4-2018

A comprehensive meta-analysis of stem cell therapy for chronic angina

Rahman Shah
University of TennesseeMemphis, Tennessee

Samuel B. Latham
University of Tennessee, Memphis, Tennessee.

Sajjad A. Khan
Aga Khan University, sajjadali.khan@aku.edu

Muhammad Shahreyar
University of Tennessee, Memphis, Tennessee.

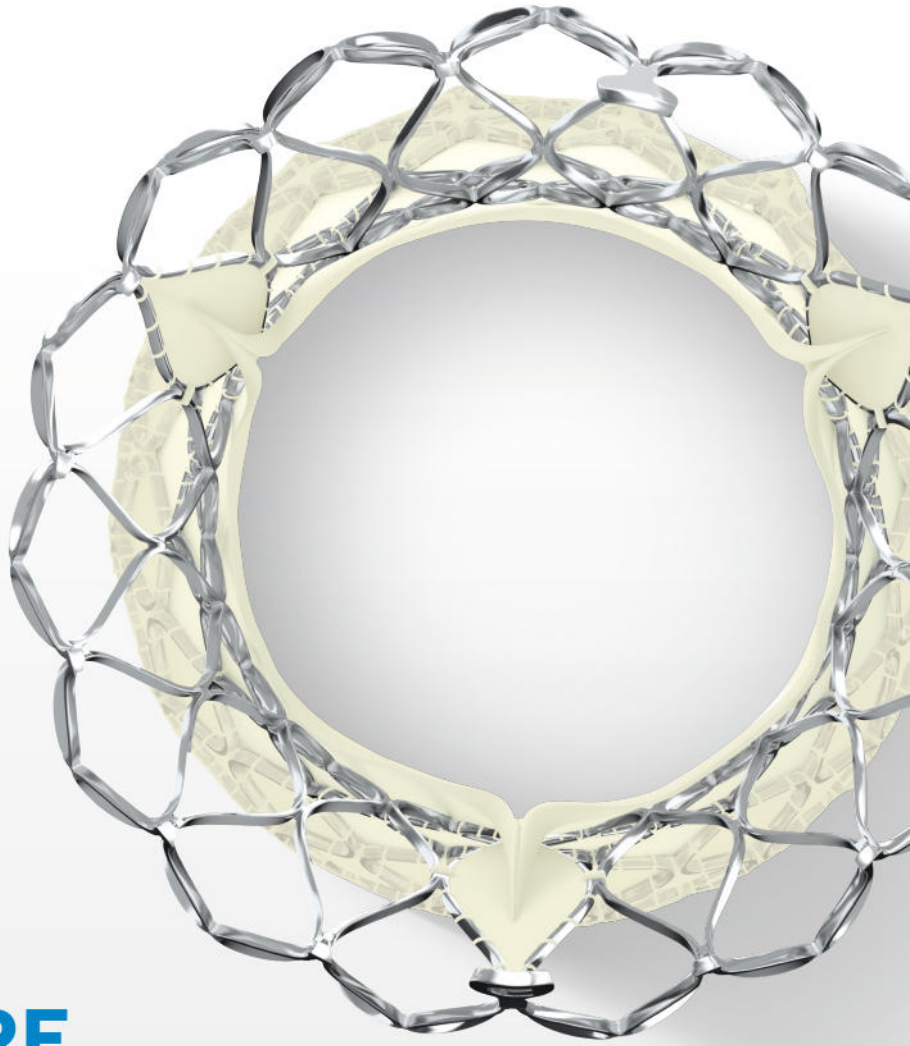
Inyong Hwang
University of Tennessee, Memphis, Tennessee.

See next page for additional authors

Authors
Rahman Shah, Samuel B. Latham, Sajjad A. Khan, Muhammad Shahreyar, Inyong Hwang, and Ion S. Jovin

ABOVE AND BEYOND

Evolut™
TAVR Platform



LEARN MORE

Medtronic

Received: 6 December 2017 | Revised: 2 February 2018 | Accepted: 4 February 2018

DOI: 10.1002/clc.22922

WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

A comprehensive meta-analysis of stem cell therapy for chronic angina

Rahman Shah[1] | Samuel B. Latham[1] | Sajjad A. Khan[2] | Muhammad Shahreyar[1] | Inyong Hwang[1] | Ion S. Jovin[3]

[1]Department of Internal Medicine, University of Tennessee, Memphis, Tennessee

[2]Department of Internal Medicine, Aga Khan University, Karachi, Pakistan

[3]Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia

Correspondence
Rahman Shah, MD, University of Tennessee, School of Medicine, Section of Cardiovascular Medicine, 1030 Jefferson Avenue, Memphis, TN 38104
Email: shahcardiology@yahoo.com

Background: A substantial proportion of patients with coronary artery disease do not achieve complete revascularization and continue to experience refractory angina despite optimal medical therapy. Recently, stem cell therapy has emerged as a potential therapeutic option for these patients. However, findings of individual trials have been scrutinized because of their small sample sizes and lack of statistical power. Therefore, we conducted an updated comprehensive meta-analysis of available randomized controlled trials (RCTs) with the largest sample size ever reported on this subject.

Hypothesis: In patients with chronic angina stem cell therapy improves clinical outcomes.

Methods: Scientific databases and websites were searched for RCTs. Data were independently collected by 2 investigators, and disagreements were resolved by consensus. Data from 10 trials including 658 patients were analyzed.

Results: Stem cell therapy improved Canadian Cardiovascular Society angina class (risk ratio: 1.53, 95% CI: 1.09 to 2.15, $P = 0.013$), exercise capacity (standardized mean difference [SMD]: 0.56, 95% CI: 0.23 to 0.88, $P = 0.001$), and left ventricular ejection fraction (SMD: 0.63, 95% CI: 0.27 to 1.00, $P = 0.001$) compared with placebo. It also decreased anginal episodes (SMD: −1.21, 95% CI: −2.40 to −0.02, $P = 0.045$) and myocardial perfusion defects (SMD: −0.70, 95% CI: −1.11 to −0.29, $P = 0.001$). However, no improvements in all-cause mortality were observed after a relatively short follow-up.

Conclusions: In patients with chronic angina on optimal medical therapy, stem cell therapy improves symptoms, exercise capacity, and left ventricular ejection fraction. These findings warrant confirmation using larger trials.

KEYWORDS

Angina, Cell Therapy, Stem Cell

1 | INTRODUCTION

The number of patients diagnosed with severe coronary artery disease is increasing because of improved survival rates and an aging population.[1] Despite continued developments and improvements in treatments that facilitate myocardial revascularization, a substantial proportion of these patients do not achieve complete revascularization and continue to experience refractory angina despite optimal medical therapy (OMT).[1] Recently, several small randomized clinical trials (RCTs) suggested that stem cell therapy may be a potential therapeutic option for these patients.[2–11] However, individual trials have been criticized for their small sample sizes and resulting lack of statistical power. Therefore, we conducted an updated comprehensive meta-analysis of available RCTs.

2 | METHODS

2.1 | Data sources and searches

This meta-analysis was performed according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[12] We performed computerized literature searches of the PubMed, http://www.Clinicaltrials.gov, and Cochrane databases from

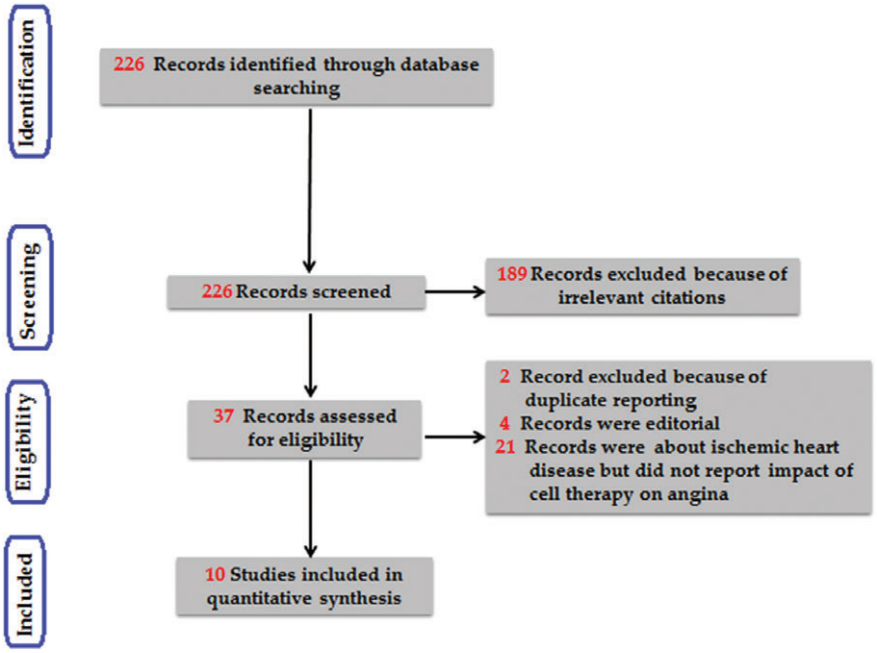


FIGURE 1 Search flow diagram

their respective inceptions to November 2017 without language restrictions. Searches were performed on various combinations of the following terms: "cell therapy," "stem cell," "angina," "ischemic heart disease," and "clinical trial." In addition, abstracts from major international cardiology scientific meetings were reviewed. We also contacted corresponding authors for those articles not reporting mean values for continuous variables.

2.2 | Data extraction and quality assessment

RCTs were included if patients suffering from angina despite OMT were randomly assigned to either stem cell therapy or placebo treatment. The data were independently collected by 2 investigators, and disagreements were resolved by consensus. The potential risk of bias of RCTs was appraised according to the Cochrane Collaboration guidelines.[13]

The primary efficacy endpoints were changes in Canadian Cardiovascular Society (CCS) angina class, anginal frequencies, and exercise capacity. The secondary efficacy endpoints were left ventricular ejection fraction (LVEF) and myocardial perfusion defects (summed score) identified using single-photon emission computed tomography (SPECT). Study definitions were used for the outcome data.

2.3 | Data synthesis and analysis

This meta-analysis was performed using the Comprehensive Meta-Analysis system, version 3 (Biostat, Inc., Englewood, NJ). For **dichotomous** variables, pooled risk ratios (RRs) were calculated using a random-effects model. For continuous variables, the data were summarized as the standardized mean difference (SMD) because the measurement units for some of the outcomes varied across studies. Because the trials by Pokushalov and Henry enrolled predominantly ischemic cardiomyopathy patients, additional sensitivity studies were performed excluding both trials.[5,8] We evaluated the presence of heterogeneity across trials using the Cochran Q test and the Higgins I^2 test.[14] When heterogeneity was discovered, a sensitivity analysis was performed by excluding 1 study at a time and evaluating the impact on the summary results.[15] Publication bias was not assessed because the number of included trials was inadequate to properly assess a funnel plot or to use more advanced regression-based assessments.[16]

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. No extramural funding was used to support this work.

3 | RESULTS

Ten RCTs including 658 patients (386 in cell groups and 272 in placebo groups) met our inclusion criteria.[2–11] All included RCTs were blinded. The search flow diagram is shown in Figure 1. Table 1 describes the characteristics of each individual trial. The majority of these trials were multicenter, but they included only a small number of patients. Four studies used $CD34^+$ cells, 3 used bone marrow mononuclear cells, 2 used $CD133^+$ cells, and 1 used adipose-derived stem cells. The techniques used to harvest these cells varied among the studies. The follow-up duration was 6 months in 5 studies, 12 months in 4 studies, and 24 months in 1 study.

In patients suffering from chronic angina, stem cell therapy decreased anginal episodes (SMD: −1.21, 95% CI: −2.40 to −0.02, $P = 0.045$) compared with the placebo-treated group (Figure 2). However, significant between-trial heterogeneity was found (Cochran's $Q = 115.8$, $P < 0.001$, $I^2 = 96.54\%$). Sensitivity analysis suggests that heterogeneity originated from the study by Wang, which was a single-center study performed in China.[4] Removing this trial eliminated the heterogeneity (Cochran's $Q = 2.9$, $P = 0.39$, $I^2 = 0.00\%$)

TABLE 1 Baseline characteristic of included trials

Characteristic		Losordo, 2007	Tse, 2007	Van Ramshorst, 2009	Wang, 2010	Pokushalov, 2010	Losordo, 2011	Jimenez-Quevedo, 2014	Henry, 2016	Posvic, 2016	Wojakowski, 2017
Study type		MC	MC	SC	SC	SC	MC	MC	MC	MC	SC
Sample size, n	Cell	18	19	25	56	55	111	19	17	50	16
	Placebo	6	9	25	56	54	56	9	14	28	15
Mean age, y	Cell	NR	65	64	61	61	60	70	64	64	64
	Placebo	NR	68	62	61	62	61	58	65	64	61
Male sex, %	Cell	NR	79	92	50	87	86	79	94	80	12
	Placebo	NR	88	80	52	85	89	100	93	86	11
Hx of MI, %	Cell	61	NR	56	9	100	79	68	82	41	63
	Placebo	50	NR	72	11	100	75	67	100	56	73
Hx of CABG, %	Cell	94	68	96	3	71	91	NR	77	91	81
	Placebo	66	63	76	2	76	96	NR	71	82	80
Baseline LVEF, %	Cell	NR	51	56	NR	27	59	51	31	52	48
	Placebo	NR	45	54	NR	26	59	55	31	52	53
Methods for LVEF estimation		Echo	Cardiac MRI	Cardiac MRI	SPECT	Echo	SPECT	SPECT, echo	Echo	NR	MRI, SPECT
Type of cell		$CD34^+$	BMMNC	BMMNC	$CD34^+$	BMMNC	$CD34^+$	$CD133^+$	ADRC	$CD34^+$	$CD133^+$
Route of injection		PTE	PTE	PTE	IC	PTE	PTE	PTE	PTE	PTE	PTE
Mean dose of cells		5×10^4, 1×10^5, 5×10^5	1×10^6, 2×10^6	100×10^6	5.6×10^7	41×10^6	1×10^5, 5×10^5[a]	30×10^6	$40–80 \times 10^6$	1×10^5 to 1×10^7	2.8×10^6 and 5.3×10^6
Follow-up duration, mo		6	6	6	6	12	12	6	12	24	12
Endpoints		Efficacy: angina frequency, CCS class, ETT, MPI, QOL. Safety: arrhythmia, LVEF	Primary: ETT. Secondary: LVEF, CCS, MPI	Primary: MPI. Secondary: CCS, LVEF. Safety: arrhythmia, MI	Efficacy: angina frequency, CCS, ETT, MPI. Safety: arrhythmia, LVEF	Primary: MPI. Secondary: arrhythmia, CCS, LVEF, mortality. Safety: CCS, LVEF	Primary: angina frequency. Secondary: ETT, use of antianginal medication, CCS, QOL	Efficacy: angina frequency, CCS, ETT, LVEF, MPI. Safety: MACE, MACVE	Efficacy: Angina frequency, CCS, ETT, LVEF, QOL, VO_2max. Safety: arrhythmia, MACE	Efficacy: angina frequency, ETT. Secondary: arrhythmia, MACE	Primary: MPI. Secondary: CCS, LVEF

Abbreviations: ADRC, adipose-derived regenerative cell(s); BMMNC, bone marrow mononuclear cell(s); CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; echo, echocardiogram; ETT, exercise tolerance test; Hx, history of; IC, intracoronary; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; MACVE, major adverse cerebrovascular events; MC, multicenter; MI, myocardial infarction; MPI, myocardial perfusion imaging; MRI, magnetic resonance imaging; NR, not reported; PTE, percutaneous transendocardial; QOL, quality of life; SC, single center; SPECT, single-photon emission computed tomography; VO_2max, maximum oxygen consumption.

[a] 55 patients used low-dose cells (1×10^5) and 56 patients received high-dose cells (5×10^5).

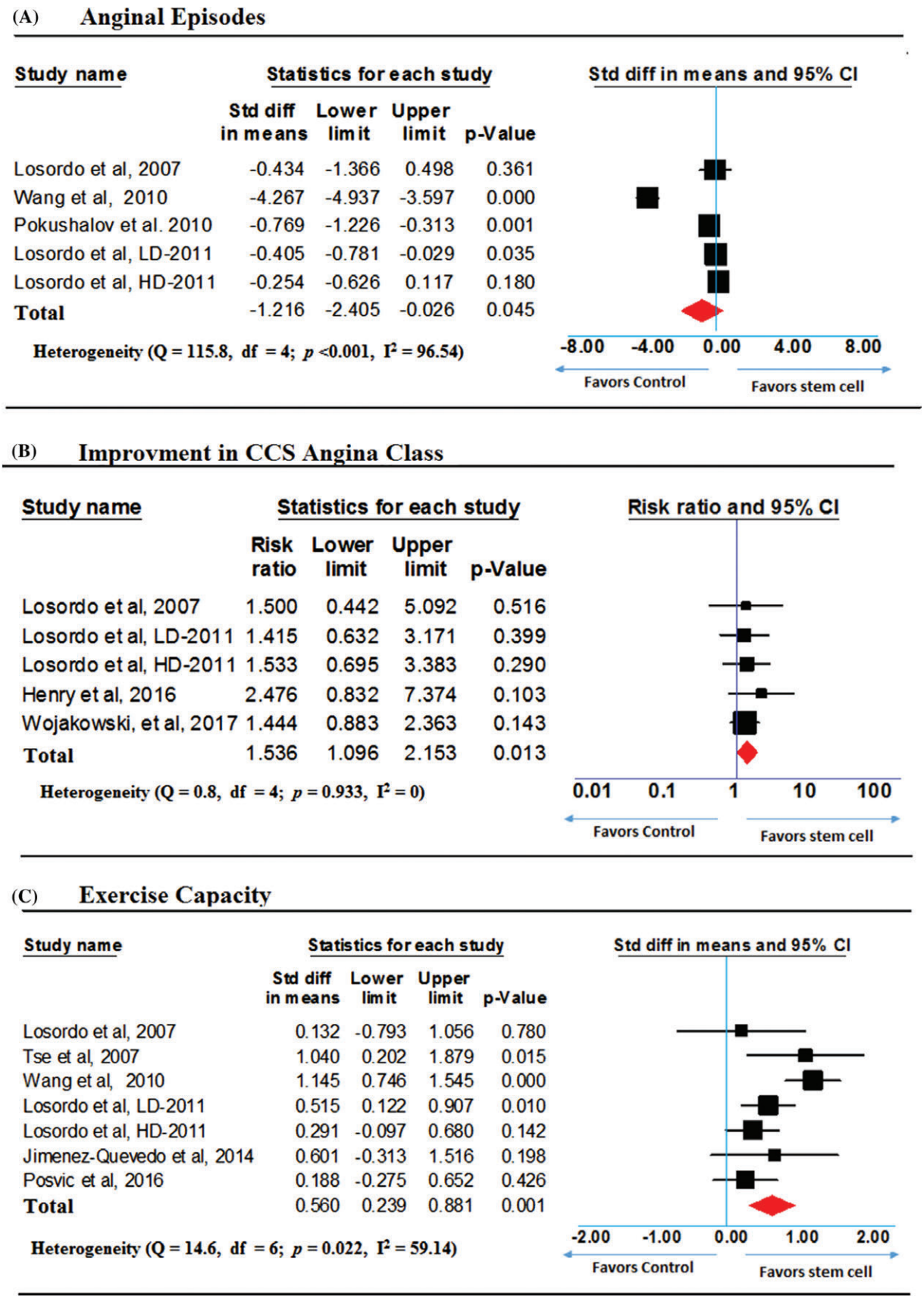


FIGURE 2 (A) Improvement in anginal episodes from baseline to the longest follow-up time point. (B) Individual and pooled RRs for improvements in CCS angina class. (C) Improvement in exercise capacity from baseline to the longest follow-up time point. The size of the square represents the relative impact of the corresponding study on the overall estimate. The overall summary estimate for the analysis is marked with a diamond. The width of the diamond represents the 95% CI. Abbreviations: CCS, Canadian Cardiovascular Society; CI, confidence interval; df, degrees of freedom; RR, risk ratio; std diff, standard difference

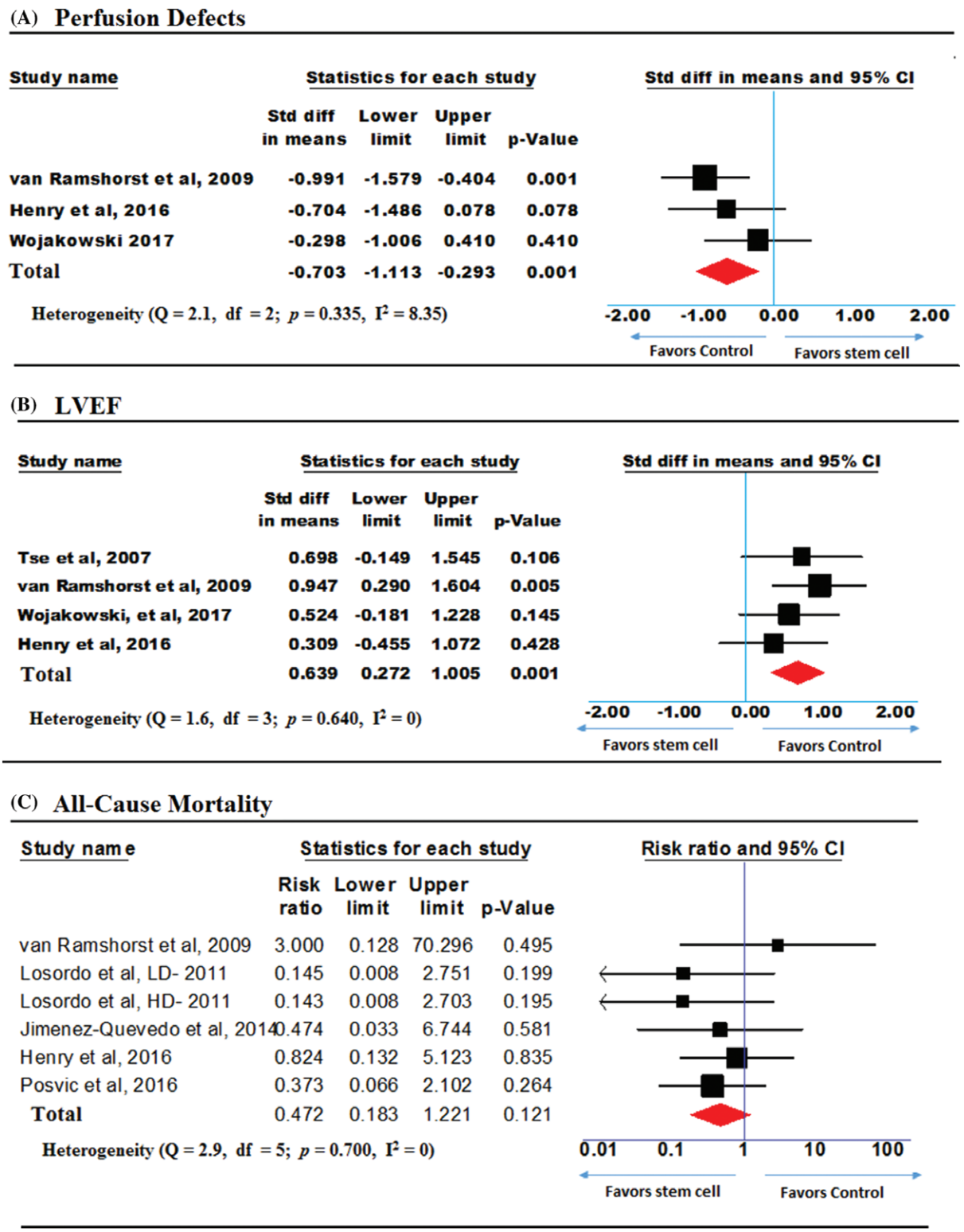


FIGURE 3 (A) Improvements in perfusion defects (by SPECT) from baseline to the longest follow-up time point. (B) Improvement in LVEF. (C) Individual and pooled RRs for all-cause mortality. Abbreviations: CI, confidence interval; df, degrees of freedom; LVEF, left ventricular ejection fraction; RR, risk ratio SPECT, single-photon emission computed tomography; std diff, standard difference

without affecting summary results (SMD: −0.44, 95% CI: −0.66 to −0.21, $P < 0.001$). On the other hand, removing any other trial did not eliminate heterogeneity.

Similarly, significantly more patients in the stem cell–treated group displayed improvements in their CCS angina class (RR: 1.53, 95% CI: 1.09 to 2.15, $P = 0.013$; Figure 2). There was no significant heterogeneity between the trials ($Q = 0.8$, $P = 0.93$, $I^2 = 0.00\%$).

Stem cell treatment also increased exercise capacity (SMD: 0.56, 95% CI: 0.23 to 0.88, $P = 0.001$) compared with the placebo-treated group (Figure 2). Again, significant heterogeneity was found

TABLE 2 Incidence of serious adverse events by trial

Author, Year	Cell Groups	Placebo
Losordo, 2007	A-arrhythmia, 1; CHF, 16; respiratory arrest, 11; CVA, 5; bleeding/anemia, 16; electrolytes disorder, 16	A-arrhythmia, 33; V-arrhythmia, 1
Tse, 2007	NR	NR
Van Ramshorst, 2009	CHF, 4	PE, 4; CVA, 4; infection, 4; breast cancer, 4
Wang, 2010	A-arrhythmia, 2; V-arrhythmia, 2; angina exacerbation, 3; CVA, 2; endocrine/electrolyte disorder, 2	A-arrhythmia, 3; V-arrhythmia, 2; angina exacerbation, 5; endocrine/electrolyte disorder, 2
Pokushalov, 2010	NR	NR
Losordo, 2011	MI, 5; MACE, 12; stroke, 3; cardiac hospitalization or ED visit, 32	MI, 12; MACE, 26; stroke, 1; cardiac hospitalization or ED visit, 37
Jimenez-Quevedo, 2014	MACE and MACVE, 10; sustained VT/VF, 5; PE, 5; repeat hospitalization for cardiac cause, 11	MACE and MACVE, 11; sustained VT/VF, 11; repeat hospitalization for cardiac cause, 25
Henry, 2016	MACE, 35; MI, 5; stroke/TIA, 11; CHF hospitalization, 11	MACE, 21; stroke/TIA, 7; CHF hospitalization, 21
Posvic, 2016	MACE, 42; MI, 10; CV hospitalization, 32; V-arrhythmia, 7	MACE, 67; MI, 7; CV hospitalization, 64; V-arrhythmia, 3
Wojakowski, 2017	PFA, 6; UA, 6	DVT, 6; UA, 6

Abbreviations: A-arrhythmia, atrial arrhythmia; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; DVT, deep venous thrombosis; ED, emergency department; MACE, major adverse cardiac events; MI, myocardial infarction; NR, none reported; PE, pericardial effusion; PFA, pseudoaneurysm of femoral artery; TIA, transient ischemic attack; UA, unstable angina; V-arrhythmia, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia. Data are presented as %.

(Cochran's Q = 14.6, P = 0.022, I^2 = 59.14%), originating from the study by Wang. Removing this study eliminated heterogeneity (P = 0.52, I^2 = 0.00%) without affecting summary results (SMD: 0.39, 95% CI: 0.17 to 0.61, P < 0.001).

Stem cell therapy also improved LVEF (SMD: 0.63, 95% CI: 0.27 to 1.00, P = 0.001; Figure 3). However, no effects on all-cause mortality were found (RR: 0.47, 95% CI: 0.183 to 1.22, P = 0.121; Figure 3). No between-trial heterogeneity was found for any of these outcomes.

Finally, sensitivity analyses excluding the studies by Pokushalov and Henry did not change our summary results or conclusion.[5,8] In addition, the incidence of adverse effects with stem cell therapy was low, as shown in Table 2.

4 | DISCUSSION

In this meta-analysis of 10 RCTs, we evaluated the efficacy of stem cell therapy in patients suffering from chronic angina. We found that stem cell therapy improved the CCS angina class and decreased angina frequency during 6 to 24 months of follow-up. The stem cell therapy also improved exercise capacity, perfusion defects (observed via SPECT), and LVEF.

Despite continued developments and improvements in treatments facilitating myocardial revascularization, about 5% to 15% of patients do not achieve complete revascularization and continue to experience refractory angina despite OMT.[1] Although it results in low mortality, refractory angina is a debilitating condition. Thus, a new therapy is needed for these patients. Recently, stem cell therapy has emerged as a potential therapeutic option for these patients.[1] Stem cell therapy is thought to improve myocardial perfusion and angina by promoting neovascularization.[1] This may be partly due to the capacity of stem cells to differentiate into endothelial cells and smooth muscle.[1] However, the predominant mechanism by which stem cells act appears to be through the secretion of paracrine factors that have cryoprotective and angiogenic effects.[17]

Several small-sized RCTs and meta-analyses have suggested that stem cell therapy may improve symptoms in patient with chronic angina.[2–10,18,19] However, since those meta-analyses, several new RCTs have been reported, arguably rendering those meta-analyses outdated.[8–10] Our updated, comprehensive meta-analysis (consisting of the largest sample size ever reported) showed that, in patients with chronic angina, stem cell therapy improved symptoms and exercise capacity. It also decreased perfusion defects measured by SPECT. In addition, stem cell therapy was associated with a statistically significant improvement in LVEF. However, in the majority of these trials, global left ventricular systolic function was preserved, and the absolute improvement in LVEF with stem cell therapy was small. Finally, because of the small sample sizes of these trials and shorter follow-up periods, no definite conclusion can be made about the impact of stem cell therapy on mortality. Therefore, additional trials with larger sample sizes and longer follow-ups are needed.

4.1 | Study limitations

This meta-analysis has several limitations. First, we did not have individual participant data; data from various studies were combined.[20] Each study had its own protocol and definitions as well as follow-up duration. Specifically, the type of stem cell, number of stem cells, and delivery method varied across studies. However, because small numbers of patients participated in each trial, subgroup analyses to determine the relative efficacy between certain types of cells or routes of administration were not performed. Therefore, additional studies must be conducted to compare cell types and routes of administration. Similarly, the definition of major adverse cardiac events varied across the studies, so we could not report on the effects related to the major adverse cardiac events rate. In addition, not all studies reported data about the class of angina and the number of episodes of angina; we were accordingly unable to include data from all of the

trials to estimate the pooled effect of stem cell on anginal symptoms. Finally, because the sample sizes of these trials were small, our findings are hypothesis-generating, and additional trials with larger samples are needed. Despite these limitations, this is the most comprehensive meta-analysis with the largest sample size ever reported on this subject.

5 | CONCLUSION

In patients suffering from chronic angina, stem cell therapy significantly improves symptoms, exercise capacity, and LVEF compared with placebo-treated groups. It also decreases myocardial perfusion defects. These findings warrant further studies in a larger clinical trial in the future.

Conflicts of interest

The authors declare no potential conflicts of interest.

ORCID

Rahman Shah http://orcid.org/0000-0001-9397-272X

REFERENCES

1. Henry TD, Satran D, Jolicoeur EM. Treatment of refractory angina in patients not suitable for revascularization. *Nat Rev Cardiol*. 2014;11:78–95.
2. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation*. 2007;115:3165–3172.
3. Tse HF, Thambar S, Kwong YL, et al. Prospective randomized trial of direct endomyocardial implantation of bone marrow cells for treatment of severe coronary artery diseases (PROTECT-CAD trial). *Eur Heart J*. 2007;28:2998–3005.
4. Wang S, Cui J, Peng W, et al. Intracoronary autologous CD34+ stem cell therapy for intractable angina. *Cardiology*. 2010;117:140–147.
5. Pokushalov E, Romanov A, Chernyavsky A, 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;3:160–168.
6. Losordo DW, Henry TD, Davidson C, et al; ACT34-CMI Investigators. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res*. 2011;109:428–436.
7. Jimenez-Quevedo P, Gonzalez-Ferrer JJ, Sabate M, et al. Selected CD133(+) progenitor cells to promote angiogenesis in patients with refractory angina: final results of the PROGENITOR randomized trial. *Circ Res*. 2014;115:950–960.
8. Henry TD, Pepine CJ, Lambert CR, et al. The Athena trials: autologous adipose-derived regenerative cells for refractory chronic myocardial ischemia with left ventricular dysfunction. *Catheter Cardiovasc Interv*. 2017;89:169–177.
9. Povsic TJ, Henry TD, Traverse JH, et al. The RENEW trial: efficacy and safety of intramyocardial autologous CD34(+) cell administration in patients with refractory angina. *JACC Cardiovasc Interv*. 2016;9:1576–1585.
10. Wojakowski W, Jadczyk T, Michalewska-Włudarczyk A, et al. Effects of transendocardial delivery of bone marrow–derived CD133+ cells on left ventricle perfusion and function in patients with refractory angina: final results of randomized, double-blinded, placebo-controlled REGENT-VSEL Trial. *Circ Res*. 2017;120:670–680.
11. van Ramshorst J, Bax JJ, Beeres SL, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. *JAMA*. 2009;301:1997–2004.
12. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1–9.
13. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
14. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
15. Sutton AJ, Abrams KR, Jones DR, et al, eds. *Methods for Meta-analysis in Medical Research*. Chichester, UK: Wiley; 2000.
16. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
17. Gnecchi M, Zhang Z, Ni A, et al. Paracrine mechanisms in adult stem cell signaling and therapy. *Circ Res*. 2008;103:1204–1219.
18. Fisher SA, Dorée C, Brunskill SJ, et al. Bone marrow stem cell treatment for ischemic heart disease in patients with no option of revascularization: a systematic review and meta-analysis. *PloS One*. 2013;8:e64669.
19. Khan AR, Farid TA, Pathan A, et al. Impact of cell therapy on myocardial perfusion and cardiovascular outcomes in patients with angina refractory to medical therapy: a systematic review and meta-analysis. *Circ Res*. 2016;118:984–993.
20. Gyöngyösi M, Wojakowski W, Lemarchand P, et al; ACCRUE Investigators. Meta-analysis of cell-based cardiac studies (ACCRUE) in patients with acute myocardial infarction based on individual patient data. *Circ Res*. 2015;116:1346–1360.

How to cite this article: Shah R, Latham SB, Khan SA, Shahreyar M, Hwang I, Jovin IS. A comprehensive meta-analysis of stem cell therapy for chronic angina. *Clin Cardiol*. 2018;41:525–531. https://doi.org/10.1002/clc.22922