# The Role of Adult Bone Marrow Stem Cells in the Heart Muscle Tissue Repair

Word Count: 4663

## Abstract

**Introduction:** Heart attacks are a significant issue for the elderly. Current methods for treating heart attacks do not account for the weakening of the heart muscle tissue following a heart attack. Studies have looked into the potential usage of bone marrow stem cells to regenerate heart tissue after heart attacks.

**Methods:** Systematic review was conducted on 15 peer reviewed studies and data was collected from the longest time between the procedure and follow up exam. Safety and efficacy were the primary factors that were considered Main endpoints taken were patients infarcted area, ejection fraction, end systolic volume, and end diastolic volume. Adverse effects and methods to obtain cardiac function data were also considered.

**Results:** Of the 915 patients analyzed in 15 different studies, there was an average change in ejection fraction of 5.85% in treatment groups and -0.41% in control groups which was a significant difference with an average p value of 0.022. End systolic volume significantly decreased (p=0.048) 12.46 mL in treatment groups and increased 5.00 mL in control groups. End diastolic volume had no significant change (p=0.65) in either group at -2.38 mL and 4.15 mL in treatment and control groups respectively. Infarcted area was not measured in most studies. Out of the five studies who did measure it, treatment groups had a 8.5% decrease and control groups a 3.4% decrease (p=0.078). Adverse events were more frequent in control groups; however, the difference was not significant (p=0.41).

**Conclusions:** The implementation of bone marrow stem cell therapy for repair of heart muscle tissue is feasible and safe . Ejection fraction frequently increases in treatment groups. Further studies need to be conducted to involve larger patient populations and more consistent and longer follow up examinations. Additionally, further studies should look into using alternative methods to measure and provide evidence for cardiac regeneration.

## Key Terms

Bone marrow stem cells, heart therapy, heart attack, infarction

## Introduction

Myocardial infarctions, or heart attacks, affect over seven million people in the US per year (Mozaffarian *et al* 2015). People affected by heart attacks suffer from chest pain, fatigue, and an abnormal heartbeat. These are caused by blood clots restricting blood flow to the heart, cutting off oxygen supply to the heart. As a result of deoxygenation, some heart tissues that were initially receiving oxygen from the now clotted artery die. These heart attacks cause long term damage to the muscle tissue in the heart and further increase heart risk through negative restructuring of the heart (Assmus *et al* 2006). Weakening of the heart muscle involves an increase in end systolic volume, the amount of blood remaining in the heart after a contraction, and a decrease in end diastolic volume, the amount of blood which fills into the heart when it lowers its pressure and relaxes. The heart then must work harder in the form of higher beats per minute (bpm) to provide adequate blood supply to the body. However, the strains this places on the heart and causes it to have a decreased lifetime and become more susceptible to further heart complications (Assmus *et al* 2006). The primary difficulty to effective recovery of the heart muscle is the limitation of cardiac tissue cells to proliferate, or multiply. Unlike muscle tissue which has a natural regenerative mechanism, cardiac tissue is difficult to heal following damage. Although there has been evidence showing limited replacement of cardiomyocytes, this rate is not sufficient enough to counteract the damage of cardiomyocytes of a myocardial infarction (Bergmann *et al* 2009).

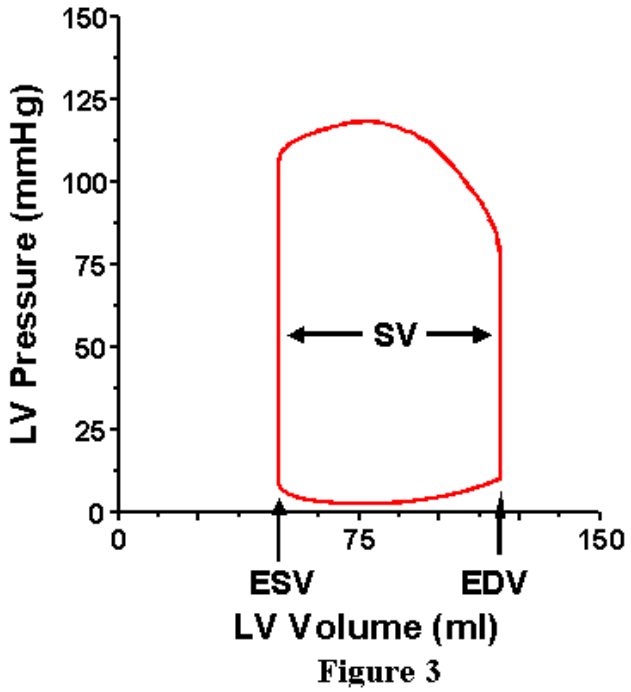



**Figure 1:** Depiction of end systolic volume (ESV) and end diastolic volume (EDV) compared with pressure in the heart. From *Mechanical Properties of the Heart I & II*

The primary causes of blocked or restricted arteries is the buildup of cholesterol. This is known as atherosclerosis and refers to a blockage in any artery throughout the body, while coronary heart disease, the main subject in this paper, is the focus for the blockage in arteries in or leading to the heart. The heart contains two to four billion cardiomyocytes, a number of which may die as a result of cardiac ischemia or reduced blood flow to the heart. If not treated quickly, this can lead to further damage in the form of a myocardial infarction which can cause about twenty five percent of cardiomyocytes to die and accumulate necrotic, or dead tissue (Laflamme & Murry 2011). The necrotic tissue further harms the patient as it does not pump blood as effectively as before.

Current methods to treat heart attacks include the use of drugs, balloon angioplasty, and surgery. Drugs such as Aspirin are used to thin the blood to allow blood to more easily flow through

arteries covered in plaque; balloon angioplasty involves implanting a long, thin tube with a balloon at the tip into the artery and inflating the balloon at the clot site to press plaque against the artery wall; and finally, surgery either creates new pathways for blood to reach the heart through bypass surgery or replaces a damaged heart valve with an artificial one by artificial heart valve surgery. Other surgical procedures include transplanting cardiomyocytes, muscle cells of the cardiac muscle, or skeletal *myoblasts*, muscle cells of the skeletal muscle group. Although these surgeries have been successfully implemented, they could not reconstruct healthy myocardial tissue or reintegrate arteries structurally into the heart. Current methods, however, only address the cause of the clot to treat the heart attack, but do not repair the permanent damage done to the heart. Necrotic tissue is not repaired and further hinders cardiac function. Healthy heart function may not be restored or only restored in a minor degree, in that around 60% of patients after myocardial infarction experience left ventricular remodeling, or changes in the shape, size, function, and structure of the heart (Pfeffer & Braunwald 1990). To address these issues, recent studies look into the usage of stem cells to restore function to those infarcted areas in the heart. The treatment aims to prevent remodeling by reconstruction of the structure of the heart which in turn would lead to functional recovery. This treatment is preferably used as a supplement to other treatments available to treat ischemic heart failure (Strauer *et al* 2011).

Stem cells are cells which are capable of differentiating, cloning, or self replicating into other types of cells. They aim to replace dead or damaged normal cells to keep the organ or tissue healthy and functional. The stem cells themselves are unspecialized, but instead give rise to specialized cells. These cells are necessary in every organism because blood, nerve, or muscle cells are unable to replicate themselves. There are many areas around the body where stem cells can be derived; for example, in circulating blood, lipid cells, or bone marrow (Chen *et al* 2004). Adult bone marrow stem cells (BMC) have been predominantly used in trials involving cardiac repair (Stamm *et al 2003,* Grajek *et al* 2009). Bone marrow stem cells contain several cell populations that have the ability to differentiate into

specialized cell types (Strauer *et al* 2011). Most notable among these are, mesenchymal cells (MSC) and hematopoietic stem cells (Heldman *et al* 2014). This allows bone marrow stem cells to have the highest capability to differentiate to become myocardial tissue more than any other cells. Another advantage of deriving stem cells from the bone marrow is its easy accessibility through minimally invasive surgical procedures and renewable populations. On the other hand, bone marrow stem cell quality varies between hosts which may have an impact on the ability for the cells to achieve desired effects (Hare *et al* 2009). A subpopulation of bone marrow stem cells, mesenchymal stem cells, are very similar to bone marrow stem cells and have shown relative success in clinical trials (Heldman *et al* 2014). Some experimental studies demonstrate improvement in left ventricular function in patients (Hare *et al* 2009). However, those same studies question the safety of mesenchymal stem cells regarding tumors, abnormal tissue growth, and organ toxicity.

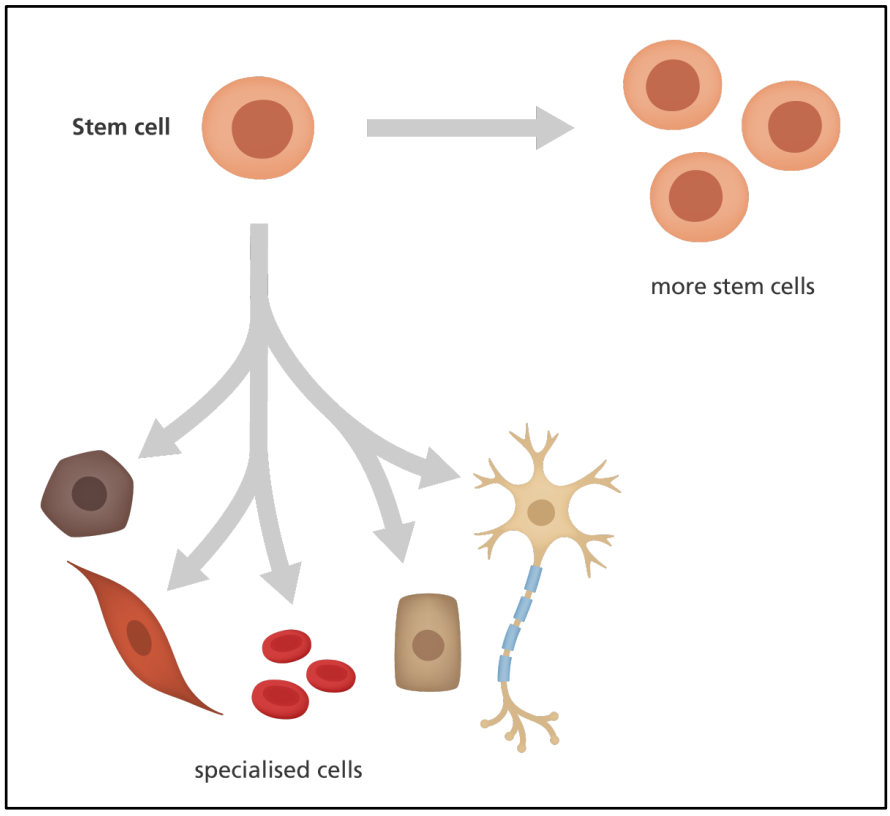



**Figure 2:** Illustrates stem cell function to be able to replicate or differentiate into specialized cells. From *What is a Stem Cell?*

The most commonly used method for stem cell therapy is by intracoronary injection (Perin *et al* 2011). Stem cells are first harvested from the patient and treated and cultured in a lab setting. The finished solution is loaded into a syringe and injected through coronary arteries to reach infarcted areas. Using this method, a balloon catheter is used in a stow-flow technique to ensure high pressure infusion of stem cells into the infarcted zone.

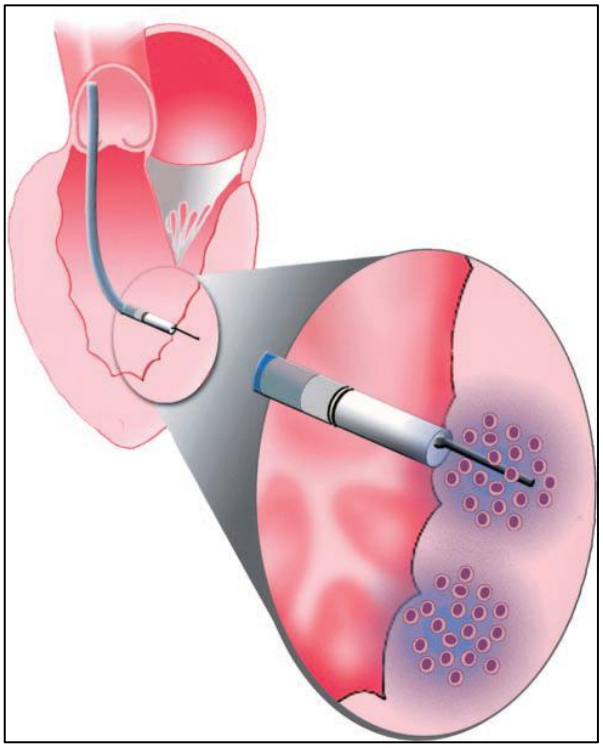


**Figure 3:** Method of injection through intracoronary injection of stem cells. From Perin *et al* 2003

By using the patient's own bone marrow stem cells, the procedure is more likely to succeed. If using donated stem cells, the cells would need to comply with the original owner's proteins on the cells, called human leukocyte antigens (HLA). There is a chance of the patient's body rejecting donor stem cells which would cause further damage. Although this may lead to more complicated and extensive

procedures in this therapy, donated stem cells are significantly more risky in that they might cause an immune response which would attack the donated cells in the patient's body.

Research and data collection was conducted by analyzing clinical trial information from peer reviewed papers. Previous studies have shown success with using stem cells. Various studies show that injecting bone marrow stem cells into the heart have regenerated damaged myocardium tissue using endpoints of cardiac function. Studies' measurements were taken by comparing blood ejection velocity, infarcted region area, end systolic volume, and end diastolic volume of treatment groups with control groups. The first examinations of stem cell potential began with Krause *et al* (2001) and Orlic *et al* (2001) who examined the potential for bone marrow stem cells to grow and differentiate in animals. Positive results which showed great potential for stem cell regeneration led researchers Strauer *et al* (2002) to test the potential for bone marrow cells to be used for recovery after myocardial infarction in clinical trials. They were one of the first to use intracoronary injection to deliver stem cells. Their promising findings led to number of other clinical trials such as Chen *et al* (2004) and Britten *et al* (2003). However, other researchers Stamm *et al* (2003) and Wollert (2004) emphasized the importance of randomized studies to ensure unbiased results. Furthermore, Assmus *et al* (2006) utilized a separate method and "criss-crossed" patients so that each patient underwent both stem cell therapy and also acted as controls at different times of the trials to eliminate any potential correlation of patient characteristics with results. This type of study allowed all patients to undergo both types of treatments, showing that the use of bone marrow stem cell treatment was effective for both groups.

However, more recent studies have shown variable success with using bone marrow stem cells. The main issue with current research is the lack of clinical trials that examine long term effects of this treatment. Few studies continue doing follow up examinations longer than a year after the procedure. A study by Grajek *et al* (2009) showed a trend toward increasing ejection fraction after a six month follow up but has noticed a trend toward a plateau in improvement after twelve months. Ejection fraction, end

systolic volume, and end diastolic volume did not differ significantly between the bone marrow stem cell group and control group in their small randomized trial. Additionally, Srimahachota *et al* (2011) conducted a trial and found little statistical significant improvement in cardiac function between their control and treatment groups. On the contrary, Yerebakan *et al* (2011) performed a study with variable follow up examination times of mean 65 ± 21 months in the stem cell group and mean 62 ± 9 months in the control group. In this extended study, the researchers showed long term improvement in ejection fraction in using stem cell therapy. It also demonstrated the safety of using this type of treatment. Those results were replicated by Rodrigo *et al* (2013) in their five year extended study which demonstrated the safety of using stem cell therapy in both the short term and long term.

There are a few ways researchers measure cardiac function in their studies. The most common method used is echocardiography, a type of test which uses ultrasound to create an image of the heart. This allows the researcher to see blood flow as well as heart wall movement. Another method, angiography, involves injecting a radiopaque substance into the bloodstream and then X-raying the patient at around two to three frames per second in order for the the researcher to evaluate the flow of blood in the vessels. Repetitive imaging cannot be done on the heart as the patient must be completely still during this procedure. Cardiac magnetic resonance imaging (MRI) uses strong magnetic fields to produce images of organs around the body, in this case the heart. Single-photon emission computed tomography (SPECT) involves injecting a radioisotope into the patient's bloodstream that emits gamma rays to be detected by a scanner,allowing a full three dimensional image of the heart.

Bone marrow stem cells have great potential to restore a patient's heart to its maximum functionality. Without proper stem cells treatment, the heart's performance will be hindered by the infarcted tissue region. Patients who have already experienced a heart attack are more likely to experience another heart attack as a result of inefficient heart function. Since older studies have shown promise with using stem cell treatment, more recent research has been conducted to examine the

potential applications of using bone marrow stem cells in animal experimentation (Behfar *et al* 2010), direct experimentation on humans (Bartunek *et al* 2013, Turan *et al* 2012, Srimahachota et al 2011), and aggregate analysis of data sets (Abdel-Latif *et al* 2007). This paper focuses on expanding the studies conducted on humans with more recent literature. This will reveal the potential of bone marrow stem cell therapy to treat patients.

## Purpose

The purpose of this study is to analyze the feasibility of using bone marrow stem cells to treat patients who have suffered heart attacks. The goal is to regenerate or reform infarcted tissue areas of the heart to restore it to its maximum function.

A major issue for heart attacks is the repeated damage to the heart muscle which weakens it for further use. The tissue necrosis caused by heart attacks causes deoxygenation in certain heart tissues and could lead to further heart problems. By using bone marrow stem cells, tissue necrosis can be repaired, and the heart can function at an improved capacity. As a result patient quality of life can be improved without further complications regarding their heart.

## Research Question

How does the use of bone marrow stem cell therapy affect cardiac function and regeneration of cardiac tissue following a myocardial infarction?

## Hypothesis

Stem cells from bone marrow can successfully be used in humans to repair infarcted heart tissue and improve cardiac function damaged by myocardial infarction.

By using stem cell therapy, ejection fraction and infarcted areas should decrease when compared to control groups. End systolic volume should also decrease and end diastolic volume should increase.

## Null Hypothesis

Stem cells from bone marrow are unable to be feasibly used to repair infarcted heart due to cost, functionality, or effectiveness. The treatment is not able to make a significant enough change in ejection fraction, end systolic volume, and end diastolic volume.

## Methods

This research was conducted by systematic literature review. Data was obtained by using other researchers finished experiments and clinical trials found on various online databases such as Ebscohost, PLOS journal, university libraries, and Google Scholar. Only data taken from trials conducted on humans using bone marrow stem cells treating myocardial infarction is used. Data from experimentation on animals for this subject is not used. Primary focus is given to human clinical trials due to the potential for this technique to be used in the medical field.

Data was obtained by taking peer reviewed papers and clinical trials to see the effects of implementing bone marrow stem cells in infarcted regions. It was recorded by taking the total number of patients in the control groups and treatment groups and comparing it to the success rate and possible side effects. If there is a high success rate and few side effects, then the current methods of implementing bone marrow stem cell therapy is sufficient and feasible.

If a patient died during the trial and before follow up exam, their results were excluded. There were very few cases were patients died due to health complications and those did not skew analysis of safety in using stem cell therapy. Adverse effects in treatment groups were compared to the control group to determine safety of this procedure.

Data collection includes change in ejection fraction, end systolic volume, end diastolic volume and infarcted area size. When multiple follow up studies were examined, data with longest follow up duration was taken for data examination. This is to fully examine the long term effects of the stem cell injection. Similar to other meta analyses such as Abdel-Latif *et al* (2007), weight data was taken for each study according to total number of patients in the study divided by total patients in the systematic review. Weight was incorporated in calculating averages of ejection fraction, end systolic volume, and end diastolic volume. Infarcted area was not calculated using weighted averages as there was too much omitted data.

Statistical analysis was performed using a t-test. All tests except for number of adverse events were considered to be two tailed as adverse events can only be positive. The data was considered statistically significant when $p<0.05$. Additionally, confidence intervals were based on 95% confidence. Used populations were based on total patients in control and treatment groups.

**Selection Criteria**

The studies were selected in the systematic review based on the following criteria:

1. The scholarly paper was peer reviewed
2. The study had a control group
3. The study was conducted post 2009
4. The study included patients who experienced recent cardiac ischemia or myocardial infarction prior to treatment
5. The study must involve autologous stem cells and were transplanted in human patients

## Results

**Table 1**: The chart displays all studies included in the data analysis, their number of patients in control groups and treatment groups, time from treatment to follow up exam, and adverse events in each group. Weight of each study is also included. Abbreviations: MSC: Mesenchymal stem cells, BMC: Bone marrow stem cells. Abbreviations include all further graphs.

| Study Analyzed | Number of patients in study (control, treatment) | Time elapsed to follow up examination | Number of Adverse Events in Control Group | Number of Adverse Events in Treatment Group | Weight |
|---|---|---|---|---|---|
| Heldman *et al* (2014) (MSC) | 11,19 | 12 months | 4 | 8 | 3.14% |
| Heldman *et al* (2014) (BMC) | 10,19 | 12 months | 4 | 10 | 3.04% |
| Perin *et al (2012)* | 27,52 | 6 months | 0 | 0 | 8.06% |
| Grajek *et al* (2009) | 12,27 | 12 months | 8 | 9 | 4.08% |
| Piepoli *et al* (2010) | 19,19 | 12 months | 9 | 7 | 3.98% |
| Quyyumi *et al* (2011) | 15,16 | 6 months | 4 | 7 | 3.25% |
| Bartunek *et al* (2013) | 15,21 | 6 months | 2 | 1 | 3.77% |
| Turan *et al* (2012) | 20,42 | 12 months | 0 | 0 | 6.49% |
| Srimahachota et al (2011) | 12,11 | 6 months | 0 | 0 | 2.41% |
| Pokushalov *et al* (2010) | 33,49 | 12 months | 21 | 6 | 8.59% |
| Traverse *et al* (2010) | 10,30 | 6 months | 0 | 1 | 4.19% |
| Yerebakan *et al* (2011) | 14,26 | 32-99 months | 2 | 2 | 4.19% |
| Strauer *et al* (2010) | 168,184 | 60 months | 32 | 7 | 36.86% |
| Perin *et al* (2011) | 10,20 | 6 months | 0 | 0 | 3.14% |
| Rodrigo *et al* (2013) | 38,8 | 12 months | 4 | 1 | 4.82% |
| Total | 412,543 | - | 90 | 51 | 100% |

A total of 955 patients were analyzed with 412 patients in control groups and 543 patients in treatment groups. Yerebakan *et al* (2011) had patients in the treatment group a mean follow up time of

65±21 months and a control group mean follow up time of 62±9 months. The total mean follow up for both groups is 64 months. Average follow up time for all groups included in this study was 16.3 months with a standard deviation of 18.8 months, which was heavily swayed by the two studies, Yerebakan et al (2011) and Strauer et al (2010).

Of all control groups combined, there were 90 total adverse events in patients. In treatment groups, there were 51 adverse events in patients. P value for difference in adverse events is 0.41, which is insignificant. Adverse events were defined as death or cardiac complications involving necessary treatment or hospitalization. Approximately 22% of patients in control groups and 9% of patients in treatment groups experienced an adverse event. Perin *et al* (2011) did not directly state number of adverse events but claimed that the number of adverse events "could not be reliably assessed due to paucity of events" and was therefore assumed to be 0 for both treatment and control groups.

Quyyumi *et al* (2011) performed a study with variable amounts of stem cells to different patients groups. Groups were arranged in a control group and three treatment groups, where the treatment groups had five million, ten million, and fifteen million cells injected in different groups. Data was collected by compiling all treatment groups together into a singular treatment group to be compared with other studies as many other studies did not conduct their experiment this way.

All studies in some form measured baseline characteristics in their treatment and control groups. There is a large range of ejection fraction (22.7-53.2%), end systolic volume (46-189.9 mL), and end diastolic volume(46-283.2). Average ejection fraction was 37.8±7.4% and 37.5±6.6% in control and treatment groups respectively. Average infarcted area in control and treatment groups was 25.4±11.4% and 29.1±7.9%. Average end systolic volume in control groups was 98.4 ±46.1 mL and 103.4±48.0 mL in treatment groups. Average end diastolic volume was 148.1±58.5 mL in control groups and 150.5±60.7

mL in treatment groups. Ejection fraction, infarcted area, end systolic volume, and end diastolic volume differences between groups was not significant

**Table 2**: Average baseline characteristics of all studies included. Omitted data was not found due to the authors not including or measuring it.

| | **Control** | | | | **Treatment** | | | |
|---|---|---|---|---|---|---|---|---|
| **Study Analyzed** | **Ejection fraction (%)** | **Infarcted area (%)** | **End systolic volume (mL)** | **End diastolic volume (mL)** | **Ejection fraction (%)** | **Infarcted area (%)** | **End systolic volume (mL)** | **End diastolic volume (mL)** |
| Heldman *et al* (2014) (MSC) | 28.1 | 27.5 | 189.9 | 261 | 35.7 | 25.9 | 186.9 | 283.2 |
| Heldman *et al* (2014) (BMC) | 36.2 | 23 | 153.9 | 153.9 | 35.9 | 25.5 | 170.3 | 170.3 |
| Perin *et al (2012)* | 30.2 | 11.8 | 65 | | 32.4 | 25.1 | 57.9 | |
| Grajek *et al* (2009) | 42.69 | | 60.64 | 120.3 | 45.39 | | 66.56 | 130.83 |
| Piepoli *et al* (2010) | 37.5 | | 76.5 | 119.2 | 36.6 | | 80.1 | 124.4 |
| Quyyumi *et al* (2011) | 53.2 | 16.6 | 76.1 | 154.7 | 47.6 | 22.7 | 88.1 | 165.8 |
| Bartunek *et al* (2013) | 27.8 | | | | 27.5 | | | |
| Turan *et al* (2012) | 45 | 29 | 73 | 132 | 43 | 31 | 78 | 129 |
| Srimahachota et al (2011) | 42.2 | 44.6 | 138 | 189 | 36.3 | 44.3 | 154 | 154 |
| Pokushalov *et al* (2010) | 26.8 | | 149 | 239 | 27.8 | | 146 | 243 |
| Traverse *et al* (2010) | 37.4 | | 40 | 77 | 38.9 | | 46 | 88 |
| Yerebakan *et al* (2011) | 40.5 | | | 58.6 | 41.1 | | | 55.7 |
| Strauer *et al* (2010) | 36.1 | | 118 | 184 | 29.4 | | 128 | 184 |
| Perin *et al* (2011) | 39 | | 81.4 | 132.2 | 37 | | 92.9 | 133.2 |
| Rodrigo *et al* (2013) | 45 | | 58 | 105 | 48 | | 50 | 95 |

Three studies (Srimahachota *et al* 2011, Traverse *et al* 2010, Perin *et al* 2011) used a combination of techniques to measure cardiac efficacy as shown in the table below. Other studies primarily used echocardiography. Echocardiography data was taken from studies who used multiple tools of measurement because the majority of other studies also used echocardiography.

## Methods of Measurement

**Table 3**: The chart lists each study's method of measuring cardiac function (ejection fraction, end systolic volume, diastolic volume). Bolded methods indicates measurement used in this data collection. Abbreviations: CMRI:Cardiac Magnetic Resonance Imaging, SPECT: Single photon emission computed tomography.

| Study Analyzed | Method of measurement |
|---|---|
| Heldman *et al* (2014) (MSC) | Echocardiography |
| Heldman *et al* (2014) (BMC) | Echocardiography |
| Perin *et al (2012)* | Echocardiography |
| Grajek *et al* (2009) | Echocardiography |
| Piepoli *et al* (2010) | Echocardiography |
| Quyyumi *et al* (2011) | CMRI |
| Bartunek *et al* (2013) | Echocardiography |
| Turan *et al* (2012) | Angiography |
| Srimahachota et al (2011) | CMRI, **Echocardiography**, and Angiography, |
| Pokushalov *et al* (2010) | Echocardiography |
| Traverse *et al* (2010) | **Echocardiography**/CMRI |
| Yerebakan *et al* (2011) | MRI |
| Strauer *et al* (2010) | Angiography |
| Perin *et al* (2011) | SPECT, **Echocardiography**, and Angiography |
| Rodrigo *et al* (2013) | Echocardiography |

## Cardiac Function

**Table 4**: Ejection fraction percent change in analyzed studies for control and treatment groups.

| Study Analyzed | Control ejection fraction % change | Treatment ejection fraction % change |
|---|---|---|
| Heldman *et al* (2014) (MSC) | 4 | 4 |
| Heldman *et al* (2014) (BMC) | 4 | 3 |
| Perin *et al (2012)* | -1.3 | 1.4 |
| Grajek *et al* (2009) | -2.89 | 0.67 |
| Piepoli *et al* (2010) | 3.5 | 9.5 |
| Quyyumi *et al* (2011) | 1 | 2.5 |
| Bartunek *et al* (2013) | 0.2 | 7 |
| Turan *et al* (2012) | 1 | 7 |
| Srimahachota et al (2011) | -0.2 | 1.7 |
| Pokushalov *et al* (2010) | -2.6 | 4.5 |
| Traverse *et al* (2010) | 9.4 | 6.2 |
| Yerebakan *et al* (2011) | 5.3 | 5.8 |
| Strauer *et al* (2010) | -3.8 | 7.4 |
| Perin *et al* (2011) | 3 | 3 |
| Rodrigo *et al* (2013) | 5 | 9 |
| Average±SD | -0.41±3.6% | 5.85±3.4% |

Eleven out of fifteen studies favor stem cell treatment over controls in changes of ejection fraction. There was an average change of -0.41% in the control groups and 5.85% in the treatment groups, with a standard deviation of 3.6 and 3.4 respectively. Calculated p value was 0.022, which is significant.

**Table 5**: Infarcted area percent change in analyzed studies in control and treatment groups. Omitted data was not provided by the authors.

| Study Analyzed | Control decrease in infarcted area (% change) | Treatment decrease in infarcted area (% change) |
|---|---|---|
| Heldman *et al* (2014) (MSC) | 1.23 | 18.9 |
| Heldman *et al* (2014) (BMC) | 5.2 | 7 |
| Perin *et al* (2012) | 2.6 | 3.8 |
| Grajek *et al* (2009) | - | - |
| Piepoli *et al* (2010) | - | - |
| Quyyumi *et al* (2011) | 6.7 | 5.2 |
| Bartunek *et al* (2013) | - | - |
| Turan *et al* (2012) | 4 | 12 |
| Srimahachota et al (2011) | 0.5 | 4 |
| Pokushalov *et al* (2010) | - | - |
| Traverse (2010) | - | - |
| Yerebakan *et al* (2011) | - | - |
| Strauer *et al* (2010) | - | - |
| Perin *et al* (2011) | - | - |
| Rodrigo *et al* (2013) | - | - |
| Average±SD | 3.4±2.38% | 8.5±5.93% |

Many studies did not measure infarcted area because it was not a viable way to measure heart efficiency. In the available data, however, four out of five studies favor bone marrow stem cells in reducing infarcted area. The average decrease in the treatment group is 8.5±5.93% while in the control group it is 3.4±2.38% and the p value 0.078, which is inconclusively insignificant. There is not enough data sets to determine a significant change. The studies primarily resorted to measuring heart function instead to determine if the heart was effectively pumping enough blood. In the few studies which did measure such data, there was relative improvement and consistent decrease in infarcted area after stem cell treatment.

**Table 6:** End systolic volume change in analyzed studies from control and treatment groups. Yerebakan *et al* (2011) was not included in this data set because their study did not measure baseline end systolic volume.

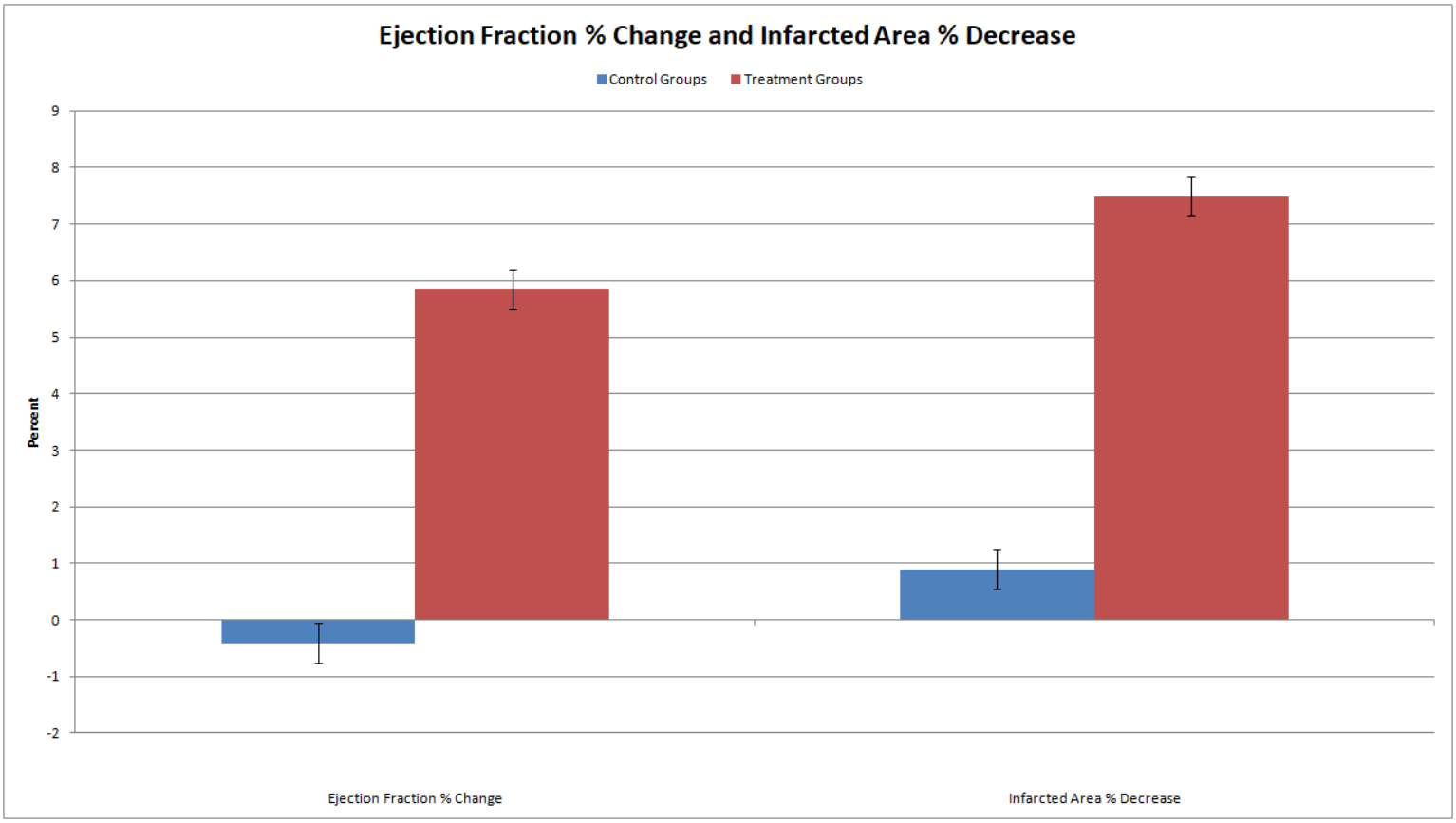
| Study Analyzed | Control end systolic volume change (mL) | Treatment end systolic volume change (mL) |
|---|---|---|
| Heldman *et al* (2014) (MSC) | 4 | -2 |
| Heldman *et al* (2014) (BMC) | 4 | 1 |
| Perin *et al (2012)* | 0 | -0.9 |
| Grajek *et al* (2009) | 19.01 | 10.12 |
| Piepoli *et al* (2010) | -0.5 | -12.5 |
| Quyyumi *et al* (2011) | -1.84 | 3.4 |
| Bartunek *et al* (2013) | -8.8 | -24.8 |
| Turan *et al* (2012) | -2 | -21 |
| Srimahachota et al (2011) | -19.8 | 5.9 |
| Pokushalov *et al* (2010) | 6 | -33 |
| Traverse *et al* (2010) | -2 | -7 |
| Yerebakan *et al* (2011) | - | - |
| Strauer *et al* (2010) | 14 | -17 |
| Perin *et al* (2011) | -9.9 | -18.9 |
| Rodrigo *et al* (2013) | -6 | -5 |
| Average±SD | 5.00±9.8 mL | -12.46±13.0 mL |

Ten out of fifteen studies favor an improved or lessened increase of end systolic volume in treatment groups compared to control groups. Average change of end systolic volume is 5.00 mL in control groups and -12.46 mL in treatment groups with a p value of 0.047, which is significant. Standard deviation for control groups and treatment groups is 9.8 and 13.0 respectively.

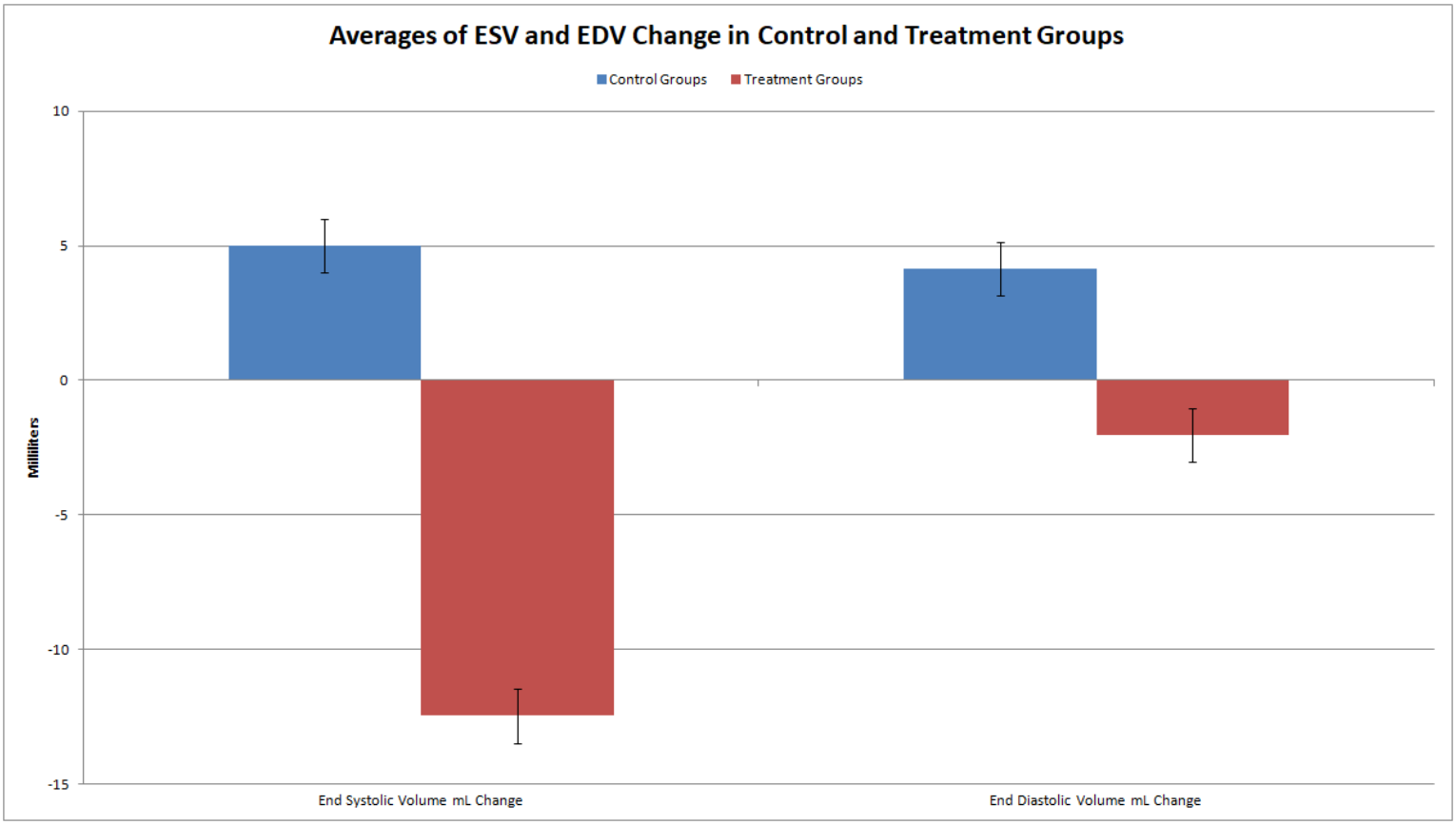
**Table 7:** End diastolic volume change in analyzed studies from control and treatment groups. Perin *et al* (2012) was not included as the study did not measure end diastolic volume as an endpoint.

| Study Analyzed | Control end diastolic volume change (mL) | Treatment end diastolic volume change (mL) |
|---|---|---|
| Heldman *et al* (2014) (MSC) | 7 | -2 |
| Heldman *et al* (2014) (BMC) | 7 | 2 |
| Perin *et al* (2012) | - | - |
| Grajek *et al* (2009) | 19.52 | 18.56 |
| Piepoli *et al* (2010) | 1.1 | -22.4 |
| Quyyumi *et al* (2011) | -0.6 | 13.4 |
| Bartunek *et al* (2013) | -9 | -18 |
| Turan *et al* (2012) | 2 | 19 |
| Srimahachota et al (2011) | -12.2 | 8.3 |
| Pokushalov *et al* (2010) | 9 | 2 |
| Traverse *et al* (2010) | 17 | -4 |
| Yerebakan *et al* (2011) | -1.5 | 1.9 |
| Strauer et al (2010) | 6 | -9 |
| Perin *et al* (2011) | -12.2 | -9.3 |
| Rodrigo *et al* (2013) | 3 | 9 |
| Average ± SD | 4.15±9.6 mL | -2.04±13.7mL |

Six out of fifteen studies favored an increased or lessened decrease of end systolic volume. Average end diastolic volume change is 4.15 mL in control groups with a standard deviation of 9.6 and -2.04 mL in treatment groups with a standard deviation of 13.7. Calculated p value was 0.65, which is not significant. Perin *et al* (2012) stated that their change was not significant and did not provide specific numbers other than the difference between treatment of control to be 2.5 mL.




**Graph 1:** Comparison of averages of ejection fraction and infarcted area change in control and treatment groups. Error bars represent 95% confidence intervals.




**Graph 2:** Comparison of averages of end systolic and end diastolic volume change in control and treatment groups. Error bars represent 95% confidence intervals.

In comparing averages of control groups and treatment groups, treatment groups are favored in decreasing ejection fraction, infarcted area, end systolic volume, and end diastolic volume.

## Discussion

The use of autologous bone marrow stem cells is feasible in all of the studies. They are a desirable source for cardiac repair due to their accessibility for harvest, attribute for self-replication, and extensive previous clinical experience (Hare *et al* 2009). A major effect cited studies hoped to discover is potential dangers of using this therapy. Therefore, most studies used patients with severe ischemic heart with little to no hope of recovery or therapy. This may have affected results in that only a small population characteristic of patients was recruited to undergo the treatment.

The compilation of these studies further provides evidence to the safety of the procedure. Although it cannot be guaranteed that the decreased amount of adverse events in treatment groups is because of the therapy, it is certainly comparable in safety to the control groups. The decreased amount of adverse events experienced by the treatment groups compared to the control groups may be due to decreased numbers of cardiac arrhythmias, an irregular beating of the heart (Strauer *et al* 2010). A weaker left ventricular function increases the likelihood of lethal cardiac arrhythmias which leads to sudden cardiac death. It is possible that the implementation of bone marrow stem cells improved left ventricular function and reduced chances of cardiac death. However, due to the high p value of 0.41, the implementation of stem cells cannot be determined to be significant in reducing adverse events.

All studies consider ejection fraction as their primary endpoint. Ejection fraction is an adequate measurement of cardiac function because it shows the heart pumping more blood per contraction. Since ejection fraction improved heart function in the treatment groups, it can be concluded that the injection of stem cells are a safe and viable method in improving the heart following heart attack. The calculated p value of 0.022 states this change as statistically significant.

The stem cells that were injected in the patient's heart successfully transformed into cardiomyocyte cells. The stem cells reinforced the heart by replacing damaged or necrotic heart tissue to healthy tissue. An increase of functional heart tissue caused the heart to be able to contract more effectively than when it carried ineffective tissue, which improved ejection fraction. An improvement of ejection fraction allowed the heart to more efficiently move blood throughout the body with fewer heartbeats, leading to longer heart longevity and health because the heart does not have to strain itself to provide oxygen to vital tissues.

As a result of being able to pump more blood, less blood remained at the end of systole, which involves a decreased end systolic volume. The heart was able to pump more blood out of its left atrium

so more blood can circulate throughout the body. The change in end systolic volume was significant (p=0.047) and demonstrates that the use of stem cells improves heart function.

However, there is substantial variation in each study's end diastolic volume change which resulted in a p value of 0.65. The injection of bone marrow stem cells did not significantly affect the end diastolic volume. The stem cells themselves did not improve or harm the capability of the heart to fill with blood. This might be controlled by additional factors along with cardiac function or another factor not associated with the heart at all.

One of the most notable mentions of all these studies combined is that they measure cardiac function as a way of providing secondary evidence cellular regeneration from stem cells. No study was able to effectively describe and provide evidence for cellular function and instead used other factors such as ejection fraction, end systolic volume, or end diastolic volume. This is due to a lack of technology to measure cardiac regeneration and is still being heavily investigated today. As a result, it is unclear whether cardiac tissue truly regenerates.

The standard deviation values of ejection fraction, end systolic volume, and end diastolic volume appear to be greater than their respective average values. This is likely due to differences between each study's methods and patient characteristics. In each study, there was a large range of improvement which could have created a number of outlier data points. This observation is consistent with other literature (Abdel Latif *et al* 2007) and was somewhat mitigated with the large patient population in this study.

## Limitations

The high degree of variance in human populations is a critical limitation in this review. The wide range of baseline patient characteristics may have resulted in skewed results. Other individual patient

factors such as age or past heart problems may have affected cardiac function after treatment. The difference in each studies' patient size as well as methods of procedure may also have affected results. There is no standardized or accepted way in stem cell treatment, as it is still highly experimental and its applications are relatively unclear. Additionally, the use of ejection fraction, end systolic volume, and end diastolic volume as endpoints do not necessarily serve to accurately measure success of stem cell therapy. These are only secondary effects of cardiac regeneration which may or may not occur in a patient.

## Conclusion

In this study designed to address further treatment regarding patients suffering from ischemic heart, it showed that bone marrow stem cell usage has promise in increasing ejection fraction and end diastolic volume while decreasing end systolic volume. It is inconclusive from this systematic review whether infarcted area can be truly decreased or replaced. As a result, most patients undergoing stem cell treatment would experience higher quality of life as a result of improved cardiac function. Blood is more easily circulated throughout the body which will also preserve the longevity of cardiac muscle tissue.

Evidence of myocardial tissue regeneration is not able to be provided. This may be due to the lack of knowledge in the field of stem cells or the improper technology to discover biological functions. The only evidence supported conclusion is the improvement of some cardiac function. This review shows the importance of determining other methods to measure effectability of treatment.

One of the most important outcomes of this review is that stem cell therapy has shown safety in treating patients suffering from myocardial infarctions. Although improvements in adverse events have not shown to significantly decrease adverse events, it is as sufficient as using standard therapy. This shows promise in the therapy producing a positive change for treated patients.

The implementation of stem cells for treatment after heart attacks favors preventing left ventricular remodeling for patients in their future. Because myocardial infarctions weaken the heart by damaging heart tissue, people are more likely to experience further heart problems. Affected areas in the heart will no longer be able to pump blood as efficiently as before. Patients who have experienced a heart attack would need to undergo medications and other treatments throughout their life to prevent another heart attack. Therefore, applications of bone marrow stem cell therapy will prevent further damage to the patient by improving cardiac function and preventing left ventricular remodeling.

## Further Work

Because there have been few experiments conducted over a extended time period with a large number of patients, future studies in this subject should focus on a much larger sample size over a time period of multiple years. Although important factors to control for include patient characteristics, it is nearly impossible to have uniform patient populations in individual studies. Therefore, randomization and controlled trials are necessary to minimize possible errors. Further clinical trials should look into standardizing measurement methods and injection methods to determine proper efficacy of stem cell treatment. With such high variance in methods, patient population, and measurements, it is necessary to determine one way to decide the efficacy of stem cell treatment.

It would be beneficial for additional basic stem cell and molecular biology research to expand current knowledge of its function and improve upon its clinical applications. All current experiments only measure cardiac function and do not determine how stem cell therapy functions. Future studies should provide physical evidence to provide definite proof of cardiac regeneration and truly examine how bone marrow stem cells function. This would ultimately decide the feasibility of using the treatment instead of trials by cardiac function as it varies between patients.

## Acknowledgments

I would like to thank Dr. Malhotra for being an instructor and mentor throughout my research as well as Dr. Jeng, Michelle, Magnusson, and Melissa Wong for providing feedback, edits, and comments about the project. Additional thanks to Dr. Zin for providing access to California State Channel Islands Library for additional research papers.

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