




Evaluation of the effectiveness of infusion of bone marrow derived cell in patients with heart failure: A network meta-analysis of randomized clinical trials and cohort studies

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Abstract

Background: The aim of this study was to investigate the effectiveness of bone marrow-derived cells (BMC) technology in patients with heart failure and compare it with alternative therapies, including drug therapy, cardiac resynchronization therapy pacemaker (CRT-P), cardiac resynchronization therapy defibrillator (CRT-D).

Methods: A systematic review study was conducted to identify all clinical studies published by 2017. Using keywords such as “Heart Failure, BMC, Drug Therapy, CRT-D, CRT-P” and combinations of the mentioned words, we searched electronic databases, including Scopus, Cochrane Library, and PubMed. The quality of the selected studies was assessed using the Cochrane Collaboration’s tool and the Newcastle-Ottawa. The primary and secondary end-points were left ventricular ejection fraction (LVEF) (%), failure cases (Number), left ventricular end-systolic volume (LVES) (ml), and left ventricular end-diastolic volume (LVED) (ml). Random-effects network meta-analyses were used to conduct a systematic comparison. Statistical analysis was done using STATA.

Results: This network meta-analysis covered a total of 57 final studies and 6694 patients. The Comparative effectiveness of BMC versus CRT-D, Drug, and CRT-P methods indicated the statistically significant superiority of BMC over CRT-P (6.607, 95% CI: 2.92, 10.29) in LVEF index and overall CRT-P (-13.946, 95% CI: -18.59, -9.29) and drug therapy (-4.176, 95% CI: -8.02, -3.33) in LVES index. In addition, in terms of LVED index, the BMC had statistically significant differences with CRT-P (-10.187, 95% CI: -18.85, -1.52). BMC was also dominant to all methods in failure cases as a final outcome and the difference was statistically significant i.e. BMC vs CRT-D: 0.529 (0.45, 0.62) and BMC vs Drug: 0.516 (0.44, 0.60).

In none of the outcomes, the other methods were statistically more efficacious than BMC. The BMC method was superior or similar to the other methods in all outcomes.

Conclusion: The results of this study showed that the BMC method, in general, and especially in terms of failure cases index, had a higher level of clinical effectiveness. However, due to the lack of data asymmetry, insufficient data and head-to-head studies, BMC in this meta-analysis might be considered as an alternative to existing treatments for heart failure.

Keywords: Bone marrow cell, CRT-D, Drug, CRT-P, Heart failure, Network meta-analysis

Conflicts of Interest: None declared

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Introduction

Heart failure is a chronic disease that is often referred to

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↑What is “already known” in this topic:

Some evidences have shown the effectiveness of bone marrow-derived stem cell therapy in patients with heart failure, and they have reported promising results. There are controversies about their effectiveness.

→What this article adds:

BMC method in general, and especially in terms of failure cases index, had a higher level of clinical effectiveness.

as congestive heart failure and is characterized by the inability of the heart to pump the blood needed for the tissues; moreover, the prevalence of this disease increases with age (1). The prevalence of cardiovascular diseases is increasing due to the increase in the incidence and prevalence of congestive heart failure, and the rise in the longevity of patients due to the use of new medical and surgical treatments (2). In addition, heart failure often occurs as an outcome of hypertension, cardiac ischemia, coronary artery disease, valvular heart disease, heart muscle disease, or cardiomyopathy, or several diseases occurring at the same time. Since the mentioned diseases increase the risk of irreversible heart failure, it is of great importance to identify and treat them (3).

Chronic heart failure and inadequate blood supply to the heart muscles (ischemic heart disease) are the most important causes of mortality in the world. The prevalence of this disease is 1% to 2% in the adult population, 6% in people over 65 years of age, and 10% in those over 75 years of age. Overall, it is estimated that around 15 million people worldwide have this disease (4). After the incidence of heart attack and chronic heart failure, the heart will not have the appropriate contractile power (5). Several methods of treatment are commonly used in the world for the treatment of this disease, among which we may note the followings: Drug Therapy, Cardiac Resynchronization Therapy Pacemaker (CRT-P), Cardiac Resynchronization Therapy Defibrillator (CRT-D), Left Ventricular Assist Device (LVAD), and RVAD (Right Ventricular Assist Device), artificial heart surgery, heart transplant, dietary regimen, and activity limitations. However, each mentioned method has its own limitations.

Nowadays, with the progress made in basic sciences and engineering, cell therapy has been introduced as a new and alternative method for the treatment of chronic diseases (6, 7). To justify cell therapy, it is said that different tissues of the body are made of cells, some of which have the ability to rebuild their own cells. For instance, the heart cells and some other cells have the ability to transform into other specialized cells (8).

Stem cells have two general sources: 1) embryonic stem cells (ESCs) and 2) adult stem cells derived from blood and bone marrow and can repair a tissue when it is damaged. These cells are more specialized than embryonic stem cells (9). Stem cells have many uses in the treatment of various diseases such as spinal cord injury, hormonal impairment, various types of syndrome, infertility, chronic hepatitis, pancreatitis, diabetes mellitus, and ischemic heart diseases such as congestive heart failure, etc. (10). Different types of therapies for heart failure are subject to some limitations; for example, in many studies, inappropriate drug therapy is reported as the most common cause of exacerbating heart failure (11).

The repair of the heart muscle cells is the latest therapeutic method. In this method, stem cells are transferred into the heart muscle, and a proper condition is created to generate new cells in the damaged area. Often, bone marrow cells are used for cell transplantation in the heart muscle (12-14), and these cells are studied in the majority of clinical trials. When applying this method, there is no need to

culture the cells before injecting them to patients, and it is the most important advantage of using these cells (15). These cells are able to replace or repair the damaged cardiac arteries and tissues. Because of the positive and promising results found in a number of clinical trials around the world, this method has received much attention (16, 17). In 2005, the US Food and Drug Administration confirmed the effectiveness of cell therapy in cardiac patients (18).

Many clinical trials have been conducted in the world to evaluate the effectiveness of bone marrow-derived stem cell therapy in patients with heart failure, and they have reported promising results (19-27). In addition, a number of studies have also reported that the use of this new technology for the treatment of heart failure is safe; however, as they stated, it is necessary to carry out clinical trials in higher phases with larger sample sizes (16, 28-31).

Despite the availability of the studies mentioned above, the use of this new technology in the health system of the country requires a comprehensive investigation in order to provide a clear picture of the effectiveness of this technology, as compared with other new therapies. In view of that, this study aimed to evaluate the clinical effectiveness of intracoronary/intra-myocardial infusion of bone marrow-derived cells (BMC) in patients with heart failure, as compared with alternative therapies including drug therapy, CRT-P, and CRT-D.

Methods

Data Resources and Search Strategy

In order to investigate the effectiveness of BMC technology in comparison with the other common therapies used for patients with heart failure, we conducted a systematic review of the studies that published from inception up until December 30, 2017, in electronic databases, including PubMed, Scopus, and Cochrane Library. We used several keywords, including (Myocardial infarction OR Chronic ischemic heart disease OR ischemic cardiomyopathy OR heart failure OR congestive heart failure), (Bone marrow cells OR bone marrow-derived cells OR stem cell OR bone marrow mononuclear cell OR MNC OR BMC OR BMNC), (Pharmacotherapy OR Drug Therapy OR Medication Therapy), (Cardiac Resynchronization Therapy Defibrillator OR CRT-D), Cardiac Resynchronization Therapy Pacemaker (CRT-P), and combinations of the mentioned keywords.

Study selection and data extraction

To select the studies for the systematic review, we set the inclusion criteria and only included articles reporting randomized controlled clinical trials and cohort studies published in English that investigated the clinical effectiveness of BMC technology and compared it with alternative therapies, including Drug Therapy (Include angiotensin-converting-enzyme (ACE) inhibitor, Beta Blockers such as Enalapril, Candesartan, Carvedilol, Metoprolol, and Nebivolol), CRT-P, and CRT-D in patients with chronic heart failure, ischemic heart disease, acute myocardial infarction, ischemic cardiomyopathy, and congestive heart failure.

Moreover, in order to include the studies in the meta-

analysis, we only selected the studies with the following PICO:

Population: Patients with heart failure

Intervention: BMC

Comparators: Drug Therapy, CRT-P, and CRT-D

Outcomes: The expected outcomes were as follows: “left ventricular ejection fraction (LVEF) (%), failure cases (Number), left ventricular end-systolic volume (LVES) (ml), and left ventricular end-diastolic volume (LVED) (ml)”. Based on the exclusion criteria, we excluded animal studies, studies without a control group, Case-Report, Case- Series, Cross-Sectional, Case-Control, review studies, and economic evaluation studies.

After the initial search, duplicated articles were removed, and the titles and abstracts of the remaining articles were evaluated by two people separately to identify and eliminate unrelated items and articles that did not meet the inclusion criteria. The results obtained by these two people were rechecked once and the controversial cases were resolved by referring to the articles. In the next step, the full texts of the articles, which were selected in the previous stage, were studied and articles that met the aforementioned inclusion criteria were selected. The PRISMA guideline was used for the systematic review of the articles (32). Using the predefined form, the necessary information was extracted from the text of selected articles based on inclusion and exclusion criteria. The outcome measures included left ventricular ejection fraction (LVEF) (%), left ventricular end-systolic volume (LVES) (ml), and left ventricular end-diastolic volume (LVED) (ml) and failure cases (Number) (Composite of all-cause mortality, stroke, rehospitalization for items that were left out of treatment.)

Quality Assessment

The quality of all RCT studies was assessed by the Cochrane Collaboration's tool (33), and the quality of cohort studies was evaluated by the Newcastle-Ottawa Quality Assessment Scale: Cohort Studies. In the Cochrane Collaboration's tool, each study is assessed based on six domains of bias: “selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias”; and all domain, assessments are included of these items: “Random sequence generation, Allocation concealment, Blinding of participants and personnel, Blinding of outcome assessment, Incomplete outcome data, Selective reporting and Anything else, ideally prespecified”; each item is assessed based on three options (high, low, or unclear). Accordingly, the mean of each option is calculated for all studies in the systematic review. To assess the cohort studies, the questions listed in the Newcastle-Ottawa Evaluation Scoreboard (34) were answered; in the four-choice questions, the two options a and b were given a star, while in questions with three or few choices, only option a was given a star. Finally, calculating the total number of answers receiving stars, i.e., Selection (4*), Comparability (2*), and Outcome (3*), the study was given stars and the quality of the study was evaluated. The maximum number of stars that a study could receive was nine stars. The studies with at least five stars or more were considered acceptable in terms of quality. Hence, in the end, the studies that met the selected criteria

and indices had an acceptable level of quality based on the Cochrane Collaboration's tool or Newcastle-Ottawa and had similar methodologies were enrolled in the network meta-analysis.

Data Analysis

The search and review of the databases mentioned above did not result in finding any study that had directly compared BMC technology with other available therapeutic methods. Hence, there was an attempt to find clinical trials and cohort studies conducted on BMC; in addition, we extracted data on the effectiveness of other different technologies that had been separately reported by various studies and then compared them with the effectiveness of BMC technology. Therefore, in order to integrate the results of the reviewed studies, we applied network meta-analysis carried out using Excel and STATA software.

Therefore, as mentioned above, in this study we first adopted a systematic review approach and extracted data on the effectiveness of BMC technology and other treatment alternatives. Then, using network meta-analysis, we compared the effectiveness of the studied methods with each other and analyzed and reported the results.

In this network meta-analysis, the data analysis was performed using indirect command and random effect method. In this type of meta-analyses, first, the available comparisons are meta-analyzed and then their results are combined to carry out an indirect meta-analysis.

For various outcomes, the pooled odds ratios from randomized trials and cohort studies in the systematic review of BMC compared with PLB and Other Alternatives with PLB were computed using meta-analysis. Cochran's Q test and I2 index were used with P-value<0.1 were applied to assess heterogeneity among the RCTs and cohort studies included in the meta-analysis. Because of heterogeneous data random-effects model was used. To assess heterogeneity and for calculation of direct & indirect effects, “mean” and “indirect” commands in STATA 11.2 were used.

Bucher et al. method was used to calculate the indirect effects (19). In this method, the effects of BMC in comparison with common treatment methods can be estimated indirectly via using the direct estimators for the effects of BMC relative to PLB (effect_{BMC, PLB}) and PLB relative to CRT (effect_{CRT-D, PLB}):

$$\text{Effect}_{\text{BMC, CRT-D}} = \text{effect}_{\text{BMC, PLB}} - \text{effect}_{\text{PLB, CRT-D}}$$

The indirect estimator variance of Effect_{BMC, CRT} is the sum of the direct estimators' variances:

$$\text{Variance}_{\text{BMC, CRT-D}} = \text{variance}_{\text{BMC, PLB}} + \text{variance}_{\text{PLB, CRT-D}}$$

To assess the indirect effects of BMC vs. PLB with Drug or CRT-P vs. PLB, we used the same formula.

The consistency and transitivity assumptions network meta-analysis were assessed. We could not investigate the consistency, because we did not have direct comparison between BMC, CRT-P, CRT-D, and Drug. For the transitivity assumption, proper inclusion and exclusion were implemented to get similarity between arms. The only potential modifier was the follow-up time. The mean duration of follow-up in the four groups was similar (p=0.343).

In this study, for each outcome, a table with nine comparisons was provided. We first conducted five direct comparisons and then combined their results, and performed four indirect comparisons; as a result, the four existing therapies were compared with BMC. For the first three outcomes, the difference in mean values after the intervention was compared between the two groups. For the outcome of failure cases, the odds ratios were compared with each other. When collecting the data, it was not possible to obtain data on standard deviations from the baseline in each treatment group; as a result, we only extracted data on standard deviations before and after the intervention separately. Therefore, by estimating the correlation between the parameters

before and after the study in each group (using the data extracted from all the studies), the standard deviation from the baseline in each group was estimated with an approximate level of accuracy.

Results

Study Screening, Characteristics, and Quality of Included Studies

A total of 21985 articles were found after conducting searches in the electronic databases and checking the references. After conducting several reviews, we conducted a meta-analysis of the studies that met the inclusion criteria and had an acceptable level of quality on the basis of the desired criteria (Fig. 1). A total of 57 studies that had been

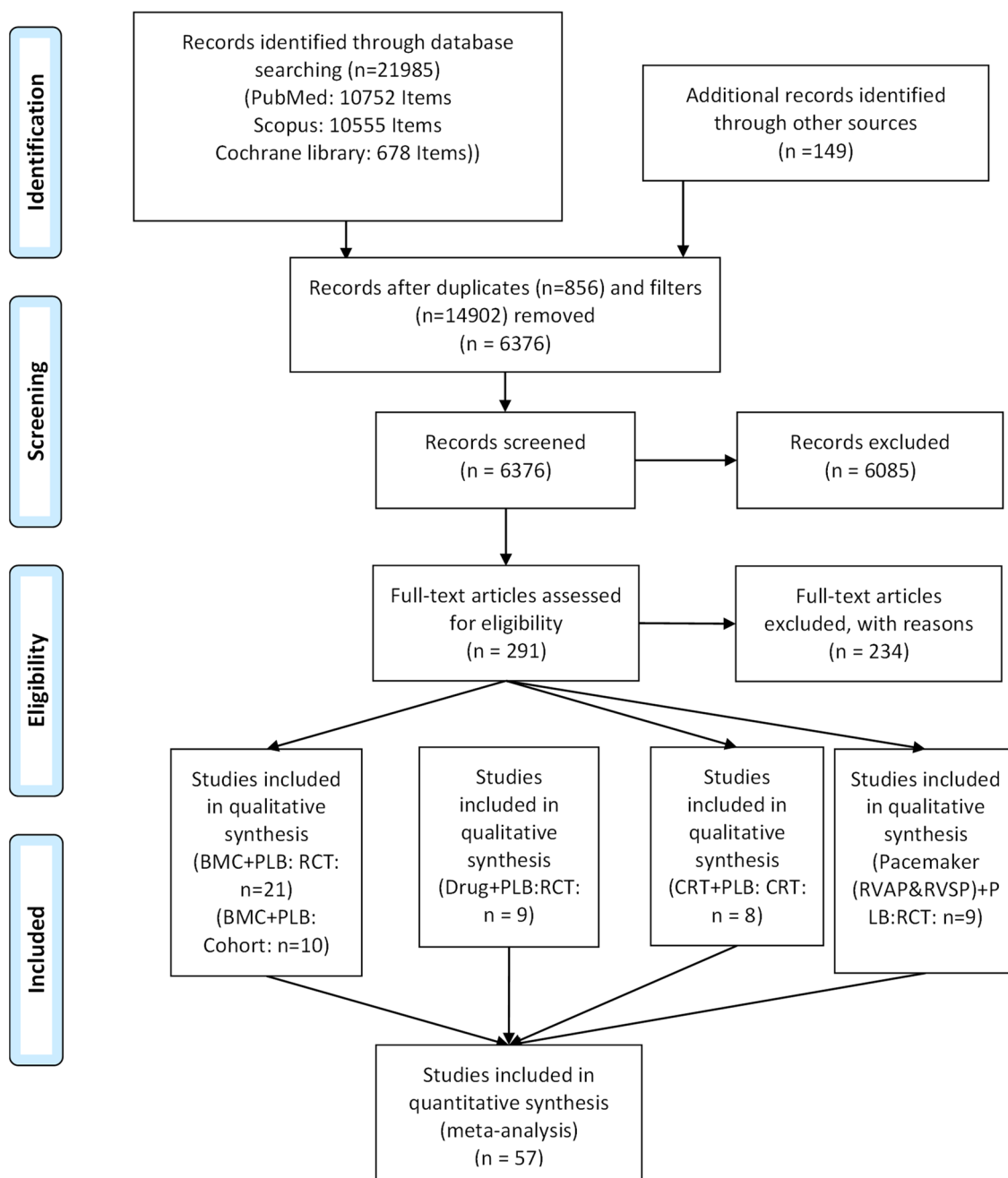


Fig. 1. Diagram of the process of selecting clinical trials and cohort studies which investigated the alternatives under the study

conducted on a total of 6694 patients were finally analyzed. Table 1 presents the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. In addition, as the results of the studies indicated, the Cochrane Collaboration's tool obtained an average for all the studies in the

systematic review was 70% low risk of bias, 14% Bias unclear and 16% High risk of bias. Total ten studies described all domain of the Cochrane Collaboration's tool and using Randomized Control Trial design; others all described over three domains, so we had not an article with high risk in all

Table 1. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials

Author/Year	Bias domain						
	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	
	Source of bias						
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified
Traverse and Colleagues (2011) USA (47)	+	+	+	+	+	+	+
Abraham and Colleagues (2004) USA (67)	+	+	+	+	+	+	+
St John Sutton and Colleagues (2003)USA (69)	+	+	+	+	+	+	+
Young and Colleagues (2003) USA (70)	+	+	+	+	+	+	+
Thibault and Colleagues (2013) Canada (71)	+	+	+	+	+	+	+
Linde and Colleagues (2008) Sweden (74)	+	+	+	+	+	+	+
Kitzman and Colleagues (2010) USA (75)	+	+	+	+	+	+	+
Van Veldhuisen and Colleagues (2009) Netherlands (76)	+	+	+	+	+	+	+
Matsumori and Colleagues (2003) Japan (78)	+	+	+	+	+	+	+
Imrie and Cirillo and Levy and Ascoli and Moccetti Colleagues (2000) Canada and Brazil and USA and italy and Switzerland (82)	+	+	+	+	+	+	+
Wohrle and Colleagues (2010) Germany (45)	+	+	+	+	+	?	+
Menardi and Colleagues (2008) Italy (73)	+	+	?	?	+	+	?
Piepoli and Colleagues (2010) Italy (52)	+	+	?	?	+	+	?
Cicoira and Colleagues (2002) Italy(80)	+	+	-	+	+	+	?
Pokushalov and Colleagues (2010) Russia (39)	+	+	+	-	+	+	?
Turan and Colleagues (2012) Germany (46)	+	+	+	+	-	+	?
Bristow and Colleagues (2004) USA (68)	+	+	-	+	+	+	?
Muto and Colleagues (2013) Italy (72)	+	+	-	+	+	+	?
Ang and Colleagues(2008) UK (37)	?	?	+	+	+	+	-
Perin and Colleagues (2011) USA (42)	+	+	-	+	+	?	?
Palazzuoli and Colleagues (2002) Italy (79)	+	+	+	+	-	?	?
Assmus and Colleagues (2006) Germany (38)	+	-	+	+	+	?	?
Silva and Colleagues (2009) Brazil (50)	+	+	?	?	+	-	+
Suarez and Colleagues (2007) Spain (49)	+	+	?	?	+	-	?
Cao and Colleagues (2009) USA (53)	+	+	?	?	+	+	-
Herbots and Colleagues (2009) Belgium (56)	+	+	-	+	+	?	?
Tsutamoto and Colleagues (2001) Japan (81)	+	+	?	?	+	-	?
Hendriks and Colleagues (2006)USA (41)	+	+	-	+	+	-	+
Yao and Colleagues (2009) China (44)	+	+	-	+	+	-	+
Quyyumi and Colleagues (2011) USA (51)	+	+	-	+	+	-	+
Muto and Colleagues (2009) Italy (85)	+	+	-	-	+	+	+
Cho and Colleagues (2011) Korea (87)	+	-	-	+	+	+	+
Chen and Colleagues (2004) China (54)	-	-	+	+	+	+	?
Grajek and Colleagues (2010) Poland (55)	+	+	-	-	+	?	+
Cano and Colleagues (2010) Spain (84)	+	+	-	+	+	-	?
Occhetta and Colleagues (2015) Italy (88)	+	+	-	-	+	+	?
Traverse and Colleagues (2010) USA (48)	+	+	-	-	+	?	?
Yao and Colleagues (2008) China (43)	-	+	-	+	+	-	+
Cohen Solal and Colleagues (2004) France (77)	+	+	+	+	-	-	-
Hamer and Colleagues (1989) Australia (83)	+	+	+	+	-	-	-
Patel and Colleagues (2005) USA (40)	+	+	-	-	+	-	?
Flevvari and Colleagues (2009) Greece (86)	+	+	-	-	+	-	?

Key: + Low risk of bias, ? Unclear risk of bias, - High risk of bias

domains. In addition, we evaluated the quality of cohort studies using the Newcastle-Ottawa Quality Assessment Scale, and the results showed that all the selected studies had a high-quality score of 7; thus, they had an acceptable level of quality (minimum score of five). Table 2 presents a summary of the characteristics of the selected studies, including the comparison arm, the duration of the study, and the number of patients.

Outcomes

Figure 2 shows the schematic of the various comparisons. Tables 3 to 6 present the number of studies that reported the outcomes of LVEF, LVES, LVED, and failure cases for BMC, CRT-D, Drug, CRT-P, and placebo group. The LVEF outcome was the most frequently studied outcome that was reported in 56 studies, and the failure cases were the least frequently studied outcome that was reported in 31 studies.

Table 2. The characteristics of the selected studies in the network meta-analysis

Study	Trial design	No. of patients		treatment duration (Mean follow-up)	
		Therapy group	Control group	Therapy group (month)	Control group (month)
BMC vs Placebo (RCT studies)					
Ang and Colleagues(2008) UK (37)	RCT	21	20	6	6
Ang and Colleagues(2008) UK (37)	RCT	21	20	6	6
Assmus and Colleagues (2006) Germany (38)	RCT	35	23	3	3
Pokushalov and Colleagues (2010) Russia (39)	RCT	55	54	12	12
Patel and Colleagues (2005) USA (40)	RCT	10	10	6	6
Hendrikx and Colleagues (2006)USA (41)	RCT	10	10	4	4
Perin and Colleagues (2011) USA (42)	RCT	20	10	6	6
Yao and Colleagues (2008) China (43)	RCT	24	23	6	6
Yao and Colleagues (2009) China (44)	RCT	12	12	12	12
Wohrle and Colleagues (2010) Germany (45)	RCT	29	13	6	6
Turan and Colleagues (2012) Germany (46)	RCT	42	20	12	12
Traverse and Colleagues (2011) USA (47)	RCT	58	29	6	6
Traverse and Colleagues (2010) USA (48)	RCT	30	10	6	6
Suarez and Colleagues (2007) Spain (49)	RCT	10	10	3	3
Silva and Colleagues (2009) Brazil (50)	RCT	10	6	6	6
Quyyumi and Colleagues (2011) USA (51)	RCT	16	15	6	6
Piepoli and Colleagues (2010) Italy (52)	RCT	19	19	12	12
Cao and Colleagues (2009) USA (53)	RCT	41	45	48	48
Chen and Colleagues (2004) China (54)	RCT	34	35	3	3
Grajek and Colleagues (2010) Poland (55)	RCT	31	14	12	12
Herbots and Colleagues (2009) Belgium (56)	RCT	33	34	4	4
BMC vs Placebo (Cohort studies)					
Akar and Colleagues (2009) Turkey (57)	Cohort	25	25	18	18
Yerebakan and Colleagues (2011) Germany (58)	Cohort	35	20	18	18
Perin and Colleagues (2004) Brazil (59)	Cohort	11	9	12	12
Manginas and Colleagues (2006) Greece (60)	Cohort	12	12	11	11
Mocini and Colleagues (2006) Italy (61)	Cohort	18	18	3	3
Stamm and Colleagues (2007) Germany (62)	Cohort	20	20	6	6
Turan and Colleagues (2010) Germany (63)	Cohort	17	15	6	6
Bartunek and Colleagues (2005) Belgium (64)	Cohort	19	16	4	4
Yousef and Colleagues (2009) Germany (65)	Cohort	62	62	60	60
Katritsis and Colleagues (2005) Greece (66)	Cohort	11	11	4	4
CRT-D vs Placebo					
Abraham and Colleagues (2004) USA (67)	RCT	85	101	6	6
Bristow and Colleagues (2004) USA (68)	RCT	599	308	6	6
St John Sutton and Colleagues (2003)USA (69)	RCT	172	151	6	6
Young and Colleagues (2003) USA (70)	RCT	187	182	6	6
Thibault and Colleagues (2013) Canada (71)	RCT	44	41	12	12
Muto and Colleagues (2013) Italy (72)	RCT	60	113	12	12
Menardi and Colleagues (2008) Italy (73)	RCT	100	20	12	12
Linde and Colleagues (2008) Sweden (74)	RCT	419	191	12	12
Drug vs Placebo					
Kitzman and Colleagues (2010) USA (75)	RCT	35	36	12	12
Van Veldhuisen and Colleagues (2009) Netherlands (76)	RCT	380	372	12	12
Cohen Solal and Colleagues (2004) France (77)	RCT	28	22	6	6
Matsumori and Colleagues (2003) Japan (78)	RCT	148	144	6	6
Palazzuoli and Colleagues (2002) Italy (79)	RCT	24	24	12	12
Cicoira and Colleagues (2002) Italy (80)	RCT	54	52	12	12
Tsutamoto and Colleagues (2001) Japan (81)	RCT	20	17	4	4
Imrie and Cirillo and Levy and Ascoli and Moccetti Colleagues (2000) Canada and Brazil and USA and Italy and Switzerland (82)	RCT	214	212	4	4
Hamer and Colleagues (1989) Australia (83)	RCT	16	14	6	6
CRT-P vs Placebo					
Cano and Colleagues (2010) Spain (84)	RCT	28	21	12	12
Cano and Colleagues (2010) Spain (84)	RCT	32	21	12	12
Muto and Colleagues (2009) Italy (85)	RCT	40	75	54	54
Flevvari and Colleagues (2009) Greece (86)	RCT	9	6	12	12
Flevvari and Colleagues (2009) Greece (86)	RCT	10	6	12	12
Cho and Colleagues (2011) Korea (87)	RCT	45	15	>7 day	>7 day
Cho and Colleagues (2011) Korea (87)	RCT	34	15	>7 day	>7 day
Occhetta and Colleagues (2015) Italy (88)	RCT	33	22	19	19
Occhetta and Colleagues (2015) Italy (88)	RCT	244	22	19	19

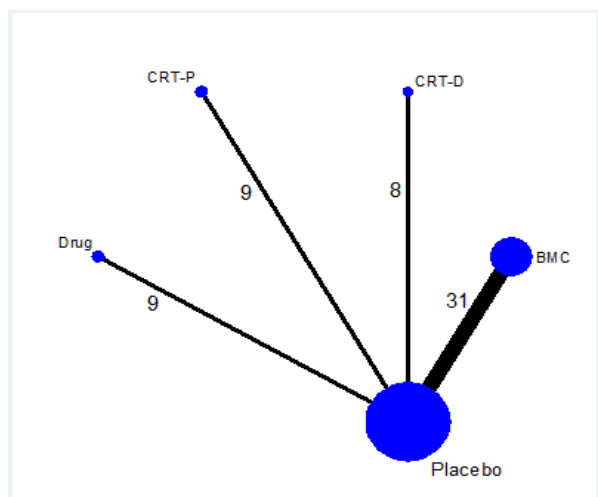


Fig. 2. Network plot between the groups (efficacy outcome) Number of studies VS Placebo in meta-analysis (31 (BMC), 8 (CRT-D), 9 (Drug) and 9 (CRT-P)).

Nodes are weighted according to the number of studies including the respective interventions. Edges are weighted according to the mean control group risk for comparisons between placebo and active treatment.

LVEF change from baseline

Based on the results of meta-analysis, as presented in Table 3, the level of LVEF in BMC, CRT-D, and Drug groups show a significant difference as compared with the placebo group. The mentioned methods, as compared with the placebo, resulted in a more significant increase in LVEF (Comparisons 1-3). However, we did not observe a significant difference between the CRT-P group, as compared with the placebo group, in terms of LVEF (Comparison 4).

Table 3. Network meta-analysis for comparison of LVEF after intervention between the two groups

Comparison		Treatment		Meta-analysis (Random effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	Mean difference (CI 95%)	p	Mean difference (CI 95%)	p
1	31	BMC	placebo	4.420 (2.779, 6.060)	<0.001		
2	7	CRT-D	placebo	5.679 (2.458, 8.901)	0.001		
3	9	Drug	placebo	3.199 (2.268, 4.131)	<0.001		
4	9	CRT-P	placebo	-2.178 (-5.479, 1.122)	0.196		
5		BMC	CRT-D			-1.259 (-4.87, 2.35)	0.495
6		BMC	Drug			1.221 (-0.66, 3.11)	0.204
7		BMC	CRT-P			6.607 (2.92, 10.29)	<0.001

Table 4. Network meta-analysis for comparison of LVES after the intervention between the two groups

Comparison		Treatment		Meta-analysis (Random effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	Mean difference (CI 95%)	p	Mean difference (CI 95%)	p
1	24	BMC	placebo	-11.201 (-14.198, -8.204)	<0.001		
2	6	CRT-D	placebo	-11 (-20.427, -1.574)	0.022		
3	6	Drug	placebo	-7.025 (-9.440, -4.610)	<0.001		
4	9	CRT-P	placebo	2.746 (-0.811, 6.302)	0.13		
5		BMC	CRT-D			-.201 (-10.09, 9.69)	0.969
6		BMC	Drug			-4.176 (-8.02, -.33)	0.033
7		BMC	CRT-P			-13.946 (-18.59, -9.29)	<0.0001

Afterward, we combined the results of the meta-analysis for indirect comparisons, and it was observed that CRT-D and Drug methods did not have a significant difference with the BMC method in terms of changes in LVEF (Comparison 5 and 6). However, there was a significant difference between the BMC method and the CRT-P method; in other words, the BMC method, as compared with the CRT-P method, resulting in a more significant increase in LVEF (Comparison 7).

LVES change from baseline

Based on the results of a meta-analysis presented in Table 4, it can be observed that BMC, CRT-D, and Drug groups had a significant difference with the placebo group in terms of LVES since the mentioned methods resulted in a more significant decrease in LVES, as compared with the placebo (Comparisons 1-3). However, the CRT-P group did not show significant differences compared to the placebo group in terms of LVES (Comparison 4).

Afterward, we combined the results of the meta-analysis for indirect comparisons, and it was observed that the CRT-D method did not have a significant difference with the BMC method in terms of the changes in LVES (Comparison 5). However, the difference between the BMC method and Drug and CRT-P methods was significant. In other words, LVES reduced more significantly in the BMC method, as compared with CRT-P and Drug methods (Comparisons 6 and 7).

LVED change from baseline

Based on the results of meta-analysis, as presented in Table 5, BMC and Drug groups had a significant difference compared to the placebo group, in terms of LVED. In other

Table 5. Network meta-analysis for comparison of LVED after the intervention between the two groups

Comparison		Treatment		Meta-analysis (Random effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	Mean difference (CI95%)	p	Mean difference (CI 95%)	p
1	25	BMC	Placebo	-6.769 (-9.579, -3.959)	<0.001		
2	6	CRT-D	Placebo	-8.305 (-31.224, 14.614)	0.478		
3	7	Drug	Placebo	-9.109 (-13.739, -4.478)	<0.001		
4	9	CRT-P	Placebo	3.418 (-4.782, 11.619)	0.414		
5		BMC	CRT-D			1.536 (-21.55, 24.63)	0.895
6		BMC	Drug			2.34 (-3.08, 7.75)	0.397
7		BMC	CRT-P			-10.187 (-18.85, -1.52)	0.021

words, the mentioned methods resulted in a more significant reduction in LVED, as compared with the placebo (Comparisons 1 and 3). However, LVED reduced more significantly in CRT-D and CRT-P groups, as compared with the placebo group. (Comparisons 2 and 4).

Then, we combined the results of the meta-analysis for indirect comparisons and it was observed that CRT-D and Drug methods did not have a significant difference compared to the BMC method in terms of the level of changes in LVED (Comparisons 5 and 6). However, the BMC method had a significant difference with the CRT-P method, as the BMC method resulted in a more significant reduction in LVED, as compared with the CRT-P method (Comparisons 7).

Failure cases after the intervention

Based on the results of meta-analysis, as presented in Table 6, BMC, CRT-D, and Drug groups had a significant difference compared to the placebo group in terms of failure cases, as the mentioned methods resulted in a more significant reduction in failure cases, as compared with the placebo (Comparisons 1-3). It should also be noted that we did not find proper data about this outcome in the pacemaker method; hence, we did not report this outcome for the pacemaker method.

We also combined the results of the meta-analysis for indirect comparisons and it was observed that CRT-D and Drug methods had a significant difference with the BMC method in terms of failure cases. In other words, the failure cases in the BMC method was significantly lower than that in the CRT-D, and Drug methods (Comparisons 5 and 6).

Discussion

The present study was the first network meta-analysis

study that indirectly evaluated the effectiveness of intracoronary / intra-myocardial infusion of bone marrow-derived cells (BMC) in patients with heart failure and compared it with common therapies in Iran including Drug Therapy, CRT-P, and CRT-D. In order to evaluate the effectiveness, first, we conducted a systematic review of the evidence on the clinical effectiveness of the methods. The available studies were selected using a set of inclusion criteria and evaluated in terms of some specific outcomes including LVEF (%), failure cases (N), LVES (ml), and LVED (ml). Finally, the studies that were eligible for meta-analysis underwent a network meta-analysis. As stated, we used the network meta-analysis method because of the absence of studies that have directly assessed and compared the mentioned methods.

Based on the results of network meta-analysis, comparison of the effectiveness of BMC with that of CRT-D, Drug, and CRT-P methods indicated a statistically significant superiority of BMC over CRT-P in LVEF index and, its superiority in LVES index over CRT-P and drug therapy. In addition, in terms of LVED index, the BMC had statistically significant differences than CRT-P. BMC was also dominant to Drug and CRT-D in failure cases as an effective index and the difference was statistically significant. Although, our findings of the effectiveness of the methods were not similar in all outcomes, according to failures cases which are considered as a final indicator and include patients' mortality, the BMC method was superior to the other methods and had a significant difference with them (p<0.05). In none of the outcomes, the other methods were statistically more efficacious than BMC. The BMC method was superior or similar to the other methods in all outcomes.

Comparing the BMC and CRT-D methods showed that the differences between the two methods in terms of LVEF,

Table 6. Network meta-analysis for comparison of failure after the intervention between the two groups

Comparison		Treatment		Meta-analysis (Fixed effect)		Indirect comparison	
id	Number of studies	Treatment 1	Treatment 2	OR (CI 95%)	p	OR (CI 95%)	p
1	20	BMC	Placebo	0.387 (0.25, 0.588)	<0.001		
2	4	CRT-D	Placebo	0.731 (0.56, 0.946)	0.017		
3	7	Drug	Placebo	0.750 (0.576, 0.977)	0.033		
4	0	CRT-P	Placebo	-	-		
5		BMC	CRT-D			0.529 (0.45, 0.62)	<0.001
6		BMC	Drug			0.516 (0.44, 0.60)	<0.001

LVES, LVED, and failure cases were - 1.259 ($p>0.05$), - 0.201 ($p>0.05$), 1.536 ($p>0.05$), and 0.529 ($p<0.05$), respectively. As it can be observed and taking into account the p-values, except for the outcome of failure cases, the other outcomes in the CRT method did not show significant differences with those in the BMC method. In other words, the BMC treatment method is superior to the CRT-D method only in terms of the mortality rate and failure cases; the two methods have a similar level of effectiveness in terms of other outcomes.

Comparison of the BMC and Drug methods revealed that the differences between the two methods in terms of LVEF, LVES, LVED, and failure cases were 1.221 ($p>0.05$), - 4.176 ($p=0.03$), 2.34 ($p>0.05$), and 0.516 ($p<0.05$), respectively. As it can be observed and taking into account the p-values, the two outcomes of LVES and failure cases in the Drug method have significant differences compared to those in the BMC method. In other words, the BMC treatment method is superior to the Drug method in terms of LVES and failure cases; the two methods have a similar level of effectiveness in terms of other outcomes.

Comparing BMC and CRT-P methods showed that the differences between the two methods in terms of LVEF, LVES, and LVED were 6.607 ($p<0.05$), -13.946 ($p<0.05$), and -10.187 ($p=0.02$), respectively. There was not enough evidence about failure cases in the Pacemaker method. As it can be observed and taking into account the p-values, all the three outcomes in the Pacemaker method have, significant differences compared to those in the BMC method. In other words, the BMC treatment method is superior to the Pacemaker method in terms of LVEF, LVES, and LVED.

Therefore, with respect to the effectiveness of BMC method with that of CRT-D, Drug, and CRT-P methods in terms of the effective indices of LVEF, LVES, and LVED, we observed significant differences in some cases and non-significant differences in other cases; thus, our findings on the effectiveness of the methods were not similar. However, considering the effectiveness index of failure cases, which includes the patients' mortality and is considered as a final indicator, the BMC method was superior to the other methods and had a significant difference.

It should be noted that we did not find any meta-analysis study that had directly or indirectly compared the BMC treatment method with the other methods mentioned in this study; therefore, it was not possible to compare the results of this study with the results of other studies. However, there were many meta-analyses and systematic reviews that compared the effectiveness of BMC treatment method between a variety of patients with heart failure, either before and after treatment or between the cases and controls. The results of such studies indicate the superiority and effectiveness of BMC method, especially in the mortality index and LVEF index, when comparing patients before and after the treatment or when comparing the cases with the controls (21, 23, 35, 36). It is in line with the results of this study, which showed the medical effectiveness of BMC treatment method, as compared with the placebo.

The difference between basic treatments in patients before receiving each method is a limitation in this study. In

addition, one of the limitations in this study is that the patients' selection may not be the same and the patients' characteristics may effect on the effectiveness of different methods.

Conclusion

The results of this study showed that the BMC method in general, and especially in terms of failure cases index, had a higher level of clinical effectiveness, as compared with the other studied treatment methods. Therefore, based on the aforementioned findings and the results of previous studies conducted on the treatment of heart failure, the use of BMC can be considered as an appropriate alternative to the existing therapies. However, due to the lack of data asymmetry, insufficient data and head-to-head studies, in this meta-analysis cannot be considered as a definitive alternative to existing treatments for heart failure. Of course, this conclusion is only in terms of clinical effectiveness. For making a better decision, when comparing this method with other methods, it is suggested that the two dimensions of cost and effectiveness should be assessed simultaneously.

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Conflict of Interests

The authors declare that they have no competing interests.

References

1. Curran JW. Economic consequences of pelvic inflammatory disease in the United States. *Am J Obstetr Gynecol.* 1980;138(7):848-51.
2. Taylor P, Molassiotis A. An exploration of the relationship between uncertainly psychological distress and type of coping standing among Chinese men after cardiac catheterization. *J Adv Nurs.* 2001;33(1):77-88.
3. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. *New Eng J Med.* 2002;347(5):305-13.
4. Chen C, Lee Y, Chiu S, Shyu W, Lee M, Huang S, et al. The application of stem cells in the treatment of ischemic diseases. *Histol Histopathol.* 2006;21(10/12):1209.
5. Rochefort GY. Mesenchymal Stem Cells in Vascular Therapy. *Stem Cell Appl Dis.* 2008:41.
6. Wu KH, Liu YL, Zhou B, Han ZC. Cellular therapy and myocardial tissue engineering: the role of adult stem and progenitor cells. *Eur J Cardiothorac Surg.* 2006;30(5):770-81.
7. Santore MT, Roybal JL, Flake AW. Prenatal stem cell transplantation and gene therapy. *Clin Perinatol.* 2009;36(2):451-71.
8. Lan L, Cui D, Nowka K, Derwahl M. Stem cells derived from goiters in adults form spheres in response to intense growth stimulation and require thyrotropin for differentiation into thyrocytes. *J Clin Endocrinol Metab.* 2007;92(9):3681-8.
9. Weissberg PL, Qasim A. Stem cell therapy for myocardial repair. *Heart.*

- 2005;91(5):696-702.
10. Zhelev N, Trifonov D, Wang S, Hassan M, El Serafi I. From Roscovitine to CYC202 to Seliciclib—from bench to bedside: discovery and development. *BioDiscovery*. 2013;10:e8956.
 11. Feenstra J, Grobbee D, Jonkman F, Hoes A, Stricker BC. Prevention of relapse in patients with congestive heart failure: the role of precipitating factors. *Heart*. 1998;80(5):432-6.
 12. Petta S, Cabibbo G, Enea M, Macaluso F, Plaia A, Bruno R, et al. Cost-effectiveness of sofosbuvir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C. *Digest Liver Dis*. 2013;45:e371.
 13. Dimarakis I, Habib NA, Gordon MY. Adult bone marrow-derived stem cells and the injured heart: just the beginning? : Elsevier Science BV; 2005.
 14. Wei H, Wong P, Hsu L, Shim W. Human bone marrow-derived adult stem cells for post-myocardial infarction cardiac repair: current status and future directions. *Singapore Med J*. 2009;50(10):935-42.
 15. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, Watt SM. Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. *Eur Heart J*. 2008;29(15):1807-18.
 16. Leistner DM, Fischer-Rasokat U, Honold J, Seeger FH, Schächinger V, Lehmann R, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI): final 5-year results suggest long-term safety and efficacy. *Clin Res Cardiol*. 2011;100(10):925-34.
 17. Assmus B, Schächinger V, Teupe C, Britten M, Lehmann R, Döbert N, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). *Circulation*. 2002;106(24):3009-17.
 18. Matsumori A, investigators aorticifjls. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. *Eur J Heart Fail*. 2003;5(5):669-77.
 19. Pokushalov E, Romanov A, Corbucci G, Prohorova D, Chernyavsky A, Lariouov P, et al. Cardiac resynchronization therapy and bone marrow cell transplantation in patients with ischemic heart failure and electromechanical dyssynchrony: a randomized pilot study. *J Cardiovasc Transl Res*. 2011;4(6):767-78.
 20. Leistner DM, Schmitt J, Palm S, Klotsche J, Estel S, Fink A, et al. Intracoronary administration of bone marrow-derived mononuclear cells and arrhythmic events in patients with chronic heart failure. *Eur Heart J*. 2010;32(4):485-91.
 21. Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. *Circulation*. 2012 Jul 31;126(5):551-68.
 22. Donndorf P, Kundt G, Kaminski A, Yerebakan C, Liebold A, Steinhoff G, et al. Intramyocardial bone marrow stem cell transplantation during coronary artery bypass surgery: a meta-analysis. *J Thorac Cardiovasc Surg*. 2011;142(4):911-20.
 23. Tian T, Chen B, Xiao Y, Yang K, Zhou X. Intramyocardial autologous bone marrow cell transplantation for ischemic heart disease: a systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis*. 2014;233(2):485-92.
 24. Assmus B, Leistner DM, Schächinger V, Erbs S, Elsässer A, Haberbosch W, et al. Long-term clinical outcome after intracoronary application of bone marrow-derived mononuclear cells for acute myocardial infarction: migratory capacity of administered cells determines event-free survival. *Eur Heart J*. 2014;35(19):1275-83.
 25. Silva GV, Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, et al. Catheter-based transcatheter delivery of autologous bone-marrow-derived mononuclear cells in patients listed for heart transplantation. *Texas Heart Institute J*. 2004;31(3):214.
 26. Moccetti T, Sürder D, Klersy C, Vassalli G, Crljenica C, Rossi MG, et al. Sustained improvement in left ventricular function after bone marrow derived cell therapy in patients with acute ST elevation myocardial infarction. A 5-year follow-up from the Stem Cell Transplantation in Ischaemic Myocardium Study. *Swiss Med Wkly*. 2012;142:w13632.
 27. Willerson JT, Perin EC, Ellis SG, Pepine CJ, Henry TD, Zhao DX, et al. Intramyocardial injection of autologous bone marrow mononuclear cells for patients with chronic ischemic heart disease and left ventricular dysfunction (First Mononuclear Cells injected in the US [FOCUS]): Rationale and design. *Am Heart J*. 2010;160(2):215-23.
 28. Trachtenberg B, Velazquez DL, Williams AR, McNiece I, Fishman J, Nguyen K, et al. Rationale and design of the Transcatheter Injection of Autologous Human Cells (bone marrow or mesenchymal) in Chronic Ischemic Left Ventricular Dysfunction and Heart Failure Secondary to Myocardial Infarction (TAC-HFT) trial: a randomized, double-blind, placebo-controlled study of safety and efficacy. *Am Heart J*. 2011;161(3):487-93.
 29. Ross G, Bever FN, Uddin Z, Hockman EM. Troponin I sensitivity and specificity for the diagnosis of acute myocardial infarction. *J Am Osteopath Assoc*. 2000;100(1):29.
 30. Strauer BE, Yousef M, Schannwell CM. The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heart failure: the STAR-heart study. *Eur J Heart Fail*. 2010;12(7):721-9.
 31. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Holschermann H, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. *Eur Heart J*. 2006;27(23):2775-83.
 32. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Int Med*. 2015 Jun 2;162(11):777-84.
 33. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
 34. Deeks J, Dinnes J, D'amico R, Sowden A, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. *Health Technol Assess (Winchester, England)*. 2003;7(27):1-173.
 35. Zhu K, Li J, Wang Y, Luo J, Zhang W, Guo C, et al. Intramyocardial autologous bone marrow-derived stem cells injection for ischemic heart disease ineligible for revascularization: a systematic review and meta-analysis. *Arch Med Res*. 2015;46(4):286-95.
 36. Wen Y, Ding J, Zhang B, Gao Q. Bone marrow-derived mononuclear cell therapy for nonischemic dilated cardiomyopathy—A meta-analysis. *Eur J Clin Invest*. 2018 Apr;48(4):e12894.
 37. Ang KL, Chin D, Leyva F, Foley P, Kubal C, Chalil S, et al. Randomized, controlled trial of intramuscular or intracoronary injection of autologous bone marrow cells into scarred myocardium during CABG versus CABG alone. *Nature Rev Cardiol*. 2008;5(10):663.
 38. Assmus B, Honold J, Schächinger V, Britten MB, Fischer-Rasokat U, Lehmann R, et al. Transcatheter transplantation of progenitor cells after myocardial infarction. *N England J Med*. 2006;355(12):1222-32.
 39. Pokushalov E, Romanov A, Chernyavsky A, Lariouov P, Terekhov I, Artyomenko S, et al. Efficiency of intramyocardial injections of autologous bone marrow mononuclear cells in patients with ischemic heart failure: a randomized study. *J Cardiovasc Transl Res*. 2010;3(2):160-8.
 40. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel HC, Jr., Kormos R, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. *J Thorac Cardiovasc Surg*. 2005;130(6):1631-8.
 41. Hendriks M, Hensen K, Clijsters C, Jongen H, Koninckx R, Bijnen E, et al. Recovery of regional but not global contractile function by the direct intramyocardial autologous bone marrow transplantation: results from a randomized controlled clinical trial. *Circulation*. 2006;114(1 Suppl):I101-7.
 42. Perin EC, Silva GV, Henry TD, Cabreira-Hansen MG, Moore WH, Coulter SA, et al. A randomized study of transcatheter injection of autologous bone marrow mononuclear cells and cell function analysis in ischemic heart failure (FOCUS-HF). *Am Heart J*. 2011;161(6):1078-87 e3.
 43. Yao K, Huang R, Qian J, Cui J, Ge L, Li Y, et al. Administration of intracoronary bone marrow mononuclear cells on chronic myocardial infarction improves diastolic function. *Heart (British Cardiac Society)*. 2008;94(9):1147-53.
 44. Yao K, Huang R, Sun A, Qian J, Liu X, Ge L, et al. Repeated autologous bone marrow mononuclear cell therapy in patients with large myocardial infarction. *Eur J Heart Fail*. 2009;11(7):691-8.
 45. Wöhrle J, Merkle N, Mailander V, Nusser T, Schauwecker P, von Scheidt F, et al. Results of intracoronary stem cell therapy after acute myocardial infarction. *Am J Cardiol*. 2010;105(6):804-12.
 46. Turan RG, Bozdogan TI, Turan CH, Ortak I, Akin I, Kische S, et al. Enhanced mobilization of the bone marrow-derived circulating progenitor cells by intracoronary freshly isolated bone marrow cells transplantation in patients with acute myocardial infarction. *J Cell Mol Med*. 2012;16(4):852-64.

47. Traverse JH, Henry TD, Ellis SG, Pepine CJ, Willerson JT, Zhao DX, et al. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. *JAMA*. 2011;306(19):2110-9.
48. Traverse JH, McKenna DH, Harvey K, Jorgensen BC, Olson RE, Bostrom N, et al. Results of a phase I, randomized, double-blind, placebo-controlled trial of bone marrow mononuclear stem cell administration in patients following ST-elevation myocardial infarction. *Am Heart J*. 2010;160(3):428-34.
49. Suarez de Lezo J, Herrera C, Pan M, Romero M, Pavlovic D, Segura J, et al. [Regenerative therapy in patients with a revascularized acute anterior myocardial infarction and depressed ventricular function]. *Rev Espan Cardiol*. 2007;60(4):357-65.
50. Silva SA, Sousa AL, Haddad AF, Azevedo JC, Soares VE, Peixoto CM, et al. Autologous bone-marrow mononuclear cell transplantation after acute myocardial infarction: comparison of two delivery techniques. *Cell Transplan*. 2009;18(3):343-52.
51. Quyyumi AA, Waller EK, Murrow J, Esteves F, Galt J, Oshinski J, et al. CD34(+) cell infusion after ST elevation myocardial infarction is associated with improved perfusion and is dose dependent. *Am Heart J*. 2011;161(1).
52. Piepoli MF, Vallisa D, Arbasi M, Cavanna L, Cerri L, Mori M, et al. Bone marrow cell transplantation improves cardiac, autonomic, and functional indexes in acute anterior myocardial infarction patients (Cardiac Study). *Eur J Heart Fail*. 2010;12(2):172-80.
53. Cao F, Sun D, Li C, Narsinh K, Zhao L, Li X, et al. Long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up. *Eur Heart J*. 2009;30(16):1986-94.
54. Chen SL, Fang WW, Ye F, Liu YH, Qian J, Shan SJ, et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol*. 2004;94(1):92-5.
55. Grajek S, Popiel M, Gil L, Breborowicz P, Lesiak M, Czepczynski R, et al. Influence of bone marrow stem cells on left ventricle perfusion and ejection fraction in patients with acute myocardial infarction of anterior wall: randomized clinical trial: Impact of bone marrow stem cell intracoronary infusion on improvement of microcirculation. *Eur Heart J*. 2010;31(6):691-702.
56. Herbots L, D'Hooge J, Eroglu E, Thijs D, Ganame J, Claus P, et al. Improved regional function after autologous bone marrow-derived stem cell transfer in patients with acute myocardial infarction: a randomized, double-blind strain rate imaging study. *Eur Heart J*. 2009;30(6):662-70.
57. Akar AR, Durdu S, Arat M, Kilickap M, Kucuk NO, Arslan O, et al. Five-year follow-up after transepical implantation of autologous bone marrow mononuclear cells to ungraftable coronary territories for patients with ischaemic cardiomyopathy. *Eur J Cardiothorac Surg*. 2009;36(4):633-43.
58. Yerebakan C, Kaminski A, Westphal B, Donndorf P, Glass A, Liebold A, et al. Impact of preoperative left ventricular function and time from infarction on the long-term benefits after intramyocardial CD133(+) bone marrow stem cell transplant. *J Thorac Cardiovasc Surg*. 2011;142(6):1530-9 e3.
59. Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Silva GV, et al. Improved exercise capacity and ischemia 6 and 12 months after transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy. *Circulation*. 2004;110(11 Suppl 1):II213-8.
60. Manginas A, Goussetis E, Koutelou M, Karatasakis G, Peristeri I, Theodorakos A, et al. Pilot study to evaluate the safety and feasibility of intracoronary CD133(+) and CD133(-) CD34(+) cell therapy in patients with nonviable anterior myocardial infarction. *Catheter Cardiovasc Interv*. 2007;69(6):773-81.
61. Mocini D, Staibano M, Mele L, Giannantoni P, Menichella G, Colivicchi F, et al. Autologous bone marrow mononuclear cell transplantation in patients undergoing coronary artery bypass grafting. *Am Heart J*. 2006;151(1):192-7.
62. Stamm C, Kleine HD, Choi YH, Dunkelmann S, Lauffs JA, Lorenzen B, et al. Intramyocardial delivery of CD133+ bone marrow cells and coronary artery bypass grafting for chronic ischemic heart disease: safety and efficacy studies. *J Thorac Cardiovasc Surg*. 2007;133(3):717-25.
63. Turan RG, Bozdogan-Turan I, Ortak J, Akin I, Kische S, Schneider H, et al. Improvement of cardiac function by intracoronary freshly isolated bone marrow cells transplantation in patients with acute myocardial infarction. *Circulation*. 2011;75(3):683-91.
64. Bartunek J, Vanderheyden M, Vandekerckhove B, Mansour S, De Bruyne B, De Bondt P, et al. Intracoronary injection of CD133-positive enriched bone marrow progenitor cells promotes cardiac recovery after recent myocardial infarction: feasibility and safety. *Circulation*. 2005;112(9 Suppl):1178-83.
65. Yousef M, Schannwell CM, Kosterling M, Zeus T, Brehm M, Strauer BE. The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. *J Am College Cardiol*. 2009;53(24):2262-9.
66. Katritis DG, Sotiropoulou PA, Karvouni E, Karabinos I, Korovesis S, Perez SA, et al. Transcoronary transplantation of autologous mesenchymal stem cells and endothelial progenitors into infarcted human myocardium. *Catheter Cardiovasc Interv*. 2005;65(3):321-9.
67. Abraham WT, Young JB, León AR, Adler S, Bank AJ, Hall SA, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* [Internet]. 2004;110(18):[2864-8 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/10.1161/01.CIR.000.133.18.11>
68. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *The New England journal of medicine* [Internet]. 2004; 350(21):[2140-50 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/10.1056/NEJMoa032422>
69. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003;107(15):1985-90.
70. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *Jama* [Internet]. 2003; 289(20):[2685-94 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/10.1001/jama.289.20.2685>
71. Thibault B, Harel F, Ducharme A, White M, Ellenbogen KA, Frasure-Smith N, et al. Cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. *Circulation*. 2013;127(8):873-81.
72. Muto C, Solimene F, Gallo P, Nastasi M, La Rosa C, Calvanese R, et al. A randomized study of cardiac resynchronization therapy defibrillator versus dual-chamber implantable cardioverter-defibrillator in ischemic cardiomyopathy with narrow QRS: the NARROW-CRT study. *Circ Arrhythm Electrophysiol*. 2013;6(3):538-45.
73. Menardi E, Vado A, Rossetti G, Racca E, Conte E, Deorsola A, et al. Cardiac resynchronization therapy modifies the neurohormonal profile, hemodynamic and functional capacity in heart failure patients. *Arch Med Res*. 2008;39(7):702-8.
74. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am College Cardiol*. 2008;52(23):1834-43.
75. Kitzman DW, Hundley WG, Brubaker PH, Morgan T, Moore JB, Stewart KP, et al. A randomized, double-blinded trial of enalapril in older patients with heart failure and preserved ejection fraction: effects on exercise tolerance and arterial distensibility. *Circulation: Heart Failure*. 2010;109:898-916.
76. van Veldhuisen DJ, Cohen-Solal A, Böhm M, Anker SD, Babalis D, Roughton M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am College Cardiol*. 2009;53(23):2150-8.
77. Solal AC, Jondeau G, Beauvais F, Berdeaux A. Beneficial effects of carvedilol on angiotensin-converting enzyme activity and renin plasma levels in patients with chronic heart failure. *Eur J Heart Fail*. 2004;6(4):463-6.
78. Matsumori A. Assessment of Response to Candesartan in Heart

- Failure in Japan Study I. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. *Eur J Heart Fail.* 2003;5(5):669-77.
79. Palazzuoli A, Bruni F, Puccetti L, Pastorelli M, Angori P, Pasqui A, et al. Effects of carvedilol on left ventricular remodeling and systolic function in elderly patients with heart failure. *Eur J Heart Fail.* 2002;4(6):765-70.
80. Ciccoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, et al. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J Am College Cardiol.* 2002;40(2):304-10.
81. Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am College Cardiol.* 2001;37(5):1228-33.
82. Investigators R. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation.* 2000;101(4):378-84.
83. Hamer AW, Arkles LB, Johns JA. Beneficial effects of low dose amiodarone in patients with congestive cardiac failure: a placebo-controlled trial. *J Am College Cardiol.* 1989;14(7):1768-74.
84. Cano O, Osca J, Sancho-Tello M-J, Sánchez JM, Ortiz V, Castro JE, et al. Comparison of effectiveness of right ventricular septal pacing versus right ventricular apical pacing. *Am J Cardiol.* 2010;105(10):1426-32.
85. Muto C, Ascione L, Canciello M, Carreras G, Iengo R, Ottaviano L, et al. Effect of right ventricular apical pacing in survivors of myocardial infarction. *Pacing Clin Electrophysiol.* 2009;32:S173-S6.
86. Flevari P, Leftheriotis D, Fountoulaki K, Panou F, Rigopoulos AG, Paraskevaidis I, et al. Long-term nonoutflow septal versus apical right ventricular pacing: Relation to left ventricular dyssynchrony. *Pacing Clin Electrophysiol.* 2009;32(3):354-62.
87. Cho GY, Kim MJ, Park JH, Kim HS, Youn HJ, Kim KH, et al. Comparison of ventricular dyssynchrony according to the position of right ventricular pacing electrode: a multi-center prospective echocardiographic study. *J Cardiovasc Ultrasound.* 2011;19(1):15-20.
88. Occhetta E, Quirino G, Baduena L, Nappo R, Cavallino C, Facchini E, et al. Right ventricular septal pacing: safety and efficacy in a long term follow up. *World J Cardiol.* 2015;7(8):490.