The Efficacy of Mesenchymal Stem Cells for Cardiomyopathy: A Meta-analysis of Randomized Controlled Trials

Yu Li, Linglong Chen, Sheng Li, Ya-Jing Pan

Intensive Care Unit, Wenzhou People's Hospital, Wenzhou, Zhejiang Province, P.R. China

ABSTRACT

Introduction: The efficacy of mesenchymal stem cells (MSCs) for cardiomyopathy remains controversial. We conducted a systematic review and meta-analysis to explore the influence of MSCs versus placebo on the treatment efficacy of cardiomyopathy.

Methods: We searched PubMed, EMbase, Web of Science, EBSCO, and Cochrane Library databases through November 2018 for randomized controlled trials (RCTs) assessing the treatment efficacy of MSCs versus placebo for cardiomyopathy. This meta-analysis was performed using the random-effect model.

Results: Five RCTs were included in the meta-analysis. Overall, compared with the control group for cardiomyopathy, MSCs treatment showed significantly positive effect on LVEF (MD = 5.85; 95% CI = 3.88 to 7.83; $P < .00001$), NYHA classification (MD = -1.11; 95% CI = -1.45 to -0.77; $P < .00001$), LVEDd (MD = -3.00; 95% CI = -5.37 to -0.64; $P = .01$), and the proportion of fixed defects (MD = -4.22; 95% CI = -6.91 to -1.52; $P = .002$), but had no obvious influence on death (RR = 0.42; 95% CI = 0.12 to 1.50; $P = 0.18$) or adverse events (RR = 1.14; 95% CI = 0.70 to 1.86; $P = .59$).

Conclusion: MSCs treatment showed favorable impact on LVEF, NYHA classification, LVEDd, and the proportion of fixed defects for cardiomyopathy patients.

INTRODUCTION

Cardiomyopathy can be caused by many factors such as non-ischemic and ischemic factors [Dadson 2017; Corrado 2017; Akhtar 2018]. For instance, dilated cardiomyopathy is regarded as the most common form of non-ischemic cardiomyopathy, and is characterized by ventricular dilatation and impaired systolic function of the left ventricular sites [Maron 2006]. Current therapies such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and mechanotherapy aim primarily to effectively control heart rate and prevent further damage to the myocardium [Viollet 2012; Hoshikawa 2011; Barasa 2018]. New therapeutic procedures should be developed to provide regenerative potential to damaged myocardium.

Bone marrow-derived cell preparations such as bone marrow mononuclear cells (MNCs) and mesenchymal stem cells (MSCs) are reported to have the potential to ameliorate left ventricular (LV) remodeling in patients with acute myocardial infarction and chronic ischemic cardiomyopathy [Assmus 2006; Leistner 2011; Perin 2012; Williams 2011; Losordo 2011]. Intracoronary delivery of autologous bone marrow stem cells is safe and effective to improve cardiac function in the treatment of post-infarct and chronic ischemic models [Assmus 2006; Wollert 2017; Wollert 2004]. However, cardiomyopathy patients commonly suffer from reduced coronary flow reserve and impaired microvascular function, and there is much controversy concerning cell therapy for these patients [Canetti 2003; Fischer-Rasokat 2009; Martino 2010; Vrtovec 2011].
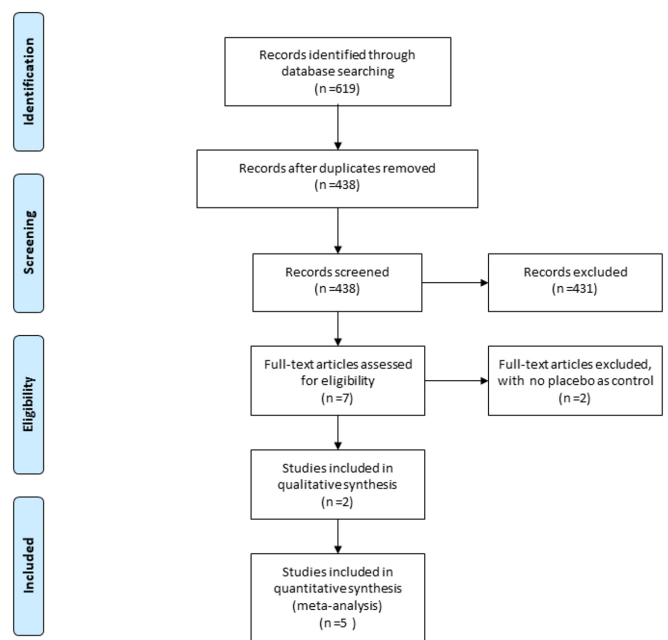
Figure 1. Flow diagram of study searching and selection process.

Characteristics of Included Studies

No.	Author and publication year	MSCs Group					
		Number	Age, y	Male, n	Hypertension, n	Diabetes, n	Methods
1	Xiao 2017	17	51.6 ± 12.2	12	4	5	Intracoronary infusion of bone marrow MSCs
2	Heldman 2014	19	57.1 ± 10.6	18	12	3	MSCs injection with an infusion catheter
3	Xiao 2012	17	51.6 ± 12.2	12	—	—	Intracoronary infusion of MSCs through the guiding catheter
4	Wang 2006	12	54 ± 11.1	9	—	—	Intracoronary injection of autologous MSCs
5	Chen 2006	22	59.3 ± 6.8	19	15	5	MSCs injections after percutaneous coronary intervention

MSCs indicates mesenchymal stem cells.

Recently, several studies regarding the effect of MSCs on cardiomyopathy have been published, and the results have been conflicting [Xiao 2017; Heldman 2014; Xiao 2012; Wang 2006]. With accumulating evidence, we therefore performed a systematic review and meta-analysis of RCTs to explore the efficacy and safety of MSCs treatment versus placebo for cardiomyopathy.

MATERIALS AND METHODS

Ethical approval and patient consent were not required because this was a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis were conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [Moher 2009].

Two investigators independently searched the following databases (inception to November 2018): PubMed, EMbase, Web of Science, EBSCO, and Cochrane Library databases. The electronic search strategy was conducted using the following key words: mesenchymal stem cell; cardiomyopathy. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria were as follows: (i) population patients were diagnosed with cardiomyopathy; (ii) intervention treatments were mesenchymal stem cell therapy versus placebo; (iii) study design was RCT.

Data Extraction and Outcome Measures

We extracted the following information: author, number of patients, age, male, hypertension, diabetes, and detail methods in each group. Data were extracted independently by two investigators, and discrepancies were resolved by consensus. We also contacted the corresponding authors to obtain data when necessary.

The primary outcome was left ventricular ejection fraction (LVEF). Secondary outcomes included New York Heart Association (NYHA) classification, left ventricular end-diastolic diameter (LVEDd), the proportion of fixed defects, death, and adverse events.

Quality Assessment in Individual Studies

Methodological quality of the included studies was independently evaluated using the modified Jadad scale [Jadad 1996]. There were 3 items for the Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad scale varied from 0 to 5 points. An article with Jadad score ≤2 was considered to be of low quality. The study was thought to be of high quality for Jadad score ≥3 [Kjaergard 2001].

Statistical Analysis

We estimated the mean difference (MD) with 95% confidence interval (CI) for continuous outcomes (LVEF, NYHA classification, LVEDd, and the proportion of fixed defects) and risk ratios (RRs) with 95% CIs for dichotomous outcomes (death and adverse events). The random-effects model was used regardless of heterogeneity. Heterogeneity was reported using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity [Higgins 2002]. Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

RESULTS

A detailed flowchart of the search and selection results is shown in Figure 1. 619 potentially relevant articles were identified initially. Finally, five RCTs that met our inclusion criteria were included in the meta-analysis [Xiao 2017; Heldman 2014; Xiao 2012; Wang 2006; Chen 2006].

The baseline characteristics of five eligible RCTs in the meta-analysis are summarized in the Table. The five studies

Characteristics of Included Studies [cont.]

No.	Author and publication year	Number	Age, y	Female, n	Hypertension, n	Diabetes, n	Methods	Jada scores
					Control Group			
1	Xiao 2017	20	54.4 ± 11.6	14	7	6	matched placebo	4
2	Heldman 2014	11	60.0 ± 12.0	10	6	3	matched placebo	5
3	Xiao 2012	20	54.4 ± 11.6	14	—	—	matched placebo	4
4	Wang 2006	12	58.4 ± 11	8	—	—	matched placebo	3
5	Chen 2006	23	57.8 ± 7.2	21	15	7	matched placebo	4

MSCs indicates mesenchymal stem cells.

were published between 2006 and 2017, and sample sizes ranged from 24 to 45. Two RCTs reported the same sample at different follow-up of 3 months [Xiao 2012] and 12 months [Xiao 2017]. MSCs were administered by intracoronary infusion [Xiao 2017; Xiao 2012; Wang 2006; Chen 2006] or injections in 10 left ventricular sites [20]. Three RCTs involved dilated cardiomyopathy [Xiao 2017; Xiao 2012; Wang 2006]; the remaining two RCTs involved ischemic cardiomyopathy [Heldman 2014; Chen 2006].

Among the five studies included here, three studies reported LVEF [Xiao 2017; Xiao 2012; Chen 2006]; two studies reported NYHA classification [Xiao 2017; Chen 2006]; two studies reported LVEDd and proportion of fixed defects [Xiao 2017; Xiao 2012]; three studies reported death [Xiao 2017; Xiao 2012; Chen 2006]; and four studies reported adverse events [Xiao 2017; Xiao 2012; Chen 2006]. Jadad scores of the five included studies varied from 3 to 5, and all five studies were considered of high-quality according to quality assessment.

Primary Outcome: LVEF

This outcome data was analyzed with the random-effects model, and compared to control group for cardiomyopathy, MSCs treatment resulted in significantly improved LVEF (MD = 5.85; 95% CI = 3.88 to 7.83; P < .00001), with no heterogeneity among the studies (I^2 = 0%, heterogeneity P = .84) (Figure 2).

Sensitivity Analysis

No heterogeneity was observed among the included studies for LVEF, and thus we did not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

Secondary Outcomes

In comparison with control group for cardiomyopathy, MSCs treatment was associated with substantially reduced NYHA classification (MD = -1.11; 95% CI = -1.45 to -0.77; P < .00001; Figure 3), LVEDd (MD = -3.00; 95% CI = -5.37 to -0.64; P = .01; Figure 4), and proportion of fixed defects (MD = -4.22; 95% CI = -6.91 to -1.52; P = .002; Figure 5). There was no statistical difference of death (RR = 0.42;

95% CI = 0.12 to 1.50; P = .18; Figure 6) or adverse events (RR = 1.14; 95% CI = 0.70 to 1.86; P = .59; Figure 7) between the two groups.

DISCUSSION

Cardiomyopathy leads to the loss of a large number of cardiomyocytes that are replaced by fibroblasts (i.e. ventricle remodeling), and is an important cause of heart failure [Dadson 2017; Maron 2006; Karkkainen 2007]. Cardiomyocytes are not terminally differentiated cells, but the number of regenerative cells is far fewer than that required for cardiac repair [Beltrami 2001]. Myocardial regenerative therapy has emerged as an increasingly important strategy for the treatment of cardiomyopathy through transplantation of exogenous functional cells to replace, repair, or enhance the biological function of non-functional cardiomyocytes [Nagaya 2005; Seth 2006]. Bone marrow MSCs exhibit the features of self-regeneration, differentiation plasticity, sufficient source, no immune rejection, and have the ability to increase LVEF and improve coronary microvascular function for acute and chronic ischemic heart disease [Blau 2001; Eydt 2016].

Our meta-analysis concludes that MSCs treatment shows a remarkably positive effect on LVEF, NYHA classification, LVEDd, and the proportion of fixed defects for cardiomyopathy patients. The proposed mechanisms of cell therapy for cardiomyopathy include cardiomyocyte regeneration, angiogenesis, and inhibition of myocardial apoptosis and ventricular remodeling through paracrine factors of the infused cells for ischemic heart disease [Assmus 2002; Lezaic 2015; Strauer 2002]. Intracoronary stem cell injection in patients with dilated cardiomyopathy is found to be effective and safe despite severely reduced coronary flow reserve and impaired microvascular function [Canetti 2003; Duran 2007].

Different stem cell subpopulations have different characteristics and plasticity, and bone marrow MSCs have great potential in proliferation and regeneration. Clinical trials have compared intracoronary infusion of bone marrow
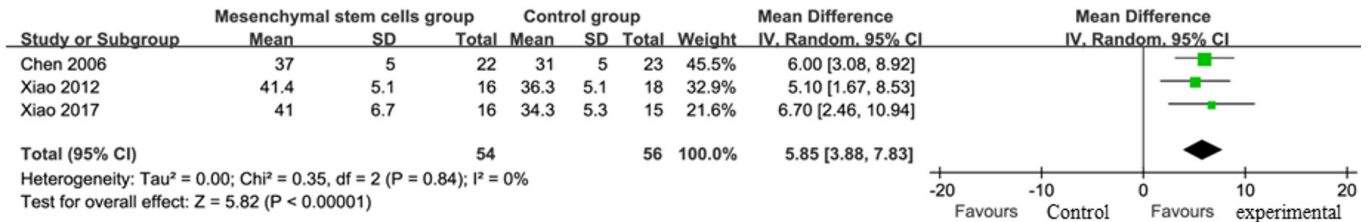
Study or Subgroup	Mesenchymal stem cells group			Control group			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Chen 2006	37	5	22	31	5	23	45.5%	6.00 [3.08, 8.92]	
Xiao 2012	41.4	5.1	16	36.3	5.1	18	32.9%	5.10 [1.67, 8.53]	
Xiao 2017	41	6.7	16	34.3	5.3	15	21.6%	6.70 [2.46, 10.94]	
Total (95% CI)			54			56	100.0%	5.85 [3.88, 7.83]	

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 5.82 (P < 0.00001)

Figure 2. Forest plot for the meta-analysis of LVEF (%).

Study or Subgroup	Mesenchymal stem cells group			Control group			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Chen 2006	1.3	0.7	22	2.5	0.6	23	77.4%	-1.20 [-1.58, -0.82]	
Xiao 2017	1.9	1.1	16	2.7	0.9	15	22.6%	-0.80 [-1.51, -0.09]	
Total (95% CI)			38			38	100.0%	-1.11 [-1.45, -0.77]	

Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 6.48 (P < 0.00001)
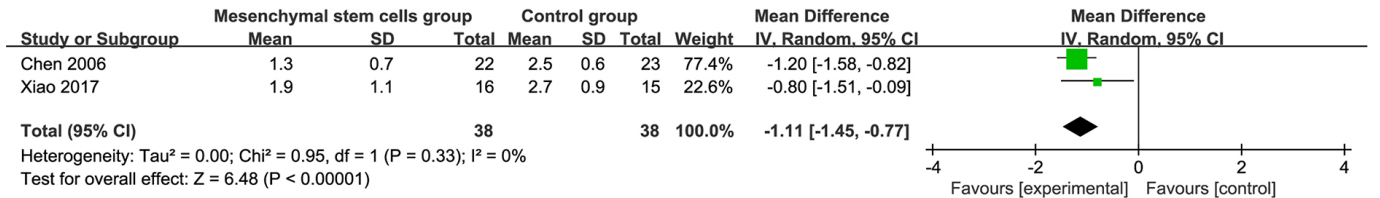
Figure 3. Forest plot for the meta-analysis of NYHA classification.

Study or Subgroup	Mesenchymal stem cells group			Control group			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Xiao 2012	59.8	5.6	16	62.2	3.7	18	53.5%	-2.40 [-5.63, 0.83]	
Xiao 2017	61.6	5.6	16	65.3	4.2	15	46.5%	-3.70 [-7.17, -0.23]	
Total (95% CI)			32			33	100.0%	-3.00 [-5.37, -0.64]	

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.49 (P = 0.01)
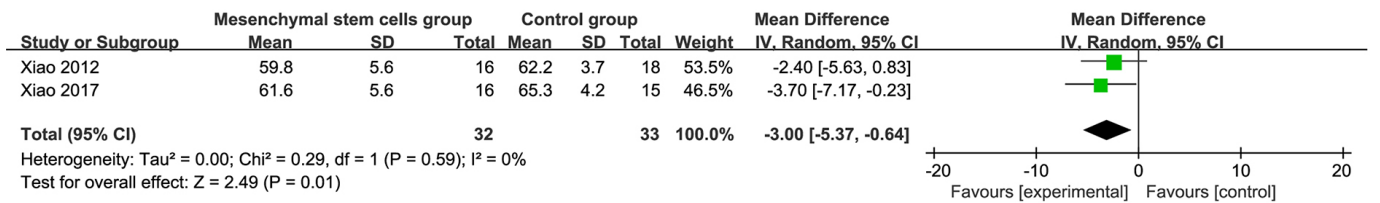
Figure 4. Forest plot for the meta-analysis of LVEDd (mm).

Study or Subgroup	Mesenchymal stem cells group			Control group			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Xiao 2012	19.6	5.2	16	23.2	5	18	61.4%	-3.60 [-7.04, -0.16]	
Xiao 2017	20.6	6.8	16	25.8	5.5	15	38.6%	-5.20 [-9.54, -0.86]	
Total (95% CI)			32			33	100.0%	-4.22 [-6.91, -1.52]	

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.07 (P = 0.002)

Figure 5. Forest plot for the meta-analysis of proportion of fixed defects (%).

MSCs with BNCs in patients with dilated cardiomyopathy, and both cell therapies have been shown to significantly improve LVEF and NYHA class, and their efficacy is comparable [Xiao 2017; Tendera 2009]. In addition, the higher number of intracoronary stem cells may contribute to the greater improvement in LVEF by improving the retention rate after cell transplantation [Abdel-Latif 2007; Quyyumi 2011]. Regarding the sensitivity analysis, there is no significant heterogeneity. However, different approaches and number of MSCs, various factors to cause cardiomyopathy and follow-up times, may have some influence on the pooling results. Previous study has confirmed the efficacy and safety of intracoronary injection of autologous MSCs [Strauer 2010]. MSCs results show no increase in death or adverse events after MSCs treatment for cardiomyopathy based on the results of our meta-analysis.

This meta-analysis has several limitations. First, our analysis is based on five RCTs, and all of them have a relatively small sample size (n < 100). Overestimation of the treatment effect was more likely in smaller trials compared with larger samples. Although there is no significant heterogeneity, different origins, delivery approaches and number of MSCs, various factors to cause cardiomyopathy, may affect the pooling results. Finally, some important indexes such as 6-minute walk distance and re-hospitalization cannot undergo the meta-analysis based on current RCTs.

Conclusion

MSCs treatment shows important efficacy and safety for the treatment of cardiomyopathy, and should be recommended in clinical work, with caution.

Figure 6. Forest plot for the meta-analysis of death.

Figure 7. Forest plot for the meta-analysis of adverse events.

REFERENCES

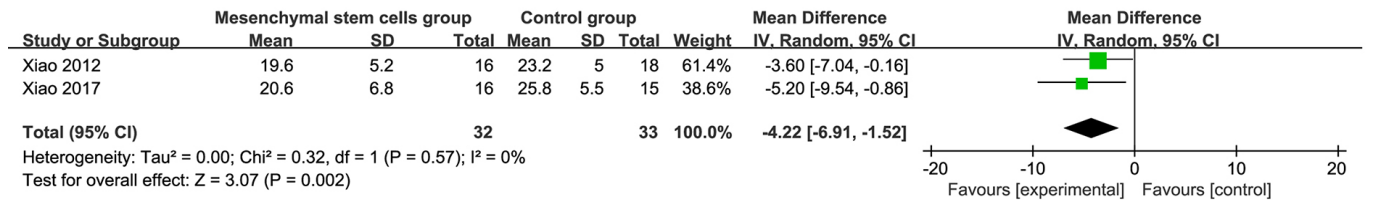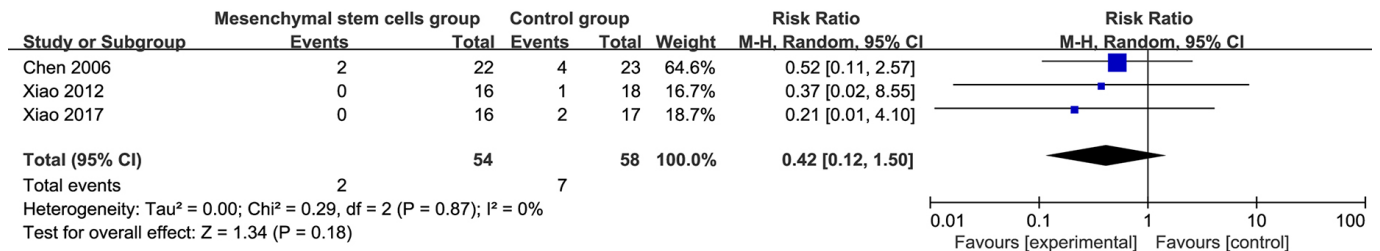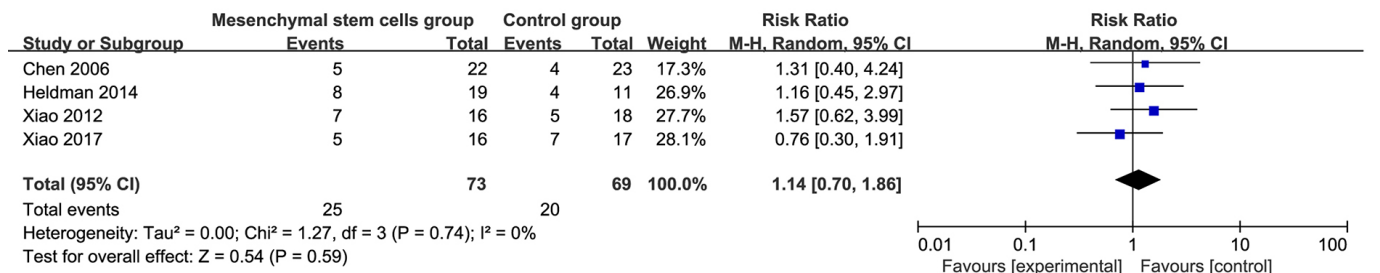Abdel-Latif A, Bolli R, Tleyjeh IM, et al. 2007. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. Archives Internal Med 167:989-97.

Akhtar MM, Elliott P. 2018. Impact of left bundle branch block (LBBB) in dilated cardiomyopathy (DCM) with intermediate left ventricular systolic dysfunction (LVSD). Int J Cardiol 278:199-201.

Assmus B, Schachinger V, Teupe C, et al. 2002. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation 106:3009-17.

Assmus B, Honold J, Schachinger V, et al. 2006. Transcoronary transplantation of progenitor cells after myocardial infarction. New Engl J Med 355:1222-32.

Barasa A, Goloskokova V, Ladfors L, Patel H, Schaufelberger M. 2018. Symptomatic recovery and pharmacological management in a clinical cohort with peripartum cardiomyopathy. J Maternal-fetal Neonatal Med 31:1342-9.

Beltrami AP, Urbanek K, Kajstura J, et al. 2001. Evidence that human cardiac myocytes divide after myocardial infarction. New Engl J Med 344:1750-7.

Blau HM, Brazelton TR, Weimann JM. 2001. The evolving concept of a stem cell: entity or function? Cell 105:829-41.

Canetti M, Akhter MW, Lerman A, et al. 2003. Evaluation of myocardial blood flow reserve in patients with chronic congestive heart failure due to idiopathic dilated cardiomyopathy. Am J Cardiol 92:1246-9.

Chen S, Liu Z, Tian N, et al. 2006. Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery. J Invasive Cardiol 18:552-6.

Corrado D, Basso C, Judge DP. 2017. Arrhythmogenic cardiomyopathy. Circ Research 121:784-802.

Dadson K, Hauck L, Billia F. 2017. Molecular mechanisms in cardiomyopathy. Clin Sci 131:1375-92.

Duran JR, 3rd, Taffet G. 2007. Coronary microvascular dysfunction. New Engl J Med 356:2324-5; author reply 5.

Eydt C, Geburek F, Schrock C, et al. 2016. Sternal bone marrow derived equine multipotent mesenchymal stromal cells (MSCs): investigations considering the sampling site and the use of different culture media. Veterinary Med and Sci 2:200-10.

Fischer-Rasokat U, Assmus B, Seeger FH, et al. 2009. A pilot trial to assess potential effects of selective intracoronary bone marrow-derived progenitor cell infusion in patients with nonischemic dilated cardiomyopathy: final 1-year results of the transplantation of progenitor cells and functional regeneration enhancement pilot trial in patients with nonischemic dilated cardiomyopathy. Circulation Heart Failure 2:417-23.

Heldman AW, DiFede DL, Fishman JE, et al. 2014. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. JAMA 311:62-73.

Higgins JP, Thompson SG. 2002. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 21:1539-58.

Hoshikawa E, Matsumura Y, Kubo T, et al. 2011. Effect of left ventricular reverse remodeling on long-term prognosis after therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and beta blockers in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 107:1065-70.

Jadad AR, Moore RA, Carroll D, et al. 1996. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clinical Trial 17:1-12.

Karkkainen S, Peuhkurinen K. 2007. Genetics of dilated cardiomyopathy. Annals of Medicine 39:91-107.

Kjaergard LL, Villumsen J, Gluud C. 2001. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals Internal Med 135:982-9.

Leistner DM, Fischer-Rasokat U, Honold J, et al. 2011. 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 100:925-34.

Lezaic L, Socan A, Poglajen G, et al. 2015. Intracoronary transplantation of CD34(+) cells is associated with improved myocardial perfusion in patients with nonischemic dilated cardiomyopathy. J Cardiac Failure 21:145-52.

Losordo DW, Henry TD, Davidson C, et al. 2011. Intramyocardial, autologous CD34+ cell therapy for refractory angina. Circulation Res 109:428-36.

Maron BJ, Towbin JA, Thiene G, et al. 2006. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 113:1807-16.

Martino HF, Oliveira PS, Souza FC, et al. 2010. A safety and feasibility study of cell therapy in dilated cardiomyopathy. Brazilian J Med Biol Res (Revista brasileira de pesquisas medicas e biologicas) 43:989-95.

Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62:1006-12.

Nagaya N, Kangawa K, Itoh T, et al. 2005. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation 112:1128-35.

Perin EC, Willerson JT, Pepine CJ, et al. 2012. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. JAMA 307:1717-26.

Quyyumi AA, Waller EK, Murrow J, et al. 2011. CD34(+) cell infusion after ST elevation myocardial infarction is associated with improved perfusion and is dose dependent. Am Heart J 161:98-105.

Seth S, Narang R, Bhargava B, et al. 2006. Percutaneous intracoronary cellular cardiomyoplasty for nonischemic cardiomyopathy: clinical and histopathological results: the first-in-man ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) trial. J Am Coll of Cardiol 48:2350-1.

Strauer BE, Brehm M, Zeus T, et al. 2002. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 106:1913-8.

Strauer BE, Yousef M, Schannwell CM. 2010. 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 failure 12:721-9.

Tendera M, Wojakowski W, Ruzyllo W, et al. 2009. Intracoronary infusion of bone marrow-derived selected CD34+CXCR4+ cells and nonselected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial. Eur Heart J 30:1313-21.

Viollet L, Thrush PT, Flanigan KM, Mendell JR, Allen HD. 2012. Effects of angiotensin-converting enzyme inhibitors and/or beta blockers on the cardiomyopathy in Duchenne muscular dystrophy. Am J Cardiol 110:98-102.

Vrtovec B, Poglajen G, Sever M, et al. 2011. Effects of intracoronary stem cell transplantation in patients with dilated cardiomyopathy. J Cardiac Failure 17:272-81.

Wang JA, Xie XJ, He H, et al. 2006. A prospective, randomized, controlled trial of autologous mesenchymal stem cells transplantation for dilated cardiomyopathy. Zhonghua xin xue guan bing za zhi 34:107-10.

Williams AR, Trachtenberg B, Velazquez DL, et al. 2011. Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling. Circulation Res. 2011;108:792-6.

Wollert KC, Meyer GP, Lotz J, et al. 2004. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet 364:141-8.

Wollert KC, Meyer GP, Muller-Ehmsen J, et al. 2017. Intracoronary autologous bone marrow cell transfer after myocardial infarction: the BOOST-2 randomised placebo-controlled clinical trial. Euro Heart J 38:2936-43.

Xiao WT, Gao LJ, Gao CY, et al. 2012. Comparative study on the efficacy of intracoronary infusion with various types of autologous bone marrow stem cells for patients with dilated cardiomyopathy. Zhonghua xin xue guan bing za zhi 40:575-8.

Xiao W, Guo S, Gao C, et al. 2017. A randomized comparative study on the efficacy of intracoronary infusion of autologous bone marrow mononuclear cells and mesenchymal stem cells in patients with dilated cardiomyopathy. International Heart J 58:238-44.