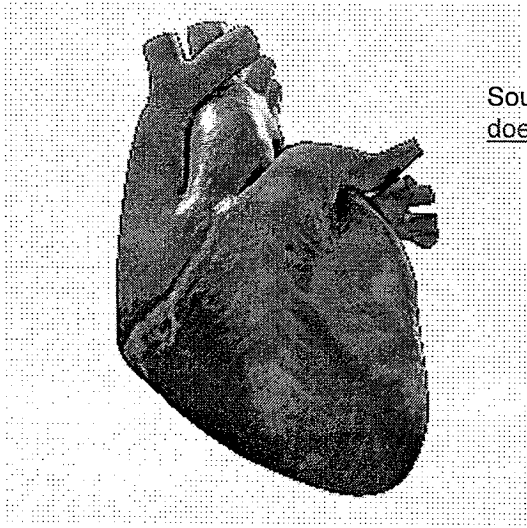
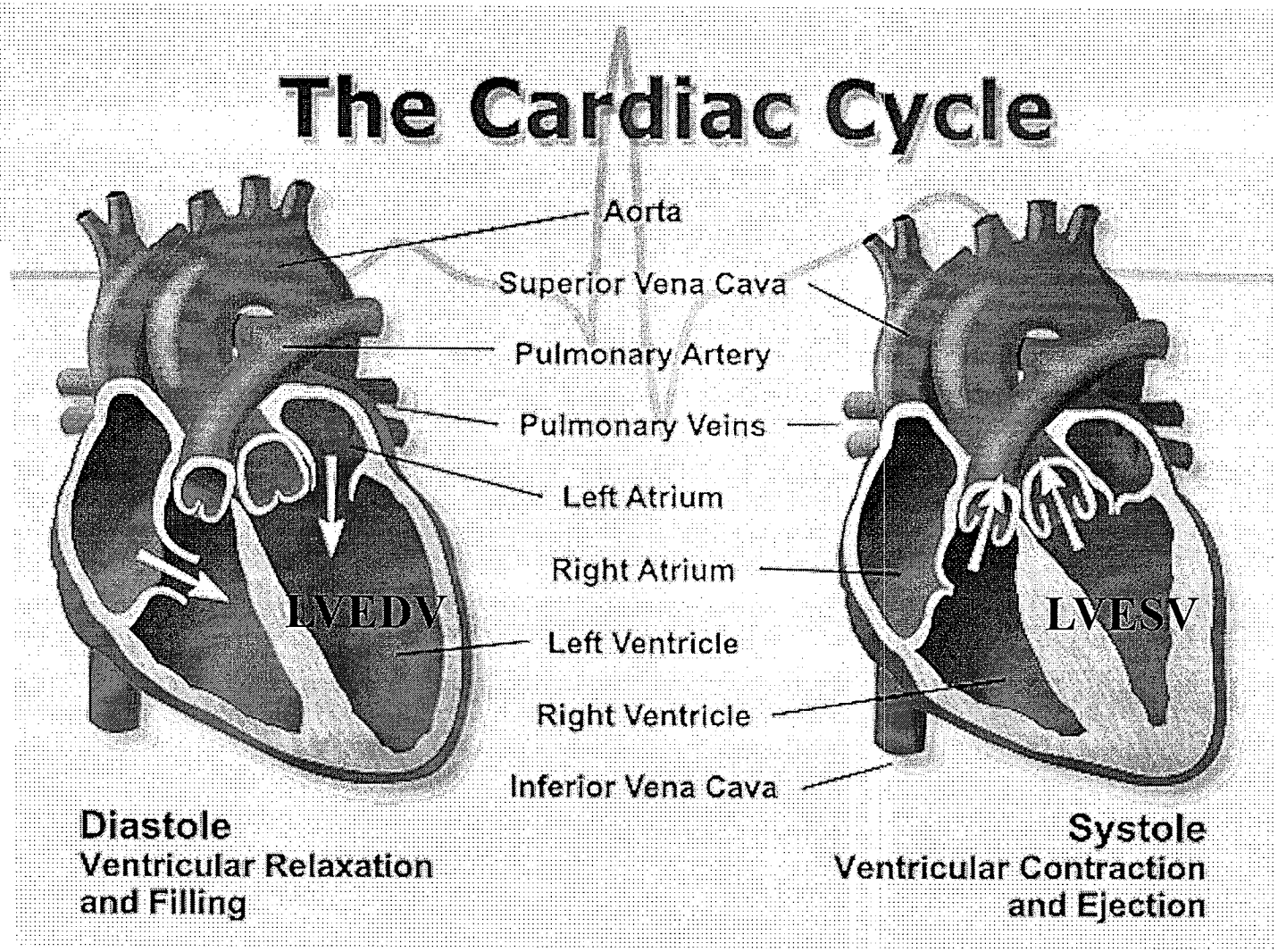


Source: http://drsvenkatesan.wordpress.com/2011/05/21/does-the-lv-ejection-fraction-change-with-every-heart-beat/

Ejection Fraction and Volumes



Source: http://students.cis.uab.edu/atrenina/Physiology.html

Meta-analysis of Adult BMC Therapy Trials

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Adult Bone Marrow Cell Therapy Improves Survival and Induces Long-Term Improvement in Cardiac Parameters : A Systematic Review and Meta-Analysis

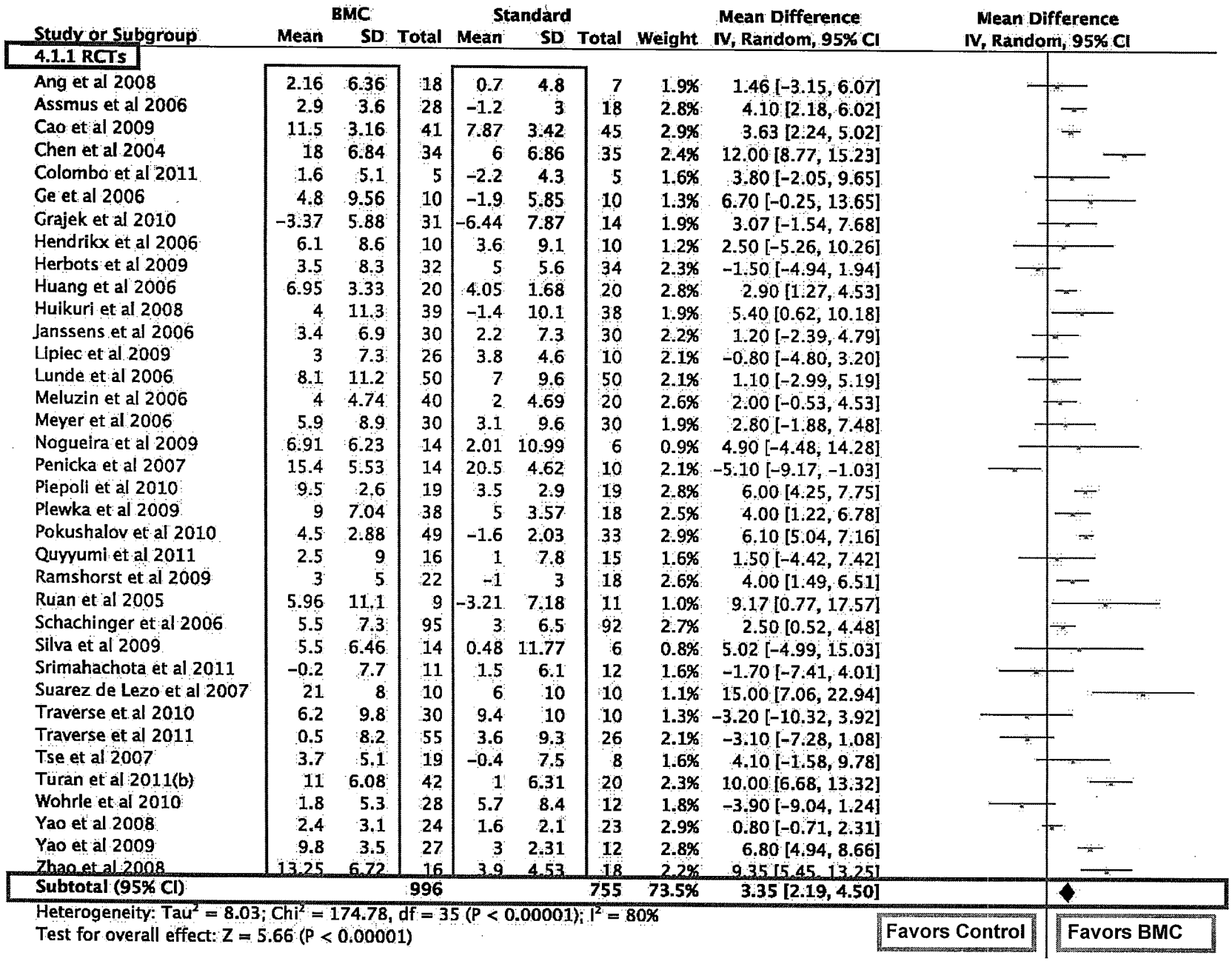
Vinodh Jeevanantham, Matthew Butler, Andre Saad, Ahmed Abdel-Latif, Ewa K. Zuba-Surma and Buddhadeb Dawn

Circulation. 2012;126:551-568; originally published online June 22, 2012;
doi: 10.1161/CIRCULATIONAHA.111.086074

- 50 studies were included in this meta-analysis

- A total of 2,625 patients
  (1,460 BMC-treated and 1,165 control patients)

Mean Change in Left Ventricular Ejection Fraction (heart function)



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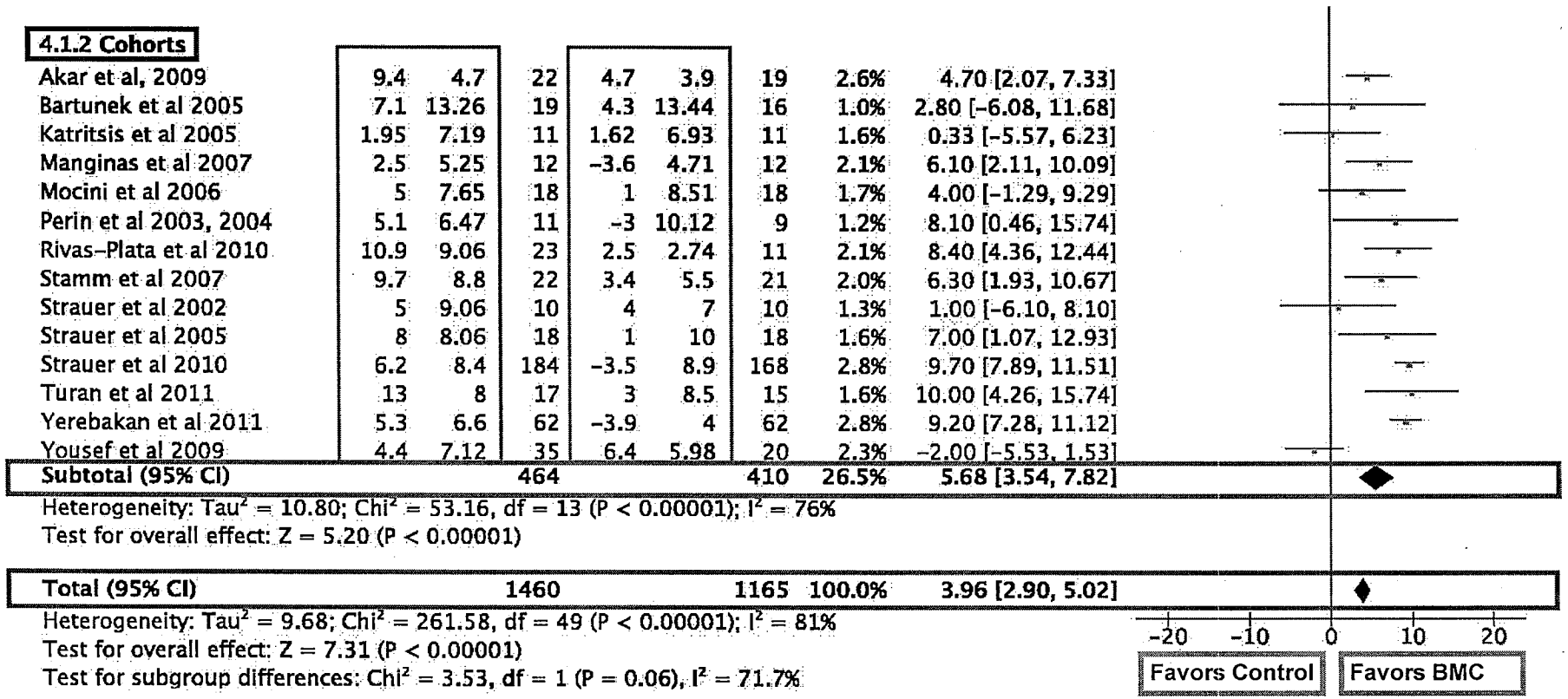


Jeevanantham *et al.* Circulation 2012;126;551-568.

Results of Analysis of Pooled Data

In BMC-treated patients (compared with standard therapy):

- Heart function improved with bone marrow cell injection (by about 4%)

- The extent of scar tissue was smaller (by about 4%)

- Heart volume was smaller (about 5 ml)

- Benefits persisted for >12-24 months

Adult BMC Therapy Reduces Adverse Events During Follow-up

Outcome	Peto OR	95% Confidence Interval	*P* value
All-Cause Mortality	0.39	0.27 to 0.55	<0.00001
Cardiac Deaths	0.41	0.22 to 0.79	0.005
Recurrent MI	0.25	0.11 to 0.57	0.001
Heart Failure	0.52	0.27 to 1.00	0.05
Stent Thrombosis	0.34	0.12 to 0.94	0.04
In-stent Restenosis	0.87	0.47 to 1.62	0.66
Target Vessel Revascularization	0.83	0.55 to 1.23	0.35
CVA	0.28	0.08 to 1.07	0.06
VT / VF	1.14	0.52 to 2.53	0.74

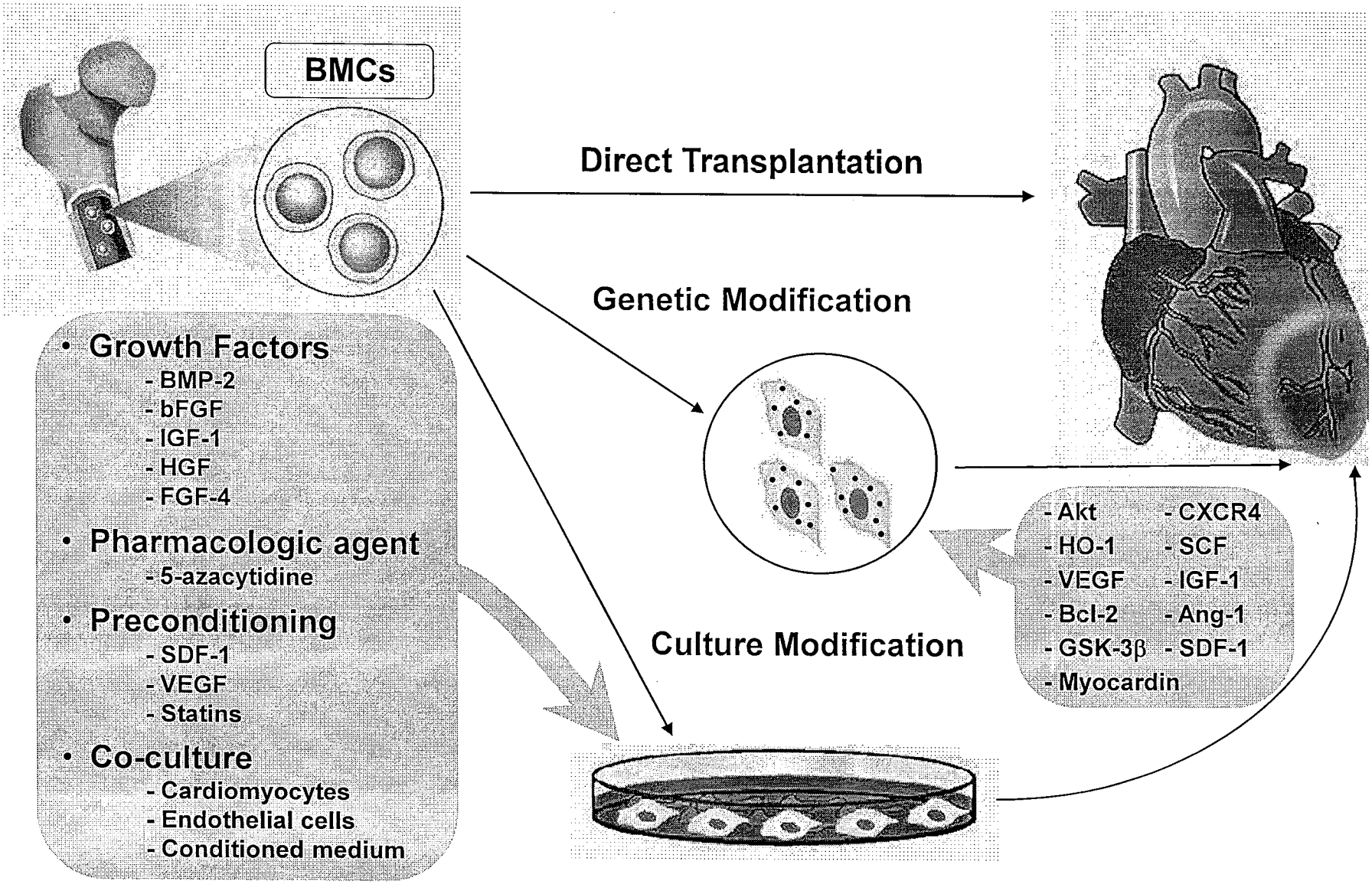
Results of Analysis of Pooled Data

- Adult bone marrow cell therapy benefits patients with acute heart attack, as well as chronic heart failure

- If heart function is worse at baseline, the improvement is greater

- Adult bone marrow cell therapy is effective over a long time interval after heart attack

Future: Modification of Adult BMCs



Chugh *et al*. Minerva Cardioangiol 2009;57:185-202.

Future: Adult-derived Induced Pluripotent Stem Cells

Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]
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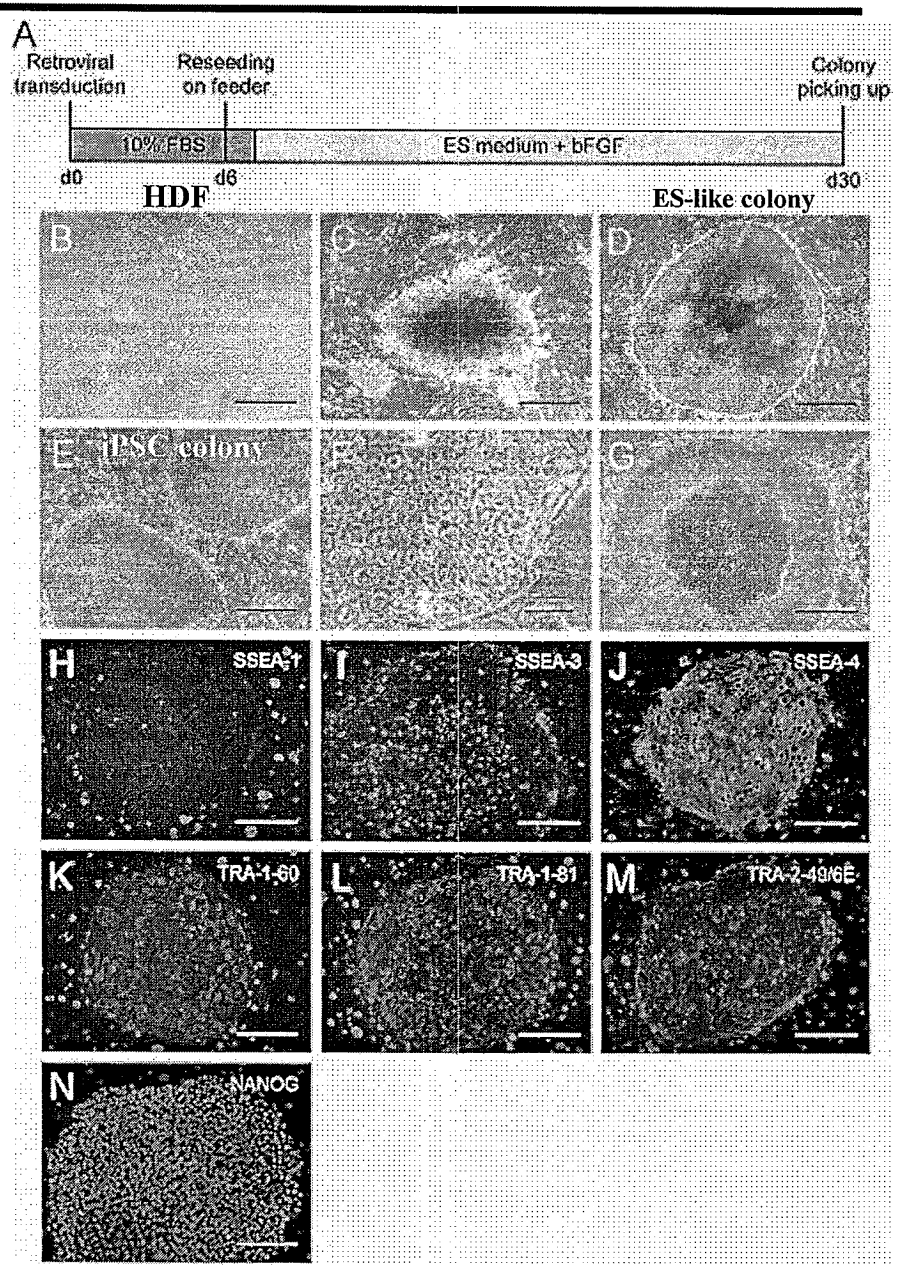
DOI 10.1016/j.cell.2007.11.019

Adult human dermal fibroblasts

Retroviral transfection with
- Oct 3/4
- Sox2
- Klf4
- c-Myc



Takahashi K, et al. *Cell* 2007;131:861-872.

Future: Increasing Targets for Adult Stem Cell Therapy

- Heart attack, heart failure, heart block
- Stroke, spinal cord injury, neuropathy
- Critical limb ischemia
- Cancer therapy
- Curative bone marrow transplant
  (e.g., for myeloma, lymphoma)
- Transplant failure, Graft versus host disease
- Joint diseases
- Cornea repair
- Autoimmune diseases (ulcerative colitis, etc.)

Adult Stem Cell Therapy As Prevention

- The average total cost of a single heart transplant in 2007 was $658,800. (source: Transplant Living)
http://www.ehow.com/about_4673173_much-does-heart-transplant-cost.html

- The estimated research cost of adult stem cell therapy in certain ongoing clinical trials is approximately $20,000 (± depending on procedures, etc.) per patient.
Note: The 'real world' costs may vary.

How An Adult Stem Cell Therapy Center May Help

- Producing autologous patient-specific adult stem cells locally

- Ensuring access to cutting-edge adult stem cell therapy for Kansans

- Help Kansas investigators initiate stem cell trials

- Enable cellular engineering with genes, molecules, and such

- Promote awareness about adult stem cell research and therapy

Conclusions

- Adult stem cell therapy can potentially cure diseases that are major health care problems
- The ability to process and manufacture clinical grade adult stem cells is a key requirement
- A systematic mechanism to deliver adult stem cell therapy will benefit patients in a large geographic territory
- This will also help generate new knowledge in adult stem cell therapy

THANK YOU