Research Paper

Stem cell-derived extracellular vesicles for myocardial infarction: a meta-analysis of controlled animal studies

Lihong Yang[1,2,*], Jialu Zhu[2,*], Cong Zhang[3], Juntao Wang[4], Fengyang Yue[2], Xingtai Jia[5], Hongzhi Liu[2,6,7]

[1]Department of Cardiac Function Evaluation, Henan Provincial People's Hospital, Zhengzhou, Henan, China
[2]Department of Cardiology, Zhengzhou University People's Hospital, Zhengzhou, Henan, China
[3]Department of Electrocardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou, Henan, China
[4]Department of Cardiology, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou, Henan, China
[5]Department of Cardiology, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
[6]Department of Cardiology, Fuwai Central China Hospital, Zhengzhou, Henan, China
[7]Department of Cardiology, Henan Provincial People's Hospital, Zhengzhou, Henan, China
[*]Equal contribution

Correspondence to: Hongzhi Liu; **email:** 834529847@qq.com

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ABSTRACT

Aims: Stem cell-derived extracellular vesicles (EVs) have emerged as a promising therapy for myocardial infarction, but its effects remain incompletely understood. We aim to systematically review the efficacy of EVs on myocardial infarction in both small and large animals.

Methods: On April 5, 2018, we searched the PubMed, Embase and Web of Science databases using variations of "myocardial infarction" and "extracellular vesicle". Controlled studies about the treatment effects of stem cell-derived EVs in myocardial infarction animal model were included. Meta-regression analysis was used to reveal the factors affecting the EVs treatments.

Results: Of 1210 studies retrieved, 24 were eligible for meta-analysis. EVs injection was associated with the improvements of left ventricular ejection fraction (12.65%), fractional shortening (7.54%) and the reduction of infarct size/area at risk (-15.55%). Meta-regression analysis did not reveal the association between treatment efficacy and type of stem cell, ligation-to-injection interval, route of delivery, dosage of delivery or follow-up period (all P values > 0.05). The median quality score of eligible studies was only 1, indicating potential risks of bias.

Conclusion: Stem cell-derived EVs improve cardiac function and reduce infarct size in myocardial infarction animals, but current pool-up study reveals no associations between common factors and treatment effects.

INTRODUCTION

Myocardial infarction (MI) remains an important component of global health loss, although pharmacological treatments and interventional strategies have been greatly developed to reduce the morbidity and mortality in the past decades [1]. One of the main goals of MI management is to salvage and even regenerate the infarcted myocardium. Despite timely coronary interventions and sufficient evidence-based pharmacological treatments, a large proportion of MI patients still suffer from cardiomyocyte apoptosis, ventricular wall thinning, cavity enlargement and finally heart failure [2]. The past decades have seen the surge of many animal studies and clinical trials conducted to reveal the role of stem cells in MI repair, yet controversies remain regarding the mechanisms and efficacy of stem cells for MI [3]. Cell therapy has some inherent disadvantages such as low immediate and long-term cell retention rate after implantation to target tissues and low cell survival rate due to the adverse environments of MI region. Recently, stem cell-free therapies including extracellular vesicles (EVs) have been proposed to repair the infarcted myocardium.

EVs are bilayer lipid-enclosed microvesicles derived from endosomes and secreted by almost all types of cells such as cancer cells, endothelial cells, and stem cells. EVs contain various bioactive components including nucleic acids, proteins, lipids and carbohydrates, functioning as intercellular message carriers under both physiologic and pathologic conditions [4]. Currently, studies have indicated stem cell-derived EVs as a promising therapeutic agent for myocardial infarction, heart failure and dilated cardiomyopathy [5]. Intramyocardial and intravenous injections of EVs have been demonstrated to have anti-apoptotic, anti-fibrotic and angiogenic effects on infarcted myocardium [6-8]. Despite various aims and setups, most animal studies

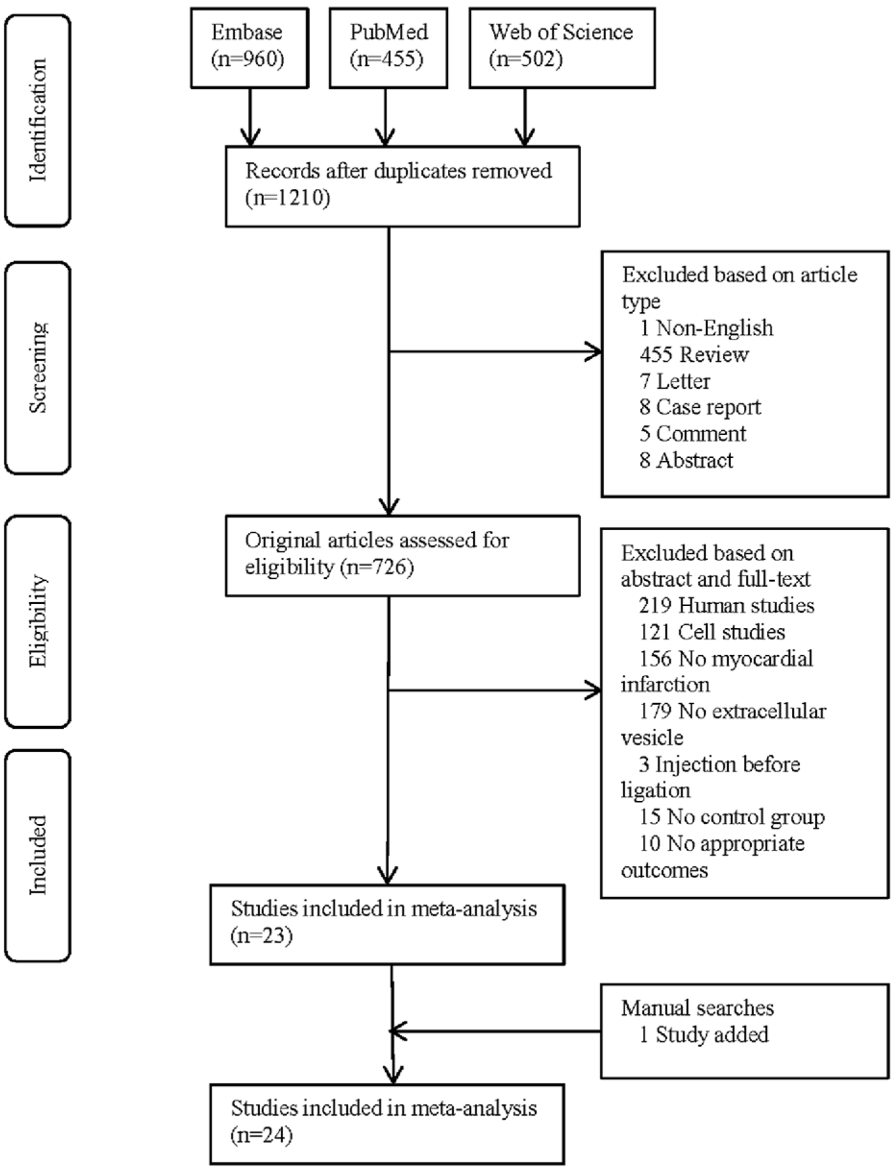

Figure 1. PRISMA flowchart of study selection.

using EVs for MI repair commonly follow four steps: isolation and characterization of EVs, ligation of coronary artery, injection of EVs to infarct zone, and assessments of cardiac function and infarct size. In this study, we quantitatively analyse the treatment effects of stem cell-derived EVs on improving cardiac function and reducing infarct size in animal models after myocardial infarction.

RESULTS

After removal of duplicates, 1210 studies were primarily screened by article type. Then 726 original articles were further screened by abstract and full-text, resulting in 23 eligible studies. One study was added by manually searching the reference lists of eligible articles and review articles [9]. Overall, 24 studies were finally included in statistical analysis (Figure 1).

Baseline characteristics

The eligible studies contained 31 comparisons and 524 MI animals, including 272 animals in EVs group and 252 animals in control group (Supplement 1). EVs were frequently isolated from mesenchymal stem cells (14/31), cardiac progenitor cells (7/31), and cardiosphere-derived cells (7/31). The size of isolated EVs ranged between 20-1000 nm (mostly 50-200 nm). Surface markers included CD 63, CD 9 and CD 81 were used to identify and sort out EVs from other components. A variety of microRNAs were reported in EVs, such as miR-210 and miR-451. Most studies ligated the left anterior descending artery and injected EVs to the animals intramyocardially (22/31) or intravenously (8/31). The median dosage was 100 µl. The median time from injection to examination was 4 weeks.

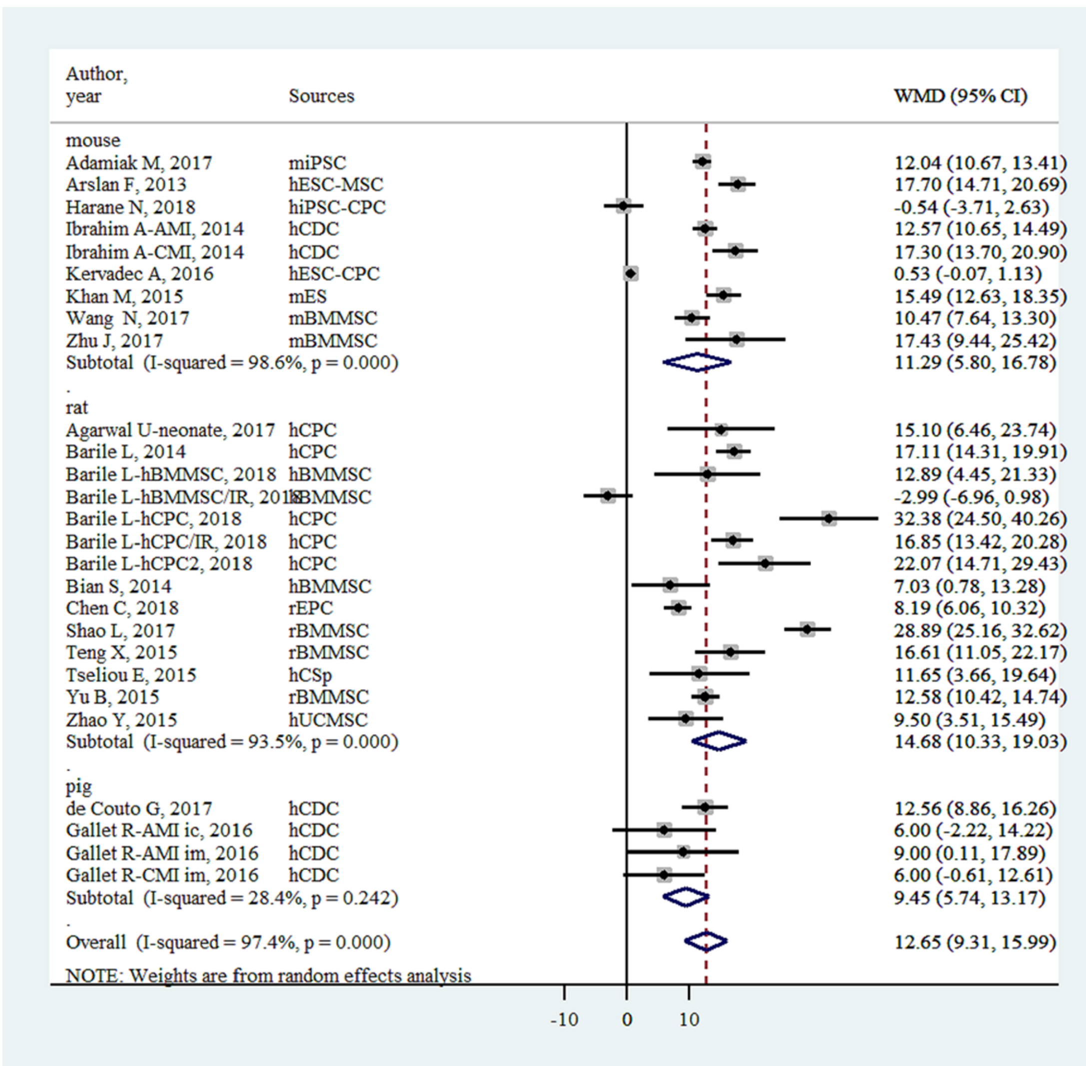

Figure 2. Improvement of left ventricular ejection fraction with injection of stem-cell-derived extracellular vesicles.

EF

EVs injection was associated with an EF improvement of 12.65% (95% confidence interval: 9.31- 15.99%, P<0.001, Figure 2). The improvement was significantly higher in small animals (13.32% [9.66%-16.98%], P < 0.001) than in large animals (9.45% [5.74-13.17%], P < 0.001).

FS

FS was only reported in small-animal studies (n = 9). EVs injection was associated with an FS improvement of 7.54% (6.08- 9.01%, P<0.001, Figure 3).

IS/AAR

EVs injection was associated with an IS/AAR reduction of -15.55% (-18.56%~ -12.55%, P < 0.001, Figure 4). The effect sizes for large animals and small animals were -17.19% (-36.17%~1.80%, P < 0.001) and -15.50% (-17.57%~ -13.42%, P < 0.001), respectively.

Meta-regression analysis

Meta-regression analysis did not show significant associations between effect size and type of stem cell, ligation-to-injection interval, route of delivery and follow-up period (Supplement 2, P > 0.05). Dosage was previously reported to be associated with efficacy of EVs injection, but our meta-regression analysis did not show statistical significance (P = 0.34 for all animals, and P = 0.88 for small animals).

Risk of bias and sensitivity analysis

The median quality score was 1 (Supplement 3). Although random allocation was reported in 10 comparisons, none of them provided sufficient details on the generation procedures of random sequence. Blinding injection was only performed in 3 comparisons. Blinding assessment was conducted in 11 comparisons. Sensitivity analysis was performed by removing the highest and lowest values. Removing the highest value did not result in marked fluctuation of EF

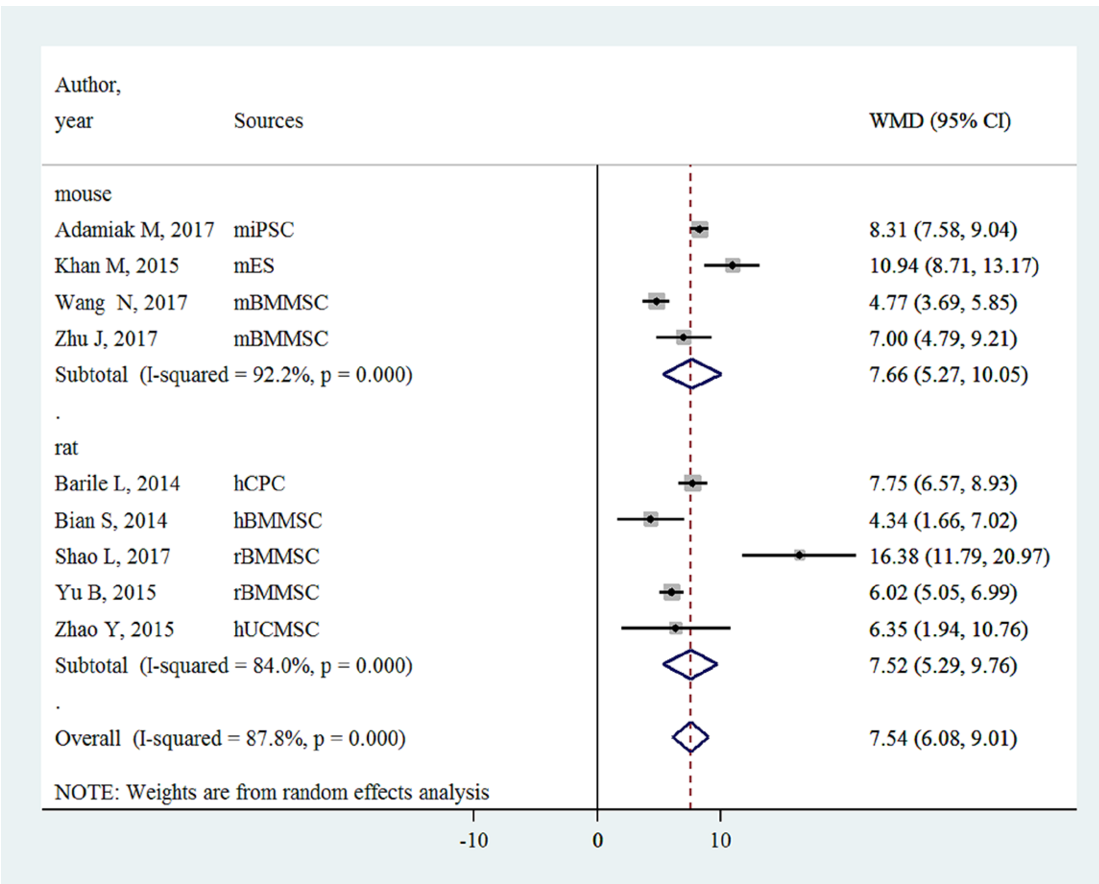

Figure 3. Improvement of left ventricular fractional shortening with injection of stem-cell-derived extracellular vesicles.

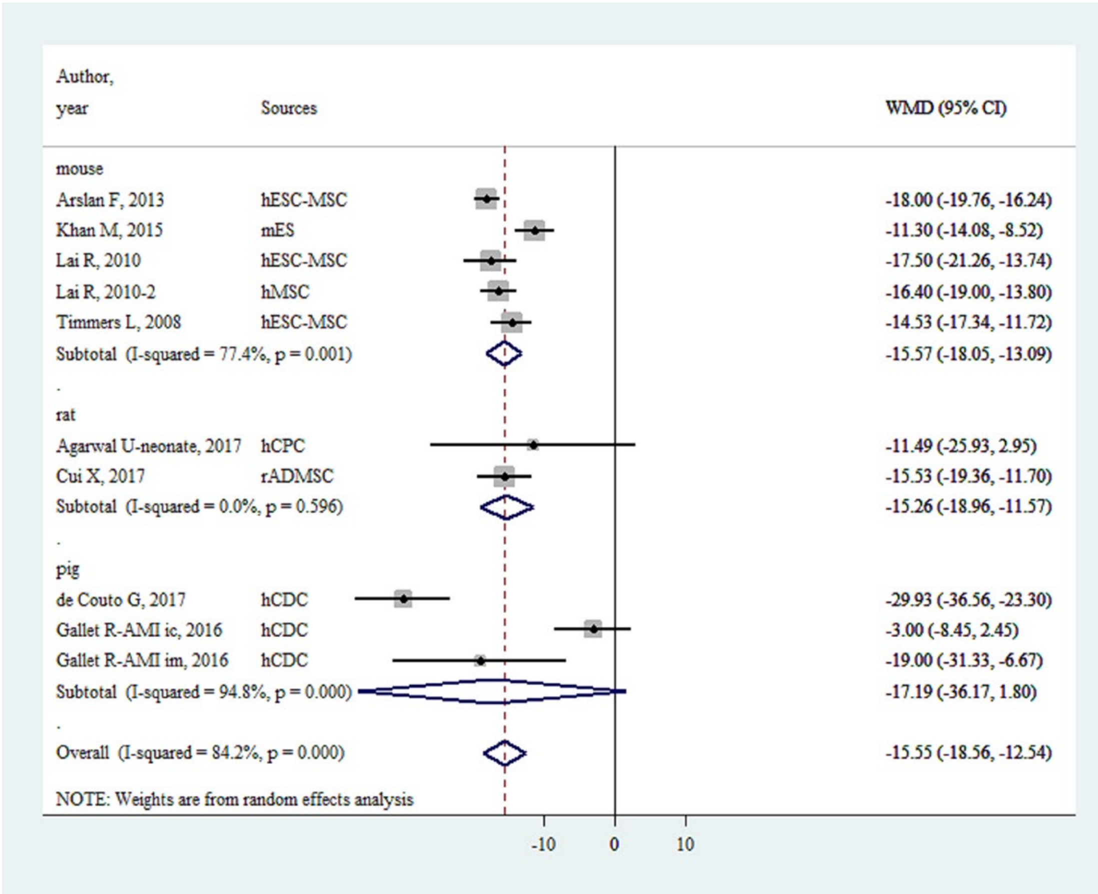

Figure 4. Reduction of infarct size/area at risk with injection of stem-cell-derived extracellular vesicles.

(10.90% [7.22-14.58%]), FS (5.19% [2.24-8.15%]) or IS/AAR (-12.84% [-16.76~-8.92%]), compared with the original results. Similarly, removing the highest and lowest values of other outcomes did not result in any significant changes of the original effect sizes.

DISCUSSION

To the best of our knowledge, this is the first preclinical systematic review and meta-analysis of large- and small- animal experiments to provide evidence summary to support the treatment efficacy of EVs injection for MI. Our major finding is that the injection of stem cell-derived EVs is effective in improving EF and FS and reducing IS/AAR in MI animals, but the overall quality of currently available studies is low and requires more improvements in the future. It is noteworthy that compared with previous preclinical meta-analyses of stem cell therapy, stem-cell-derived EVs injection seems to be more effective than cardiac stem cell injection and mesenchymal stem cell injection in improving cardiac function (improvement of EF: 12.65% *vs*. 10.66% *vs*. 10.79%) in animal models [10, 11]. Embryonic stem cell-derived EVs appear to be more effective in improving EF, based on the evidence from small animals. Mouse embryonic stem cell-derived EVs promote endogenous repair mechanisms by augmenting cardiac progenitor cell survival and proliferation, indicating the complicated interactions of exogenous and endogenous stem cells during cardiac remodeling [8]. This kind of interactions among various types of cells may provide synergetic effects to allow better regeneration of infarcted myocardium. Moreover, EVs may also exert beneficial effects on myocardial infarction through the conversion of inactivated cells to activated cells. For instance, CDCs-derived EVs are capable of converting inert cells (e.g., fibroblasts) to therapeutically active cells [6].

As a cell-free therapy, EVs injection does not have the inherent problems of cell therapy such as low cell survival and teratoma formation, thereby serving as an efficient and safe alternative to cell therapy [12]. EVs injection facilitates post-infarct cardiac remodelling by reducing TUNEL-positive area and fibrotic area and promoting angiogenesis [13]. These beneficial effects of EVs have been mainly attributed to the intracellular components, e.g., microRNAs and growth factors.

Similarities of intracellular components such as microRNAs (miR-126, miR-146a and miR-210) between EVs and parent cells have been recently demonstrated by a study, which also showed the abundance of some microRNAs specifically in EVs [14]. These special microRNAs are likely to confer better cardioprotective effects to EVs than their parent stem cells. More importantly, exogenous microRNAs and other bioactive molecules may also be delivered by EVs to heal ischemic myocardium. By far, the cardioprotective effects of EVs have been associated with the activation of multiple signalling pathways such as the Wnt/β-catenin signaling pathway, PI3K/Akt pathway and ERK1/2 signaling pathway [7, 15, 16]. The modification and pretreatment of EVs may further empower them to become a useful tool for cardiac repair after myocardial infarction. EVs secreted from the stem cells with GATA-4 overexpression, Akt overexpression and hypoxia-pretreatment have shown better improvements of cardiac function in animal models, as compared with the EVs derived from unmodified stem cells [17-19]. Although all these methods have been proposed to cultivate the benefits of EVs for post-infarct cardiac repair, currently our understandings of the underlying pathophysiological mechanisms remain incomplete and need further investigations.

Follow-up period is crucial for the beneficial effects of stem cell therapy for animal model of MI, as shown by previous meta-analyses that the treatment effect often drops with time [20,21]. However, our analysis did not reveal the association between follow-up period and treatment effects of EVs injection. This may be due to the fact that in our eligible studies, EVs were derived from various stem cells and injected at different dosages, so the effect of follow-up period on MI might have been somehow offset by these factors. As shown in our meta-analysis, EVs have been isolated and identified using different methods across various studies. Thus, standardization and optimization of isolation and identification techniques serve as the cornerstone for the better translation of EVs from laboratory to clinic. The overall quality of experiment conduction was low in eligible animal studies as reflected by a low SYCLE score of 1. The lack of randomization and blinding in animal studies might have introduced the risks of overestimation of treatment effects of EVs into original studies as well as into our meta-analysis. Considering all these factors which might have affected the results of animal studies to different extents, we believe that our findings of no associations between type of EVs, or the route, dosage and timing of injection have been more likely affected by interstudy heterogeneities than by the real treatment effect of EVs. In the future, *in-vivo* studies may be designed in a more rigorous way and with reference to the requirements of human randomized controlled trials.

Study limitations

First, although we have shown that stem cell-derived EVs injection could generally improve cardiac function, we did not identify any factors which might affect the efficacy of EVs treatments. More rigorously designed animal studies are in fact needed to reveal the treatment effect of EVs. Second, our meta-analysis has included mostly small animal models (mice and rats, 22/24) which might have been less clinically relevant than large animals (rabbits, dogs and pigs). The inclusion of a large amount of small-animal studies might have also overestimated the treatment effect of stem cell-derived EVs on MI.

CONCLUSIONS

Stem cell-derived EVs are effective in improving cardiac function and reducing infarct size in animal MI models, but current meta-analysis did not reveal any significant associations between treatment effects and relevant factors such as timing, route and dosage of injection. More rigorously designed animal studies are needed to investigate the treatment effects of EVs.

MATERIALS AND METHODS

Our study has been registered on the CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) website (http://www.dcn.ed.ac.uk/camarades/research.html#protocols). Study protocol is freely downloadable. We followed a previously published guideline of reporting preclinical systematic review and meta-analysis [22].

Literature search

On April 5, 2018, we searched the PubMed, Embase and Web of Science using various combinations of "myocardial infarction" and "extracellular vesicle" (Supplement 4). Publication date was from inception to April 5, 2018. Publication language was limited to English. We also examined the reference lists of eligible studies and review articles to identify possible relevant publications.

Study selection

After removal of duplicates, the studies were screened according to the following inclusion criteria and exclusion criteria. Inclusion criteria: 1) original articles; 2) MI animals; 3) intervention group injected with stem-cell-derived EVs diluted in vehicles; 4) control group injected with vehicles alone (phosphate buffer saline, normal saline or culture medium); 5) reporting of at least one of the following outcomes: left ventricular ejection fraction (EF), left ventricular fractional shortening (FS), or infarct size/area at risk (IS/AAR). Exclusion criteria: 1) article type: review, case report and letter; 2) EVs injected before coronary ligation; 3) control group untreated. Two investigators independently screened the studies. Differences were resolved by consensus.

Data extraction

Data were extracted from eligible studies to a predesigned electronic table which included publication details, study design, and outcomes. If data were only reported in figures, we would extract the data with a digitalized tool WebPlotDigitizer [23]. The authors of potential eligible studies would also be contacted via email for experimental data if they were not reported in their papers. The paper would be excluded from statistical analysis if the emails were not responded before the initiation of statistical analysis (~ 3 weeks). The data extraction table was completed by two investigators independently and then checked by the third investigator.

Quality assessment

We assessed the quality of eligible studies using the following three items adapted from the SYRCLE risk of bias tool: random allocation, blinding injection, and blinding evaluation [24]. Each item was scored “Yes” (given 1 point) or “No” (given 0 point). Two investigators independently scored the eligible studies. Differences were resolved by consensus.

Statistical analysis

In our meta-analysis, small animals were defined as rats and mice, while large animals as pigs. Weighted mean difference (WMD) and the corresponding 95% confidence interval (CI) were calculated for each comparison of studies. DerSimonian-Laird random-effects model was used to pool up the extracted data because we expected a huge heterogeneity across different eligible studies. Q statistic and I^2 statistic were used to quantify the interstudy heterogeneity. Meta-regression analysis was performed to identify how factors including type of stem cell, ligation-to-injection interval, route of delivery, dosage of delivery and follow-up period affected the treatment effects of stem cell-derived EVs. Sensitivity analysis was conducted by removing extreme values and recalculating the effect size and 95% confidence interval. The difference was compared between before and after the removal of extreme values.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

None declared.

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SUPPLEMENTARY MATERIAL

Supplement 1. Baseline characteristics of eligible studies.
Supplement 2. Meta-regression analysis.
Supplement 3. Quality of eligible studies.
Supplement 4. Search strategies.
Supplementary References

Supplement 1. Baseline characteristics of eligible studies.

Author, year	class	Species	Strain	Sex, age, weight	Ligation	Reperfusion	Control		L-to-I time (min)	Route	Total dose (μl)	Follow-up	Imaging	N	EF (%)		Con.		FS (%)		Con.		IS/AAR (%)		Con.	
de Couto G, 2017 [1]	CDC	pig	Yucatan	F, adult, 80 kg	LAD	1	IMDM	2	120	im		48 h	ventriculography	9	56.49	2.31	43.93	3.34					51.56	6.53	81.49	1.98
Gallet R-AMI ic, 2016 [2]	CDC	pig	Yucatan	F, adult, 80 kg	LAD	1	IMDM	2	120	ic	10000	48 h	ventriculography	13	48	6	42	9					77	5	80	5
Gallet R-AMI im, 2016 [2]	CDC	pig	Yucatan	F, adult, 80 kg	LAD	1	IMDM	2	120	im	2000	48 h	ventriculography	11	51	6	42	9					61	12	80	5
Gallet R-CMI im, 2016 [2]	CDC	pig	Yucatan	F, adult, 80 kg	LAD	1	IMDM	2	4 w	im	2000	1 m	ventriculography	11	40	4	34	7								
Ibrahim A-AMI, 2014 [3]	CDC	mouse	SCID	M, 3 m	LAD	0	IMDM	2	0	im	80	4 w	echo	16	44	1.57	31.43	2.28								
Ibrahim A-CMI, 2014 [3]	CDC	mouse	SCID	M, 3 m	LAD	0	IMDM	2	3 w	im	80	3 w	echo	12	42.75	3.6	25.45	2.7								
Tseliou E, 2015 [4]	CDC	rat	Wistar	F, 5-6 w	LAD	0	PBS	1	4 w	im	120	4 w	echo	14	44.07	10.82	32.42	3.44								
Agarwal U-neonate, 2017 [5]	CPC	rat	Crl:NIH-Foxn1rnu	250 g	LAD	1	saline	1	30	im	100	25 d	echo	8	73.26	4.76	58.16	7.42					45.56	7.43	57.05	12.7
Barile L, 2014 [6]	CPC	rat	Wistar	M, 250-300 g	LAD	0	PBS	1	60	im	150	5 d	echo	19	64.13	2.95	47.02	3.25	28	1.33	20.25	1.3				
Barile L-hCPC, 2018 [7]	CPC	rat	Wistar	250-300 g	LAD	0	PBS	1	60	im	100	4 w	echo	20	81.54	1.61	49.16	8.94								
Barile L-hCPC/IR, 2018 [7]	CPC	rat	Wistar	250-300 g	LAD	1	PBS	1	30	im	100	4 w	echo	11	77.16	2.19	60.31	3.36								
Barile L-hCPC2, 2018 [7]	CPC	rat	Wistar	250-300 g	LAD	0	PBS	1	60	im	100	4 w	echo	14	68.1	2.06	46.03	8.25								

Author, year	class	Species	Strain	Sex, age, weight	Ligation	Reperfusion	Control		L-to-I time (min)	Route	Total dose (µl)	Follow-up	Imaging	N	EF (%)		Con.		FS (%)		Con.		IS/AAR (%)		Con.	
Harane N, 2018 [8]	CPC	mouse	199 nude		LAD	0	PBS	1	3 w	im	40	7 w	echo	36	41.28	4.77	41.82	4.9								
Kervadec A, 2016 [9]	CPC	mouse	Rj/NMRI-Foxn1nu/Foxn1nu	M, 8 w	LAD	0	alpha-MEM	2	3 w	im	30	6 w	echo	28	2.83	0.84	2.3	0.77								
Chen C, 2018 [10]	EPC	rat	Wistar	M	LAD	0	PBS	1	0	im	100	4 w	ventriculography	19	39.34	2	31.15	2.72								
Khan M, 2015 [11]	ES	mouse	C57BL/7	M, 8-12w	LAD	0	PBS	1	0	im	20	8 w	echo	12	43.42	2.53	27.93	2.52	28.74	1.32	17.8	2.45	20.8	2.6	32.1	2.3
Adamiak M, 2017 [12]	iPSC	mouse	C57BL6/J	M, 23-29 g, 11-13 w	LAD	1	PBS	1	48 h	im	150	33 d	echo	21	49.66	1.46	37.62	1.67	29.97	0.92	21.66	0.78				
Arslan F, 2013 [13]	MSC	mouse	C57BL6/J	M,10-12 w, 25-30 g	LCA	1	saline	1	25	iv		4 w	MRI	20	53.83	3.6	36.13	3.21					21	2.2	39	1.8
Barile L-hBMMSC, 2018 [7]	MSC	rat	Wistar	250-300 g	LAD	0	PBS	1	60	im	100	4 w	echo	13	62.05	4.54	49.16	8.94								
Barile L-hBMMSC/IR, 2018 [7]	MSC	rat	Wistar	250-300 g	LAD	1	PBS	1	30	im	100	4 w	echo	10	57.32	3.03	60.31	3.36								
Bian S, 2014 [14]	MSC	rat	Wistar	M, adult, 200 g	LAD	0	PBS	1	30	iv	80	4 w	echo	20	55.44	7.5	48.41	6.73	25.76	3.19	21.42	2.93				
Cui X, 2017 [15]	MSC	rat	SD	M, 275-300 g	LAD	1	PBS	1	35	iv	200	3 h		20									21.61	3.54	37.14	5.06
Lai R, 2010 [16]	MSC	mouse	C57BL16/J	M,10-12 w, 25-30 g	LCA	1	saline	1	25	iv	200	24 h	echo	15									17	3.6	34.5	3.3
Lai R, 2010-2]17]	MSC	mouse	C57BL16/J	M,10-12 w, 25-30 g	LCA	1	saline	1	25	iv	200	24 h	echo	16									18.1	2	34.5	3.3

Author, year	**class**	**Species**	**Strain**	**Sex, age, weight**	**Ligation**	**Reperfusion**	**Control**		**L-to-I time (min)**	**Route**	**Total dose (µl)**	**Follow-up**	**Imaging**	**N**	**EF (%)**		**Con.**		**FS (%)**		**Con.**		**IS/AAR (%)**		**Con.**	
Shao L, 2017 [18]	MSC	rat	SD	M, 260-280 g	LAD	0	PBS	1	0	im	40	7 d	echo	20	59.66	4.38	30.77	4.13	31.31	7.03	14.93	2.31				
Teng X, 2015 [19]	MSC	rat	SD	M, 250-300 g	LAD	0	PBS	1	60	im	100	4 w	echo	12	79.24	5.08	62.63	4.74								
Timmers L, 2008 [20]	MSC	mouse	BALB/c	10-12 w, 25-30 g	LCA	1	saline	1	25	iv	20	24h		18									20.16	2.91	34.69	3.16
Wang N, 2017 [21]	MSC	mouse	C57BL/6J	M, 8 w	LAD	0	PBS	1	1	iv		4 w	echo	12	50.35	2.93	39.88	1.99	20.47	1.26	15.7	0.5				
Yu B, 2015 [22]	MSC	rat	SD	F, 2-3 m	LAD	0	saline	1	0	im	50	4 w	echo	26	47.71	3.85	35.13	1.56	20.7	1.83	14.68	0.47				
Zhao Y, 2015 [23]	MSC	rat	SD	M, 220-250 g	LAD	0	PBS	1	0	iv	200	4 w	echo	12	59.97	4.58	50.47	5.92	32.76	3.85	26.41	3.94				
Zhu J, 2017 [24]	MSC	mouse	C57BL/6, 20-25 g	M, 6-8 w	LAD	0	PBS	1	30	im	30	4 w	echo	36	38.19	17.2	20.76	5.39	18.95	3.95	11.95	2.8				

Supplement 2. Meta-regression analysis.

EF

Variable	Coefficient	LCI	UCI	P value
class	1.137701	-1.264895	3.540297	0.339
randomization	-5.218478	-12.01666	1.579708	0.126
blinding injection	.859003	-9.458939	11.17695	0.865
blinding assessment	-1.892155	-8.400234	4.615924	0.555
quality score	-1.877796	-5.479191	1.723599	0.293
species	-4.700754	-13.83159	4.430085	0.299
ligation-to-injection time	-3.227312	-7.725924	1.2713	0.152
route	-1.139511	-5.523777	3.244754	0.597
follow up	-1.352479	-3.148747	.4437895	0.134

FS

Variable	Coefficient	LCI	UCI	P value
class	1.004528	-2.38594	4.394996	0.506
randomization	-.8295799	-9.834547	8.175387	0.834
blinding injection	-3.751959	-12.2494	4.745479	0.331
blinding assessment	-.1332895	-5.896159	5.62958	0.958
quality score	-.7855705	-4.346688	2.775547	0.618
species	-	-	-	-
ligation-to-injection time	-1.490393	-7.062023	4.081236	0.547
route	-1.877727	-4.272445	.5169902	0.106
follow up	-.1646326	-1.630776	1.30151	0.798

IS/AAR

Variable	Coefficient	LCI	UCI	P value
class	1.177793	-2.966831	5.322416	0.531
randomization	5.755156	-3.527084	15.0374	0.191
blinding injection	-.4579897	-14.26349	13.34751	0.941
blinding assessment	.3146597	-11.19345	11.82277	0.951
quality score	1.631681	-3.803592	7.066955	0.508
species	-1.439353	-13.26043	10.38172	0.786
ligation-to-injection time	-4.895186	-20.59604	10.80567	0.493
route	.487758	-5.188615	6.164131	0.848
follow up	.6046283	-1.570909	2.780166	0.540

Supplement 3. Quality of eligible studies.

Author, year	Randomization	Blinding injection	Blinding assessment	Total score
de Couto G, 2017 [1]	0	0	0	0
Gallet R-AMI ic, 2016 [2]	1	0	0	1
Gallet R-AMI im, 2016 [2]	1	0	0	1
Gallet R-CMI im, 2016 [2]	1	0	0	1
Ibrahim A-AMI, 2014 [3]	0	0	0	0
Ibrahim A-CMI, 2014 [3]	0	0	0	0
Tseliou E, 2015 [4]	1	0	0	1
Agarwal U-neonate, 2017 [5]	1	1	1	3
Barile L, 2014 [6]	0	0	0	0
Barile L-hCPC, 2018 [7]	0	0	0	0
Barile L-hCPC/IR, 2018 [7]	0	0	0	0
Barile L-hCPC2, 2018 [7]	0	0	0	0
Harane N, 2018 [8]	0	0	1	1
Kervadec A, 2016 [9]	1	0	1	2
Chen C, 2018 [10]	1	0	1	2
Khan M, 2015 [11]	0	0	0	0
Adamiak M, 2017 [12]	0	0	1	1
Arslan F, 2013 [13]	0	1	1	2
Barile L-hBMMSC, 2018 [7]	0	0	0	0
Barile L-hBMMSC/IR, 2018 [7]	0	0	0	0
Bian S, 2014 [14]	0	1	1	2
Cui X, 2017 [15]	1	0	0	1
Lai R, 2010 [16]	0	0	0	0
Lai R, 2010-2 [17]	0	0	0	0
Shao L, 2017 [18]	0	0	1	1
Teng X, 2015 [19]	0	0	0	0
Timmers L, 2008 [20]	1	0	1	2
Wang N, 2017 [21]	0	0	1	1
Yu B, 2015 [22]	0	0	0	0
Zhao Y, 2015 [23]	0	0	0	0
Zhu J, 2017 [24]	1	0	1	2

Supplement 4. Search strategies.

Search strategies were developed with references to a number of articles, especially review articles [25-29]. It's noteworthy that the nomenclature of EVs has been evolving with time. Currently, a variety of names have been adopted by the researchers of different fields around the world. On April 5, 2018, we searched the PubMed, Embase and Web of Science databases with the following strategies:

PubMed (455):

((((vesicle OR vesicles OR microvesicle OR microvesicles OR micro-vesicle OR micro-vesicles OR nanovesicle OR nanovesicles OR nano-vesicle OR nano-vesicles OR microparticle OR microparticles OR micro-particle OR micro-particles OR exovesicle OR exovesicles OR "platelet dust" OR "platelet dusts" OR "apoptotic body" OR "apoptotic bodies" OR exosome OR exosomes OR secretome OR secretomes OR dexosome OR dexosomes OR texosome OR texosomes OR epididymosome OR epididymosomes OR tolerosome OR tolerosomes OR prostasome OR prostasomes OR ectosome OR ectosomes OR "extracellular vesicles"[MeSH Terms] OR "cell-derived microparticles"[MeSH Terms] OR "exosomes"[MeSH Terms])) AND ("myocardial infarction" OR "myocardial infarctions" OR "myocardial infarct" OR "myocardial infarcts" OR "cardiac infarction" OR "cardiac infarctions" OR "ventricular infarction" OR "ventricular infarctions" OR "myocardium infarction" OR "heart infarction" OR "heart infarctions" OR "myocardial ischemia" OR "myocardial ischemias" OR "myocardial necrosis" OR "myocardial necroses" OR "myocardial reperfusion" OR "myocardial reperfusions" OR "myocardial remodel" OR "myocardial remodeling" OR "ventricular remodeling" OR "atrial remodeling" OR "heart attack" OR "heart attacks" OR "coronary occlusion" OR "coronary occlusions" OR "coronary ligation" OR "coronary ligations" OR "myocardial infarction"[MeSH Terms] OR "myocardial ischemia"[MeSH Terms] OR "myocardial reperfusion"[MeSH Terms] OR "ventricular remodeling"[MeSH Terms] OR "atrial remodeling"[MeSH Terms] OR "coronary occlusion"[MeSH Terms])) AND ((("animal experimentation"[MeSH Terms] OR "models, animal"[MeSH Terms] OR "invertebrates"[MeSH Terms] OR "Animals"[Mesh:noexp] OR "animal population groups"[MeSH Terms] OR "chordata"[MeSH Terms:noexp] OR "chordata, nonvertebrate"[MeSH Terms] OR "vertebrates"[MeSH Terms:noexp] OR "amphibians"[MeSH Terms] OR "birds"[MeSH Terms] OR "fishes"[MeSH Terms] OR "reptiles"[MeSH Terms] OR "mammals"[MeSH Terms:noexp] OR "primates"[MeSH Terms:noexp] OR "artiodactyla"[MeSH Terms] OR "carnivora"[MeSH Terms] OR "cetacea"[MeSH Terms] OR "chiroptera"[MeSH Terms] OR "elephants"[MeSH Terms] OR "hyraxes"[MeSH Terms] OR "insectivora"[MeSH Terms] OR "lagomorpha"[MeSH Terms] OR "marsupialia"[MeSH Terms] OR "monotremata"[MeSH Terms] OR "perissodactyla"[MeSH Terms] OR "rodentia"[MeSH Terms] OR "scandentia"[MeSH Terms] OR "sirenia"[MeSH Terms] OR "xenarthra"[MeSH Terms] OR "haplorhini"[MeSH Terms:noexp] OR "strepsirhini"[MeSH Terms] OR "platyrrhini"[MeSH Terms] OR "tarsii"[MeSH Terms] OR "catarrhini"[MeSH Terms:noexp] OR "cercopithecidae"[MeSH Terms] OR "hylobatidae"[MeSH Terms] OR "hominidae"[MeSH Terms:noexp] OR "gorilla gorilla"[MeSH Terms] OR "pan paniscus"[MeSH Terms] OR "pan troglodytes"[MeSH Terms] OR "pongo pygmaeus"[MeSH Terms]) OR ((animals[tiab] OR animal[tiab] OR mice[Tiab] OR mus[Tiab] OR mouse[Tiab] OR murine[Tiab] OR woodmouse[tiab] OR rats[Tiab] OR rat[Tiab] OR murinae[Tiab] OR muridae[Tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[Tiab] OR rodent[Tiab] OR rodents[Tiab] OR pigs[Tiab] OR pig[Tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[Tiab] OR "guinea pig"[Tiab] OR cavia[Tiab] OR callithrix[Tiab] OR marmoset[Tiab] OR marmosets[Tiab] OR cebuella[Tiab] OR hapale[Tiab] OR octodon[Tiab] OR chinchilla[Tiab] OR chinchillas[Tiab] OR gerbillinae[Tiab] OR gerbil[Tiab] OR gerbils[Tiab] OR jird[Tiab] OR jirds[Tiab] OR merione[Tiab] OR meriones[Tiab] OR rabbits[Tiab] OR rabbit[Tiab] OR hares[Tiab] OR hare[Tiab] OR diptera[Tiab] OR flies[Tiab] OR fly[Tiab] OR dipteral[Tiab] OR drosphila[Tiab] OR drosophilidae[Tiab] OR cats[Tiab] OR cat[Tiab] OR carus[Tiab] OR felis[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematoda[Tiab] OR nematode[Tiab] OR nematodes[Tiab] OR sipunculida[Tiab] OR dogs[Tiab] OR dog[Tiab] OR canine[Tiab] OR canines[Tiab] OR canis[Tiab] OR sheep[Tiab] OR sheeps[Tiab] OR mouflon[Tiab] OR mouflons[Tiab] OR ovis[Tiab] OR goats[Tiab] OR goat[Tiab] OR capra[Tiab] OR capras[Tiab] OR rupicapra[Tiab] OR chamois[Tiab] OR haplorhini[Tiab] OR monkey[Tiab] OR monkeys[Tiab] OR anthropoidea[Tiab] OR anthropoids[Tiab] OR saguinus[Tiab] OR tamarin[Tiab] OR tamarins[Tiab] OR leontopithecus[Tiab] OR hominidae[Tiab] OR ape[Tiab] OR apes[Tiab] OR pan[Tiab] OR paniscus[Tiab] OR "pan paniscus"[Tiab] OR bonobo[Tiab] OR bonobos[Tiab] OR troglodytes[Tiab] OR "pan troglodytes"[Tiab] OR gibbon[Tiab] OR gibbons[Tiab] OR siamang[Tiab] OR siamangs[Tiab] OR nomascus[Tiab] OR symphalangus[Tiab] OR chimpanzee[Tiab] OR chimpanzees[Tiab] OR prosimians[Tiab] OR "bush baby"[Tiab] OR prosimian[Tiab] OR bush babies[Tiab] OR galagos[Tiab] OR galago[Tiab] OR pongidae[Tiab] OR gorilla[Tiab] OR gorillas[Tiab] OR pongo[Tiab] OR pygmaeus[Tiab] OR "pongo pygmaeus"[Tiab] OR orangutans[Tiab] OR pygmaeus[Tiab] OR lemur[Tiab] OR lemurs[Tiab] OR lemuridae[Tiab] OR horse[Tiab] OR horses[Tiab] OR pongo[Tiab] OR equus[Tiab] OR cow[Tiab] OR calf[Tiab] OR bull[Tiab] OR chicken[Tiab] OR chickens[Tiab] OR gallus[Tiab] OR quail[Tiab] OR bird[Tiab] OR birds[Tiab] OR quails[Tiab] OR poultry[Tiab] OR poultries[Tiab] OR fowl[Tiab] OR fowls[Tiab] OR reptile[Tiab] OR reptilia[Tiab] OR reptiles[Tiab] OR snakes[Tiab] OR snake[Tiab] OR lizard[Tiab] OR lizards[Tiab] OR alligator[Tiab] OR alligators[Tiab] OR crocodile[Tiab] OR crocodiles[Tiab] OR turtle[Tiab] OR turtles[Tiab] OR amphibian[Tiab] OR amphibians[Tiab] OR amphibia[Tiab] OR frog[Tiab] OR

frogs[Tiab] OR bombina[Tiab] OR salientia[Tiab] OR toad[Tiab] OR toads[Tiab] OR "epidalea calamita"[Tiab] OR salamander[Tiab] OR salamanders[Tiab] OR eel[Tiab] OR eels[Tiab] OR fish[Tiab] OR fishes[Tiab] OR pisces[Tiab] OR catfish[Tiab] OR catfishes[Tiab] OR siluriformes[Tiab] OR arius[Tiab] OR heteropneustes[Tiab] OR sheatfish[Tiab] OR perch[Tiab] OR perches[Tiab] OR percidae[Tiab] OR perca[Tiab] OR trout[Tiab] OR trouts[Tiab] OR char[Tiab] OR chars[Tiab] OR salvelinus[Tiab] OR "fathead minnow"[Tiab] OR minnow[Tiab] OR cyprinidae[Tiab] OR carps[Tiab] OR carp[Tiab] OR zebrafish[Tiab] OR zebrafishes[Tiab] OR goldfish[Tiab] OR goldfishes[Tiab] OR guppy[Tiab] OR guppies[Tiab] OR chub[Tiab] OR chubs[Tiab] OR tinca[Tiab] OR barbels[Tiab] OR barbus[Tiab] OR pimephales[Tiab] OR promelas[Tiab] OR "poecilia reticulata"[Tiab] OR mullet[Tiab] OR mullets[Tiab] OR seahorse[Tiab] OR seahorses[Tiab] OR mugil curema[Tiab] OR atlantic cod[Tiab] OR shark[Tiab] OR sharks[Tiab] OR catshark[Tiab] OR anguilla[Tiab] OR salmonid[Tiab] OR salmonids[Tiab] OR whitefish[Tiab] OR whitefishes[Tiab] OR salmon[Tiab] OR salmons[Tiab] OR sole[Tiab] OR solea[Tiab] OR "sea lamprey"[Tiab] OR lamprey[Tiab] OR lampreys[Tiab] OR pumpkinseed[Tiab] OR sunfish[Tiab] OR sunfishes[Tiab] OR tilapia[Tiab] OR tilapias[Tiab] OR turbot[Tiab] OR turbots[Tiab] OR flatfish[Tiab] OR flatfishes[Tiab] OR sciuridae[Tiab] OR squirrel[Tiab] OR squirrels[Tiab] OR chipmunk[Tiab] OR chipmunks[Tiab] OR suslik[Tiab] OR susliks[Tiab] OR vole[Tiab] OR voles[Tiab] OR lemming[Tiab] OR lemmings[Tiab] OR muskrat[Tiab] OR muskrats[Tiab] OR lemmus[Tiab] OR otter[Tiab] OR otters[Tiab] OR marten[Tiab] OR martens[Tiab] OR martes[Tiab] OR weasel[Tiab] OR badger[Tiab] OR badgers[Tiab] OR ermine[Tiab] OR mink[Tiab] OR minks[Tiab] OR sable[Tiab] OR sables[Tiab] OR gulo[Tiab] OR gulos[Tiab] OR wolverine[Tiab] OR wolverines[Tiab] OR minks[Tiab] OR mustela[Tiab] OR llama[Tiab] OR llamas[Tiab] OR alpaca[Tiab] OR alpacas[Tiab] OR camelid[Tiab] OR camelids[Tiab] OR guanaco[Tiab] OR guanacos[Tiab] OR chiroptera[Tiab] OR chiropteras[Tiab] OR bat[Tiab] OR bats[Tiab] OR fox[Tiab] OR foxes[Tiab] OR iguana[Tiab] OR iguanas[Tiab] OR xenopus laevis[Tiab] OR parakeet[Tiab] OR parakeets[Tiab] OR parrot[Tiab] OR parrots[Tiab] OR donkey[Tiab] OR donkeys[Tiab] OR mule[Tiab] OR mules[Tiab] OR zebra[Tiab] OR zebras[Tiab] OR shrew[Tiab] OR shrews[Tiab] OR bison[Tiab] OR bisons[Tiab] OR buffalo[Tiab] OR buffaloes[Tiab] OR deer[Tiab] OR deers[Tiab] OR bear[Tiab] OR bears[Tiab] OR panda[Tiab] OR pandas[Tiab] OR "wild hog"[Tiab] OR "wild boar"[Tiab] OR fitchew[Tiab] OR fitch[Tiab] OR beaver[Tiab] OR beavers[Tiab] OR jerboa[Tiab] OR jerboas[Tiab] OR capybara[Tiab] OR capybaras[Tiab]) NOT medline[subset])))))
Embase (960): **#3 (960)** #1 NOT #2 **#2 (402)** #1 AND [embase]/lim NOT [medline]/lim AND 'conference abstract'/it **#1 (1362)** (vesicle OR vesicles OR microvesicle OR microvesicles OR 'micro vesicle' OR 'micro vesicles' OR nanovesicle OR nanovesicles OR 'nano vesicle' OR 'nano vesicles' OR microparticle OR microparticles OR 'micro particle' OR 'micro particles' OR exovesicle OR exovesicles OR 'platelet dust' OR 'platelet dusts' OR 'apoptotic body' OR 'apoptotic bodies' OR exosome OR exosomes OR secretome OR secretomes OR dexosome OR dexosomes OR texosome OR texosomes OR epididymosome OR epididymosomes OR tolerosome OR tolerosomes OR prostasome OR prostasomes OR ectosome OR ectosomes OR 'exosomes'/exp) AND ('myocardial infarction' OR 'myocardial infarctions' OR 'myocardial infarct' OR 'myocardial infarcts' OR 'cardiac infarction' OR 'cardiac infarctions' OR 'ventricular infarction' OR 'ventricular infarctions' OR 'myocardium infarction' OR 'heart infarction' OR 'heart infarctions' OR 'myocardial ischemia' OR 'myocardial ischemias' OR 'myocardial necrosis' OR 'myocardial necroses' OR 'myocardial reperfusion' OR 'myocardial reperfusions' OR 'myocardial remodel' OR 'myocardial remodeling' OR 'ventricular remodeling' OR 'atrial remodeling' OR 'heart attack' OR 'heart attacks' OR 'coronary occlusion' OR 'coronary occlusions' OR 'coronary ligation' OR 'coronary ligations' OR 'heart infarction'/exp OR 'heart muscle ischemia'/exp OR 'heart muscle reperfusion'/exp OR 'heart ventricle remodeling'/exp OR 'coronary artery occlusion'/exp) AND ('animal experiment'/exp OR 'animal model'/exp OR 'invertebrate'/exp OR 'animal'/exp OR 'chordata'/exp OR 'invertebrate chordata'/exp OR 'vertebrate'/exp OR 'amphibian'/exp OR 'bird'/exp OR 'fish'/exp OR 'reptile'/exp OR 'mammal'/exp OR 'primate'/exp OR 'artiodactyla'/exp OR 'carnivora'/exp OR 'cetacea'/exp OR 'chiroptera'/exp OR 'elephant'/exp OR 'hyraxe' OR 'insectivora'/exp OR 'lagomorpha'/exp OR 'marsupialia'/exp OR 'monotremata'/exp OR 'perissodactyla'/exp OR 'rodentia'/exp OR 'scandentia'/exp OR 'sirenia'/exp OR 'xenarthra'/exp OR 'haplorhini'/exp OR 'strepsirhini'/exp OR 'platyrrhini'/exp OR 'tarsii'/exp OR 'catarrhini'/exp OR 'cercopithecidae'/exp OR 'hylobatidae'/exp OR 'hominidae'/exp OR 'gorilla gorilla'/exp OR 'pan paniscus'/exp OR 'pan troglodyte' OR 'pongo pygmaeus'/exp OR animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR 'sus scrofa' OR ferrets OR ferret OR polecat OR polecats OR 'mustela putorius' OR 'guinea pigs' OR 'guinea pig' OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR

pan OR paniscus OR 'pan paniscus' OR bonobo OR bonobos OR troglodytes OR 'pan troglodytes' OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR 'bush baby' OR prosimian OR 'bush babies' OR galagos OR galago OR pongidae OR gorilla OR gorillas OR 'pongo pygmaeus' OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR 'epidalea calamita' OR salamander OR salamanders OR eel OR eels OR fish OR fishes OR pisces OR catfish OR catfishes OR siluriformes OR arius OR heteropneustes OR sheatfish OR perch OR perches OR percidae OR perca OR trout OR trouts OR char OR chars OR salvelinus OR 'fathead minnow' OR minnow OR cyprinidae OR carps OR carp OR zebrafish OR zebrafishes OR goldfish OR goldfishes OR guppy OR guppies OR chub OR chubs OR tinca OR barbels OR barbus OR pimephales OR promelas OR 'poecilia reticulata' OR mullet OR mullets OR seahorse OR seahorses OR 'mugil curema' OR 'atlantic cod' OR shark OR sharks OR catshark OR anguilla OR salmonid OR salmonids OR whitefish OR whitefishes OR salmon OR salmons OR sole OR solea OR 'sea lamprey' OR lamprey OR lampreys OR pumpkinseed OR sunfish OR sunfishes OR tilapia OR tilapias OR turbot OR turbots OR flatfish OR flatfishes OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR 'xenopus laevis' OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR 'wild hog' OR 'wild boar' OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)
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Indexes=SCI-EXPANDED Timespan=All years

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